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

2015 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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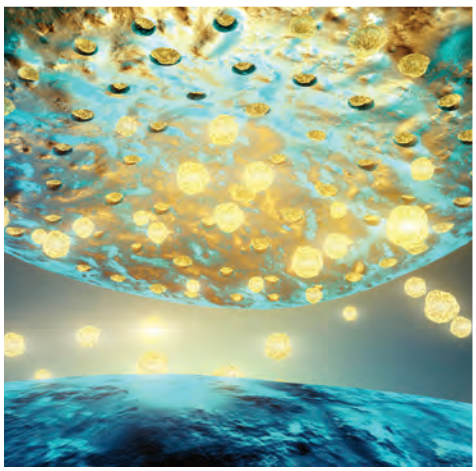

UFHealth
UNIVERSITY OF FLORIDA HEALTH

Office of UF Senior Vice President for Health Affairs

1515 SW Archer Road, Suite 23C1
Gainesville, FL 32608
P.O. Box 100014
Gainesville, FL 32610-0014
Phone: 352.733.1700
Fax: 352.733.1201
UFHealth.org

January 12, 2016

The McKnight Brain Research Foundation
The SunTrust Bank
Mail Code FL-ORL-2160
300 South Orange Avenue, Suite 1600
Orlando, FL 32801

Dear Trustees:

We would like to extend our continuing gratitude to the McKnight Brain Research Foundation (MBRF) for its generous support of the University of Florida's Age-related Memory Loss and Cognitive Aging and Memory research programs in 2015, a productive year for both programs. We are pleased to see the ongoing McKnight inter-institutional collaborations and the progress of the Epigenetics and Bio-informatics Core (funded by the MBRF). Additionally, extramural support for these MBRF sponsored programs has grown significantly with several key investigators in each program earning and renewing NIH funding. The numerous publications and current pilot studies toward understanding and alleviating age-related cognitive decline are impressive.

With the newly formed Evelyn F. McKnight Chair for Clinical Translational Research in Cognitive Aging, we now have two McKnight Endowed Chairs leading and expanding these respective research teams. We look forward to the ongoing accomplishments from these programs and thank you again for your 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
Professor of Epidemiology and Medicine
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Michael L. Good, M.D.
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Senior Associate Dean, Research Affairs
College of Medicine

Age-related Memory Loss (ARML) Program and the Evelyn F. McKnight Chair for Brain Research in Memory Loss

2015 Progress Report

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

PO Box 100015
Gainesville, FL 32610-0015
352-273-8500 Office
352-846-0185 Fax
mbi.ufl.edu

January 15, 2016

The McKnight Brain Research Foundation
SunTrust Bank
Mail Code FL-ORL-2160
300 South Orange Avenue, Suite 1600
Orlando, FL 32801

Dear MBRF Trustees,

It is my pleasure to submit this 2015 Annual Report of the Age Related Memory Loss (ARML) program and the Cognitive Aging and Memory Clinical Translational Research Program (CAM-CTRP). Submitting this report turned out to be one of my very last duties as Executive Director of the Evelyn F. & William L. McKnight Brain Institute (MBI) of the University of Florida (UF). It has been a great privilege to serve the MBI since October 1, 2010, and I would like to express my deepest appreciation to the MBRF for the strong support of our programs.

When I came aboard, the CAM-CTRP had just been established at the Institute on Aging (IoA) at UF to facilitate clinical translation of research on cognitive aging and memory by allocating half of the annual revenue from the MBRF fund at the UF Foundation. However, the transition took some time to appoint Ronald Cohen, PhD as the inaugural Director of the CAM-CTRP. Halving the budget of the ARML program also required a major adjustment of the research program at the MBI. Despite the slow start, subsequent years have shown strong progress. Recruitment of Jennifer Bizon, PhD, Sara Burke, PhD, and Andrew Maurer, PhD allowed Thomas Foster, PhD, Director of the ARML program, to develop an interdisciplinary basic research team for ARML at MBI. Meanwhile, Dr. Foster received the prestigious NIH Merit Award, evidence that he is an undisputed national leader of ARML research. The ARML program has significantly increased its NIH funding and is expected to further increase funding from the NIH and other grant agencies in coming years. The CAM-CTRP was not idle either; Dr. Cohen took no time in organizing a productive team of clinical scientists, which quickly became functional at the IoA. Leaders of the two programs regularly met in the respective institutes' monthly executive committees. Both programs significantly contributed to the inter-institutional collaboration with three other MBIs, which are located at the University of Alabama Birmingham, University of Arizona and University of Miami. In this collaboration, Dr. Foster's team has become a key component of epigenetics studies of learning and memory in aging, and Dr. Cohen has taken a key leadership

role to facilitate the magnetic resonance imaging studies on cognitive aging. Thus, the initial organization of research teams and the return of investments showed clear progress.

While mechanistic basic science research and descriptive clinical studies are fundamentally important on their own right, the next challenge is strengthening the collaborations between CAM-CTRP and ARML program to develop a machinery for seamless clinically meaningful translational research from bench to bedside. The current programs have outstanding scientists at bench and those at bedside, and they understand translational research at their respective conceptual contexts. However to make the translational pipeline work, we will need a handful of researchers who can closely work with both basic scientists and clinical scientists to connect the two programs at the operational level. They may be UF faculty, outside industry scientists, or a group of paid consultants, who have specialized expertise and track record in developing the pipeline from basic bench research to clinical investigations. Such a team may be supported by new NIH grant opportunities envisioning the seamless translational research from the proof of concept to clinical trials. Thus in my view, the team approach with appropriate gap-filling expertise and close communications between the two programs should be a key to the successful conversion of the return of investment from the total grant amount to clinically meaningful values.

It will be the next Executive Director of the MBI who can further nurture these programs. I look forward to learning the new Executive Director's vision and innovative measures to propel the clinically meaningful translational research on cognitive aging.

Sincerely yours,

Tetsuo Ashizawa, M.D.
Executive Director

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 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 (32% FTE), Jennifer Bizon (42%FTE), Sara Burke (90% FTE) and Andrew Maurer (85% FTE).

Promoting Collaboration and Communication across MBRF Institutes

During the past year members of the ARML program have presented posters at the McKnight Brain Research Foundation poster session at the Society for Neuroscience. Dr. Joseph McQuail from Dr. Bizon's lab received 1st place in recognition for his poster. In addition, ARML members attended the 8th Inter-Institutional Meeting of the Evelyn F. McKnight Brain Research Foundation (April 29-May 1, 2015). At the April meeting, Dr. Foster presented an Overview of the Epigenetics Core. The Epigenetics Core brings together the four Institutes to address projects related to examining transcriptional markers of age-related cognitive decline.

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

1) **Cognitive Aging Core:**
   The members of the ARML program (particularly Drs. Bizon and Burke) 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.

2) **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 Eveyln F. McKnight Brain Institutes. The basic infrastructure has been established and currently analysis and manuscript preparation is ongoing a study involving cross institute collaboration examining transcription across three regions of the hippocampus (CA1, CA3, dentate gyrus). Data collection is complete and phone conferences and e-mail correspondences are directed at bioinformatics analysis. It is expected that a manuscript will be submitted in 2016.

Collaborations within UF:

A number of collaborations are ongoing between ARML members and in association with other researchers at the University of Florida. The following represents a subset of collaborations related to funded projects, published papers, grants submitted to NIH, or emphasize collaborations between ARML and CAM-CTRP.

1) **Functional connectivity during aging:** Dr. Burke received a fundable score on an R01 proposal to examine the hypothesis that variability in memory performance across the lifespan is due to differences in functional connectivity among medial temporal lobe and prefrontal cortical areas. This work in collaboration with Drs. Maurer and Bizon, will examine behavior following inactivate specific brain regions with intracerebral infusions.

2) **Role of neurogenesis in in hippocampal-dependent memory:** This collaboration is between Drs. Burke, Maurer, and Ormerod, and received funding from a UF Research Seed Opportunity Fund as well as an R03 from the NIA. Currently, animals are tested in Dr. Foster's behavioral core.

3) **Role of Systemic Inflammation in Age-Related Cognitive Decline.** This project was funded in 2015 (Foster PI) and involves an interaction between ARML members and the biomarkers core at the Institute of Aging. Blood biomarkers of inflammation are correlated with cognition and brain transcription. A similar study examining markers of systemic inflammation and cognition in humans is being conducted by CAM-CTRP and involves the same core and many of the same markers.

4) **Transcriptional profiling:** This work was funded by NIH (Foster PI) and involves collaboration between members of the Foster lab (Ianov, Kumar) and the Bizon lab (Beas). Furthermore, the project utilized the Bio-informatics core and parallels the cross institute collaboration, except that the focus is on the prefrontal cortex. This work examined the transcriptional profiling of

the prefrontal cortex in animals characterized on a battery of cognitive tasks. In addition, age-related changes in the animal model were compared to changes reported in the dorsolateral cortex of aging humans. A manuscript is in preparation.

Currently, we plan to examine human exosome RNA from plasma and DNA single nucleotide polymorphisms from blood cells. Members of the Foster lab (Rani, Ianov) have institutional review board approval for examining blood from humans. The results of the bioinformatics analysis from the cross institute collaboration and the prefrontal cortex collaboration, in addition to theoretical considerations, will direct which subset of DNA single nucleotide polymorphisms to examine. Pilot studies are ongoing to standardize and improve protocols for examine exosome RNA and DNA from blood samples. Once we are confident of these procedures, we will begin examination of samples provided by CAM-CTRP from the ACTIVE project.

5) **Synaptic dysfunction in a mouse model of amyloidosis:** A collaborative project examined behavior and protein expression (Bizon lab) and synaptic function (Dr. Kumar) in a mouse analog of an associative "transfer learning" task that has previously been used to identify risk for prodromal Alzheimer's disease in humans. This collaboration resulted in a published paper (Montgomery et al., 2015).

SUMMARY OF SCIENTIFIC ACHIEVEMENTS SINCE LAST REPORT:

Jennifer Bizon, PhD

Our laboratory had a productive year investigating mechanisms of age-related cognitive decline. Evidence of productivity includes 14 manuscripts at various stages of publication and upwards of 15 presentations at national and international scientific meetings. Highlights include a paper in *The Journal of Neuroscience* from Dr. Caitlin Orsini, a postdoctoral fellow co-mentored by Dr. Barry Setlow and myself. Dr. Orsini's manuscript describes new circuitry underlying risky behavior that we believe may be altered in aging, contributing to to maladaptive decision making in older adults. This work served as the basis for Dr. Orsini's successful Thomas H. Maren Postdoctoral Fellowship awarded in 2014 and a K99 application which recently received an Impact Score of 24 and that has a high likelihood of funding. We also published an invited review for *Trends in Molecular Medicine* (Impact Factor 10.11). This review highlighted several key findings from our laboratory and others regarding age-related dysfunction in GABAergic neurotransmission in the hippocampus and prefrontal cortex and the impact of such alterations on cognition. In addition, we have recently completed a manuscript which describes unique deficiencies in excitatory signaling in the prefrontal cortex that contribute to working memory decline and a novel pharmacological approach for improving this aspect of executive function. Data from this manuscript have been presented by my postdoctoral fellow, Dr. Joseph McQuail at both the International Behavioral Neuroscience Society meeting (where he received 3rd place for his presentation) and at the McKnight Foundation poster session in Chicago (where he received 1st place). This work also served as the basis for Dr. McQuail's successful F32 NRSA fellowship which was awarded earlier this year. Two additional manuscripts are currently under review from our laboratory which directly link GABAergic signaling alterations in the aged prefrontal cortex to cognitive inflexibility and show improvements in this aspect of executive function with the GABA(B) agonist baclofen. Over the past year, we have continued to strengthen our collaboration with Dr. Sara Burke and other ARML affiliates. I am a co-I on Dr. Burke's R01 which received an outstanding score and is likely to be funded. Moreover, Dr. Burke and I co-authored numerous posters at the most recent Sociey for Neuroscience meeting in Chicago, and have three manuscripts submitted or in the final stages of preparation. At the national level, I continue as a Senior Editor at *Neurobiology of Aging* and will Chair the NIH F03 (Neurodevelopment, Synaptic Plasticity and Neurodegeneration Fellowship) Study Section for two years beginning in October 2016. I also regularly serve on other NIH and private foundation grant review panels, including for the National Institute on Aging and Alzheimer's Drug Discovery Foundation.

Sara N. Burke, PhD

The focus of my research continues to be on determining the neurobiology of age-related memory loss. My lab addresses this question using multiple levels of analysis that include molecular imaging techniques, high-channel count in vivo neurophysiology, and behavioral assessment. Particularly, we are taking the novel approach of trying to understand how aging impacts communication across brain areas that are critical for adaptive behaviors. Within the past year we made the novel observation that aged rats are impaired at acquiring object-place associations, which rely on interactions between the prefrontal cortex, perirhinal cortex and hippocampus. The manuscript of these data was recently published in the journal *Behavioral Neuroscience*. To follow up on these data, in collaboration with Dr. Bizon, my lab was able to learn methods for inactivating specific brain regions with intracerebral infusions. We have used this approach to elicit deficits in young rats that resemble those of aged animals by "reversibly disconnecting brain regions to further characterize the neural circuitry that is involved in object-place associations. Furthermore, an additional manuscript is under review at the *Journal of Neuroscience Methods*. Currently, my lab is also incorporating physical performance measures into our models of cognitive aging. This endeavor is being supported by a Pepper Pilot grant as well as my Pepper Scholar Award, which is covering 45% of my research effort.

In addition to making significant progress on our behavioral models, we have also acquired pilot data of immediate-early gene expression (using FISH) and electrophysiological recordings. These were instrumental for my R01 resubmission, which received a fundable score (impact: 14, 3%) and an R21 that was submitted on November 16, 2016 that will be reviewed in February. My lab has also collected substantial amounts of pilot to support a collaborative grant to be submitted with Dr. Jennifer Bizon this winter.

Finally, as my research efforts have continued to focus on further establishing my lab, I have recruited additional personnel to assist with molecular, behavioral and electrophysiological studies. This includes an IDP graduate student, Abigail Rosen, a fulltime OPS employee/lab manager, Jack-Morgan Mizell, who has expertise in data analysis and database management, and several undergraduate students. Two of my undergraduate students, Sean Turner and Patricia Sacks, earned University Scholar Awards from the College of Medicine. I had another undergraduate student defend an honor's thesis and earn High Honors from the Department of Psychology. I had another student who was admitted to the Junior Honor's program and defended an honor's thesis in July before beginning medical school. This student will be returning in the summer to do research with me.

Thomas C. Foster, PhD

Estrogen and cognition over the life span:

We have published 3 papers on effects of estrogen on cognition. One paper examined the receptors that mediate the rapid effets of estradiol (E2) on hippocampal synaptic transmission (Kumar et al., 2015). These results suggest that enhancement of synaptic transmission by E2 involves multiple estrogen receptor subtypes; however, a relatively new receptor, GPER1, is the major contributor to the rapid increase in synaptic transmission. Furthmore, the study suggests that if rapid signaling and enhanced synaptic transmission contribute to learning and memory, then the contribution of each receptor will depend on the expression/function and localization of each receptor. In this case, GPER1 agonists may provide a good alternative to E2 treatment. A second study (Bean et al., in press), employed viral expression of estrogen receptors in the hippocampus to examine the therapeutic window for E2 treatment. This is the first demonstration that the window for E2-mediated benefits on cognition and hippocampal E2-responsiveness can be reinstated by increased expression of ERα. A third project was a collaboration examing the role of estrogen receptors on food intake (Minervini et al., 2015).

Synaptic plasticity and age-related cognitive decline:

We have published 4 papers on synaptic plasticity during aging. One paper examined the involvement of a redox mediated decline in N-methyl-D-aspartate receptor (NMDAR) function to the emergence of impaired executive function (attention) (Guidi et al., 2015a). The results indicate that the emergence and variability of impaired executive function is linked to oxidative stress and a functional decline in NMDARs. A second study examined the behavioral effects of NMDAR blockade (Guidi et al., 2015b). A decrease in NMDAR function is associated with age-related cognitive impairments. However, memantine an NMDAR antagonists is prescribed for mild cognitive impairment and age-related neurodegenerative disease, raising questions as to the role of NMDAR activity in cognitive function during aging. The current studies examined effects of NMDAR blockade on cognitive task that are sensitive to aging. Low doses of NMDAR antagonist enhanced attention and impaired episodic memory. Our results confirm that NMDARs contribute to rapidly acquired and flexible spatial memory and support the idea that a decline in NMDAR function contributes to the age-related impairments in cognition. A third project examined to role of metabotropic glutamate receptors in regulating synaptic plasticity during aging (Kumar and Foster, 2014). Finally, Dr Kumar was an author on a collaborative project examining synaptic dysfunction in a mouse model of amyloidosis (Montgomery et al., 2015).

Role of peripheral inflammation on the onset and progression of cognitive decline:

Behavior was examined in young, middle-age, and aged animals. Cytokines were examined in the serum, hippocampus, and prefrontal cortex. Markers of inflammation in the serum were predictive of the emergence of cognitive decline and cytokines in different brain regions were diagnostic of the type of cognitive impairment. Our data add to the emerging picture of how age-related changes in immune and neuroimmune system signaling impacts cognition (Scheinert et al., 2015).

Other Projects:

We condtibuted to a review on successful aging (Anton et al., 2015) and a paper on transcription during learning (Gomez-Chacon et al., in press).

Andrew Maurer, PhD

Presently, I am working towards developing preliminary data for an R01 proposal investigating age-associated alteration in dentate function with aging. 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. We have managed to secure Seed Opportunity Funding, an R03 and McKnight Seed money for this project which has allowed progress on multiple fronts. Specifically, we have completed an age-related charachterization of spatial discrimination, requiring the integrity of the dentate gyrus. Moreover, we have continued to collect electrophysiology data while using the McKnight support to investigate functional connectivity of the entate circuitry across the lifespan. We anticipate this grant to submitted in the next 18 months.

Since the last progress report, I have managed to support 20 percent of my effort from the previously mentioned R03 as well as a joint R21 with Dr. Barry Setlow, Department of Psychiatry. Furthermore, I have supported an R01 application (Co-I) directed by Dr. Sara Burke which has received a Impact Score of 14 and we are anticipating will be funded.

In the past calendar year, I have published a shared first-author manuscript. Moreover, I have three papers under review and another two in preparation. Moving towards the future, Drs. Jen Bizon, Sara Burke and I are developed a outline to investigate the role of the basal forebrain on prefrontal and hippocampal dynamics. We believe that this should provide a unique intersection to our common research interests by which to develop a competitive grant application.

PUBLICATIONS IN PEER REVIEWED JOURNALS:

Jennifer Bizon, PhD

1. Montgomery, KA, Edwards, E, Kumar, A, Levites, Y, Setlow, B and **Bizon, JL** (2015). Deficits in hippocampal-dependent transfer generalization learning and synaptic function in mouse models of amyloidosis. *Hippocampus*. doi: 10.1002/hipo.22535. [Epub ahead of print]

2. McQuail, JA, Frazier, CJ, **Bizon, JL** (2015). Molecular aspects of age-related cognitive decline: Role of GABA signaling. *Trends in Molecular Medicine*. Jul;21(7):450-60. doi: 10.1016/j.molmed.2015.05.002

3. Paul, S, Jeon, WK, **Bizon, JL** & Han, JS (2015). Interaction of basal forebrain cholinergic neurons with the glucocorticoid system in stress regulation and cognitive impairment. *Frontiers in Aging Neuroscience*. doi: 10.3389/fnagi.2015.00043.

4. Yoder, WM, Gaynor, L, Windham, E, Lyman, M, Munizza, O, Setlow, B, **Bizon, JL** & Smith, DW (2015). Characterizing olfactory binary mixture interactions in Fischer 344 rats using behavioral reaction times. *Chemical Senses*. 40(5):325-34. doi: 10.1093/chemse/bjv014.

5. Orsini, CA, Trotta, RT, **Bizon, JL** & Setlow, B (2015). Dissociable Roles for the Basolateral Amygdala and Orbitofrontal Cortex in Decision-Making under Risk of Punishment. *Journal of Neuroscience*. 35(4):1368-79. doi: 10.1523/JNEUROSCI.3586-14.2015.

6. Shimp, KM, Mitchell, MR, Beas, BS, **Bizon, JL** & Setlow, B (2015). Affective and cognitive mechanisms of risky decision making. *Neurobiology of Learning and Memory*. pii: S1074-7427(14)00048-3. doi: 10.1016/j.nlm.2014.03.002.

7. Orsini, CA, Gilbert, RJ, Willis, M, **Bizon, JL** & Setlow, B. Sex differences in a rat model of risky decision making. *Behavioral Neuroscience. In Press.*

8. Carpenter, HE, Kelly, KB, **Bizon, JL** & Frazier, CJ. *Age related changes in tonic activation of pre- and post-synaptic GABA(B) receptors in medial prefrontal cortex. Under Revision.*

9. Beas, BS, Setlow, B & **Bizon, JL**. *"The GABA(B) receptor agonist baclofen facilitates behavioral flexibility in rats". Under Revision.*

10. Beas, BS, McQuail, JA, Simpson, K, Setlow, B & **Bizon, JL**. *"Reduction in prefrontal GABA(B)R predicts behavioral inflexibility in aged rats: reversal with the GABA(B)R agonist baclofen". Submitted November 2015.*

11. McQuail, JA, Beas, BS, Simpson, K, Kyle, K, Frazier, CJ, Setlow, B, **Bizon, JL**. *"NR2A-containing NMDA receptors in the prefrontal cortex are required for working memory and predict age-related cognitive decline." Submitted December 2015.*

12. Johnson, SA, Sacks, PK, Turner, SM, Gaynor, LS, Ormerod, BK, Maurer, AP, **Bizon, JL** & Burke SN. *Spatial discrimination performance: influence of difficulty, age, and cumulative interference. Submitted December 2015.*

13. Yoder, WM, Lyman, M, Muizza, O, Burke, SN, Setlow, B, Smith, DW & **Bizon, JL**. *"Interaction between age and perceptual difficulty in olfactory discrimination learning: relationship with hippocampal-dependent spatial learning." Final Stages of Preparation.*

14. Hernandez, AR, Reasor, JE, Truckenbrod, L, Johnson, SA, **Bizon, JL**, Maurer, AP & Burke, SN. *"Disconnection of Medial Prefrontal-Perirhinal Cortical Circuits Severely Disrupts Object-Place Paired-Associative Memory." Final Stages of Preparation.*

Sara N. Burke, PhD

1. **Burke, SN**, Barnes, CA (2015). The Neural Representation of 3-Dimensional Objects in Rodent Memory Circuits. *Behavioural Brain Research*, 285: 60-6.

2. Hernandez, AR*, Maurer, AP*, Reasor, J, Turner, S, Barthle, SE, Johnson, SA & **Burke, SN** (2015). Age-related Impairments in Object-Place Associations Signify a Decline in Systems-level Neural Communication. *Behavioral Neuroscience*, 129(5):599-610.

3. Sheremet, A, **Burke, SN**, Maurer, AP (2015). Movement Enhances the Nonlinearity of Hippocampal Theta. *Preliminary acceptance, The Journal of Neuroscience.*

Submitted:

1. Maurer, AP, Topper, NC, Ndum, R, Hernandez, AR, Johnson, SA, Reasor, JE, McEwen, C, Mizell, JM, Turner, SM & **Burke, SN** (2015). An Open Source Software Suite for Collecting and Analyzing Behavioral Exploration Data in Rodents. *Under review, Journal of Neuroscience Methods.*

2. Hernandez, AR, Reasor, JE, Truckenbrod, L, Johnson, SA, Bizon, JL, Maurer, AP & **Burke, SN**. *Disconnection of Medial Prefrontal-Perirhinal Cortical Circuits Severely Disrupts Object-Place Paired-Associative Memory. Final Stages of Preparation.*

3. Yoder, WM, Lyman, M, Muizza, O, Ormerod, BK, **Burke, SN**, Setlow, B, Smith, DW & Bizon, JL. *Interaction between age and perceptual difficulty in olfactory discrimination learning: relationship with hippocampal-dependent spatial learning. Final Stages of Preparation.*

4. Johnson, SA, Sacks, PK, Turner, SM, Gaynor, LS, Ormerod, BK, Maurer, AP, Bizon, JL & **Burke, SN**. *Spatial discrimination performance: influence of difficulty, age, and cumulative interference. To be submitted in December.*

Thomas C. Foster, PhD

1. Guidi, M, Kumar, A & **Foster, TC**. Impaired attention and synaptic senescence of the prefrontal cortex involve redox regulation of NMDA receptors. *J Neurosci*, 2015, 35(9) 3966-3977. **PMCID: 434819**

2. Minervini, V, Rowland, NE, Robertson, KL & **Foster, TC**. Role of estrogen receptor-α on food demand elasticity. *Journal of the Experimental Analysis of Behavior*, 2015, 103(3) 553-561. **PMCID: 25869426**

3. Kumar, A, Bean, LA, Rani, A & **Foster, TC**. Contribution of estrogen receptor subtypes, ERalpha, ERbeta, and GPER1 in rapid estradiol-mediated enhancement of hippocampal synaptic transmission in mice. Hippocampus 2015 in press. **PMCID: 4644731**

4. Scheinert, RB, Asokan, A, Rani, A, Kumar, A & **Foster, TC**. Ormerod, B.K. Some hormone, cytokine and chemokine levels that change across lifespan vary by cognitive status in male Fischer 344 rats. *Brain, Behavior, and Immunity* 2015, 49 216-232. **PMCID: 4567443**

5. Guidi, M, Rani, A, Karic, S, Severance, B, Kumar, A & **Foster, TC**. Contribution of N-methyl-D-aspartate receptors to attention and episodic spatial memory during senescence. *Neurobiology of Learning and Memory*, 2015, 125 36-46. **PMCID: 4648716**

6. Gomez-Chacon, B, Gamiz, F, **Foster, TC** & Gallo, M. Neuroplastic Mechanisms Underlying Perceptual and Cognitive Enhancement. *Neural Plasticity. In press 11/2015.*

7. Anton, SD, Woods, AJ, Ashizawa, T, Barb, D, Buford, TW, Carter, CS, Clark, DJ, Cohen, RA, Corbett, DB, Cruz-Almeida, Y, Dotson, V, Ebner, N, Efron, PA, Fillingim, RB, **Foster, TC**, Gundermann, DM, Joseph, A-M, Karabetian, C, Leeuwenburgh, C, Manini, TM, Marsiske, M, Mutchie, HL, Perri, MG, Ranka, S, Sandesara, B, Scarpace, PJ, Sibille, KT, Solberg, LM, Someya, S, Uphold, C, Wu, SS & Pahor, M. Successful Aging: Advancing the Science of Physical Independence in Older Adults. *Ageing Research Reviews. In Press 10/2015.*

8. Bean, LA, Kumar, A, Rani, A, Guidi, M, Rosario, A, Cruz, P, Golde, T & **Foster, TC**. Re-opening the critical window for estrogen therapy. *Journal of Neuroscience. In press 11/2015.*

9. Montgomery, KS, Edwards, G, **Kumar, A**, Myers, CE Gluck, MA, Setlow, B, Bizon, JL. Deficits in hippocampal-dependent transfer generalization learning accompany synaptic dysfunction in a mouse model of amyloidosis (2015) *Hippocampus. In press.*

Andrew Maurer, PhD

1. Hernandez, AR, **Maurer, AP**, Reasor, JE, Turner, SM, Barthle, SE, Johnson, SA & Burke, SN. Age-related impairments in object-place associations are not due to hippocampal dysfunction. *Behav Neurosci*. 2015 Oct;129(5):599-610.

PUBLICATIONS (OTHER):

Jennifer L. Bizon, PhD

1. Beas, BS, Setlow, B, Samanez-Larkin, GR, **Bizon, JL** (2015). 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

Society for Neuroscience Abstracts:

1. Gaynor, LS, Johnson, SA, Sacks, PK, Maurer, AP, Bizon, JL & **Burke, SN** (2015). *Cholinergic modulation of spatial discrimination performance in young and aged rats. SfN abstract.*
2. Hernandez, AR, Reasor, JE, Turner, SM, Barthle, SE, Johnson, SA, Bizon, JL, Maurer, AP & **Burke, SN** (2015). *Object-place paired associations require interactions between prefrontal and perirhinal cortices. SfN abstract.*
3. Johnson, SA, Gaynor, LS, Sacks, PK, Turner, SM, Yoder, YM, Ormerod, BK, Maurer, AP, Bizon, JL & **Burke, SN** (2015). *Age-related decline of spatial discrimination performance based on difficulty may reflect pattern separation deficits. SfN abstract.*
4. Maurer, AP, **Burke, SN** & Sheremet, A (2015). *Nonlinear oscillations of the hippocampus. SfN abstract.*
5. Ndum, R, Topper, NC, Hernandez, AR, **Burke, SN** & Maurer AP (2015). *A low-cost, open-source gait tracker for rodents. SfN abstract.*
6. Reasor, JE, Hernandez, AR, Turner, SM, Barthle, SE, Johnson, SA, Maurer, AP & **Burke, SN** (2015). *Age-related impairments in object-place associations signify a decline in systems-level neural communication. SfN abstract.*
7. Topper, NC, Ndum, R, Hernandez, AR, Johnson, SA, Reasor, JE, Mizell, JM, Turner, SM, Maurer, AP & **Burke, SN** (2015). *An open-source software suite for collecting and analyzing spontaneous object recognition data. SfN abstract.*

PRESENTATIONS AT SCIENTIFIC MEETINGS:

Jennifer Bizon, PhD

Invited

- *"Molecular aspects of prefrontal cortical-dependent cognitive decline in aging"* Tulane Center for Aging, New Orleans, Louisiana.
- *"GABAergic dysfunction and behavioral inflexibility in a rodent model of age-related cognitive decline"* International Behavioral Neuroscience Society Meeting, Victoria, Canada.
- *"Excitatory-inhibitory imbalance and age-related decline of prefrontal-cortical dependent cognition"* Winter Conference on Brain Research, Big Sky, Montana.
- *"Using olfaction to understand mechanisms of age-related cognitive decline"* Smell and Taste Center Workshop, University of Florida, Gainesville, FL.
- *"How to succeed in science"* (Career Development Panel), North Florida Chapter Society of Neuroscience Symposium, Gainesville, FL.

Poster Presentations

- McQuail, JA, Beas, BS, Kelly, KB, Simpson, K, Frazier, CJ, Setlow, B & **Bizon, JL**. Subtypes of NMDA receptors in working memory and normal aging. *American College of Neuropsychopharmacology Meeting*, Hollywood, FL.
- Orsini, CA, Trotta, R, **Bizon, JL** & Setlow B (2015). Neural Activity in Basolateral Amygdala Encodes reward magnitude and risk of punishment in a risky decision making task in rats. *American College of Neuropsychopharmacology Annual Meeting*, Phoenix, AZ.
- McQuail, JA, Beas, BS, Simpson, K, Setlow, B & **Bizon, JL**. Subtypes of NMDA receptors in working memory and normal aging. *Society for Neuroscience Meeting*, Chicago, IL. ***First place in McKnight Reception Poster Competition***
- Beas, BS, McQuail, JA, Setlow, B & **Bizon, JL** (2015). Reductions in GABABR signaling contribute to aged related impairments in behavioral flexibility. *Society for Annual Neuroscience Meeting*, Chicago, IL.
- Hernandez, C, McQuail, JA, Beas, BS, Setlow, B & **Bizon, JL** (2015). Subregional and behaviorally relevant transcriptional changes related to GABA and glutamate signaling in the aged prefrontal cortex. *Society for Annual Neuroscience Meeting*, Chicago, IL.
- Bruner, MM, McQuail, JA, Backes, IM, Clifton, RR, Setlow, B, Scheuer, DA & **Bizon, JL** (2015). Chronic variable stress recapitulates changes to GABA and glutamate receptors in the aged PFC. *Society for Annual Neuroscience Meeting*, Chicago, IL.
- Orsini, CA, Febo, M, **Bizon, JL** & Setlow, B (2015). Neural activity in basolateral amygdala encodes reward magnitude and risk of punishment in risky decision making task. *Society for Annual Neuroscience Meeting*, Chicago, IL.

- Kelly, KB, McQuail, JA, Hernandez, C, **Bizon, JL** & Frazier, CJ (2015). Aging alters excitatory and inhibitory modulation of GABAergic interneurons in layer 2/3 of the rodent medial prefrontal cortex. *Society for Annual Neuroscience Meeting*, Chicago, IL.
- Gaynor, LS, Johnson, SJ, Sacks, P, Mauer, AP, **Bizon, JL** & Burke, SN (2015). Cholinergic Modulation of spatial pattern discrimination performance in young and aged rats. *Society for Annual Neuroscience Meeting*, Chicago, IL.
- Johnson, SA, Gaynor, LS, Yoder, WM, Ormerod, BK, Maurer, AP, **Bizon, JL** & Burke, SN. Age-related decline of spatial discrimination performance based on difficulty may reflect pattern separation deficits. *Society for Annual Neuroscience Meeting*, Chicago, IL.
- Hernandez, AR, Reasor, JE, Turner, SM, Barthle, SE, Johnson, SA, **Bizon, JL** & Burke, SN. Object-place paired associations require interactions between prefrontal and perirhinal cortices. *Society for Annual Neuroscience Meeting*, Chicago, IL.
- Ianov, L, Rani, A, Kumar, A, Beas, BS, **Bizon, JL** & Foster, TC. Region specific expression of aging and cognitive genes. *Society for Annual Neuroscience Meeting*, Chicago, IL.
- McQuail, JA, Beas, BS, Simpson, K, Setlow, B & **Bizon, JL**. Subtypes of NMDA receptors in working memory and normal aging. *International Behavioral Neuroscience Meeting*, Victoria, Canada.
- McQuail, JA*, Beas, BS, Simpson, K, Setlow, B & **Bizon, JL** (2015). Subtypes of NMDA receptors in working memory and normal aging. *International Behavioral Neuroscience Meeting*, Victoria, Canada. **** Third place in poster competition***

Sara N. Burke, PhD

- January 8, 2015, *Department of Neuroscience Faculty Data Blitz*, Gainesville, FL, "Age-related cross-modal declines in perceptual discrimination."
- January 31, 2015, *Creativity in Arts and Sciences Event* (Presentation by Jordan Reasor), University of Florida, "Disrupted Paths."
- April 27, 2015, **Invited talk**, *Institute for Brain and Machine Cognition Symposium*, Gainesville, FL, "Age-related neural communication deficits."
- May 18, 2015, **Invited talk**, *Institute on Aging Seminar*, Gainesville, FL, "Working towards a systems-level understanding of cognitive aging."
- June 7, 2015, **Invited talk**, *Spring Hippocampal Research Conference*, Taormina, Italy, "Age-related deficits in the acquisition of object-place associations: the role of perirhinal-hippocampal interactions."
- Oct 8, 2015, **Invited talk**, *Department of Neuroscience Seminar*, Gainesville, FL. "Working towards a systems-level understanding of cognitive aging"
- Sept 30, 2015, **Invited talk**, *Rehabilitation Science Seminar*, Gainesville, FL. "Understanding the Bi-directional relationship between physical and cognitive performance with aging"

Thomas C. Foster, PhD

Invited

- Rodent models of synaptic senescence: Relevance to discovery of AD therapies. (2015) **Foster, TC**. *Soc for Neurosci*. 377.11.
- Effect of NMDA receptor blockade on attention and episodic spatial memory during aging (2015). Kumar, A, Guidi, M, Rani, A, Karic, S, Severance, B & **Foster, TC**. *Soc for Neurosci*. 442.06.
- Upregulation of estrogen receptor alpha restores spatial memory and NMDA receptor synaptic function (2015). Beal, LA, Kumar, A, Rani, A, Guidi, M, Cruz, P & **Foster, TC**. *Soc for Neurosci*. 626.28.
- Region specific expression of aging and cognitive genes (2015). Ianov, L, Rani, A, Kumar, A, Beas, BS, Bizon, JL & **Foster, TC**. *Soc for Neurosci*. 628.02.

Poster Presentations

- Synaptic plasticity meets oxidative stress on the path to age-related cognitive decline, *Department of Neuroscience, UF College of Medicine*, 3/12/2015.

- Overview of the Epigenetics Core, data generated at UF and UA on aged animals, samples prepped, and general experimental design for the entire project. *MBRF Inter-Institute Meeting*, 4/2015.
- The senescent synapse: Linking brain aging to cognitive decline. *Department of Physiology and Functional Genomics, UF College of Medicine*, 10/26/2015.
- Cognitive aging – what is it? *Neurology Grand Rounds, UF College of Medicine*, 11/3/2015.

Andrew Maurer, PhD

- Sat, Oct 17, 1:00 - 5:00 PM 84.01/X22 – Age-related decline of spatial discrimination performance based on difficulty may reflect pattern separation deficits *Johnson, SA[1], Gaynor, LS[1], Sacks, PK[1], Turner, SM[1], Yoder, WM[1], Ormerod, BK[1], **Maurer, AP**[1,2], Bizon, JL[1], Burke, SN[1,3]; [1]Dept. of Neurosci., Univ. of Florida, Gainesville, FL; [2]Biomed. Engin., Gainesville, FL; [3]Inst. on Aging, Gainesville, FL.
- Sat, Oct 17, 1:00 - 5:00 PM 84.02/X23 – Nonlinear oscillations of the hippocampus ***Maurer, AP**[1], Burke, SN[1], Sheremet, A[2]; [1]Evelyn F. McKnight Brain Inst., [2]Engin. Sch. of Sustainable Infrastructure & Envrn., Univ. of Florida, Gainesville, FL.
- Sat, Oct 17, 1:00 - 5:00 PM 84.04/X25 – Age-related impairments in object-place associations signify a decline in systems-level neural communication *Reasor, JE[1], Hernandez, AR[1], Turner, SM[1], Barthle, SE[1], Johnson, SA[1], **Maurer, AP**[1,2], Burke, SN[1]; [1]Neurosci., McKnight Brain Institute, Univ. of Florida, Gainesville, FL; [2]Biomed. Engin., Gainesville, FL.
- Sat, Oct 17, 1:00 - 5:00 PM 84.06/X27 – An open-source software suite for collecting and analyzing spontaneous object recognition data *Topper, N[1], Ndum, R[1], Hernandez, AR[1], Johnson, SA[1], Reasor, JE[1], Mizell, JM[1], Turner, SM[1], **Maurer, AP**[1,2], Burke, SN[1,3]; [1]Neurosci., McKnight Brain Institute, Univ. of Florida, Gainesville, FL; [2]Biomed. Engin., Gainesville, FL; [3]Inst. on Aging, Gainesville, FL.
- Sat, Oct 17, 1:00 - 5:00 PM 84.07/X28 – Object-place paired associations require interactions between prefrontal and perirhinal cortices *Hernandez, AR[1], Reasor, JE[1], Turner, SM[1], Barthle, SE[1], Johnson, SA[1], Bizon, JL[1], **Maurer, AP**[1,2], Burke, SN[1]; [1]Neurosci., McKnight Brain Institute, Univ. of Florida, Gainesville, FL; [2]Biomed. Engin., Gainesville, FL.
- Sat, Oct 17, 1:00 - 5:00 PM 84.10/X31 – Cholinergic modulation of spatial discrimination performance in young and aged rats Gaynor, LS[1], Johnson, SA[1], Sacks, PK[1], **Maurer, AP**[1,2], Bizon, JL[1], *Burke, SN[1,3]; [1]Neurosci., Univ. of Florida, Gainesville, FL; [2]Biomed. Engin., Gainesville, FL; [3]Inst. on Aging, Gainesville, FL.
- Sat, Oct 17, 1:00 - 5:00 PM 84.12/X33 – A low-cost, open-source gait tracker for rodents *Ndum, R[1], Topper, N[1], Hernandez, AR[1], Burke, SN[1,2], **Maurer, AP**[1,3]; [1]Neurosci., McKnight Brain Institute, Univ. of Florida, Gainesville, FL; [2]Inst. on Aging, Gainesville, FL; [3]Biomed. Engin., Gainesville, FL.

PRESENTATIONS AT NON-SCIENTIFIC MEETINGS OR EVENTS:

Jennifer Bizon, PhD

- *"Strategies for Healthy Cognitive Aging"* Gainesville Newcomers Club Luncheon, Gainesville, FL.

Sara N. Burke, PhD

- November 20, 2014, **Invited talk**, *Howard Hughes Medical Institute, Science for Life Seminar* "Behavioral Insights into the Neurobiology of Aging."
- April 16, 2015, **Invited talk**, *Oak Hammock Institute for Learning in Retirement Seminar*, Gainesville, FL, "The discovery of cells that constitute a positioning system in the brain."

AWARDS (OTHER):

Jennifer Bizon, PhD

1. UF College of Medicine Excellence in Teaching Award

Sara N. Burke, PhD

1. January 2014, Neuroscience Seminar Data Blitz, voted Best Talk
2. 2014-2015, Exemplary Teaching Award, University of Florida College of Medicine

FACULTY BIOGRAPHICAL SKETCHES: See page 83

TRAINEES:

Jennifer Bizon, PhD

a. **Post-doctoral**

Dr. Joseph McQuail In the past year, Dr. McQuail received a NRSA from the National Institute on Aging to fund his research in my laboratory investigating the mechanisms of prefrontal cortical mediated executive decline in aging. Dr. McQuail has several manuscripts in various stages of publication, including a recent review in Trends in Molecular Medicine. Dr. McQuail has received awards for the presention of his work at several international conferences, including 3rd place at the International Behavioral Neuroscience Society meeting and 1st place at the McKnight reception at the Society for Neuroscience meeting in Chicago.

Dr. Caitlin Orisini (co-Mentored with Dr. Barry Setlow) In the past year, Dr. Orsini has received a Maren Postdoctoral fellowship from the College of Medicine and a very promising score on a recently submitted K99 award from NIH to fund her research related to the neural mechanisms of decision making. She has been instrumental in establishing optogenetic tools in our laboratory, which we are now poised to apply to questions pertaining to cognitive aging. Dr. Orsini has published several manuscripts in the past year, including a study on the neural circuitry of risky decision making in the Journal of Neuroscience.

b. **Pre-doctoral**

Dr. Blanca Sofia Beas Dr. Beas recently completed her Ph.D. in my laboratory. In the past year she has published an invited chapter on animal models of decision making in aging and has two first-author manuscripts under review that are related to cognitive inflexibility in aging. The first of these manuscripts directly links age-related deficits in cognitive flexibility to deficits in GABAergic signaling in the aged prefrontal cortex. The second manuscript demonstrates that the GABA(B) receptor agonist baclofen can facilitate cognitive flexibility in rats. Dr. Beas received several postdoctoral offers and is currently deciding between positions at University of Maryland Collge of Medicine and the National Institute of Mental Health.

Caesar Hernandez Caesar entered my laboratory last year to pursue his Ph.D. on topics related to age related cognitive decline. He has been exceptionally productive and has already presented first-author work related to subregional differences in gene expression in the prelimbic and infralimbic cortex at the recent Society for Neuroscience meeting. He is currently in the process of preparing his initial first author manuscript.

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.

b. **Pre-doctoral:**
Abigail R. Hernandez (Rosen), M.S., joined my laboratory in March 2015. She has been examining the neural circuitry that supports object-place assocations and how this is compromised in old age. Ms. Hernandez (Rosen) is also testing the efficacy of a ketogenic diet intervention for treating cognitive aging and frailty. Leslie Gaynor, is a Clinical neuropsychology student that is working in laboratory as well as the lab of Dr. Russell Bauer. She will be conducting cognitive tests in rats and elderly humans to enhace the translational potential of our research.

c. **Other:**
Sean Turner, is an undergraduate student who will be working with me for 1 year after graduating. Mr. Turner is a University Scholar and a talented young researcher who is examining age-related deficits in changes in object discrimination.

Thomas C. Foster, PhD

b. **Pre-doctoral**
(i) **Linda Bean**, Graduate Student, Department of Neuroscience, University of Florida (Graduated 2015)

(ii) **Lara Ianov**, Graduate Student, Department of Genetics, University of Florida

(iii) **Constantinos Kyritsopoulos**, Graduate Student, Department of Neuroscience, University of Florida

c. **Other**
Mentor for Dr. Amy Brewster (Purdue) as part of the Mentoring Institute for Neuroscience Diversity Scholars (MINDS) program.

Asha Rani (Technical)

Andrew Maurer, PhD

b. **Pre-doctoral:**
Rotation Student, **Douglas Miller**, Neuroscience IDP

CLINICAL/TRANSLATIONAL PROGRAMS:

Jennifer Bizon, PhD

a. **New programs**
We have continued to seek funding for a translational drug discovery program for pharmacological approaches to treat age-related cognitive decline. We were successful last year in obtaining a contract with Sanford Burnham to pursue a medicinal chemistry effort related to GABA(B) receptor antagonists. Unfortunately, changes in the funding structure of Sanford Burnham have left the future of this collaboration uncertain. We also submitted applications to the McKnight Brain Institute Drug Discovery program and the Alzheimer's Drug Discovery Foundation to fund this project. While the latter was well-received, this application was ultimately not funded. In the coming year, we will continue to seek funding mechanisms to move promising pharmacological compounds toward the clinic.

Thomas C. Foster, PhD

a. **New programs**
A new NIH grant has been funded, Systemic inflammation in regulating the onset and progression of brain aging. The 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. A paper has been published which shows that markers of inflammation in the serum are predictive of the emergence of cognitive decline and cytokines in different brain regions are diagnostic of the type of cognitive impairment (Scheinert et al., 2015).

b. **Update on existing clinical studies**
University of Florida Bio-Informatics Core: *Transcription and cognitivefunction:* Behavior on two tasks that depend on

the prefrontal cortex and hippocampus have been completed. Lara Ianov has completed the RNA analysis for the medial prefrontal cortex and region CA1. A manuscript is currently being prepared. *Epigenetics (DNA methylation):* 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.

TECHNOLOGY TRANSFER:

Andrew Maurer, PhD

Patents applications

I am considering submitting an IP for an Operant Conditioning Chamber WiFi interface.

BUDGET UPDATE: See page 66

EDUCATIONAL PROGRAMS FOCUSING ON AGE RELATED MEMORY LOSS: NA

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

Drs. Sara N. Burke and Andrew Maurer (UF), along with Dr. Carol Barnes (UofA) may utilize an older database to conduct a small, collaborative analysis on perirhinal dynamics and aging.

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

Jennifer Bizon, PhD

I currently collaborate with Dr. Greg Samanez-Larkin at Yale University on research related to decision making in aging. Dr. Samanez-Larkin has several R01s to investigate dopaminergic signaling in age-related changes in probabilistic and temporal decision making in humans. We have been establishing a parallel rodent arm of this research to enable mechanistic studies. We have thus far shipped one cohort of young and aged rats to Yale University for PET imaging. We have secured these brains and are in the process of conducting additional molecular analyses.

Thomas C. Foster, PhD

Relationship between transcription and cognitive decline: Inter-institute collaboration The behavior is complete, RNA has been processed and a first pass of analysis has been preformed. We will meet again in December for the second round of analysis. We are hoping to have a paper submitted before the next inter-institute meeting.

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

Jennifer Bizon, PhD

Dr. Sara Burke and I are currently preparing a new R01 as MPIs (target submission February 2016) that is focused on identifying the mechansims of perceptual deficits in aging and their contribution to episodic mnemonic decline. I have additional grants under development with ARML affiates Dr. C Jason Frazier, Dr. Andrew Maurer, and Dr. Barry Setlow as well as with Dr. Debbie Scheuer

(Dept of Physiology) and Dr. Eric Krause (Department of Pharmacodynamics). We have been working with Dr. Scheuer and Krause for the past year to develop a new research avenue focused on prefrontal cortical regulation of the hypothalamic-pituitary-adrenal axis. We have collected preliminary data showing that a chronic variable stress regimen in young adults disrupts GABAergic signaling in the prefrontal cortex and cardiovascular function, both of which can negatively impact cognition. A future grant application will focus on both mechanistic questions and interventions targeting stress as a modifiable risk factor for improving cognitive function at advanced ages.

Sara N. Burke, PhD

I am continuing to foster multiple collaborations within the Department of Neuroscience as well as other departments on campus. In collaboration with Dr. Jennifer Bizon (Neuroscience), we are examining the effects of age and inhibitory/excitatory neurotransmission on olfactory perception. With Dr. Maurer (neuroscience) and Brandi Ormerod (Biomedical Engineering), we are investigating the roles of age-related declines in neurogenesis of hippocampal-dependent memory. This project received funding from UF Research Seed Opportunity Fund as well and an R03 from the NIA (1R03AG049411). 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. This has been submitted to NSF (CRCNS program). Each are these collaborations are directly aligned with ongoing research in my laboratory and are enriching already established research trajectories.

Thomas C. Foster, PhD

Pilot studies will be conducted examine plasma RNA and DNA single-nucleotide polymorphisms (snps) in humans. Based on the litureature and current transcriptional studies, a panel of DNA snps is being designed.

IF APPLICABLE, PLEASE PROVIDE ENDOWMENT INVESTMENT RESULTS FOR THE REPORT PERIOD: See page 74

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

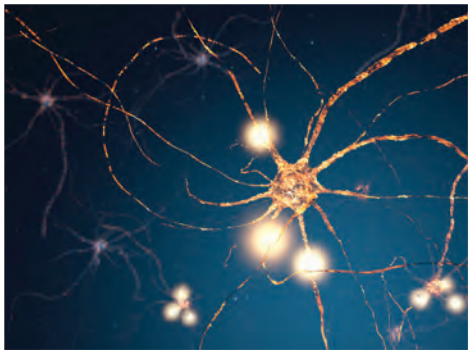
NEGATIVE EVENTS (LOSS OF PERSONNEL, SPACE, BUDGET ETC.): NA

ADDITIONAL COMMENTS: See letter on page 5

SIGNATURE, DATE AND TITLE OF PERSON SUBMITTING THE REPORT:

Cognitive Aging and Memory – Clinical Translational Research Program and the Evelyn F. McKnight Chair for Clinical Translational Research in Cognitive Aging

2015 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

December 21, 2015

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 2015. The past year has been extremely busy and productive for the CAM-CTRP, continuing the progress made over the past three years. 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.

Two areas of continued development that had been raised in past reviews of the CAM-CTRP were 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. The recruitment of a preeminent neurologist to bolster our clinical translational efforts was accomplished. We were very happy when Dr. Steven DeKosky joined the UF faculty with a joint appointment in neurology and also aging and geriatric research. Dr. DeKosky is committed to our work in the CAM-CTRP and has already taken an active role in facilitating two R01 grant submissions. His academic effort is being supported by the CAM-CTRP. He is working closely with Drs. Cohen, Woods and other members of the CAM-CTRP and also IOA on new initiatives, and with neuroscience investigators at the MBI on clinical translational efforts aimed at integrating animal neuroimaging models with human approaches. His new role as interim director of the MBI should greatly enhance all of these collaborations in the coming years. Furthermore, significant strides were made towards the clinical-translational objectives as well, including collaborations with Dr. Foster on the epigenetic initiatives, collaborations with MBI animal researchers on models for translation of laboratory neuroimaging for clinical assessment in humans, and NSF-supported grant proposals aimed brain microstimulation methods in animal models that we hope will eventually lead to human interventions. These research initiatives are described in greater detail in the full report.

Dr. Ron Cohen is currently co-mentoring 3 graduate students, and 3 young faculty who have training awards from NIH. Dr. Woods has also been extremely productive. He was awarded KL2 career development award in March 2014, and recently submitted a K01 to NIA, which received an excellent score and will likely be funded. Dr. Woods is currently mentoring two graduate students, and co-mentoring 3 additional graduate students. Dr. John Williamson who has a VA career development award recently was awarded a R56 with Dr. Cohen as co-I that focuses on HF and cerebral perfusion. We have also had two other young faculty members (Drs. Kim Sibille and Yenisel Cruz- Almeida) funded by career development awards from NIH. Dr. Eric Porges was a post-doctoral fellow and is now joining our faculty as a research assistant professor. He is submitting a K-01 proposal to NIAAA. 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. 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 is underway, providing insights into the 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. Dr. Cohen was also the recipient of a renewal of Research Component 1 of the ARCH from NIAAA to study HIV and alcohol consumption effects. It was originally funded at Brown University, but now will include UF as a primary site as well.

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.

Of particular note, are grants awarded to Dr. Ebner to study oxytocin effects in aging and a pending nutriceutical grant to Dr. Woods to study phosphorus MRS and cerebral metabolic function in the elderly, We have also resubmitted the ACT grant, a MBI-institute R01 of cognitive training and brain stimulation on the suggestion of NIA. The ENRGISE R01 which was recently funded (Pahor, PI) has also been followed by EMRGISE-COG, a R01 focusing on anti-inflammatory agents and their ability to improve cognitive function in the elderly.

There continue to be number of pilot studies (15) 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 expect to continue that trend with enthusiasm and continued productivity. .

Sincerely,

Ronald Cohen, Ph.D., ABPP, ABCN
Professor, Aging, Neurology, and Psychiatry
Director, CAM-CTRP, and Evelyn McKnight Endowed Chair
for Clinical Translation in Cognitive Aging

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

SUMMARY OF SCIENTIFIC ACHIEVEMENTS SINCE LAST REPORT:

There have been a number of achievements since the last annual report, including faculty and affiliate faculty recruitment, new research collaborations, the initiation of the McKnight Inter-Institutional neuroimaging and cognitive initiatives to establish normative databases for successful cognitive aging in people over 85 years, newly funded NIH and industry grants, submission of multiple new R01 grant proposals, including resubmission of a modified ACT grant to study brain stimulation effects on cognitive training on the request of NIA, career development grant submissions with likely funding of a K01 (Woods), and initiation of studies of chemotherapy effects for breast cancer in older women (IOA-Cancer Institute initiative), Specific scientific achievements are outlined later in this report.

A. The CAM-CTRP has continued to focus on responding to the recommendations of the External Review Board Meeting and have made considerable progress in meeting most objectives. These are objectives are listed below along with:

Clinical translation: The board emphasized the value of integrating basic neuroscience findings coming from the AMRL faculty into the human realm with a focus on clinical translation and developing new clinical outcome and biomarkers for cognitive aging and also novel interventions. We have addressed this through several initiatives: 1) Collaboration with Dr. Bizon and her group to develop agents to enhance cognitive and behavioral function in the elderly; 2) Studies bridging high field in vitro and in vivo MR methods in laboratory animals with human MRI and MRS approaches to study neuroinflammation, blood-brain-barrier function, and epigenetic mechanisms contributing to age-associated cognitive decline (Febo, Plant, Miller, DeKosky, Woods, Cohen); 3) Genetic and epigenetic analyses of blood from the CAM ACTIVE brain study of older adults (Foster, Woods, Cohen); and 4) Closed-loop microelectrode brain stimulation for the control of diabetes and obesity (Judy, Porges, Lamb, Febo, Setlow, Cohen). The status of theses initiatives are outlined later in this report.

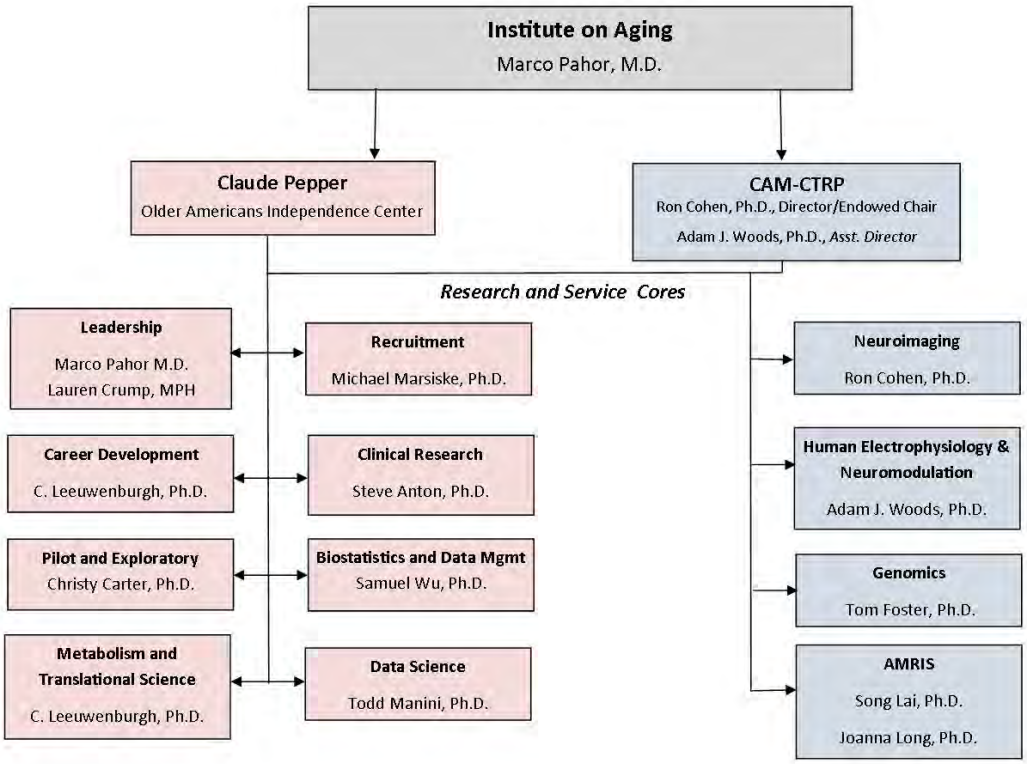
Collaborations across UF and McKnight institutes: The CAM-CTRP has developed a number of collaborations that meet these objectives. These include: 1.CTSI investigators in epidemiology, biostatistics, and health outcomes (e.g., SHARC U-grant, ARCH-2); Veterans Administration Hospital Brain Rehabilitation Research Center investigators (multiple projects including TBI and aging, heart failure, and HIV); 3) biomedical engineering and nanotechnology (closed end feedback brain stimulation grant with Jack Judy, PhD); 4) cardiology (cardiac resynchronization for heart failure); 5) neuroradiology (Erik Middlebrooks, MD-MR biomarker development) and; 6) the involvement of faculty from across the University.

Physician researcher: As part of the recruitment of Dr. Steven DeKosky, the CAM-CTRP negotiated for him to have a joint appointment in the IOA to provide clinical trial and neurological expertise. Dr. DeKosky has moved on to become interim director of the MBI. We believe that his involvement in CAM-CTRP will play an important role in our future studies. He has already contributed as a co-investigator on one NIA grant being submitted, as pilot studies that have been planned as described earlier. Dr. DeKosky is a world renowned neurology researcher with expertise in not only AD, but also cognitive aging and many of the areas of research the CAM-CTRP is engaged in.

The Administrative Chart on the next page 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 Neurophysiology and Neuromodulation, and Genomic Science.

McKnight Brain Research Foundation

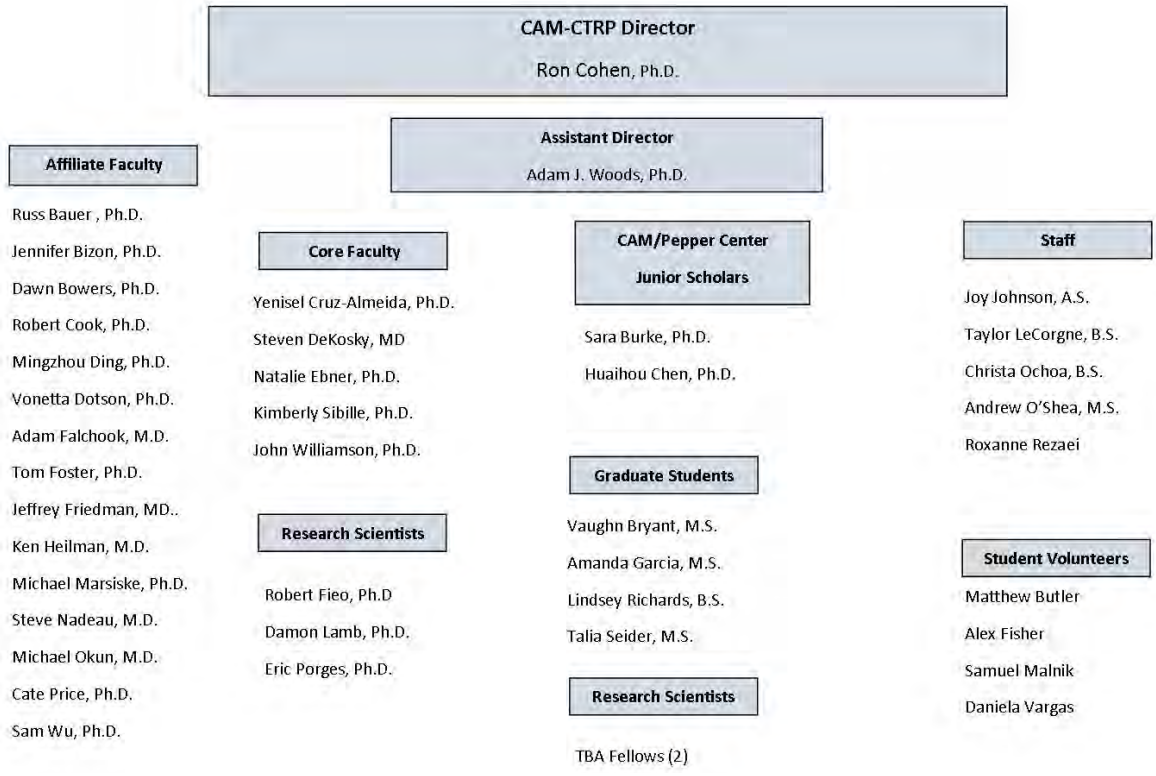
CAM –CTRP Organizational Core Collaboration Chart



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



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 AND NSF FUNDED STUDIES:

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 completed year 1. 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. We have begun to analyze baseline data and will be preparing initial manuscript for publication.

2. **ARCH-2:** (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 now approved by NIAAA with recent IRB approval.

3. **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.

4. **HEART-BRAIN STUDY:** Williamson, Cohen, Heilman, Woods, and other CAM faculty were recently awarded a R56 grant from NHLBI to study the effects of increasing cerebral perfusion via cardiac resynchronization therapy in patients with HF. This study continues a line of research initiated by Dr. Cohen two decades ago that examines the effects of cardiovascular disease factors on the development of brain dysfunction in older adults. This R56 employs neuroimaging methods to achieve greater understanding of the functional, hemodynamic and cerebral metabolic changes that occur when systemic perfusion is improved in people with HF.

5. **LIFE-STUDY:** Secondary analyses of the data from the LIFE study of exercise in older adults has been performed over the past two years in collaboration with investigators at the other LIFE sites to examine effects on cognitive function. This has led to several publications, including a JAMA paper showing only minimal effects of mild-moderate exercise in older adults, though greater benefits among those who are frail and sedentary at baseline. Another finding in a second paper that has been submitted shows greater benefits in people with Type 2 diabetes.

MBRF FUNDED INITIATIVES:

1. **McKnight Brain Aging Registry and Neuroimaging Core:** The aim is to create a normative neuroimaging database consisting of people over 85 years who are aging successfully without neurodegenerative disease. This is an MBI-inter-institute effort in which 200 participants will be recruited (50 at each MBI site). Neuroimaging measures of brain structure, function (FMRI), and cerebral hemodynamic and metabolic function are being obtained, along with serum and a limited cognitive assessment and extensive medical history and functional data.

2. **McKnight Brain Aging Cognitive Core:** The aims of this initiative parallel that of the neuroimaging core, and will establish a more extensive set of normative data on cognitive, sensory, motor, affective, and daily function measures in this same cohort. Blood samples collected in this study will be analyzed in future epigenetic studies. will be unction, and of neuroimaging is block-grant.

CAM SUPPORTED PROJECTS:

1. **ACTIVE BRAIN STUDY** *(Cerebral metabolic, vascular and functional neuroimaging, NIH Toolbox Cognitive Measures, and physical activity as predictors of age associated cognitive dysfunction.)* 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. We have collected three types of data from 150 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 includes a broad age range from 60-85 years, to establish a database of neuroimaging and cognitive performance data for analysis, which will serve as the foundation for gathering independent peer review grant funding. Several papers have been submitted for publication and others are in preparation.

2. **AGING EFFECTS ON SEMANTIC NEURAL NETWORKS (TALKING BRAIN STUDY):** *(Garcia, Cohen, Heilman, Nadeau, Porges, Woods, Chen)* 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. The neuroimaging study has been initiated and 38 participants studied.

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. We are developing the stimuli and tasks and in the process of obtaining normative data in older adults using Amazon. The neuroimaging acquisition will follow.

4. **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 underway with a number of participants recruited. The study has expanded its recruitment base to include Urology (V. Bird) and is receiving 24 hr recruitment support from the Emergency Department, providing optimal coverage for identification and enrollment of the target population.

5. **PROTEOMICS AND GENOMICS OF COGNITIVE AGING:** *(Cohen, Leeuwenburgh, Foster)* This pilot currently is processing serum from 124 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.

6. **STIMULATED BRAIN STUDY:** This is an investigation of neuromodulation of cognition in older adults: *(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. The study has enrolled 19 subjects to date, with 9 completing the 3-month intervention and currently in the one-year follow-up period. This study has achieved an overall 92% adherence rate. The remaining participants are either currently in intervention or awaiting baseline testing prior to intervention. This study and resulting pilot data have led to both a K01 and R01 submission by Woods. The K01 received a fundable score and awaits a funding decision in January NIA Council. The R01 score is still pending.

7. **FACES:** This study examines the effects of oxytocin on socio-emotional decisions in aging (FACES): *(Ebner, Woods, Chen, 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. We have published one manuscript from this study, have another submitted, and two in prepartation.

8. **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.

9. **MIND STUDY:** Development of 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. This study is currently enrolling participants.

10. **STRONG BRAIN STUDY:** This study examines 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. The study is currently completing final follow-up testing in participants and is nearing completion.

11. **Attentive Brain Study:** Age associated changes in attention and arousal: *(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.

NEW INITIATIVES:

1. **McKnight Inter-Institute Initiatives:** As described earlier, neuroimaging and cognitive cores were funded and initiated over the past year as part of the larger effort to develop a MBRF Brain Aging Registry.

2. **ENRGISE-COG:** A multicenter R01 grant was awarded to the IOA UF *(Pahor, PI)* to examine the effects of two different anti-inflammatory drugs/supplements on mobility and physical function. An ancillary R01 was developed *(Woods, Cohen, DeKosky, multiple PIs)* to study the cognitive and brain benefits of reducing systemic inflammation in older adults. This R01, which involves a RCT of McKnight sites was submitted in December.

3. **ACT-2:** This R01 is a revision and resubmission of the ACT grant that previously was submitted to NIA in response to a special RFA. The original grant proposal scored very well (Priority Score = 17) but was not funded because only one project was funded nationally. The program officer suggested that we consider submitting to a new NIA PA focused on RCTs for cognitive aging and AD. This was submitted in December.

4. **CANE:** NSF Engineering Research Center for Autonomic Neural Engineering *(Judy PI)*. This proposal was in response to a NSF RFA for projects to design biomedical devices employing microstimulation and recording methods. Cohen, Porges, Lamb, and Williamson collaborated on a major component of the proposal, which focused on developing a test bed for a closed-end stimulation and feedback system for hypothalamic control of obesity.

5. **SHARC-U01:** The SHARC (Southeastern HIV Alcohol Research Center) is currently up for renewal. Drs. Cook (CTSI, Epidemiology) and Cohen are submitting a U01 proposal as dual PIs for this renewal. The proposed project would examine the effects of reduced alcohol consumption via contingency management on cognitive, behavior, and brain function in HIV infected people with heavy alcohol use, with additional focus on aging influences.

INFRASTRUCTURE AND PROGRAM DEVELOPMENT: *(Cohen, Woods)*

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 and Program 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. The system is now operational and initial pilot data is being obtained to support subsequent R01 submissions. It will be used in the context of the ENRGISE-COG and also the HIV projects.

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. These have now been implemented in several of our studies involving diffusion imaging of the brain.

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

6. Transcranial Direct Current Stimulation studies are now underway.
7. A SuperRapid Magstim TMS system with neuronavigation was purchased for the Neurophysiology and Neuromodulation Core in the CAM.
8. Dr. Woods and colleagues have expanded their CME certified tDCS fellowship (a worldwide first).
9. University-wide Neuroimaging User Group comprised of over 80 UF investigators continues to grow and has been hugely successful *(Cohen, Woods)*.
10. University-wide monthly Human Neuroimaging Lecture Series has been now going on for over a year and is 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. This stalled because of problems with finalizing the drug formulation. We hope that this effort will move forward in the coming months.

G. 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:

Dawn Bowers, PhD

1. Scott, BM, Maye, J, Jones, J, Thomas, K, Mangal, PC, Trifilio, E, Hass, C, Marsiske, M, **Bowers, D**. Post-exercise pulse pressure is a better predictor of executive function than pre-exercise pulse pressure in cognitively normal older adults. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2015 Dec 2:1-13. [Epub ahead of print] **PubMed PMID: 26629911.**
2. Jones, JD, Hass, C, Okun, MS, **Bowers, D**. Reply: The 'cognitions' index of the Parkinson's disease questionnaire-39 relates to sleep disturbances and hallucinations. *Parkinsonism Relat Disord*. 2015 Mar;21(3):351-2. doi: 10.1016/j.parkreldis.2014.12.002. Epub 2014 Dec 11. **PubMed PMID: 25616693.**
3. Jones, JD, Butterfield, LC, Song, W, Lafo, J, Mangal, P, Okun, MS, **Bowers, D**. Anxiety and Depression Are Better Correlates of Parkinson's Disease Quality of Life Than Apathy. *J Neuropsychiatry Clin Neurosci*. 2015 Summer;27(3):213-8. doi: 10.1176/appi.neuropsych.13120380. Epub 2014 Oct 31. PubMed PMID: 25162776; **PubMed Central PMCID: PMC4344415.**
4. Schwab, NA, Tanner, JJ, Nguyen, PT, Schmalfuss, IM, **Bowers, D**, Okun, M, Price, CC. Proof of principle: Transformation approach alters caudate nucleus volume and structure-function associations. *Brain Imaging Behav*. 2015 Dec;9(4):744-53. doi: 10.1007/s11682-014-9332-x. PubMed PMID: 25413122; **PubMed Central PMCID: PMC4440856.**
5. Jones, JD, Marsiske, M, Okun, MS, **Bowers, D**. Latent growth-curve analysis reveals that worsening Parkinson's disease quality of life is driven by depression. *Neuropsychology*. 2015 Jul;29(4):603-9. doi: 10.1037/neu0000158. Epub 2014 Nov 3. **PubMed PMID: 25365564.**
6. LeMonda, BC, Peck, CP, Giles, KJ, **Bowers, D**. Neurocognitive Profile of a Woman with Susac's Syndrome: Further Evidence of Cognitive Variability. *Clin Neuropsychol*. 2015;29(5):689-706. doi: 10.1080/13854046.2015.1076891. **PubMed PMID: 26367343.**
7. Tanner, JJ, Mareci, TH, Okun, MS, **Bowers, D**, Libon, DJ, Price, CC. Temporal Lobe and Frontal-Subcortical Dissociations in Non-Demented Parkinson's Disease with Verbal Memory Impairment. *PLoS One*. 2015 Jul 24;10(7):e0133792. doi: 10.1371/journal.pone.0133792. eCollection 2015. **PubMed PMID: 26208170; PubMed Central PMCID: PMC4514873.**

8. Lafo, JA, Jones, JD, Okun, MS, Bauer, RM, Price, C, **Bowers, D**. Memory similarities in Essential Tremor and Parkinson's disease: A final common pathway. *The Clinical neuropsychologist*. (2015, in press)

9. Price, CC, Levy, SA, Tanner, J, Garvan, C, Ward, J, Akbar, G, **Bowers, D**, Rice, M, Okun, MS. (Orthopedic surgery and post-operative cognitive decline in idiopathic Parkinson's disease: Considerations from a Pilot Study. *J. of Parkinson's Disease*. (2015, in press)

10. Renfroe, JB, Bradley, MM, Okun, MS, **Bowers, D**. Motivational engagement in Parkinson disease: perception and preparation for action. *International Journal of Psychophysiology*. (2015, in press)

11. Jones, J, Mangal, P, Lafo, P, Okun, MS, **Bowers, D**. Mood differences among Parkinson disease patients with mild cognitive impairment. *J. Neuropsychiatry and Clinical Neuroscience*. (2015, in press)

12. Renfroe, J, Bradley, M, **Bowers, D**. Aging and emotion modulation of late positive during affective picture viewing. *Psychology and Aging* (2015, in press).

Huaihou Chen, PhD

1. **Chen, H**, Kelly, C, Castellanos, FX, He, Y, Zuo, XN & Reiss, PT. (2015). Quantile rank maps: A new tool for understanding individual brain development. *NeuroImage*, 111, 454-463.

2. Kantrowitz, JT, Woods, SW, Petkova, E, Cornblatt, B, Corcoran, CM, **Chen, H**, ... & Javitt, DC. (2015). D-serine for the treatment of negative symptoms in individuals at clinical high risk of schizophrenia: a pilot, double-blind, placebo-controlled, randomised parallel group mechanistic proof-of-concept trial. *The Lancet Psychiatry*, 2(5), 403-412.

3. Seider, Talia R; Gongvatana, Assawin; Woods, Adam J; **Chen, H**, Porges, Eric C; Cummings, Tiffany; Correia, Stephen; Tashima, Karen; Cohen, Ronald A; Age exacerbates HIV-associated white matter abnormalities. *Journal of Neurovirology*, 12 Jan 2015, Springer.

Ron Cohen, PhD

1. 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. *Journal of Geriatric Psychiatry and Neurology* 2015;28:57-66.

2. Alosco, ML, Spitznagel, MB, **Cohen, R**, et al. Decreases in daily physical activity predict acute decline in attention and executive function in heart failure. *Journal of Cardiac Failure* 2015;21:339-46.

3. 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. *European Journal of Cardiovascular Nursing: Journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology* 2015;14:334-41.

4. Alosco, ML, Spitznagel, MB, Strain, G, et al. Improved serum leptin and ghrelin following bariatric surgery predict better postoperative cognitive function. *J Clin Neurol* 2015;11:48-56.

5. Alosco, ML, Spitznagel, MB, Strain, G, et al. Pre-operative history of depression and cognitive changes in bariatric surgery patients. *Psychology, Health & Medicine* 2015;20:802-13.

6. Anderson, AM, Harezlak, J, Bharti, A, et al. Plasma and Cerebrospinal Fluid Biomarkers Predict Cerebral Injury in HIV-Infected Individuals on Stable Combination Antiretroviral Therapy. *J Acquir Immune Defic Syndr* 2015;69:29-35.

7. Anton, SD, Woods, AJ, Ashizawa, T, et al. Successful aging: Advancing the science of physical independence in older adults. *Ageing Research Reviews* 2015;24:304-27.

8. Aubertin-Leheudre, M, Woods,, AJ, Anton, S, **Cohen, R**, Pahor, M. Frailty Clinical Phenotype: A Physical and Cognitive Point of View. *Nestle Nutrition Institute Workshop Series* 2015;83:55 63.

9. Clark, US, Walker, KA, **Cohen, RA**, et al. Facial emotion recognition impairments are associated with brain volume abnormalities in individuals with HIV. *Neuropsychologia* 2015;70:263-71.

10. **Cohen, RA**, Seider, TR, Navia, B. HIV effects on age-associated neurocognitive dysfunction: premature cognitive aging or neurodegenerative disease? *Alzheimer's Research & Therapy* 2015;7:37.

11. Daiello, LA, Gongvatana, A, Dunsiger, S, **Cohen, RA**, Ott, BR. Association of fish oil supplement use with preservation of brain volume and cognitive function. *Alzheimer's & Dementia: the Journal of the Alzheimer's Association* 2015;11:226-35.

12. Ebner, NC, Horta, M, Lin, T, Feifel, D, Fischer, H, **Cohen, RA**. Oxytocin modulates meta-mood as a function of age and sex. *Frontiers in Aging Neuroscience* 2015;7:175.

13. Ebner, NC, Kamin, H, Diaz, V, **Cohen, RA**, MacDonald, K. Hormones as "difference makers" in cognitive and socioemotional aging processes. *Frontiers in Psychology* 2014;5:1595.

14. Galioto, R, Alosco, ML, Spitznagel, MB, et al. Glucose regulation and cognitive function after bariatric surgery. *Journal of Clinical and Experimental Neuropsychology* 2015;37:402-13.

15. Hawkins, MA, Alosco, ML, Spitznagel, MB, et al. The Association Between Reduced Inflammation and Cognitive Gains After Bariatric Surgery. *Psychosomatic Medicine* 2015;77:688-96.

16. Monnig, MA, Kahler, CW, Lee, H, et al. Effects of smoking and alcohol use on neurocognitive functioning in heavy drinking, HIV-positive men who have sex with men. *AIDS Care* 2015:16.

17. Seider, TR, Gongvatana, A, Woods, AJ, et al. Age exacerbates HIV-associated white matter abnormalities. *Journal of Neurovirology* 2015.

18. Sink, KM, Espeland, MA, Castro, CM, et al. Effect of a 24-Month Physical Activity Intervention vs Health Education on Cognitive Outcomes in Sedentary Older Adults: The LIFE Randomized Trial. *JAMA* 2015;314:781-90.

19. Thompson, PM, Andreasen, OA, Buckner, RA, .. **Cohen, RA**, …the ENIGMA Consortium. ENIGMA and the individual: Predicting factors that affect the brain in 35 countries worldwide. *Neuroimage*. In press.

Robert L. Cook, MD, MPH

1. Okafor, C, Hu, X, **Cook, RL**. Racial/ethnic disparities in HPV vaccine uptake among a sample of college women. In press, *Journal of Racial and Ethnic Health Disparities*, 2015.

2. Marshall, BDL, Operario, D, Bryant, KJ, **Cook, RL**, Edelman, EJ, Gaither, JR, Gordon, AJ, Kahler, CW, Maisto, SA, McGinnis, KA, van den Berg, JJ, Zaller, ND, Justice, AC, Fiellin, DA. Drinking trajectories among HIV-infected men who have sex with men: A cohort study of United States veterans. **Drug and Alcohol Dependence** 2015 Mar 1;148:69-76. doi: 10.1016/j. **PMID: 25596785.**

3. Delcher, C, Wagenaar, AC, Goldberger, BA, **Cook, RL**, Maldonado-Molina, MM. Abrupt decline in oxycodone-caused mortality after implementation of Florida's Prescription Drug Monitoring Program. *Drug Alcohol Depend*. 2015 May 1;150:63-8. doi: 10.1016/j. **PMID: 25746236.**

4. McGinnis, KA, Fiellin, DA, Tate, JP, **Cook, RL**, Braithwaite, RS, Bryant, KJ, Edelman, EJ, Gordon, AJ, Kraemer, KL, Maisto, S, Justice, AC. Number of drinks to "Feel a Buzz" varies by HIV status and viral load in men. (In press), *AIDS and Behavior*, 2015.

5. Harle, CA, Bauer, SE, Hoang, HQ, **Cook, RL**, Hurley, RW, Fillingim, RB. Toward decision support for chronic pain care: How do primary care physicians decide when to prescribe opioids? A qualitative study. *BMC Family Practice*, 2015 Apr 14;16:48. doi: 10.1186/s12875-015-0264-3.

6. Azarian, T, **Cook, RL**, Johnson, JA, Guzman, N, McCarter, YS, Gomez, N, Rathore, MH, Morris, JG, Jr., Salemi, M. Whole-genome sequencing for outbreak investigations of methicillin-resistant Staphylococcus aureus in the neonatal intensive care unit: Time for routine practice? *Infection Control & Hospital Epidemiology*, 2015 Jul;36(7):777-85. doi: 10.1017/ice.2015.73. Epub 2015 May 8. **PMID: 25998499.**

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8. **Woods, AJ**, Bryant, V, Sacchetti, D, Gervits, F, Hamilton, R. (2015). Effects of electrode drift on transcranial direct current stimulation. *Brain Stimulation*, 8(3): 515-519. Impact Factor: 5.43.

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:

Dawn Bowers, PhD

1. Altmann, L, Stegemoller, E, **Bowers, D**, Okun, MS, Hass, CJ. (2015, February). *Effects of aerobic exercise intervention in Parkinson's disease.* Presented at 43rd annual meeting of the International Neuropsychological Society, Denver CO. (Abstract: Journal International Neuropsychological Society).

2. Scott, BM, Maye, J, Jones, J, Thomas, K, Trifilio, E, Hass, C, Marsiske, M, **Bowers, D**. (2015, February). *Walking as a stressor in cognitively normal older adults: Post-exercise pulse pressure better predicts executive function than pre-exercise pulse pressure.* Presented at 43rd annual meeting of the International Neuropsychological Society, Denver, CO.

3. Scott, BM, Strutt, AM, Lundberg-Love, PK, Schmitt, AL, Trifilio, ER, & **Bowers, D**. (2015, February). *Comparison of psychogenic movement disorders patients with non-epileptic seizsures vs. other hyperkinetic motor manifestations.* Presented at 43rd annual meeting of the International Neuropsychological Society, Denver, CO.

4. Wald, D, Jones, JD, Cummings, T, Mikos, A, Rodriguez, R, Okun, MS, **Bowers, D**. (2015, February). *Is exercise more important for cognitive and mood functioning among Parkinson 's disease patients than normal elderly?* Presented at 43rd annual meeting of the International Neuropsychological Society, Denver CO.

5. Jones, J, Helphrey, J, Thomas, K, Marsiske, M, **Bowers, D**. (2015, February). *Influence of everyday walking on cognition: Multilevel modeling results from the Village Interactive Training and Learning study.* Presented at 43rd annual meeting of the International Neuropsychological Society, Denver, CO.

6. Jones, JD, Marsiske, M, Okun, MS, **Bowers, D**. (2015, February). *Latent growth curve analysis reveals worsening Parkinson's disease quality of life is driven by depression.* Presented at 43rd annual meeting of the International Neuropsychological Society, Denver, CO.

7. Lafo, J, **Bowers, D**, Marsiske, M, Marra, D, Thomas, K, Jones, JD, Reynolds, B, Hass, H, Steindler, D, Bauer, RM. (2015, February). *Effects of combined cognitive training and physical exercise on spatial navigation and learning in older adults.* Presented at 43rd annual meeting of the International Neuropsychological Society, Denver, CO.

8. Mangal, P, Lafo, J, Okun, MS, Bradley, MM, **Bowers, D**. (2015, February). *Emotional memory, the late positive potential, and Parkinson's disease.* Presented at 43rd annual meeting of the International Neuropsychological Society, Denver, CO.

9. Trifilio, E, Scott, B, Thomas, K, Jones, JD, Marsiske, M, **Bowers, D**. (2015, February). *Age related changes in apathy, but not anticipatory anhedonia in cognitively normal older adults.* Presented at 43rd annual meeting of the International Neuropsychological Society, Denver, CO.

10. Thomas, KR, Marsiske, M, Jones, JD, Reynolds, B, Steindler, D, **Bowers, D**. (2015, February). *Effects of Wii, aerobic exercise and cognitive interventions on older adults' self-evaluation of intellectual aging.* Presented at 43rd annual meeting of the International Neuropsychological Society, Denver, CO.

11. Maye, J... (2015, February). *Relationships of pulse pressure and cognitive functioning in cognitively normal older adults in the VITAL study.* Presented at 43rd annual meeting of the International Neuropsychological Society, Denver, CO.

12. Butterfield, L, Jones, J, Thomas, K, Marsiske, M, **Bowers, D**. (2015, February). *Apathy and fatigue are better predictors of cognitive performance than other mood variables in a sample of healthy older adults.* Presented at 43rd annual meeting of the International Neuropsychological Society, Denver, CO. (Abstract: Journal of the International Neuropsychological Society).

13. Hazamy, A, Altmann, Troche, M, Cowles, W & **Bowers, D**. (2015, February). *Emotional sentence processing in persons with Parkinson's disease.* Presented at 43rd annual meeting of the International Neuropsychological Society, Denver, CO. (Abstract: Journal of the International Neuropsychological Society).

14. Morishito,... (2015, April). *Interdisciplinary Deep Brain Stimulation Screening and the Relationship to Unintended Hospitalizations and Quality of Life.* Paper presented at 67th annual meeting of the American Academy of Neurology, Washington DC.

15. **Bowers, D**, Sapienza, C, Rodriguez, R, Fernandez, H, Okun MS. (2015, June). *Unmasking the face of Parkinson disease. Immediate and 3 month followoup from a randomized control behavioral intervention.* International Congress of Parkinson disease and Movement Disorders, San Diego, CA.

16. Scott, B, Scott, BM, Strutt, AM, Lundberg-Love, PK, Schmitt, AL, Trifilio, ER & **Bowers, D**. (2015, June). *Psychogenic movement disorders: Are there neurocognitive differences between patients with non-epileptic seizures vs those with other hyperkinetic motor manifestations?* International Congress of Parkinson disease and Movement Disorders, San Diego, CA.

17. Butterfield, L, Cimino, C, Salazar, R, Lee, C, Haley, W, Sanchez-Ramos, J, Okun, MS, **Bowers, D**. (2015, June). *A Behavioral Intervention Targeting Apathy in Parkinson's Disease: PAL*. International Congress of Parkinson disease and Movement Disorders, San Diego, CA.

18. CC, Price, JJ, Tanner, SAT, Levy, MS, Okun, **Bowers, D** (2015, June). *Gray and white predictors of cognitive frontal-striatal deficits in Parkinson disease.* International Congress of Parkinson disease and Movement Disorders, San Diego, CA.

19. Levy, SA, Tanner, JJ, Okun, MS, **Bowers, D**, Price, CC. (2015, June). *Cognitive change in Parkinson's disease and progression of frontal-striatal deficits.* International Congress of Parkinson disease and Movement Disorders, San Diego, CA. Presented at the annual meeting of the International Congress of Parkinson disease and Movement Disorders, San Diego, CA.

20. L, Almeida, MS, Okun, **Bowers, D**, H, Ward, S, Fayad, C, Jacobson, N, McFarland. (2015, June). *Prevalence of depression in atypical Parkinsonian disorders versus Parkinson's disease.* Presented at the annual meeting of the International Congress of Parkinson disease and Movement Disorders, San Diego, CA.

21. M, Higuchi, H, Morita, **Bowers, D**, H, Ward, L, Warren, M, DeFranco, MS, Troche, S, Kulkarni, EH, Monari, D, Martinez-Ramirez, KD, Foote, Y, Tsuboi, MS, Okun (2015, June). *Interdisciplinary deep brain stimulation screening and the relationship to unintended hospitalizations and quality of life.* Presented at the annual meeting of the International Congress of Parkinson disease and Movement Disorders, San Diego, CA.

22. L, Almeida, MS, Okun, **Bowers, D**, H, Ward, S, Fayad, C, Jacobson, N, McFarland (2015, June). *Prevalence of anxiety in atypical Parkinsonian patients.* Presented at the annual meeting of the International Congress of Parkinson disease and Movement Disorders, San Diego, CA.

23. Thomas, KR, Maye, J, **Bowers, D**, Marsiske, M. (2015, November). *Effects of cognitive impairment on complex everyday tasks process scores.* Presented at the annual meeting of the Gerontologic Society of America. Orlando, FL.

24. Marsiske, M, Thomas, KR, Butterfield, L, Trifilio, E, Jones, J, Reynolds, B, Steindler, D, **Bowers, D**. (2015, November). *Visual processing training, exergaming, & aerobic exercise effects on mood and cognition.* Presented at the annual meeting of the Gerotologic Society of America. Orlando, FL.

Ron Cohen, PhD

1. *Role of the Anterior Cingulate Cortex for Intention.* Pre-INS University of Florida Winter Gator Meeting. Keystone, CO, USA, February 2-6, 2015.

2. McKnight Brain Inter Institute Meeting. *"Clinical Translation Approaches to Cognitive Aging."* Miami, FL. April 27, 2015.

3. Brown University Alcohol Research Center for HIV. (ARCH Summer Meeting). *"Updating on Research Component Number 1"*

Robert L. Cook, MD, MPH

1. Burrell, II LE, Stubbs, L, Bryant, VE, Diggins, A, Whitehead, NE, **Cook, RL**. Centers for Disease Control and Prevention (2015). *STIs and Disclosure of Same-Sex Attraction: Implications for Prevention as Treatment*. Poster presentation at the National AIDS Education and Service for Minorities (NAESM) Leadership Meeting. Atlanta, Georgia. January 2015.

2. Bryant, VE, Porges, EC, Woods, AJ, **Cook, RL**, Kahler, CW, Monti, PM, Cohen, RA. *The Effect of Current Alcohol Consumption on Cognitive Impairment Varies as a Function of HIV Status and Age.* 2015 Southern HIV and Alcohol Research Consortium (SHARC) Conference. Gainesville, FL. January 28-29, 2015.

3. Burrell, LE, Whitehead, N, Bryant, V, Mannes, Z, **Cook, RL**. *Disclosure of Same-Sex Sexual Attraction: Associations with STIs and Risky Sexual Behavior.* 2015 Southern HIV and Alcohol Research Consortium (SHARC) Conference. Gainesville, FL. January 28-29, 2015.

4. Canidate, SS, Cook, CL, **Cook, RL**, Carnaby, GD. *A Systematic Review of NatItrexone for Women with Alcohol Use Disorders.* 2015 Southern HIV and Alcohol Research Consortium (SHARC) Conference. Gainesville, FL. January 28-29, 2015.

5. Dunne, EM, **Cook, RL**, Whitehead, NE. *Misuse of Prescription Drugs Associated with Binge Drinking, Poor Medication Adherence, and Mental Health Diagnoses Among Those Living with HIV.* 2015 Southern HIV and Alcohol Research Consortium (SHARC) Conference. Gainesville, FL. January 28-29, 2015.

6. Jin, J, **Cook, RL**, Hu, X. *Recent Trends in Youth Substance Use in Florida: 2004-2013.* 2015 Southern HIV and Alcohol Research Consortium (SHARC) Conference. Gainesville, FL. January 28-29, 2015.

7. Kelso, NE, Okafor, C, Miguez, MJ, **Cook, RL**. The Influence of Alcohol Consumption on Metabolic Risk Among Women with HIV-infection Who Drink. 2015 Southern HIV and Alcohol Research Consortium (SHARC) Conference. Gainesville, FL. January 28-29, 2015.

8. Mills, J, Kinsell, H, Harman, JS, Cook, CL, **Cook, RL**. *Depression, Alcoholism and HIV: Prevalence and Impact on HIV-Related Hospitalizations.* 2015 Southern HIV and Alcohol Research Consortium (SHARC) Conference. Gainesville, FL. January 28-29, 2015.

9. Okafor, C, Kelso, N, Harman, JS, Cook, CL, **Cook, RL**. *The Relationship Between Complementary and Alternative Medicine (CAM) Use and Immunologic Parameters Among Persons Living with HIV/AIDS (PLWHA) in Florida.* 2015 Southern HIV and Alcohol Research Consortium (SHARC) Conference. Gainesville, FL. January 28-29, 2015.

10. Rahim-Williams, B, Hu, X, Miguez, MJ, **Cook, RL**. *The Weight of Pain and Alcohol Consumption Among Women Living with HIV.* 2015 Southern HIV and Alcohol Research Consortium (SHARC) Conference. Gainesville, FL. January 28-29, 2015.

11. Stubbs, L, Maldonado-Molina, MM, Whitehead, NE, **Cook, RL**, Harman, JS, Cook, C. *Risk Factors Associated with Unmet Service Needs Among HIV-Positive Individuals in the Florida Medical Monitoring Project.* 2015 Southern HIV and Alcohol Research Consortium (SHARC) Conference. Gainesville, FL. January 28-29, 2015.

12. A team science approach to monitoring and improving HIV health outcomes in Florida. Oral presentation: *Turning Research into Prevention (TRIP).* National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention (CDC). Atlanta, GA. March 2, 2015.

13. Okafor, CN, Zhou, Z, **Cook, RL**. *Marijuana use and antiretroviral therapy adherence among persons living with HIV in Florida.* Poster presentation at the College of Public Health and Health Professions Research Day, University of Florida. Gainesville, FL. April 8, 2015.

14. **Cook, RL**, Zhou, Z, Okafor, E, Cook, C, Burrell, L, Whitehead, NE, Harman, JE. *Marijuana use and undetectable HIV viral load in persons living with HIV (PLWH) in Florida.* Poster for College on Problems of Drug Dependence (CPDD). Phoenix, AZ. June 14-17, 2015.

15. **Cook, RL**, Hu, X, Weber, KM, Mai, D, Karki, M, Thomas, K, Brumback, B, Rathore, M, Bryant, KJ, Young, M, Cohen, M. *Pharmacotherapy for Hazardous Drinking in Women with HIV: A Pilot Randomized Clinical Trial.* Poster for Research Society on Alcoholism (RSA) Scientific Meeting. June 22, 2015.

16. Kelso, NE, Sheps, DS, **Cook, RL**. *The association between alcohol consumption and cardiovascular disease among people living with HIV: A systematic review.* Poster presentation at the 2015 Research Society on Alcoholism. San Antonio, TX. June 22, 2015.

17. **Cook, RL**, Zhou, Z, Harman, J, Kelso, N, Miguez, MJ. *Challenges when assessing potential causes of racial disparities in HIV from existing data sources.* Abstract for invited session at the 2015 combined session of the RSA and Research Society on Alcoholism and the National Hispanic Science Network (NHSN) meeting. San Antonio, TX. June 24, 2015.

18. National Hispanic Science Network (NHSN) Panel: HIV, Alcohol and Health Disparities Panel included: Kendall Bryant, PhD, Patricia Molina, MD, PhD, Maria Miguez-Burbano, MD, PhD, **Robert L. Cook, MD**, Carmen Albizu, MD, and David Perez-Jimenez, PhD, San Antonio, TX. June 24, 2015.

Yenisel Cruz-Almeida, MSPH, PhD

1. **Cruz-Almeida, Y**. *Healthy Brain Project: Neuroepidemiology Study of 15-year exposure to Risk Factors for Brain Aging: Pain.* Symposium Speaker – Gerontological Society of America, 2015. Orlando, FL.
2. **Cruz-Almeida, Y**. *Aging, Central Nervous System and Mobility: Follow-up from a 3-year NIA Funded GSA Pre-Conference.* Symposium Speaker – Gerontological Society of America, 2015. Orlando, FL.
3. **Cruz-Almeida, Y**. *Intersecting mechanisms of pain in older adults.* Starke Neuroscience Institute, October 22nd, 2015, Indiana University, Indiannapolis, IN.
4. **Cruz-Almeida, Y**. *Neurobiological mechanisms of pain in older adults.* PRICE Data Blitz, September 21st, 2015, University of Florida, Gainesville, FL.
5. **Cruz-Almeida, Y**. *Pain in Older Adults: Predictors, Functional Consequences and Considerations for Treatment.* Symposium Speaker – American Pain Society, 2015. Palm Springs, California.
6. **Cruz-Almeida, Y**. *Pain Measurement Across the Lifespan.* Speaker at the Shared Interest Group Meeting – Measurement of pain and its impact. American Pain Society, 2015. Palm Springs, California.
7. **Cruz-Almeida, Y**. *Pain and Aging: Interactions with cognition and physical function.* Claude D. Pepper for Older Adults. University of Pittsburgh, PA. March 3, 2015.

Mingzhou Ding, PhD

1. *"Multimodal Imaging of Human Brain Function,"* Department of Clinical and Health Psychology, University of Florida, January, 2015.
2. *"Multimodal Imaging of Pain,"* The Facial Pain Research Foundation Scientific Meeting, Naples, Florida, March, 2015.
3. *"Imaging Human Brain Function with Simultaneous EEG-fMRI,"* The 2015 International Symposium on Computational Psychophysiology, Jinan, China, April, 2015.
4. *"Imaging Human Brain Function with Simultaneous EEG-fMRI,"* The Kavli Futures Symposium on Emerging Technologies for Neuroscience, Santa Barbara, June, 2015.
5. *"Imaging Human Brain Function with Simultaneous EEG-fMRI,"* BrainModes: Neuronal Oscillations and Large-scale Brain Networks, Atlanta, December, 2015.

Vonetta Dotson, PhD

1. Szymkowicz, SM, McLaren, ME, O'Shea, A, Woods, AJ, Manini, TM, Anton, SD & **Dotson, VM**. (2015). *Subthreshold depressive symptoms are associated with age-related structural brain changes.* Poster presented at the 43rd annual International Neuropsychological Society meeting, Denver, CO.
2. McLaren, ME, Szymkowicz, SM, O'Shea, A, Woods, AJ, Manini, TM, Anton, SD, **Dotson, VM**. (2015). *Symptom dimensions of depression and frontal brain volume in older adults.* Poster presented at the 43rd annual International Neuropsychological Society meeting, Denver, CO.
3. Kirton, JW & **Dotson, VM**. *Moderating effects of age and education on the relationship between body mass and memory function in community adults.* Poster presented at the 43rd annual International Neuropsychological Society meeting, Denver, CO.

Natalie Ebner, PhD

1. Horta, M, Lin, T, Fischer, H, Cohen, RA, Feifel, D & **Ebner, NC**. (May, 2015). *Does Oxytocin Affect Emotional Competence and Prosocial Decision-Making in Aging?* Poster at the 27th Annual Convention of the Association for Psychological Science, New York, NY, USA.
2. Lin, T, Horta, M, Fischer, H, Cohen, RA, Feifel, D & **Ebner, NC**. (May, 2015). *Effects of intranasal oxytocin on trust–related decision making in aging.* Poster at the 27th Annual Convention of the Association for Psychological Science, New York, NY, USA.

3. Szymkowicz, S, Fischer, H, Persson, J & **Ebner, NC**. (May, 2015). *Hippocampal volume predicts accuracy and speed of emotional face recognition in older adults.* Poster at the 27th Annual Convention of the Association for Psychological Science, New York, NY, USA.

4. Ziaei, M, Hippel, W, Henry, J, **Ebner, NC** & Burianová, HA. (April, 2015). *Multivariate analysis of brain networks involved in facial gaze and emotion processing.* Poster at the Annual Meeting of the Australasian Experimental Psychology Conference, Sydney, Australia.

5. Ziaei, M, Hippel, W, Henry, J, **Ebner, NC** & Burianová, HA. (June, 2015). *Multivariate analysis of brain networks involved in facial gaze and emotion processing.* Talk at the Annual Meeting of the Australasian Social Neuroscience Society, Brisbane, Australia.

6. Horta, M, Lin, T, Fischer, H, Cohen, RA, Feifel, D & **Ebner, NC**. (March, 2015). *Effects of age and intranasal oxytocin on prosocial decision-making.* Poster at the Decision Neuroscience and Aging Conference, Miami, FL, USA.

7. Lin, T, Horta, M, Fischer, H, Cohen, RA, Feifel, D & **Ebner, NC**. (March, 2015). *Effects of intranasal oxytocin on trust–related decision making in aging.* Poster at the Decision Neuroscience and Aging Conference, Miami, FL, USA.

8. Dillon, K, Strickland-Hughes, CM, West, RL & **Ebner, NC**. (February, 2015). *Own-age bias in face-name associations: Evidence from memory and visual attention in younger and older adults.* Poster at the ILR Student Research on Aging Exposition, Gainesville, FL, USA.

9. Horta, M, Lin, T, Fischer, H, Cohen, RA, Feifel, D & **Ebner, NC**. (February, 2015). *Does intranasal oxytocin affect emotional competence in aging?* Poster at the ILR Student Research on Aging Exposition, Gainesville, FL, USA.

10. Strickland-Hughes, CM, **Ebner, NC** & West, RL. (February, 2015). *Influences of age-salient false feedback and beliefs on name memory in younger and older adults.* Poster at the ILR Student Research on Aging Exposition, Gainesville, FL, USA.

11. Strickland-Hughes, CM, **Ebner, NC** & West, RL. (February, 2015). *Influences of age-salient false feedback and beliefs on name memory in younger and older adults.* Talk at Oak Hammock, Gainesville, FL, USA.

12. Rana, M, **Ebner, NC** & Sitaram, R. (February, 2015). *Real-time functional magnetic resonance imaging (rtfMRI) demonstration.* Poster at the 2nd International Conference on Real-time Functional Imaging and Neurofeedback, Gainesville, FL, USA.

13. Varan, AQ, Rana, M, Cohen, RA, Sitaram, R & **Ebner, NC**. (February, 2015). *Executive functioning and neurofeedback success in aging.* Poster at the 2nd International Conference on Real-time Functional Imaging and Neurofeedback, Gainesville, FL, USA.

Eric S. Porges, PhD

1. AD Falchook, **EC 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.

2. Natalie Ebner; **Eric 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.

Kimberly Sibille, MA, PhD

1. **Sibille, K**, Fillingim, RB, Williams, D (2015). *Enhanced Classification and Assessment of Chronic Pain: Moving Beyond Dichotomy.* Presentation at the 34th Annual Scientific Meeting of the American Pain Society, May 13-16, 2015 in Palm Springs, CA.

2. **Sibille, K** (May 2015). *Allostatic Load Composite Predicts Knee OA Pain, Physical Functioning, and Protective Factors.* Invited poster presentation at the 2015 NIH Pain Consortium Symposium, Washington, DC.

John Williamson, PhD

1. **Williamson, JB**, Lamb, DL, Harciarek, M, Porges S, Heilman, K. *The identification of emotional facial expressions in people with mild traumatic brain injury and symptoms of PTSD.* Presented at the annual meeting of the International Neuropsychological Society 2015.

2. Harciarek, M, Michalwoski, J, Biedunkiewicz, B, **Williamson, JB**, Beska-Slizien, A, Rutkowski, B. *What do the event related potentials tell us about the anterior attentional system in dialyzed patients with end-stage renal disease?* Presented at the Annual meeting of the International Neuropsychological Society 2015.

3. Harciarek, M, Michalwoski, J, Biedunkiewicz, B, **Williamson, JB**, Beska-Slizien, A, Rutkowski, B. *Anterior attentional/executive system in adequately hemodyalized patients with end-stage renal disease.* Evidence from the ROBBIA. Presented at the Annual meeting of the international neuropsychological Society 2015.

4. Stead, T, Ratogi, R, Penumudi, R, Lamb, D, **Williamson, JB**, Hedna, V. *Hemispheric differences in malignant middle cerebral artery stroke.* Presented at 2015 annual meeting of the American Academy of Neurology.

Adam J. Woods, PhD

1. **Woods, AJ**. *Updates on cognitive training and tDCS clinical trials in cognitive aging.* Updates on Clinical Trials in tDCS Symposium, City College of New York, New York, NY, USA, November 14, 2015.
2. **Woods, AJ**. *Updates on cognitive training and tDCS clinical trials in cognitive aging.* Updates on Clinical Trials in tDCS Symposium, City College of New York, New York, NY, USA, November 14, 2015.
3. **Woods, AJ**. *Preliminary data from the STIMULATED BRAIN study: a novel transcranial direct current stimulatgion intervention for cognitive aging.* 3rd International GABA MRS Symposium, Orlando, FL, USA, October, 15, 2015.
4. **Woods, AJ**. *A Novel Non-Invasive Intervention for Cognitive Aging.* University of Florida Clinical Translational Science Institute Research Day, Gainesville, FL, USA, June 12, 2015.
5. Porges, EC, **Woods, AJ**, Bryant, VE, Cohen, RA. *The effect of current alcohol consumption on cognitive impairment varies as a function of HIV status and age.* Research Society on Alcoholism, invited symposium, San Antonio, TX, USA, June 20, 2015.
6. **Woods, AJ**, Bryant, V, Sacchetti, D, Gervits, F, Hamilton, R. *Effects of electrode drift on transcranial direct current stimulation.* International Brain Stimulation Conference. Singapore, March 5, 2015.
7. **Woods, AJ**, Bikson, M. *Research Uses of tDCS.* Invited Symposium, International Brain Stimulation Conference. Singapore, March 5, 2015.
8. **Woods, AJ**, Bryant, V, Sacchetti, D, Gervits, F, Hamilton, R. *Reducing variability of effects in transcranial direct current stimulation.* Pre-INS Gator Meeting. Keystone, CO, USA, February 3, 2015.
9. **Woods, AJ**. *Reducing alcohol abuse in people living with HIV using tDCS.* Annual Southeastern HIV and Alcohol Research Consortium (SHARC) Conference. Gainesville, FL, USA, January 28-29, 2015.
10. **Woods, AJ**. *Effects of electrode drift and localization on transcranial direct current stimulation.* NYC Neuromodulation 2015. New York, NY, USA, January 11, 2015.

PRESENTATIONS TO THE COMMUNITY (NON-SCIENTIFIC MEETINGS):

Huaihou Chen, PhD

Chen, H, Reiss, PT, Tarpey, T. *Optimally Weighted L2 Distance for Functional Data.* Department of Math and Statistics, Auburn University. November, 2014.

Robert L. Cook, MD, MPH

2015 *Fogarty Indo-U.S. Training Program.* Bangalore, India, January 13, 2015.

2014-Present *P.A.U.S.E.*, Alachua County, Teen training designed to teach students how to overcome barriers they face when trying to facilitate peer access to local resources.

Yenisel Cruz-Almeida, MSPH, PhD

IOA Translational Science Meeting

Oak Hammock Lecture Series

Vonetta Dotson, PhD

Dotson, VM. *Effects of Depression on Cognitive and Brain Aging.* Presented at the San Diego State University Advancing Diversity in Aging seminar, San Diego, CA, October 7, 2015.

Natalie Ebner, PhD

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.

John Williamson, PhD

2015 Pepper Center Meeting. *Cognitive impairment reversion: Predictors*

2015 Neurostimulation tech meeting: *Methods and approaches to deep brain stimulation in post traumatic stress disorder.*

AWARDS:

Dawn Bowers, PhD

2015 Doctoral Mentoring Award – College or Public Health and Health Professions

2015 Audrey Shumacher Teaching Award – Department of Clinical & Health Psychology

T32 NS82168	Bowers/Vaillancourt	05/2015-04/2020	NIH/NINDS

Interdisciplinary Training in Movement Disorders and Neurorestoration.

This T32 for Interdisciplinary Training in Movement Disorders is designed to support research oriented advanced PhD students from multiple disciplines (neuroscience, movement science, cognitive-emotion neuroscience, biomedical engineering, rehabilitation science) who are using varied approaches (cellular/genetic to physiologic to behavior) to study movement disorders.

N/A	Bowers/Marsiske (MPI)	03/2014-02/2017	Sante Fe/AvMed

Vitality Mind-Brain Health: Re-Vitalize, Cedar, & Neuroadvantage

This project tests various hypotheses regarding the basis for cognitive improvement in older adults undergoing various cognitive and behavioral interventions i.e., mindfulness, exergames, LED NIR.

R21 NS079767	Bowers	2012-2015	NINDS

Emotion Regulation, Executive Function, and Parkinson Disease

This study examines the role of executive function in upregulating and downregulating emotional reactivity in Parkinson patients, as indexed by ERP (LPP) and other physiological measures.

R01 NS082386	Price	2013 -2018	NINDS

White Matter Connectivity and PD Cognitive Phenotype

This grant examines several cognitive subtypes of PD in relation to white matter connectivity using diffusiontensor imaging.

Role: Co-I

R03-MH109333	Dotson	2015-2017	NIMH

Dissociating Components of Anhedonia: Pilot Behavioral and fMRI Data for the Effort Expenditure for Rewards Task

The goal of this study is to examine the neural correlates of anhedonia in older and younger adults.

Role: Co-I

N/A	Okun	2015-2017	Michael J. Fox Foundation

A Responsive Closed-Loop Approach to Treat Freezing of Gait in Parkinson's Disease

The major goal of this study is to provide a rapid, automated closed-loop algorithm prototyping. The approach involves identifying local field potentials (LFP) occurring in GPi and PPN during normal walking and during maneuvers known to instigate freezing episodes. The Nexus-D algorithm will be used to facilitate a responsive train of stimulation to break freezing episodes.

Role: Co-I

Pending

R21-NS098071	Bowers	06/01/16 – 05/31/18	NINDS

Apathy and Parkinson's Disease

The goal of this study is to examine methods for bolstering physiological reactivity to emotional stimuli in Parkinson patients with apathy and the relationship to executive function and everyday activities.

R43- EB021913 Benton/Bowers 06/2016-05/2019 NIBIBB

Online Treatment for Anxiety and Depression in Older Adults

This joint industry - university initiative (SBIR) intends to develop and pilot online anxiety and depression treatment modules for older adults in rural settings.

State of Florida Bowers 02/2016-01/2018

Pilot Intervention in Mild Cognitive Impairment: A Proof of Concept Study with Transcranial Near Infrared Stimulation

This pilot study will test in a randomized sham controlled trial whether a novel intervention, near infrared brain stimulation, has potential for improving cognitive symptoms in individuals with amnestic mild cognitive impairment.

State of Florida Wicklund 02/2016-01/2018

Consortium for Diagnostic Algorithm with Novel Markers in Early Alzheimer's Disease

The goal of this study is to develop an automated algorithm for enhancing sensitivity of diagnostic decision making and clinical efficiency regarding MCI and early AD drawing from multiple data sources (i.e., clinical, neuropsychological, experimental cognitive, imaging)

Role: Co-I

R01 Okun 07/01/16-06/30/21 NIH

The Human Thalamocortical Network In Tourette Syndrome.

The goal of this study is to develop a closed loop neuromodulation solution for Tourette syndrome and to explore the humanthalamocortical newtwork in Tourette syndrome

Role: Co-I

Huaihou Chen, PhD

Active

Pepper Scholar, UF Claude D. Pepper Center (OAIC)

Chen (PI) 8/1/2015-3/31/2017

Statistical learning methods for incorporating multimodal imaging biomarkers to advance aging research

The goal of this study is to develop and apply statistical learning methods for multimodal imaging analysis with application to aging studies.

Pending

NSF Chen (PI) 7/1/2016-6/31/2021

Functional and graphical models for multimodal neuroimaging analysis

The goal of this study is to develop novel functional and graphical methods for efficient analysis of multimodal neuroimaging.

Ron Cohen, PhD

Active

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

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

The tudy 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

2 P01 AA019072 (Monti)	9/1/15-5/31/20	NIAAA	$893,352

Alcohol and HIV: Biobehavioral Interactions and Intervention

The goals of this program project are to study the effects of alcohol use on HIV disease progression, the effects of interventions to reduce alcohol use in HIV-infected populations, and the effects of alcohol on sexual decision making. The project also fosters multidisciplinary collaborations and training in research on alcohol and HIV and dissemination of research findings to clinicians treating addictions and HIV. Research Component 1 (Cohen, PI) is a continuation of the study being conducted in the parent ARCH, but will now examine the effects of reducing alcohol consumption via a motivational interviewing approach in HIV-infected heavy drinkers, with a specific focus on changes in cognitive performance, functional brain response on FMRI, and cerebral metabolite abnormalities (MRS).

Role: Co-1; Research Component-1: PI (20% effort)

U24 AA022002	Cook (PI)	09/01/13-08/31/16	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-I

P01 AA019072	Monti (PI)	09/30/10 - 08/31/16	NIAAA

Alcohol and HIV: Biobehavioral Interactions and Intervention (ARCH)

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 the R01 type project (RC1) overseeing all aspects of the study.

Role: Co-Investigator; PI: Research Component 1

P01 AA019072	Monti (PI)	08/30/10 - 08/31/16	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 the R01 type project (RC1) overseeing all aspects of the study.

Role: Co-Investigator; PI: Research Component 1

RO1 NS080655 Thompson (PI) 8/1/2012-7/31/2016 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 by 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

Awards

2015 Evelyn McKnight Chair, Cognitive Aging and Memory

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

Active

K01 AG048259-01A1 (PI: Cruz-Almeida) 05/2015 - 04/2020 National Institute on Aging

Neuroimaging Age-Related Changes in Pain Modulation

Role: PI

P30AG028740-07 (PI: Cruz-Almeida) 05/2015 – 04/2017 National Institute on Aging OAIC Pilot Project

Pain and Mobility Function in Older Adults

Role: PI

N/A (PI: Cruz-Almeida) 06/2014 – 05/2016 University of Florida Clinical Translational Sciences Institute

Cortico-striatal connectivity predicting pain and physical function in older adults

Role: PI

R01AG039659 (PI: Riley) 04/2015 - 03/2017 National Institute on Aging

The effects of aging on experimental models of pain inhibition and facilitation

Role: Co-Investigator

P30AG028740-07 (PI: Buford) 11/2013 – 03/2016 National Institute on Aging Research Development Project

Development of clinical methods to evaluate neural function in aging

Role: Co-Investigator

Mingzhou Ding, PhD

Active

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

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.

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

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.

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

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

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

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

Kenneth M. Heilman, MD

Active

I01 CX000744 VA Clinical Science Research & Development – Merit Review 10/1/2012 – 9/30/2016

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.'

Role: PI

XZ302 DOEA State of Florida, Department of Elder Affairs Memory Disorder Clinics 7/1/88 – 6/30/15

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.

Role: PI

R21 AG044449 National Institute of Health/National Institute on Aging 9/30/13 – 6/30/15

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.

Role: PI

IK2 RX000707 VA Rehabilitation Research & Development - Career Development 2 4/1/2012 – 3/31/2017

White Matter Changes and Mild TBI: Emotional and Autonomic Consequences

Research on the brain mechanisms that may induce the behavioral deficits caused by mild TBI is important for several reasons. Perhaps the most important reason is the frequency of these injuries and the disability and suffering caused by TBI. Understanding the pathophysiology of a disorder is often an important initial step in finding a successful treatment.

Role: Mentor (PI: John B. Williamson, PhD)

RX000958-01A2	Leon (PI)	01/01/2014-12/31/2016	0.60 Calendar Months
VA Career Development Award	$168,800		

Treatment of Emotional Prosodic Disorders in Parkinson's Disease

The goal of this CDA1 proposal is to determine effect size for treating individuals with Parkinson's disease (PD) who have deficits in the production of emotional prosodic speech.

Role: Mentor

	Stamps (PI)	12/01/2014-11/31/2015
Alzheimer's Art Quilt Initiative	$44,473	

A brief, clinical test of odor detection for diagnosing early Alzheimer's disease – The purpose of this study is to replicate and build upon the findings of our preliminary study that demonstrated the left nostril was significantly worse at detecting an odor than the right nostril of individuals with early Alzheimer's disease.

Role: Mentor

1P50AG047266-01A1	(PI T. Golde)	08/15/2015-05/31/2020

Alzheimer's Disease Research Center (ADRC) – NIA $5,763,027

University of Florida - Mt. Sinai Medical Center AD Research Center

Role: Co-Investigator Alzheimer's Disease Research Center (ADRC) – NIA

Damon Lamb, PhD

Active

IK2 RX000707 VA Rehabilitation Research & Development 4/1/2012 -3/31/2017

White matter changes and mild TBI: Emotional and autonomic consequences

Principal Investigator: John B. Williamson

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 (8/26/2013 – present)

I01 CX000744 VA Clinical Science Research & Development – Merit Review 10/1/2012 - 9/30/2016

Vertical Neglect

Principal Investigator: Kenneth M. Heilman

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 (8/26/2013 – present)

Michael Okun, MD

Active

NIH R01 Okun and Butson (multi-PI) 09/01/14-08/31/19

Mobile Decision Support System for Nurse Management of Neuromodulation Therapy

The major goal of this study is to assess improvements in DBS patient outcomes from use of mobile computing platform. The UF site will use an iPad mobile computing platform and measure outcomes compared to standard of care DBS programming. We will identify anatomical regions where stimulation provides the most effective symptomatic relief or most significant side effects.

Role: PI

R01 NS052318 Vaillancourt (PI) 11/01/11-07/31/15 NIH

Scaling and Sequencing Motor Output in Humans: fMRI study

The major goal of this project is use fMRI and DTI to understand how structural and functional deficits in the

basal ganglia and cortex change longitudinally in early stage PD.

Role: Co-Investigator

1R01 NS082386-01A1 Price (PI) 04/01/14-03/31/18 NIH

White Matter Connectivity and PD Cognitive Phenotypes

The major goal of this grant is to define white matter connectivity and changes associated with Parkinson's disease and to develop a technique to better define the cognitive phenotypes of Parkinson's disease.

Role: Co-Investigator

The Bachmann-Strauss Dystonia & Parkinson's Disease COE Okun (PI) 07/16/13-07/01/16

Bachmann-Strauss FDN & Tyler's' Hope FND
The major goal of this grant is to develop a clinical research center for dystonia and Parkinson's disease. The center projects include translational animal models, biomarker and and drug discovery paradigms.

Role: PI

C-11-07 3004369.005 Okun (PI) 07/01/11-06/30/16

St. Jude Medical/Advanced Neuro Systems

Brain Bank for subjects implanted with the LibraTM Deep Brain Stimulation System

The goal of this project is to pair well standardized clinical data from major DBS trials to collection of post-mortem tissue. The project aims to uncover tissue based changes results from DBS.

Role: PI

R01NS075012-01A1 Vaillancourt (PI) 07/16/12-07/15/17 NIH

Non-Invasive Markers of Neurodegeneration in Movement Disorders

The Major Goal of this project is to examine the imaging aspects of neurodegenerative disorders such as Parkinson's disease and no examine imaging changes that may serve as markers of disease.

Role: Co-Investigator

TSA International Data Base Okun (PI) 11/01/12-06/3019

TSA International Database of deep Brain Stimulation Studies in Tourette Syndrome

The Major Goal of this project is to create an international registry of Tourette DBS procedures. The database contains DBS procedure parameters, scale measurements, and more information on an individual's deep brain stimulation surgery for the treatment of Tourette Syndrome.

Role: PI

NEUROMODULATION 2014 Okun (PI) 01/16/15-01/15/17 Michael J Fox Foundation (MJFF)

A Responsive Closed-Loop Approach to Treat Freezing of Gait in Parkinson's Disease

The major goal of this study is to provide a rapid, automated closed-loop algorithm prototyping. Our approach will identify the local field potentials (LFP) occurring in GPi and PPN during normal walking and during maneuvers known to instigate freezing episodes. We will use an algorithm to facilitate a responsive train of stimulation to break freezing episodes.

Role: PI

NIH CTSI KL2 Gunduz (PI) 01/15/15-01/14/17

The Human Tic Detector: A Responsive Deep Brain Stimulator for the Treatment of Tourette Syndrome

The goal of this study is to detect the neural signatures of Tourette Syndrome to initiate and terminate deep brain stimulation.

Role: Mentor

UF Research Foundation Gunduz (PI) 06/01/15-05/31/17

Uncovering an Electrical Biomarker for Freezing of Gait in Parkinson's Disease

The goal of this study is to investigate biomarkers of freezing of gait in Parkinson's Disease during ambulation using wireless EEG systems.

Role: Co-PI

Academic Awards & Honors

2015 I received the White House Champion of Change Award for Parkinson's disease

Eric S. Porges, PhD

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

Kimberly Sibille, MA, PhD

Active

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

Active

VAMC BRRC Pilot 2014

Awarded 2014

External Non –invasive vagal nerve stimulation for the treatment of post-traumatic stress disorder.

The goal of this funding was to provide pilot data for the effect of transcutaneous vagal nerve stimulation on emotional cognition and physiology in patients with TBI and PTSD. Preliminary data analyses demonstrate alleviation of anxiety (state) in patients with TBI/PTSD.

Role: PI

NIH 1R56HL127175-01 10/01/2015-10/01/2016

Awarded

Brain and cognition effects of cardio resychronization therapy in heart failure.

The goal of this funding is to characterize brain changes as a result of improved cardiac output in heart failure including hemodynamic, task dependent regional brain activation and brain metabolic changes associated with improved cognitive performance and brain health.

NIH R01, submitted

Brain and cognition effects of cardio resychronization therapy in heart failure.

The goal of this funding is to characterize brain changes as a result of improved cardiac output in heart failure including hemodynamic, task dependent regional brain activation and brain metabolic changes associated with improved cognitive performance and brain health.

VA Merit Review submitted

Brain and cognition effects of cardio resychronization therapy in heart failure.

The goal of this funding is to characterize brain changes as a result of improved cardiac output in heart failure including hemodynamic, task dependent regional brain activation and brain metabolic changes associated with improved cognitive performance and brain health.

VA Merit Review submitted

Treatment of Mild TBI and PTSD with external vagal nerve stimulation.

The goal of this funding is to continue my line of research on chronic emotional dysregulation after mild TBI and understand a potential treatment option (tVNS) and how it impacts limbic system behavior.

VA Spire submitted

Treatment of Mild Cognitive Impairment with external vagal nerve stimulation

Vagal nerve stimulation has previously been shown to improve memory performance. Through the locus coeruleus and inputs from the nucleus of the solitary tract, vagal nerve stimulation can interact directly with brain systems impacted by Alzheimer's disease pathology. This project is designed to understand the cognitive enhancing properties of tVNS in patients with mild cognitive impairment.

Adam J. Woods, PhD

Active

CTSI KL2TR001429-01 (Woods; PI) 03/15/14-03/15/16 9.00 calendar

NIH & Clinical Translational Science Institute KL2 Career Award $200,234

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 NIH	(Thompson; PI)	09/29/14-09/30/18	0.60 calendar $180,000

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

NIA R01AG044424 NIH	(Clark; PI)	09/1/14-08/31/18	0.60 calendar $1,376,867

Neural mechanisms of dynapenia: The UNCODE study

This translational physiology study seeks to determine the neurological mechanisms (or contributors) to muscle weakness (i.e., Dynapenia) classically observed in older adults.

Role: Co-I

NIAAA P01AA019072 NIH	(Monti; PI) Renewal	09/1/15-08/31/20	0.60 calendar $7,499,996

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

NHLBI R56HL127175 NIH	(Williamson; PI)	09/08/15-08/31/16	1.2 calendar $478,898

Brain and cognition effects of cardio resynchronization therapy in heart failure

The goal of this study is to evaluate cognitive and brain consequences of cardiac resynchronization therapy in heart failure patients using functional neuroimaging, magnetic resonance spectroscopy, & arterial spin labeling.

Role: Co-I

2 P30 AG028740-06 NIH	(Pahor; PI)	04/15/12-03/31/17	0.12 calendar $63,150

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 NIH	(Pahor; PI)	04/15/12-03/31/17	0.12 calendar $47,532

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 Neuroimaging Consortium Grant	(Wright; PI)	05/01/15-05/01/17	0.12 calendar $400,000

UF Neuroimaging Consortium Cohort (Site PI: Cohen)

The goal of this project is to develop a cohort of 200 adults 85 years and older across four sites using multimodal neuroimaging and

cognitive assessment – including structure MRI, DTI, and MRS, in addition to the NIH toolbox.

Role: Co-I

McKnight Brain Research Foundation (Cohen; PI) 10/1/15-09/30/17 0.12 calendar

Cognitive Assessment Consortium Grant $400,000

UF Cognitive Assessment Consortium Cohort (Site PI: Cohen)

The goal of this project is to develop norms for the NIH toolbox for adults 85 years and older in a cohort of 200 older adults across four sites using comprehensive cognitive assessment – including the NIH Toolbox Cognitive Battery and a variety of common cognitive and sensory measures. Novel measures will also be developed at each site.

Role: Co-I

NIA K99AG048762 (Fazeli; PI) 09/15/14-05/31/16 0.00 calendar
NIH $1,712,409

A novel neurorehabilitation approach for cognitive aging with HIV

The goal of this study is to investigate the efficacy of cognitive training paired with tDCS on remediation of cognitive deficits in HIV positive older adults. Dr. Fazeli will receive training in aging and tDCS research methods.

Role: Co-mentor

McKnight Brain Research Foundation (Cohen; PI) 10/15/13-10/15/16 0.12 calendar
McKnight Brain Research Foundation $179,414

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) 11/1/14-11/1/16 0.60 calendar
McKnight Brain Research Foundation $73,164

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 (Cohen; PI) 01/1/14-01/1/16 0.12 calendar
McKnight Brain Research Foundation $95,176

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 (Cohen; PI) 01/01/14-01/01/16 0.12 calendar
McKnight Brain Research Foundation $101,164

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) 07/1/14-07/1/16 0.60 calendar
McKnight Brain Research Foundation $114,164

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

Fund to Cure Stroke (Mennemeier; PI) 05/15/14-05/15/16 0.00 calendar
Fund to Cure Stroke $35,593

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

NIAAA F31AA024060 (Bryant; PI) 05/01/15-04/30/18 0.0 calendar
NIH $109,474

Working memory: a critical factor underlying alcohol reduction intervention response

The goal of this project is to evaluate the role of working memory function in response to an effective alcohol reduction intervention (Motivational Interviewing) in HIV and non-HIV older adults. The student will receive training in functional and structural magnetic resonance imaging methods.

Role: Co-Mentor

2 P30 AG028740-06 (Pahor; PI) 04/15/12-03/31/17 0.0 calendar
NIH $98,494

UF Claude D. Pepper Older Americans Independence Center (OAIC) KL2 Award:

A study of cross-cultural differences in analgesic effects of transcranial direct current stimulation (tDCS) in white and Asian older adults with chronic pain: KL2 awardee (Ahn).

Role: Co-Mentor

Other Support

L30 AG051178 (Woods; PI) 07/01/15-06/31/17 0.0 calendar

NIH Loan Repayment Program; National Institute on Aging (NIA)

Study Title: Neuromodulation of Cognition in Older adults

Two-year loan repayment support for research on the use of transcranial direct current stimulation paired with cognitive training to enhance cognitive function in older adults.

Role: PI

Pending

NIA K01AG050707-A1 (Woods; PI) Impact Score: 17 $617,768
NIH 9.0 calendar

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

Industry Sponsored Trial (Woods; PI) $239,360
Osato Research Institute 0.6 calendar

Impact of Fermented Papaya Product on brain energetics, neuroinflammation, and cognition

The goal of this study is to perform a pilot clinical trial investigating the influence of Fermented Papaya Product on brain energetics, neuroinflammation, and cognition in older adults with elevated systemic inflammation using multimodal neuroimaging (fMRI, DWI) and spectroscopy (31P, 1H-MRS), as well as assessment of systemic inflammation and cognition.

Role: PI

NIA R01 (Woods/Cohen/DeKosky; MPIs) $2,459,654
NIH 3.0 calendar

ENRGISE-COG: augmenting cognitive and brain function through anti-inflammatory intervention

The goal of this study is to investigate the impact of systemic low grade chronic inflammation on cognition, brain function,

and neuroinflammation in 200 older adults across 5 sites and evaluate the benefit of low-cost anti-inflammatory interventions: omega-3 and losartan.

Role: PI

NIA R01	(Woods/Cohen/Marsiske; MPIs)	$6,018,978
NIH		3.0 calendar

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: PI

NIAAA U24AA022002	(Cook; PI); Administrative Supplement	$200,000
NIH		1.2 calendar

Southeastern HIV Alcohol Research Consortium (SHARC)

The goal of this study is to develop a 1500 person HIV cohort across Florida with varied degrees of at-risk alcohol behavior. The project will facilitate future studies of HIV and alcohol interactions through cohort development. The supplement will provide support for increased acquisition of adults over the age of 70 years in the cohort.

Role: Co-I

NIA R21	(Clark; PI)	(October Submission)	$189,233
NIH			1.2 calendar

Combining tDCS and neurorehabilitation to treat age-related deficits of mobility and cognition

The goal of this study is to obtain pilot data for a full-scale clinical trial combining transcranial direct current stimulation (tDCS) and complex walking intervention to enhance mobility in older adults.

Role: Co-I

NIDA R01	(Cook; PI)	(October Submission)	$3,145,217
NIH			0.6 calendar

Health effects of marijuana in persons living with HIV

The goal of this study is to investigate the acute and chronic impact of marijuana use on the cognitive and physical health of persons living with HIV.

Role: Co-I

NIA R01	(Sibille; PI)	$2,013,783
NIH		0.6 calendar

Promoting Adaptive Neuroplasticity and Affective Resilience in the Treatment of Chronic Pain

The goal of this study is to investigate the beneficial effects of Omega-3, glucose administration, and guided imagery interventions on the chronic pain.

Role: Co-I

Ethel Moore Fund	(Bowers, PI)	$62,102
State of Florida		0.6 calendar

Pilot Intervention in Mild Cognitive Impairment: A proof of concept study with Transcranial Near Infrared Stimulation

The goal of this study is to obtain pilot data for effectiveness of TNIS in treatment of cognitive impairment in MCI, with acquisition of mechanistic phosphorous magnetic resonance spectroscopy data investigating change in brain ATP metabolism.

Role: Co-I

Academic Awards & Honors

2015-2017 NIH Loan Repayment Program Recipient, Funding Agency: National Institute on Aging

2015 Young Investigator Award, NYC Neuromodulation 2015, New York, NY, USA

FACULTY BIOGRAPHICAL SKETCHES: See page 83

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.

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 projects 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.

Robert Fieo, PhD, joined the CAM team in 2015 as a Research Assistant Professor. He is housed within the Center of Cognitive Aging & Memory (CAM). He is primary interested in how Cognitive Enrichment models can serve to attenuate cognitive decline in older adults. Dr. Fieo is also interested in the application of psychometrics to help enhance health outcome measures, particularly, hard to define subjective constructs of self-report, e.g., fatigue or motivation.

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 3rd 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 fifth 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.

Nicole Nissam is a second 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 second year master's 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 fourth 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 4 of the very brightest and best qualified undergraduate students serving as research assistants. Dr. Cohen mentors 2 of these, and Dr. Woods mentors 2.

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, Ph.D., and Ron Cohen, Ph.D.)* 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 66

EDUCATIONAL PROGRAMS FOCUSING ON AGE RELATED MEMORY LOSS:

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.

T-32 Physical, Cognitive and Mental Health in a Social Context *(Marsiske, PI; Cohen: Co-I)*. 2015-2020. This NIA supported T32 focuses on training predoctoral graduate students from UF on research topics related to the psychosocial and behavioral manifestations of aging. Dr. Cohen currently mentors two graduate students who were awarded in T32 grants in this program.

Neuroscience of Aging *(Woods)*. This is one of the online courses within the Aging and Clinical Practices certificate and masters degree program of the Institute on Aging. The focus of this course is the psychosocial, behavioral, and neurobiological bases of aging, and their clinical implications.

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, M.D., Dept. of Neurology, Adam J. Woods, Ph.D., Ron Cohen, Ph.D.

E. Study of Semantic Networks – Kenneth Heilman, M.D., Steve Nadeau, M.D., Robert Cook, M.D., Amanda Garcia, M.S.

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, Ph.D.

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, Ph.D., Ron Cohen, Ph.D., Kenneth Heilman, M.D. – 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, Ph.D., Ron Cohen, Ph.D., Kenneth Heilman, M.D., Michael Jansen, M.D., James Hill, M.D. (cardiologists at University of Florida).

C. HIV and the Aging Brain – Robert Cook, M.D., Ron Cohen, Ph.D. – 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, Ph.D., Collaborations with investigators from Brown University and Tufts.

E. Cognitive Effects of Cardiac Rehabilitation in Heart Failure – Ron Cohen, Ph.D., 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 Ph.D., 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, M.D., and other collaborators at the UF CTSI.

J. Obesity and Type II Diabetes – Collaborations among Kfir Ben-David M.D., UF Surgery, Kenneth Cusi, M.D., Diabetes Center of Excellence, Christina McCrae Ph.D., UF Sleep Research Lab, Ron Cohen, Ph.D., 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 provide 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. Thomas Foster (Genetics Core). This project will investigate genetic markers of GABA expression in conjunction with magnetic resonance spectroscopy markers of GABA and other genetic 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 initiative is underway, though the study is on hold while we await compounding of a new agent. The plan is to test a GABAergic antagonist that has been studied in the MBI AMRL program (Bizon, Foster).

IF APPLICABLE, PLEASE PROVIDE ENDOWMENT INVESTMENT RESULTS FOR THE REPORT PERIOD: See page 74

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

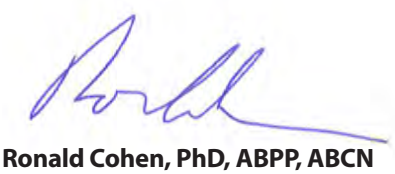
DO YOU RECOMMEND ANY MODIFICATIONS TO THE PURPOSE OR MANDATES IN THE GIFT AGREEMENT? No

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

NEGATIVE EVENTS (LOSS OF PERSONNEL, SPACE, BUDGET): None to Report

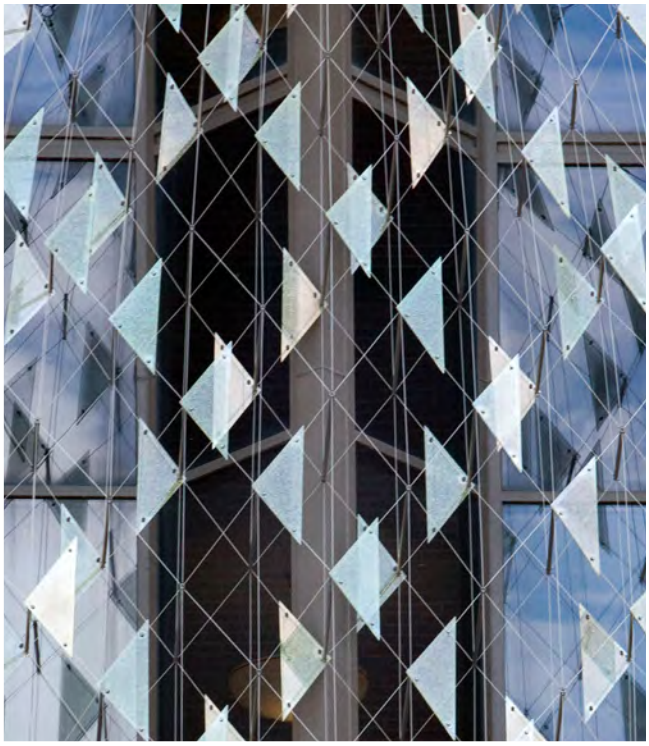
ADDITIONAL COMMENTS: See letter on page 21

SIGNATURE, DATE AND TITLE OF PERSON SUBMITTING THE REPORT:



Ronald Cohen, PhD, ABPP, ABCN
Professor, Aging, Neurology, and Psychiatry
Evelyn McKnight Endowed Chair
Director, CAM-CTRP

William G. Luttge Lectureship in Neuroscience



In 2012, the McKnight Brain Research Foundation endowed the University of Florida with $300,000 to establish a permanent annual lectureship as a memorial tribute to the late William G. "Bill" Luttge, PhD, the first director of UF's MBI. Held each year, the William G. Luttge Lectureship in Neuroscience explores inventive ideas and approaches to ensure healthy cognitive aging and to counter brain diseases.

Dr. Luttge spearheaded efforts to organize the vast amount of brain research conducted at the University of Florida into a comprehensive program, eventually resulting in the establishment of the $60 million Brain Institute on the UF Health Science Center campus that was dedicated in 1998. He passed away March 24, 2012, after being diagnosed with multiple myeloma.

On May 4, 2015, renowned neuroscientist and University of Florida alumnus Fred H. Gage, PhD, returned to campus to deliver this year's lecture. Dr. Gage, who received a bachelor's degree in psychology in 1972, is a professor and researcher in the Laboratory of Genetics at the Salk Institute for Biological Studies in La Jolla, California. His lecture, titled "Neuronal Plasticity and Genomic Diversity," was delivered to a standing-room crowd of more than 150 people at the MBI.

Gage's lecture focused on the evolutionary impact of mobile DNA, which can cause a host of genetic variations and mutations by changing places in the genome. More broadly, mobile DNA may influence normal brain function, contribute to some neurological disorders and have a role in genome evolution.

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 is now organizing the fourth Luttge Lectureship scheduled for March 14th, 2016, during National Brain Awareness Week. Carol A. Barnes, PhD, Director of the Evelyn F. McKnight Brain Institute at the University of Arizona has agreed to speak. Dr. Barnes is a Regents' Professor in the Departments of Psychology, Neurology and Neuroscience, the Evelyn F. McKnight Endowed Chair for Learning and Memory in Aging, Director of the ARL Division of Neural Systems, Memory & Aging, and Associate Director of the BIO5 Institute at the University of Arizona, Tucson, AZ. Dr. Barnes is past-president of the 42,000 member Society for Neuroscience, an elected Fellow of the American Association for the Advancement of Science, and an Elected Foreign Member of the Royal Norwegian Society of Sciences and Letters.

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

Age-related Memory Loss Program

Financial Summary
January 1 to December 31, 2015

Foundation Spendable Account		Amount	
Endowment income transferred in:			
Mar 31, 2015	$ 279,070		
Jun 30,2015	280,654		
Sept 30, 2015	299,311		
Dec 31, 2015	269,478		
Total endowment income transferred in		1,128,512	
Additional funds from MBRF:			
Reimb. for 8th Annual Inter-inst. Meeting (travel)	5,062		
Reimbursement for Epigenomics Core expenditures	136,418		
UFF administrative fee	(253)		
Total additional funds from MBRF		141,227	
Total funds available		1,269,739	
Transferred to UF Peoplesoft spendable accounts		1,237,709	(a)
Net change in foundation spendable account		32,030	
Beginning balance, Jan. 1, 2015		300,162	
Ending balance, Dec. 31, 2015		**$ 332,192**	

UF PeopleSoft Accounts		Amount	
Received from foundation spendable account		$ 1,237,709	(a)
Residual funds from closed seed grants		4,875	
Total funds available		1,242,583	
Transferred out:			
Dr. Maurer seed grant	50,000		
Dr. Burke startup (year 2 partial)	100,000		
CAM-CTRP transfer	415,567		
Total transferred out		565,567	
Expenditures:			
ARML faculty salaries	360,178		
Travel and other	5,623		
Epigenomics Core	154,919		
Total expenditures		520,720	
Total transfers out and expenditures		1,086,287	
Net change in UF Peoplesoft accounts		156,296	
Beginning balance, Jan. 1, 2015		648,736	
Ending balance, Dec. 31, 2015		**$ 805,032**	
Due to the Institute on Aging / CAM-CTRP		550,443	(b)
Due to the McKnight Chair for CAM account		27,373	(c)
Total funds available to ARML, Dec. 31, 2015		**$ 586,781**	

(a) Transfers from foundation spendable account to Peoplesoft account in 2015.

(b) Accumulation of the CAM-CTRP portion of the endowment interest income (50%), per the 2009 Gift Agreement Amendment. Scheduled to be transferred in Jan. 2016.

(c) Spendable mount due to the new chair account for CAM to adjust for Sept. 30, 2015 overage sent to chair account for ARML. Scheduled to be transferred in Jan. 2016.

McKnight Endowed Chair for Brain Research in Memory Loss
Tom Foster, PhD

Financial Summary
January 1 to December 31, 2015

Foundation Spendable Account		Amount	
Endowment income transferred in:			
March 31, 2015	$ 42,551		
June 30,2015	42,793		
Sept 30, 2015	45,637		[b]
Dec 31, 2015	36,183		
Total endowment income transferred in		167,164	
Transferred to UF Peoplesoft spendable accounts		173,532	[a]
Net change in foundation spendable account		(6,368)	
Beginning balance, January 1, 2015		42,551	
Ending balance, Dec. 31, 2015		**$ 36,183**	

UF PeopleSoft Accounts		Amount	
Received from foundation spendable account		$ 173,532	[a]
Expenditures:			
Faculty and research staff salaries	18,975		
Research equipment, supplies, and services	44,811		
Travel and other	4,817		
Total expenditures		68,603	
Net change in UF Peoplesoft accounts		104,929	
Beginning balance, January 1, 2015		369,522	
Ending balance, Dec. 31, 2015		**$ 474,451**	
Due to the McKnight Chair for CAM account		9,124	[b]
Total funds avail. to McKnight ARML Chair, Dec. 31, 2015		**$ 465,326**	

[a]Transfers from foundation spendable account to Peoplesoft account in 2015.

[b]Spendable amount due to the new chair account for CAM to adjust for Sept. 30, 2015 overage sent to chair account for ARML. Scheduled to be transferred in Jan. 2016.

Cognitive Aging & Memory
Clinical Translational Research Program

Financial Summary
January 1 to December 31, 2015

UF PeopleSoft Accounts			Amount
Received from McKnight Brain Research Grant		$	415,567
Program expenditures and commitments:			
Faculty and research staff salaries	590,202		
Research equipment, supplies, and services	331,666		
Travel and other	48,045		
Sponsored research studies in cognitive aging and memory	803,944		
Total program expenditures and commitments			1,773,858
Net change in UF Peoplesoft accounts			(1,358,291)
Beginning balance, Jan. 1, 2015			2,179,132
Ending balance, Dec. 31, 2015		**$**	**820,841**
Due from McKnight Brain Research Grant			550,443
Total funds available to CAM-CTRP, Dec. 31, 2015		**$**	**1,371,284**

McKnight Endowed Chair for Clinical Translational Research in Cognitive Aging
Ron Cohen, PhD

Financial Summary
July 1 to December 31, 2015

Foundation Spendable Account			Amount	
Endowment income transferred in:				
Sept 30, 2015 (due from other accounts)	$	36,497		
Dec 31, 2015		36,167		
Total endowment income transferred in				72,664
Transferred to UF Peoplesoft spendable accounts				-
Net change in foundation spendable account				72,664
Beginning balance, July 1, 2015				- [(a)]
Ending balance, Dec. 31, 2015			**$**	**72,664**

UF PeopleSoft Accounts			Amount	
Received from foundation spendable account			$	-
Expenditures:				
Faculty and research staff salaries		-		
Research equipment, supplies, and services		-		
Travel and other		-		
Total expenditures				-
Net change in UF Peoplesoft accounts				-
Beginning balance, July 1, 2015				- [(a)]
Ending balance, Dec. 31, 2015			**$**	**-**
Total funds avail. to McKnight CAM Chair, Dec. 31, 2015			**$**	**72,664**

[(a)] Account established July 1, 2015.

Dr. William G. Luttge
Lectureship in Neuroscience

Financial Summary
January 1 to December 31, 2015

Endowment account balance, Dec. 31, 2015	**$**	**259,739**

Spendable account activity	**Amount**
Endowment income transfers, 4 quarters ending Dec. 31, 2015	9,706
Less UF Foundation gift overhead fees	0
Total funds available	9,706
Expenses for May 2015 lectureship	5,409
Net change in spendable funds	4,297
Beginning balance, January 1, 2015	55,626
Ending balance, December 31, 2015	**$ 59,923**

McKnight Brain Research Grant Fund Report

with related accounts
Balances through December 31, 2015

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	$ 1,117,603	$ (1,596,541)	$ 169,626	$ 359,165
	$ 28,096,584	2016	$ 541,415	$ (631,103)	$ 62,715	$ 332,192 [1,2]
Life-to-date Totals			**$ 14,417,952**	**$ (14,883,523)**	**$ 797,763**	

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	9/17/09	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	$ 1,117,603	$ (558,802)	$ -	$ 695,429
		2016	$ 541,415	$ (270,708)	$ 415,459	$ 550,678
	Life-to-date Totals		**$ 6,690,772**	**$ (4,979,603)**	**$ 4,428,925**	

[1]Endowment market value balance as of Nov. 30, 2015. All other balances as of Dec. 31, 2015.

[2]The McKnight Brain Research Grant had a spendable account balance of $332,192 as of Dec. 31, 2015. 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. Additional revenues starting in 2015 are reimbursements from MBRF for Epigenetics Core expenses.

Evelyn F. McKnight Chair Endowments

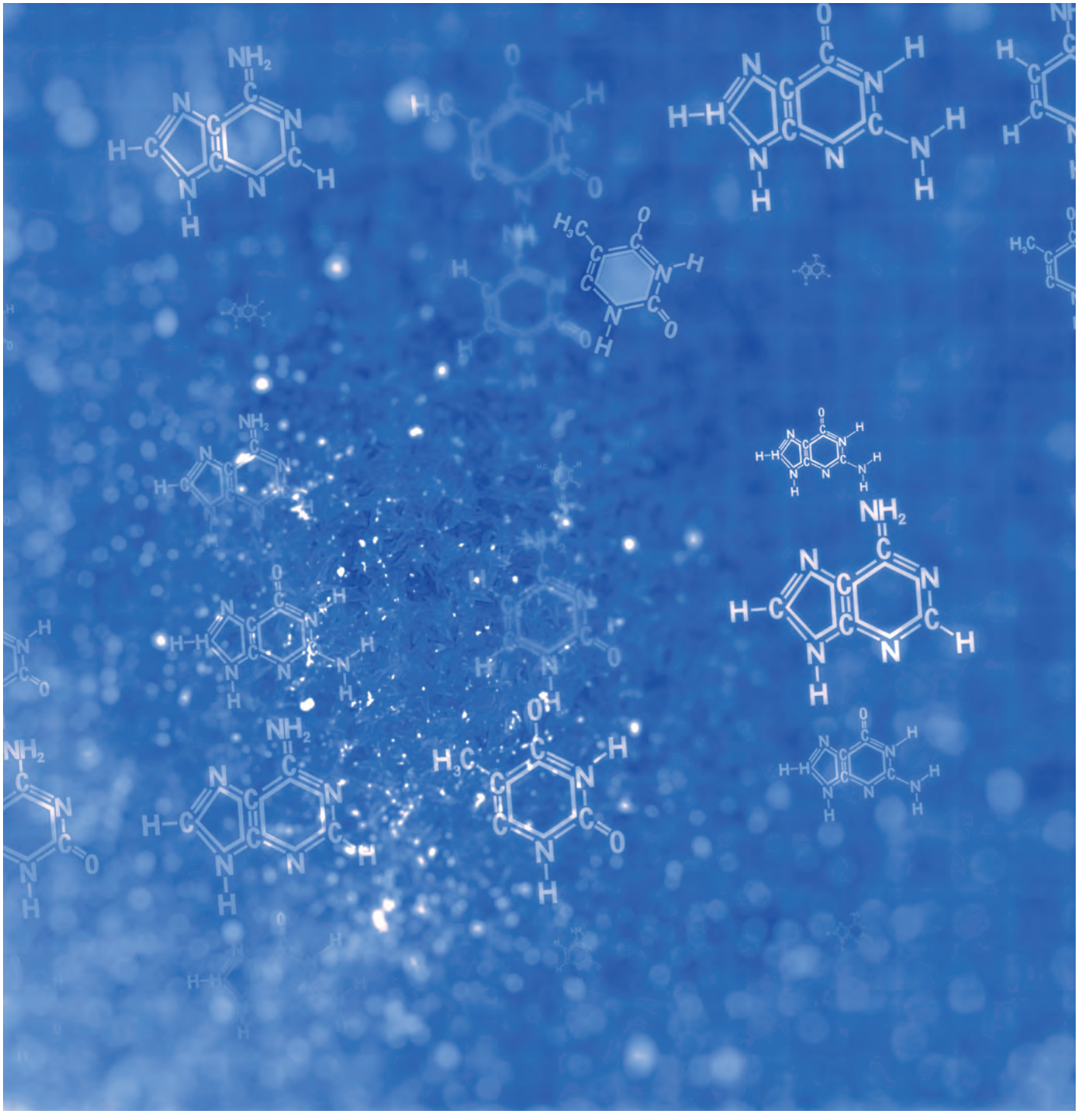
Balances through December 31, 2015

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	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	$ 170,407	$ (282,515)	$ -	$ 42,793
	$ 3,772,528	2016	$ 72,696	$ (79,306)	$ -	$ 36,183 [1]
Life-to-date Totals			**$ 2,231,640**	**$ (2,465,238)**	**$ 269,781**	

Evelyn F. McKnight Chair for Clinical Transl. Research in Cognitive Aging	Market Value Balance of Endowment	Fiscal Year Ending	Annual Endowment Transfers from Principal	Total Expenses / Net Transfers	Additional Investment Revenue	Ending Spendable Fund Balance
	F020105		F020106			
F020105 / 06	$ 3,807,064	2016	$ 72,664	$ -	$ -	$ 72,664 [1]
Life-to-date Totals			**$ 72,664**	**$ -**	**$ -**	

[1] Endowment market value balance as of Nov. 30, 2015. All other balances as of Dec. 31, 2015.

UF Foundation Endowment Reports



Evelyn F. McKnight Brain Research Grant

BOOK VALUE as of 09/30/15	**$25,967,781**
MARKET VALUE as of 09/30/15	**$28,366,062**
PROJECTED SPENDABLE INCOME for 2015/16	**$1,077,910**

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 09/30/15	**$3,995,677**
MARKET VALUE as of 09/30/15	**$3,808,711**
PROJECTED SPENDABLE INCOME for 2015/16	**$144,731**

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 09/30/15	**$250,225**
MARKET VALUE as of 09/30/15	**$262,230**
PROJECTED SPENDABLE INCOME for 2015/16	**$9,965**

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)

Evelyn F. McKnight Chair for Clinical Translational Research in Cognitive Aging

BOOK VALUE as of 09/30/15	**$4,000,000**
MARKET VALUE as of 09/30/15	**$3,807,064**
PROJECTED SPENDABLE INCOME for 2015/16	**$144,668**

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 # 020105)

McKnight Brain Research Foundation

Evelyn F. McKnight Brain Research Grant (008057)

Spendable Fund Transfers since endowment inception

FY 2015/2016	**$271,938**	**(09/30/15 YTD)**
FY 2014/2015	**$1,117,603**	
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	**$14,148,474**	

McKnight Brain Research Foundation

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

Spendable Fund Transfers since endowment inception

FY 2015/2016	**$36,513**	**(09/30/15 YTD)**
FY 2014/2015	**$170,407**	
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	**$2,195,458**	

McKnight Brain Research Foundation

William G. Luttge Lectureship in Neuroscience (018093)

Spendable Fund Transfers since endowment inception

FY 2015/2016	**$2,514**	**(09/30/15 YTD)**
FY 2014/2015	**$9,386**	
FY 2013/2014	**$9,074**	
FY 2012/2013	**$6,754**	
TOTAL	**$27,728**	

Evelyn F. McKnight Chair for Clinical Translational Research in Cognitive Aging (020106)

Spendable Fund Transfers since endowment inception

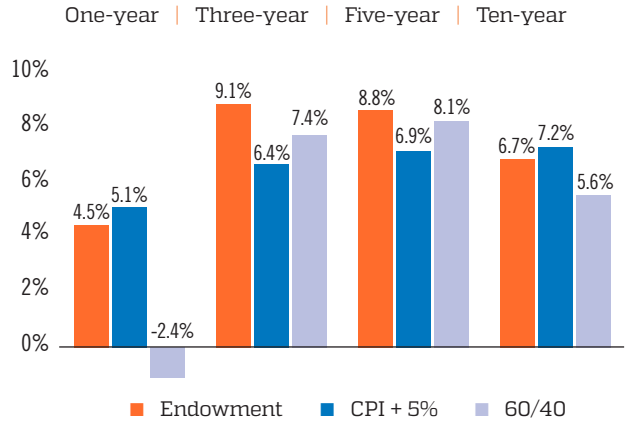
FY 2015/2016	**$36,497**	**(09/30/15 YTD)**
TOTAL	**$36,497**	

The University of Florida

INVESTMENT PERFORMANCE REPORT

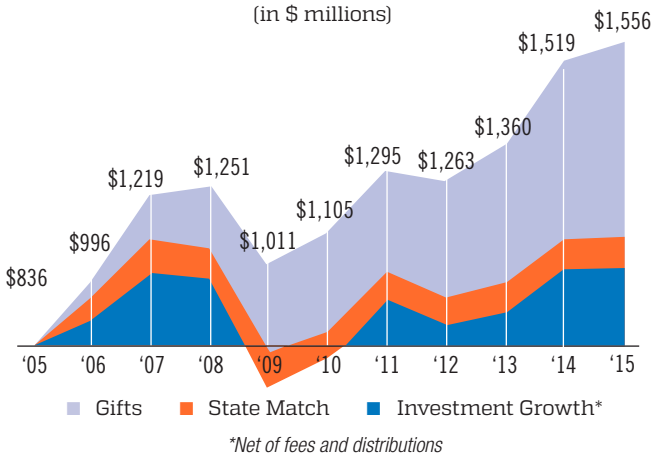
The endowment investment pool is managed by the University of Florida Investment Corporation (UFICO) and has a long-term goal to earn a total return sufficient to provide an income stream to support the university activity you designated. To measure performance of preserving the purchasing power and achieving long-term growth, investment returns are compared against the Consumer Price Index plus 5% and also a composite comprised of 60% MSCI All Country World Index and 40% Barclays Global Aggregate Bond Index. The investment returns and growth are summarized below for the fiscal years ended June 30th.

Investment Return*



*Returns are net of investment manager fees, before endowment spending

Ten-Year Endowment Growth



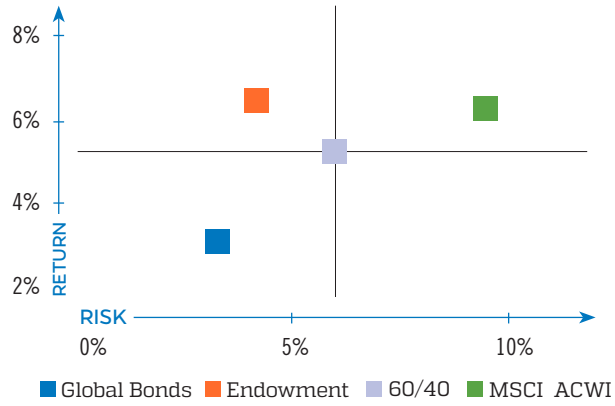
*Net of fees and distributions

To achieve the long-term goal, UFICO has constructed a strategic asset allocation, shown below, for the endowment portfolio prioritizing positive real returns, liquidity, maximum risk adjusted returns, and growth. Importantly, the endowment investment pool has outperformed the 60/40 benchmark by 110 basis points, or 1.1 percentage points, over ten years with 36% less risk, as demonstrated in the Ten-Year Risk & Return chart below.

Strategic Asset Allocation

Strategy	Asset Classes	Target Allocation
Growth	Public Equities Hedged Strategies Private Equity	80%
Inflation	Natural Resources Real Estate	12.5%
Liquidity	Fixed Income Cash	7.5%

Ten-Year Risk & Return



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

Faculty Biographical Sketches

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: Anton, Stephen

eRA COMMONS USER NAME (agency login): antonsd

POSITION TITLE: Associate Professor

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

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Florida State University , Tallahassee, FL	BA	06/1997	Psychology
University of Florida, Gainesville, FL	MS	06/1999	Clinical and Health Psychology
University of Florida, Gainesville, FL	PHD	06/2003	Clinical and Health Psychology
Pennington Biomedical Research Center, Baton Rouge, LA	Fellow	06/2006	Postdoctoral Fellow

A. Personal Statement

I am a tenured Associate Professor, Chief of the Clinical Research Division in the Department of Aging and Geriatric Research, and have served as the leader of the Clinical Research Core for the Cognitive Aging and Memory Program (CAM) since 2013. By training, I am a Clinical and Health psychologist, with a specific emphasis on the delivery of lifestyle and health promotion interventions to improve cognitive and physical function.

Following my graduate training at the University of Florida, I completed a post-doctoral fellowship at the Pennington Biomedical Research Center. During this fellowship, I had the opportunity to lead lifestyle interventions targeting the treatment of obesity and age-related metabolic disease conditions on two multi-site NIH funded clinical trials (i.e., CALERIE and POUNDS LOST). I also served as the Principal Investigator for studies examining the effects that the natural compounds chromium picolinate and stevia have on metabolic parameters and food intake regulation.

Following the completion of my post-doctoral fellowship in June of 2007, I accepted a joint Assistant Professor position within the Department of Aging and Geriatric Research and Department of Clinical and Health Psychology at the University of Florida. Since joining the University of Florida, I had the good fortune of being selected to be a Pepper Scholar from 2007-2011 and thus had the opportunity to directly benefit from the unique mentoring program available within the University of Florida's Older American's Independence Center. I not only received outstanding mentoring from my specific mentoring team but was also able to meet with leaders across campus and interact with fellow junior colleagues during regularly scheduled scholar meetings. This experience provided me with the support and direction I needed to move my career forward and thus was pivotal to my career development. Additionally, I believe it has provided me with a unique perspective and position to facilitate the development of current and future junior scholars in my current role as leader of the clinical research core.

My 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 cognitive and physical function during aging, as well as age-related disease conditions. Since joining the University of Florida, I have successfully obtained and conducted multiple grants examining the effects that lifestyle interventions and natural compounds have on mobility and other biological and functional outcomes relevant to older adults. A few relevant publications are listed below:

1. **Anton SD**, Woods AJ, Ashizawa T, Barb D, Buford TW, Carter CS, Clark DJ, Cohen RA, Corbett DB, Cruz-Almeida Y, Dotson V, Ebner N, Efron PA, Fillingim RB, Foster TC, Gundermann DM, Joseph AM, Karabetian C, Leeuwenburgh C, Manini TM, Marsiske M, Mankowski RT, Mutchie HL, Perri MG, Ranka S, Rashidi P, Sandesara B, Scarpace PJ, Sibille KT, Solberg LM, Someya S, Uphold C, Wohlgemuth S, Wu SS, Pahor M. Successful aging: Advancing the science of physical independence in older adults. *Ageing Res Rev*. 2015 Nov;24(Pt B):304-27. **PubMed PMID: 26462882; PubMed Central PMCID: PMC4661112.**

2. **Anton SD**, Karabetian C, Heekin K, Leeuwenburgh C. Caloric Restriction to Moderate Senescence: Mechanisms and Clinical Utility. *Curr Transl Geriatr Exp Gerontol Rep*. 2013 Dec 13;2(4):239-246. **PubMed PMID: 24466503; PubMed Central PMCID: PMC3899841.**

3. **Anton SD**, Karabetian C, Naugle K, Buford TW. Obesity and diabetes as accelerators of functional decline: can lifestyle interventions maintain functional status in high risk older adults?. *Exp Gerontol*. 2013 Sep;48(9):888-97. **PubMed PMID: 23832077; PubMed Central PMCID: PMC3817488.**

4. Nocera J, Buford TW, Manini TM, Naugle K, Leeuwenburgh C, Pahor M, Perri MG, **Anton SD**. The impact of behavioral intervention on obesity mediated declines in mobility function: implications for longevity. *J Aging Res*. 2011;2011:392510. **PubMed PMID: 22013527; PubMed Central PMCID: PMC3195552.**

B. Positions and Honors

Positions and Employment

1997 - 2002 Research Assistant, University of Florida, Gainesville, FL
1999 - 2000 Instructor, Santa Fe Community College, Gainesville, FL
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, Baton Rouge, LA
2007 - 2014 Assistant Professor, University of Florida, Department of Aging and Geriatric Research, Department of Clinical and Health Psychology, College of Medicine, Gainesville, FL
2011 - 2012 Interim Clinical Research Division Chief, University of Florida, Department of Aging and Geriatric Research , Gainesville, FL
2013 - Clinical Research Division Chief, University of Florida, Department of Aging and Geratric Research, Gainesville, FL
2014 - Associate Professor, University of Florida, Department of Aging and Geriatric Research, Department of Clinical and Health Psychology, College of Medicine, Gainesville, FL

Other Experience and Professional Memberships

2007 - Member, Society of Behavioral Medicine
2007 - Member, Obesity Society
2014 - Planning Committee Member , Obesity Society

Honors

1997 J. Hills Miller Presidential Fellowship, awarded each year to a small number of students based on campus wide competition, University of Florida, Gainesville, FL, University of Florida
2000 UF Clinical & Health Psychology Award for Outstanding Research (Nomination), University of Florida
2001 Society of Behavioral Medicine Paper Citation – "Effects of exercise prescriptions on exercise adherence", Society of Behavioral Medicine
2008 Research Travel Award, National Institute on Aging Conference on Idiopathic Fatigue and Aging, National Institute on Aging
2009 Research Travel Award, National Institute on Aging Bench to Bedside Conference on Inflammation and Nutrient Metabolism, National Institute on Aging
2009 Outstanding Young Alumni honoree, College of Public Health and Health Professions, University of Florida, Gainesville, FL
2010 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, University of Florida
2015 Recognized as a Master Mentor by University of Florida Mentor Academy, University of Florida, Gainesville, FL

C. Contribution to Science:

1. To date, I have authored or co-authored a total of 99 peer-reviewed manuscripts including 34 as first or senior author. My work has contributed significantly to the field of aging in regards to the role lifestyle interventions have in affecting function in older adults. The major findings from randomized controlled trials that I have led have demonstrated that (A) comprehensive lifestyle intervention consisting of dietary restriction and supervised, multi-component (aerobic, resistance, and flexibility) exercise have synergistic effects in improving muscle composition and physical function in at risk obese, older adults, (B) improvements in muscle composition in the lower extremities are strongly related to increases in walking speed in obese, older adults, (c) comprehensive lifestyle-based weight loss interventions increase expression of genes and proteins known to be involved in autophagy and mitochondrial biogenesis. Some of the key findings from my studies are described in the publications listed below.
    a. **Anton SD**, Manini TM, Milsom VA, Dubyak P, Cesari M, Cheng J, Daniels MJ, Marsiske M, Pahor M, Leeuwenburgh C, Perri MG. Effects of a weight loss plus exercise program on physical function in overweight, older women: a randomized controlled trial. *Clin Interv Aging*. 2011;6:141-9. **PubMed PMID: 21753869; PubMed Central PMCID: PMC3131984.**

b. Wohlgemuth SE, Lees HA, Marzetti E, Manini TM, Aranda JM, Daniels MJ, Pahor M, Perri MG, Leeuwenburgh C, **Anton SD**. An exploratory analysis of the effects of a weight loss plus exercise program on cellular quality control mechanisms in older overweight women. *Rejuvenation Res*. 2011 Jun;14(3):315-24. **PubMed PMID: 21631380; PubMed Central PMCID: PMC3136739.**

c. **Anton SD**, Karabetian C, Naugle K, Buford TW. Obesity and diabetes as accelerators of functional decline: can lifestyle interventions maintain functional status in high risk older adults? *Exp Gerontol.* 2013 Sep;48(9):888-97. **PubMed PMID: 23832077; PubMed Central PMCID: PMC3817488.**

d. Manini TM, Buford TW, Lott DJ, Vandenborne K, Daniels MJ, Knaggs JD, Patel H, Pahor M, Perri MG, **Anton SD**. Effect of dietary restriction and exercise on lower extremity tissue compartments in obese, older women: a pilot study. *J Gerontol A Biol Sci Med Sci.* 2014 Jan;69(1):101-8. **PubMed PMID: 23682155; PubMed Central PMCID: PMC4158399.**

2. In addition to my research on the effects of lifestyle interventions on biological and functional outcomes, I have also been actively involved in a line of research evaluating the potential that natural compounds and/or nutritional formulations (i.e., nutraceuticals) may have in improving function, quality of life, and age-related metabolic conditions. The major findings of this line of research have shown (a) some nutritional compounds may enhance effects of exercise on physical function while other may blunt the effects of exercise training, (b) resveratrol is generally safe and well-tolerated and improves some metabolic parameters in older adults, (c) saffron supplementation can improve symptoms of depression in adults with major depressive disorder. Some of the key findings from this line of research are described in the publications listed below.

   a. Hausenblas HA, Saha D, Dubyak PJ, **Anton SD**. Saffron (Crocus sativus L.) and major depressive disorder: a meta-analysis of randomized clinical trials. *J Integr Med.* 2013 Nov;11(6):377-83. **PubMed PMID: 24299602; PubMed Central PMCID: PMC4643654.**

   b. Buford TW, **Anton SD**. Resveratrol as a supplement to exercise training: friend or foe? *J Physiol*. 2014 Feb 1;592(Pt 3):551-2. **PubMed PMID: 24488074; PubMed Central PMCID: PMC3930439.**

   c. **Anton SD**, Embry C, Marsiske M, Lu X, Doss H, Leeuwenburgh C, Manini TM. Safety and metabolic outcomes of resveratrol supplementation in older adults: results of a twelve-week, placebo-controlled pilot study. *Exp Gerontol*. 2014 Sep;57:181-7. **PubMed PMID: 24866496; PubMed Central PMCID: PMC4149922.**

   d. Mankowski RT, **Anton SD**, Buford TW, Leeuwenburgh C. Dietary Antioxidants as Modifiers of Physiologic Adaptations to Exercise. *Med Sci Sports Exerc*. 2015 Sep;47(9):1857-68. **PubMed PMID: 25606815; PubMed Central PMCID: PMC4690615.**

Complete List of Published Work in My Bibliography: http://1.usa.gov/1YfOL3w

D. Research Support:

Ongoing Research Support:

Active

R01 AT007564-02 *(Anton, SD)* 09/01/13 - 05/31/18
National Center for Complementary and Integrative Health (NCCIH)
REVIVE – Resveratrol to enhance vitality and vigor in elders
The goal of this clinical trial is to determine whether resveratrol supplementation improves mitochondrial function and physical performance in generally healthy but moderately functioning older men and women.
Role: PI

1 U01 AG022376 *(Pahor, M)* 12/01/08 – 11/30/16 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 P01 AG028740-06 *(Pahor, M)* 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, J)* 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, M)* 04/01/13-03/31/16
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)* 09/01/14-05/31/19
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: Investigator

Baylor College of Medicine *(Johnston, Weight Watchers Foundation)* 03/01/15 – 12/31/15
Two dietary approaches for weight management
The objective of this study is to examine the differences in weight loss between two conditions that incorporate a program similar to the Weight Watchers Monthly Pass. The difference between the groups is in the coding of the foods consumed by the participants.
Role: Site PI

Completed Research Support (past 3 years):
NIH/NIA 1 U01 AG030644-01A1 *(Snyder, P)* 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: Site Co-PI

1K23AT004251 *(Anton, S)* 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: 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
Jennifer L. Bizon	
eRA COMMONS USER NAME (credential, e.g., agency login) jbizon	Associate Professor

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	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 of Neuroscience Graduate Program, University of Florida College of Medicine
2013-2015	Director, Neuroscience 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 (2011-2012)

Exemplary Teaching Award, University of Florida College of Medicine (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 (CNN) Washington DC (2010, 2011, 2015)
NIH Review Panel (CDIN) Washington DC (2012)
NIH Review Panel (F02B), Bethesda, MD (2013)
NIH Special Emphasis Review Panel (ZES1 LWJ-K), Chapel Hill, NC (2014)
NIH Review Panel (NIA-N), National Institute on Aging Study Section (2015)
NIH Review Panel (F03A), 2013- present
NIH Review Panel (F03A), co-Chair, 2014-present (accepted invitation to Chair beginning in October 2016)
Section Editor, Behavior, Cognition and Physiology Section, *Neurobiology of Aging* (2014-present)

C. Selected Peer-reviewed Publications (2014 and selected from 2013-2015):

1. Montgomery KA, Edwards, E, Kumar, A, Levites, Y, Setlow, B and **Bizon, JL** (2015) Deficits in hippocampal-dependent transfer generalization learning and synaptic function in mouse models of amyloidosis. *Hippocampus*. doi: 10.1002/hipo.22535. [Epub ahead of print]
2. McQuail JA, Frazier CJ, **Bizon JL** (2015) Molecular aspects of age-related cognitive decline: Role of GABA signaling. *Trends in Molecular Medicine*. Jul;21(7):450-60. doi: 10.1016/j.molmed.2015.05.002
3. Paul S, Jeon WK, **Bizon JL**, Han, JS (2015) Interaction of basal forebrain cholinergic neurons with the glucocorticoid system in stress regulation and cognitive impairment. *Frontiers in Aging Neuroscience*. doi: 10.3389/fnagi.2015.00043.
4. Yoder, WM, Gaynor L, Windham E, Lyman M, Munizza O, Setlow B, **Bizon JL**, Smith DW (2015) Characterizing olfactory binary mixture interactions in Fischer 344 rats using behavioral reaction times. *Chemical Senses*. 40(5):325-34. doi: 10.1093/chemse/bjv014.
5. Orsini CA, Trotta RT, **Bizon JL**, Setlow B (2015) Dissociable Roles for the Basolateral Amygdala and Orbitofrontal Cortex in Decision-Making under Risk of Punishment. *Journal of Neuroscience*. 35(4):1368-79. doi: 10.1523/JNEUROSCI.3586-14.2015.
6. Shimp, KM, Mitchell, MR, Beas, BS, **Bizon JL** & Setlow, B (2015) Affective and cognitive mechanisms of risky decision making. *Neurobiology of Learning and Memory*. pii: S1074-7427(14)00048-3. doi: 10.1016/j.nlm.2014.03.002.
7. Orsini, CA, Gilbert RJ, Willis M, **Bizon JL** & Setlow B. Sex differences in a rat model of risky decision making. *Behavioral Neuroscience*. In Press.
8. 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. (2014) *Journal of Neuroscience* 34(10): 3457-66. doi: 10.1523/JNEUROSCI.5192-13.2014
9. Adolescent Risk Taking, Cocaine Self-Administration, and Striatal Dopamine Signaling. Mitchell MR, Weiss VG, Beas BS, Morgan D, **Bizon JL**, Setlow B (2014) *Neuropsychopharmacology* 39(4): 955-62. doi: 10.1038/npp.2013.295.
10. Yoder, WM, Setlow, B, **Bizon, JL** & Smith, DW (2014) Characterizing olfactory perceptual similarity using carbon chain discrimination in behaviorally-trained Fischer 344 rats. *Chemical Senses*. 39(4):323-31. doi: 10.1093/chemse/bju001.
11. Regenhardt RW, Mecca AP, Desland F, Ritucci-Chinni PF, Ludin JA, Greenstein D, Banuelos C, **Bizon JL**, Reinhard MK, Sumners C (2014) Centrally administered angiotensin-(1-7) increases the survival of stroke prone spontaneously hypertensive rats. *Experimental Physiology* 99(2): 442-53. doi: 10.1113/expphysiol.2013.075242.
12. Griffith WH, Dubois DW, Fincher A, Peebles KA, **Bizon JL**, Murchison DA (2014) Characterization of age-related changes in synaptic transmission onto F344 rat basal forebrain cholinergic neurons using a reduced synaptic preparation. *Journal of Neurophysiology* 111(2): 273-86. doi: 10.1152/jn.00129.2013.
13. Beas BS, Setlow B, **Bizon JL** (2013) Distinct manifestations of executive decline in aged rats. *Neurobiology of Aging* 34(9): 2164-74. doi: 10.1016/j.neurobiolaging.2013.03.019.
14. 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.
15. 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.
16. 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.

D. Research Support:

Ongoing

2R01 AG029421 5/1/14- 5/1/19 $1,025,000.00 (direct)
"Neural mechanisms of age-related cognitive decline"
Role: **Bizon, PI (35% effort)**
National Institute on Aging

2R01 AG029421-07S1 8/1/14-8/1/16 $66, 938.00 (direct)
"Neural mechanisms of age-related cognitive decline"
Role: **Bizon PI**
National Institute on Aging

R01 DA036534 3/15/15-3/31/20 $1,250,000.00 (direct)
"Risk taking and cocaine use: interactions, mechanisms, and therapeutic targets"
Role: **Bizon Co-I, 15% effort** (Setlow, PI)
National Institute on Drug Abuse

R01 Pending $1,250,000.00 (requested)
Title: "The contribution of declines in functional connectivity to cognitive aging"
Role: **Bizon co-I, 5% effort** (Burke PI)
Agency: National Institute on Aging
Score-13, 3rd Percentile

Current Mentored Support

F32AG051371 (Joseph A McQuail) $171,018.00 (direct)
"Molecular and physiological determinants of age-related working memory decline"
6/1/15-5/31/18
National Institute on Aging
Sponsor: Bizon

McKnight Brain Institute Postdoctoral Fellowship Award (Caitlin Orsini) $10,000.00 (direct)
"Risk-taking and the amygdala: Neural circuitry and impact of chronic cocaine"
12/2014-12/2016
co-Sponsor: Bizon

Maren Junior Investigator Postdoctoral Fellowship (Caitlin Orsini) $50,000.00 (direct)
"Risk taking and the nucleus accumbens: Neural circuitry and impact of cocaine"
3/2014-3/2016
co-Sponsor: Bizon

K99 (Caitlin Orsini) $175,000.00 (requested)
"Neural circuits and mechanisms underlying maladaptive risk-taking following cocaine self-administration"
Pending
National Institute on Drug Abuse
Co-Sponsor: Bizon
Score: 24

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: Dawn Bowers, Ph.D.

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

POSITION TITLE: Professor of Clinical & Health Psychology and Neurology

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Emory University	--	1968-1970	Chemistry
University of Florida	B.S.	1972	Psychology
University of Florida	M.S.	1974	Clinical Psychology
Boston University	internship	1977	Neuropsychology
University of Florida	Ph.D.	1978	Clinical & Health Psychology

A. Personal Statement

I am university professor, a board certified clinical neuropsychologist, and a clinical researcher. I have longstanding research and clinical expertise in cognitive and emotional changes that are associated with neurologic disease and aging, particularly apathy, depression, memory and executive function. As lead neuropsychologist for the UF Movement Disorders Center, I oversee the neurocognitive module of the INFORM database, which currently has neurocognitive data on over 1600 individuals with movement disorders. I have a keen understanding of the cognitive and emotional sequalae of Parkinson disease, along with statistical methods inherent in conducting reliable change analyses over time. Current research focuses on psychophysiological signatures of apathy and depression, emotion regulation and executive function, and the interactive effects of mindfulness, cognitive training, and novel therapies on mood and cognition. I have been a funded researcher for many years and currently serve as MPI, along with Dr. Vaillancourt, of an NINDS funded T32 predoctoral training grant focusing on interdisciplinary training in movement disorders. My Cognitive Neuroscience Laboratory includes five doctoral students, who are using various tools (startle, pupillometry, ERP, computational modeling, advanced statistical approaches) to better understand mechanisms that underlie emotional and cognitive changes in individuals with movement disroders. I also serve as the Neuropsychology Area head within the Department of Clinical and Health Psychology and have taught an advanced graduate course on Adult Neuropsychological Assessment for over a decade. As such, I have the clinical, research, and experimental expertise to facilitate hypothesis driven research and supervise doctoral and post-doctoral trainees.

B. Positions and Honors

Positions & Employment

1976-1977 Teaching Fellow in Neurology, Boston University College of Medicine
1976-1977 Internship in Clinical Psychology/Neuropsychology, Boston VAMC
1976-1977 Externship in Geriatric Neuropsychology, Framingham Heart Study, MA
1979 Post-doctoral Fellowship, Behavioral Neurology, UF College of Medicine
1980- 1998 Associate Professor in Neurology [Assistant 1980-85], UF College of Medicine
1984-1998 Neuropsychologist, State of Florida Memory Disorders Clinic
1998- Professor of Clinical & Health Psychology [Associate 1998-2002]
1998- Director, Cognitive Neuroscience Laboratory, McKnight Brain Institute
2006- Area head, Neuropsychology Area, Dept. Clinical & Health Psychology
2006- Director, Neuropsychology Post-doctoral Program

Other Positions and Professional Memberships

2013-17	Merit Review Panel for Mental Health and Behavioral Sciences-B, BLRD and SCR&D; Department of Veterans Affairs
2013-	Fellows Committee, Division 40, APA
2012-14	Chair & Vice Chair, Faculty Council, College of PHHP
2012-15	Board of Governors, International Neuropsychological Society
2012	Panel Member, NIH Review of LRP proposals
2011-12	Ad hoc Member, Special Emphasis Panel, Clinical and Imaging Translations Study Section (ZRG1 DTCS Y(81)].
2009-10	Ad hoc Member, NIH Adult Psychopathology & Disorders of Aging Study Section
2006	Member, NIH Special Emphasis Panel (ZRR1 BT-801), Interdisciplinary Research Consortium
2005	Member, NIH Special Emphasis Panel (2006/01) Cognition and Perception Study Section
2004-05	Ad hoc Member, NIH Biobehavioral Mechanisms of Emotion, Stress, and Health Study Section
2000-	Editorial Boards, The Clinical Neuropsychologist, Journal of International Neuropsychological Society
1999-2003	Special Review Panel, Minority Research Infrastructure Support Program (MRISP), NIMH
1995-1998:	Member, Merit Review Committee, Mental Health &d Behavioral Science, Dept. Veterans Affairs
Membership	American Psychological Association (Divisions 12, 20, & 40), International Neuropsychology Society, American Academy of Clinical Neuropsypchology, Society for Neuroscience, Cognitive Neuroscience Society
Journal Reviews:	*Neuropsychologia, Lancet, Neurology, New England Journal of Medicine, Cortex, Movement Disorders, Journal of International Neuropsychological Society, The Clinical Neuropsychologist, J. Neurology, Neuropsychiatry & Neurosurgery, Neuropsychology, Neuropsychologia, J. Cognitive Neursocience, Brain, JCCP, J.Abnormal Psychology, Archives Clinical Neuropsychologia*

Honors

2006-	UF Foundation Research Professor
2012	Fellow, American Psychological Association, Division 40
2013	Board Certification in Clinical Neuropsychology (ABBP/cn)
2014	Paul Satz Career Mentoring Award, International Neuropsychology Society
2014	Edith Kaplan Neuropsychology Award, Massachusetts Psychological Society
2015	Audrey Shumacher Teaching Award, Department of Clinical & Health Psychology
2015	Departmental Research Award, Department of Clinical & Health Psychology
2015	Doctoral Mentoring Award, College of Public Health and Health Professions, UF

C. Selected Peer-reviewed Publications (2015)

1. Scott BM, Maye J, Jones J, Thomas K, Mangal PC, Trifilio E, Hass C, Marsiske M, **Bowers D**. Post-exercise pulse pressure is a better predictor of executive function than pre-exercise pulse pressure in cognitively normal older adults. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2015 Dec 2:1-13. [Epub ahead of print] **PubMed PMID: 26629911.**
2. Jones JD, Hass C, Okun MS, **Bowers D**. Reply: The 'cognitions' index of the Parkinson's disease questionnaire-39 relates to sleep disturbances and hallucinations. *Parkinsonism Relat Disord*. 2015 Mar;21(3):351-2. doi: 10.1016/j.parkreldis.2014.12.002. Epub 2014 Dec 11. **PubMed PMID: 25616693.**
3. Jones JD, Butterfield LC, Song W, Lafo J, Mangal P, Okun MS, **Bowers D**. Anxiety and Depression Are Better Correlates of Parkinson's Disease Quality of Life Than Apathy. *J Neuropsychiatry Clin Neurosci*. 2015 Summer;27(3):213-8. doi: 10.1176/appi.neuropsych.13120380. Epub 2014 Oct 31. **PubMed PMID: 25162776; PubMed Central PMCID: PMC4344415.**
4. Schwab NA, Tanner JJ, Nguyen PT, Schmalfuss IM, **Bowers D**, Okun M, Price CC. Proof of principle: Transformation approach alters caudate nucleus volume and structure-function associations. *Brain Imaging Behav*. 2015 Dec;9(4):744-53. doi: 10.1007/s11682-014-9332-x. **PubMed PMID: 25413122; PubMed Central PMCID: PMC4440856.**
5. Jones JD, Marsiske M, Okun MS, **Bowers D**. Latent growth-curve analysis reveals that worsening Parkinson's disease quality of life is driven by depression. *Neuropsychology*. 2015 Jul;29(4):603-9. doi: 10.1037/neu0000158. Epub 2014 Nov 3. **PubMed PMID: 25365564.**
6. LeMonda BC, Peck CP, Giles KJ, **Bowers D**. Neurocognitive Profile of a Woman with Susac's Syndrome: Further Evidence of Cognitive Variability. *Clin Neuropsychol*. 2015;29(5):689-706. doi: 10.1080/13854046.2015.1076891. **PubMed PMID: 26367343.**
7. Tanner JJ, Mareci TH, Okun MS, **Bowers D**, Libon DJ, Price CC. Temporal Lobe and Frontal-Subcortical Dissociations in Non-Demented Parkinson's Disease with Verbal Memory Impairment. *PLoS One*. 2015 Jul 24;10(7):e0133792. doi: 10.1371/journal.pone.0133792. eCollection 2015. **PubMed PMID: 26208170; PubMed Central PMCID: PMC4514873.**
8. Lafo JA, Jones JD, Okun MS, Bauer RM, Price C, **Bowers, D**. Memory similarities in Essential Tremor and Parkinson's disease: A final common pathway. *The Clinical neuropsychologist*. (2015, in press).

9. Price, C.C., Levy, S.A., Tanner, J., Garvan, C., Ward, J., Akbar, G., **Bowers, D.**, Rice, M., Okun, M.S. (Orthopedic surgery and post-operative cognitive decline in idiopathic Parkinson's disease: Considerations from a Pilot Study. *J. of Parkinson's Disease.* (2015, in press).
10. Renfroe, J.B., Bradley, M.M., Okun, M.S., **Bowers, D**. Motivational engagement in Parkinson disease: perception and preparation for action. *International Journal of Psychophysiology*. (2015, in press).
11. Jones, J., Mangal, P., Lafo, P., Okun, M.S., **Bowers, D**. Mood differences among Parkinson disease patients with mild cognitive impairment. *J. Neuropsychiatry and Clinical Neuroscience*. (2015, in press).
12. Renfroe, J., Bradley, M., **Bowers, D**. Aging and emotion modulation of late positive during affective picture viewing. *Psychology and Aging*. (2015, in press).

D. Research Support

Ongoing Research Support

T32- NS082168 MPI: **Bowers** & Vaillancourt 2015-2020
Interdisciplinary Training in Movement Disorders and Neurorestoration
This predoctoral training grant is designed to support research oriented advanced PhD students from multiple disciplines (neuroscience, movement science, cognitive-emotion neuroscience, biomedical engineering, rehabilitation science) who are using varied approaches (cellular/genetic to physiologic to behavior) to study movement disorders.
Role: **MPI**

NIH R21NS079767 PI: **Bowers** 2012-2015
Emotion Regulation, Executive Function, and Parkinson Disease.
This grant tests whether Parkinson patients can learn to "upregulate" their emotional reactivity, as measured by electrophysiological measures (LPP, ERP), and whether the ability to do so is related to executive functioning.
Role: **PI**

Village-UF Partnership PI: **Bowers** 2014-2016
Sante Fe/AvMed
Vitality Mind-Brain Health: Re-Vitalize, Cedar, & Neuroadvantage
This project tests various hypotheses regarding the basis for cognitive improvement in older adults undergoing various cognitive and behavioral interventions i.e., mindfulness, exergames, LED NIR, etc.)

NIH R03-MH109333 PI: Dotson 2015-2017
Dissociating Components of Anhedonia: Pilot Behavioral and fMRI Data for the Effort Expenditure for Rewards
The goal of this study is to examine the neural correlates of anhedonia in older and younger adults.
Role: **Co-I**

NIH R01 NS082386 PI: Price 2013 -2018
White Matter Connectivity and PD Cognitive Phenotype
This grant examines several cognitive subtypes of PD in relation to white matter connectivity using diffusion tensor imaging.
Role: **Co-I**

N/A PI: Okun 2015-2017
Michael J. Fox Foundation
A Responsive Closed-Loop Approach to Treat Freezing of Gait in Parkinson's Disease
The major goal of this study is to provide a rapid, automated closed-loop algorithm prototyping. The approach involves identifying local field potentials (LFP) occurring in GPi and PPN during normal walking and during maneuvers known to instigate freezing episodes. The Nexus-D algorithm will be used to facilitate a responsive train of stimulation to break freezing episodes.
Role: **Co-I**

Completed Research Support

State of Florida PI: Lowenstein/Wicklund 02/2015-03/30/15
Novel Markers in Alzheimer's Disease
This is multi-site project across 5 institutions in Florida that is focused on examining novel experimental measures that might be more sensitive in detecting preclinical changes associated with early Alzheimer's disease.
Role: **Co-I**

F31 NS073331-01 PI: J Dietz 2011-2014
Psychophysiology of Emotion in Parkinson disease
This predoctoral NRSA examines temporal trajectory of psychophysiological and ERP changes associated with approach and avoidance in Parkinson disease.
Role: **Mentor**

McKnight Brain Research Foundation PI: **Bowers** 2010-2013
The VITAL Study: A Multimodal Platform for the Enhancement of Cognition in Normal Elderly
This study examines whether exercise predosing improves effects of cognitive training in older adults, the trajectory of change over time, and the extent to which pure "aerobic" vs exergames are more beneficial.

R21-AG033284 Multiple PI: Altman & Hass 2010-2013
Language and Executive function in Parkinson's disease: Effects of dual task and exercise.
This project examines the influence of aerobic exercise and multi-tasking on language processing in patients with Parkinson disease.
Role: **Co-I**

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: BURKE, SARA

eRA COMMONS USER NAME (agency login): sburke

POSITION TITLE: Assistant Professor

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

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

A. Personal Statement

My research program is broadly focused on improving health outcomes in the elderly by determining the biological mechanisms that are responsible for the physical and cognitive decline that occur in later stages of life. Even in the absence of pathology, a large proportion of elderly people experience memory decline that interferes with their quality of life. Thus, understanding the neurobiology of memory impairments in advanced age is paramount both improving health outcomes in the elderly as well as distinguishing normal aging from dementia. A significant barrier to uncovering the neurobiology of age-related cognitive decline is that memory processes are distributed throughout the brain and a fundamental gap exists in our understanding of how different brain structures interact over the lifespan. The long-term goal of my laboratory is to determine the alterations in network-level interactions that underlie cognitive impairment in advanced age and dementia. Current projects are focused on uncovering mechanisms of age-related impairments in sensory discrimination across modalities, identifying age-associated changes in medial temporal lobe-prefrontal functional connectivity that contribute to memory deficits, and testing whether diet can globally improve neural network function in old animals. To answer these questions, my lab integrates neurophysiology and anatomy with behavioral analysis in order to determine the extent that age-related memory impairments manifest from dysfunction in inter-regional communication. Our rationale is that by elucidating how aging influences systems-level dynamics, we will be better positioned to develop interventions that broadly improve cognition.

B. Positions and Honors

Positions & Employment

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

Other Experience and Professional Memberships

2002 - Member, Society for Neuroscience
2008 - 2009 Mentor and small group leader, Undergraduate Biology Research Program, University of Arizona
2010 - 2012 Membership Enhancement Plan Working Group, Society for Neuroscience
2010 - 2011 Mentor, University of Arizona Assurance Program
2014 - Mentor, HHMI Science for Life
2014 - Member, North Central Florida Chapter of the Society for Neuroscience
2014 - Mentor, University of Florida Scholar Award

2015 - Judge for speaker competition, Junior Science, Engineering and Humanities Symposium
2015 - Member Faculty for Undergraduate Neuroscience

Honors

1999 Departmental Honor's in Psychology, University of Oregon
1999 Magna Cum Laude, University of Oregon
1999 Inducted, Phi Beta Kappa
2002 National Institute of Health Training Grant Recipient, University of Arizona
2005 Society for Neuroscience, Travel Award Recipient
2006 Recipient of the Ruth L. Kirschstein National Research Service Award, National Institute of Health
2008 D.G. Marquis Behavioral Neuroscience Award, American Psychology Association
2009 Mentor of the Year Award, Undergraduate Biology Research Program, University of Arizona
2010 D.G. Marquis Behavioral Neuroscience Award , American Psychology Association
2012 Honorable Mention, Mentor of the Year, Undergraduate Biology Research Program, University of Arizona
2014 Best Talk, Department Data Blitz, Department of Neuroscience, University of Florida
2015 Claude D. Pepper Older Americans Independence Center Scholar Awardee

C. Contribution to Science

1. My prior publications were the first to demonstrate that age-related deficits in object recognition memory are mediated by perirhinal cortical dysfunction. The perirhinal cortex is an area of the brain that receives sensory information from all modalities and is interconnected with the hippocampus to support memory. Using neurophysiological approaches (ref a) and activity-induced gene expression (ref b), my work showed that perirhinal activity is blunted in aged rats during an object exploration task and that this decline in perirhinal activity is tightly related to behavioral performance. This work demonstrates my experience is linking neural activity to behavioral performance, which is a central feature of the current proposal.
   a. **Burke SN**, Hartzell AL, Lister JP, Hoang LT, Barnes CA. Layer V perirhinal cortical ensemble activity during object exploration: a comparison between young and aged rats. *Hippocampus*. 2012 Oct;22(10):2080-93. **PubMed PMID: 22987683; PubMed Central PMCID: PMC3523702.**
   b. **Burke SN**, Maurer AP, Nematollahi S, Uprety A, Wallace JL, et al. Advanced age dissociates dual functions of the perirhinal cortex. *J Neurosci*. 2014 Jan 8;34(2):467-80. **PubMed PMID: 24403147; PubMed Central PMCID: PMC3870932.**

2. A long-standing presumption in the field of cognitive aging had been that aged animals have difficulty recognizing stimuli because they "forget" items that have been previously experienced. This idea, however, was difficult to reconcile with other data showing that aged subjects have an increase in false memories. I designed a series of experiments to elucidate the origins of age-associated recognition memory impairments that led to the novel observation that old animals have recognition memory deficits because they have a reduced ability to discriminate novel stimuli from those that are familiar, which manifests as a false memory (ref a). This work led to foundational insights regarding age-associated declines in recognition memory, which presumably arise from perirhinal cortical dysfunction, and was later replicated in monkeys (ref b) and humans (ref c). Moreover the paper published in 2010, of which I designed and implemented the experimental procedures, analyzed the data, and prepared the manuscript earned the D.G. Marquis Behavioral Neuroscience Award in 2010, which is indicative of my expertise in the cognitive assessment of rodent memory.
   a. **Burke SN**, Wallace JL, Nematollahi S, Uprety AR, Barnes CA. Pattern separation deficits may contribute to age-associated recognition impairments. *Behav Neurosci*. 2010 Oct;124(5):559-73. **PubMed PMID: 20939657; PubMed Central PMCID: PMC3071152.**
   b. **Burke SN**, Wallace JL, Hartzell AL, Nematollahi S, Plange K, et al. Age-associated deficits in pattern separation functions of the perirhinal cortex: a cross-species consensus. *Behav Neurosci*. 2011 Dec;125(6):836-47. **PubMed PMID: 22122147; PubMed Central PMCID: PMC3255096.**
   c. **Burke SN**, Ryan L, Barnes CA. Characterizing cognitive aging of recognition memory and related processes in animal models and in humans. *Front Aging Neurosci*. 2012;4:15. **PubMed PMID: 22988437; PubMed Central PMCID: PMC3439640.**

3. Although the spatial correlates of hippocampal firing properties have been extensively described, less is known regarding the influence on non-spatial sensory information (e.g., 3-dimensional objects) on the activity patterns of these neurons. The perirhinal cortex is extensively interconnected with the hippocampus and receives sensory input related to non-spatial information. Prior to my research it was believed that this structure supported recognition memory with changes in firing rate as a stimulus goes from novel to familiar. My work produced two foundational insights regarding the perirhinal cortex and its interactions with the hippocampus. First, we showed the perirhinal cortical neurons selectively respond to objects, but that firing rates do not change as a function of novelty (ref a). This observation called for a refinement of standard models

of recognition memory. Second, we found that the neurons in the hippocampal subregion receiving direct perirhinal input are robustly modulated by objects (ref b).

a. **Burke SN**, Maurer AP, Hartzell AL, Nematollahi S, Uprety A, et al. Representation of three-dimensional objects by the rat perirhinal cortex. *Hippocampus*. 2012 Oct;22(10):2032-44. **PubMed PMID: 22987680; PubMed Central PMCID: PMC3447635.**
b. **Burke SN**, Hartzell AL, Lister JP, Hoang LT, Barnes CA. Layer V perirhinal cortical ensemble activity during object exploration: a comparison between young and aged rats. *Hippocampus*. 2012 Oct;22(10):2080-93. **PubMed PMID: 22987683; PubMed Central PMCID: PMC3523702.**
c. **Burke SN**, Barnes CA. The neural representation of 3-dimensional objects in rodent memory circuits. *Behav Brain Res*. 2014 Sep 6; **PubMed PMID: 25205370.**

4. In young animals, dynamic hippocampal activity patterns support learning and memory. I have been involved in a series of papers that show how behavior-dependent modulation of hippocampal activity is compromised in aged animals to produce memory deficits. Moreover, we have shown that altering NMDA receptor currents with the Alzheimer's disease therapeutic memantine can restore experience-dependent plasticity in aged memory-impaired rats (ref a). This paper, on which I was first author, received the D.G. Marquis Behavioral Neuroscience Award from the American Psychological Association for the best paper published in Behavioral Neuroscience in 2008. These papers demonstrate my expertise regarding the in vivo physiological signatures of hippocampal dysfunction that are a component of the current proposal (Aims 1 and 2).
   a. **Burke SN**, Maurer AP, Yang Z, Navratilova Z, Barnes CA. Glutamate receptor-mediated restoration of experience-dependent place field expansion plasticity in aged rats. *Behav Neurosci*. 2008 Jun;122(3):535-48. **PubMed PMID: 18513124; PubMed Central PMCID: PMC2773228.**
   b. Gerrard JL, **Burke SN**, McNaughton BL, Barnes CA. Sequence reactivation in the hippocampus is impaired in aged rats. *J Neurosci*. 2008 Jul 30;28(31):7883-90. **PubMed PMID: 18667620; PubMed Central PMCID: PMC2703197.**
   c. Hartzell AL, **Burke SN**, Hoang LT, Lister JP, Rodriguez CN, et al. 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. *J Neurosci*. 2013 Feb 20;33(8):3424-33. **PubMed PMID: 23426670; PubMed Central PMCID: PMC3711759.**

5. The size of hippocampal spatial receptive fields increases along the dorsal to ventral longitudinal axis. Working with my longtime collaborator Dr. Andrew Maurer (co-I on current proposal), we elaborated on the differences in the firing properties between neurons in the dorsal versus ventral hippocampus (ref a,b) and showed that the spatial metric of hippocampal receptive fields is changed when objects are added to an environment (ref c). This work produced new insights regarding the impact of sensory information along the hippocampal longitudinal axis and highlights the productive collaborative efforts of Dr. Maurer and myself.
   a. Maurer AP, Cowen SL, **Burke SN**, Barnes CA, McNaughton BL. Organization of hippocampal cell assemblies based on theta phase precession. *Hippocampus*. 2006;16(9):785-94. **PubMed PMID: 16921501.**
   b. Maurer AP, Cowen SL, **Burke SN**, Barnes CA, McNaughton BL. Phase precession in hippocampal interneurons showing strong functional coupling to individual pyramidal cells. *J Neurosci*. 2006 Dec 27;26(52):13485-92. **PubMed PMID: 17192431.**
   c. **Burke SN**, Maurer AP, Nematollahi S, Uprety AR, Wallace JL, et al. The influence of objects on place field expression and size in distal hippocampal CA1. *Hippocampus*. 2011 Jul;21(7):783-801. **PubMed PMID: 21365714; PubMed Central PMCID: PMC3314262.**

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

D. Research Support

Ongoing Research Support

2013/10/01-2018/09/30
0011249, McKnight Brain Research Foundation
Sara N. Burke (PI)
Neural system dysfunction and cognitive aging
This goal of this award is to provide institutional support in order to establish a rigorous research program aimed and determining the neurobiological basis of cognitive impairments in the elderly and to identify potential therapeutic strategies.
Role: **PI**

2014/06/01-2016/05/30
00115480, University of Florida Research Seed Opportunity Fund
BURKE, SARA (PI)
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.
Role: **PI**

2015/08/15-2017/08/14
1R03AG049411-01A1, National Institute on Aging (Primary)
BURKE, SARA (Contact - PI)
Neurogenesis and Memory Network Dynamics during Normal Aging
As part of the continuation of the Seed fund (see above), the current proposal seeks to determine the integrity of dentate function in the aged animal.
Role: **M-PI**

2015/08/01-2017/3/31
Sub-award for P30 AG028740
Claude D. Pepper Older Americans Independence Center Junior Scholar Award and Pilot Grant Recipient
Sara N. Burke (PI)
A Novel Rodent Model of Age-related Motor-Cognition Dual-Task Deficits
The goal of this award, which was nationally reviewed by faculty at other Pepper Centers, is to development a rodent model of the association between motor and cognitive frailty in order to test potential interventions for maintaining positive health outcomes in the elderly.

2016/01/01-2020/11/30
1R01AG049722-01A1, National Institute on Aging
Sara N. Burke (PI)
The Contribution of Declines in Functional Connectivity to Cognitive Aging
The major goal of this proposal is to determine how alterations in systems-level neural coordination in old animals produce cognitive impairments.
Role: **PI**

Completed Support
2006/01/09-2009/01/08
F31 NS054465-03, National Institute of Neurological Disorders and Stroke (NINDS)
BURKE, SARA N (PI)
Aging and Neural Ensembles in the Perirhinal Cortex
Role: **PI**

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: CARTER, CHRISTY S.

eRA COMMONS USER NAME (agency login): chrcarte

POSITION TITLE: Leader

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

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Colorado, Colorado Spring, CO	BA	12/1991	Psychology
University of North Carolina, Chapel Hill, NC	PHD	12/1998	Experimental and Biological Psychology

A. Personal Statement

Dr. Carter received her PhD in Experimental and Biological Psychology from the University of North Carolina at Chapel Hill and her post-doctoral training at The Wake Forest University School of Medicine in Winston-Salem, North Carolina. While at Wake Forest, Dr. Carter participated as one of the first OAIC junior scholars. Through this mentorship, Dr. Carter successfully obtained RO1 funding and has since received several smaller grants, allowing her to also pursue her educational career objective as developer of the Department of Aging and Geriatric Research's online graduate programs. Globally, Dr. Carter's current research interests lie in preserving physical function and health-span during aging; and in particular focuses on the use of a preclinical rodent models of aging to test a variety of late-life interventions designed to mitigate loss of mobility. Furthermore, Dr. Carter has demonstrated that the application of standardized physical performance measures to a variety of animal models of aging may help to define similarities between species in the underlying mechanisms of loss of mobility, the age-related decline in performance, disability, and longevity. She has extended this area of research to other special aging populations such as the frail and obese, and has developed combinatorial therapies, using these compounds in conjunction with behavioral modification such as diet and exercise. Dr. Carter performs multiple roles for the CAM-CTRP. Most notably she has extensive experience in promoting and administering pilot studies, as she capitalizes on her combined 13 years of experience with the WFU and UF OAIC PESC (from 2002 to present). Dr. Carter supports Junior Faculty through administering their Educational Research Projects. Finally Dr. Carter supports preclinical projects through her expertise in applying preclinical batteries of physical and cognitive decline.

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

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

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

4. Justice JN, Cesari M, Seals DR, Shively CA, **Carter CS**. Comparative Approaches to Understanding the Relation Between Aging and Physical Function. *J Gerontol A Biol Sci Med Sci*. 2015 Apr 23; **PubMed PMID: 25910845.**

B. Positions and Honors

Positions and Employment

1992 - 1994 Research Assistant, Center for Environmental Medicine and Lung Biology, University of North Carolina, Chapel Hill, NC
1994 - 1995 Trainee, Toxicology Training Grant, University of North Carolina, Chapel HIll, NC
1995 - 1998 NIMH Pre-doctoral Fellow, NRSA F31MH11292, University of North Carolina, Chapel HIll, NC
1999 - 2001 Research Associate, Department of Internal Medicine, Division of Geriatrics and Gerontology, Winston-Salem, NC

2001 - 2004 Instructor, Department of Internal Medicine, Division of Geriatrics and Gerontology, Winston-Salem, NC
2003 - 2005 Co-Director, Claude D. Pepper Older Americans Independence Center, Pilot and Exploratory Studies Core, Winston-Salem, NC
2003 - 2005 Assistant Professor, Department of Internal Medicine, Division of Geriatrics and Gerontology, Winston-Salem, NC
2005 - Leader, Pilot and Exploratory Studies Core, Claude D. Pepper Older Americans Independence Center, Gainesville, FL
2005 - Assistant Professor, Department of Aging and Geriatric Research, University of Florida College of Medicine, Gainesville, FL
2005 - 2008 Associate Director for Research, North Florida/South Georgia GRECC, Gainesville, FL
2006 - 2008 Chair, Research and Development Committee, North Florida/South Georgia VMAC, Gainesville, FL

Other Experience and Professional Memberships

2001 - Member, Gerontological Society of America
2002 - Member, American Aging Association
2009 - National Scientific Advisory Board, AFAR
2013 - Chair, BS Memebership Committe, Gerontological Society of America

Honors

1995 Pre-doctoral fellowship, NRSA
1996 Travel Award, Neurobehavioral Teratology Society
2001 Austin Bloch Post-Doctoral Fellowship Award, Gerontological Society of America
2003 New Investigator Award, American Geriatrics Society
2004 Travel Award, American Aging Association
2014 Fellow, Gerontological Society of America

C. Contribution to Science

1. The study of mimetics of diet and exercise and the combination thereof may provide additional treatments for a vulnerable elderly population; however, how and when to initiate such interventions requires consideration in developing the most safe and efficacious treatment strategies. Our group has tested multiple pharmacological and behavioral interventions for the prevention of functional decline in established animal models of aging. Preclinical models, represent a critical translational link for the more rapid translation of treatments to the clinical arena insofar as they may serve as a tool for the relatively rapid systematic assessment of traditional and nontraditional interventions, initiated late in life.
   a. Marzetti E, Groban L, Wohlgemuth SE, Lees HA, Lin M, Jobe H, Giovannini S, Leeuwenburgh C, **Carter CS**. Effects of short-term GH supplementation and treadmill exercise training on physical performance and skeletal muscle apoptosis in old rats. *Am J Physiol Regul Integr Comp Physiol*. 2008 Feb;294(2):R558-67. **PubMed PMID: 18003794.**
   b. Xu J, Knutson MD, **Carter CS**, Leeuwenburgh C. Iron accumulation with age, oxidative stress and functional decline. *PLoS One*. 2008 Aug 6;3(8):e2865. **PubMed PMID: 18682742; PubMed Central PMCID: PMC2481398.**
   c. Xu J, Seo AY, Vorobyeva DA, **Carter CS**, Anton SD, Lezza AM, Leeuwenburgh C. Beneficial effects of a Q-ter based nutritional mixture on functional performance, mitochondrial function, and oxidative stress in rats. *PLoS One*. 2010 May 11;5(5): e10572. **PubMed PMID: 20485503; PubMed Central PMCID: PMC2868025.**
   d. Groban L, Lindsey S, Wang H, Lin MS, Kassik KA, Machado FS, **Carter CS**. Differential effects of late-life initiation of low-dose enalapril and losartan on diastolic function in senescent Fischer 344 x Brown Norway male rats. *Age (Dordr)*. 2012 Aug; 34(4):831-43. **PubMed PMID: 21720770; PubMed Central PMCID: PMC3682061.**

2. Evidence in animals suggest that modulation of the RAS is associated with metabolic and biochemical changes in a variety of tissues including influence on oxidative stress, metabolic and inflammation pathways. Our group has established such preclinical models of RAS intervention for declining cardiovascular, cognitive and physical decline. Understanding the molecular mechanisms governing these effects has been critical to the design of human clinical trials, especially with regards to declining physical function (described below). Pharmacological approaches may be particularly relevant late in life because not all older individuals benefit from or are capable of participating in traditional diet and/or exercise programs.
   a. **Carter CS**, Cesari M, Ambrosius WT, Hu N, Diz D, Oden S, Sonntag WE, Pahor M. Angiotensin-converting enzyme inhibition, body composition, and physical performance in aged rats. *J Gerontol A Biol Sci Med Sci*. 2004 May;59(5):416-23. **PubMed PMID: 15123750.**
   b. Kasper SO, **Carter CS**, Ferrario CM, Ganten D, Ferder LF, Sonntag WE, Gallagher PE, Diz DI. Growth, metabolism, and blood pressure disturbances during aging in transgenic rats with altered brain renin-angiotensin systems. *Physiol Genomics*. 2005 Nov 17;23(3):311-7. **PubMed PMID: 16131528.**
   c. **Carter CS**, Groban L. Role of the renin-angiotensin system in age-related sarcopenia and diastolic dysfunction. *Aging health*. 2008 Feb 1;4(1):37-46. **PubMed PMID: 20445808; PubMed Central PMCID: PMC2863036.**

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

3. Our preclinical studies suggest that modulating the RAS may have the most potential for preserving the physical capabilities of older adults when combined with regular exercise. We have translated these findings to human studies and have demonstrated that for older adults at risk for disability, exercise-derived improvements in physical function were greater for ACEi users than users of other antihypertensive drugs and antihypertensive nonusers. These findings add to those of previous studies in indicating that heterogeneity exists in the relative effects of exercise on the physical function of older adults. Thus, exercise alone may not be sufficient to prevent physical disability in many older individuals. If confirmed, these findings will have important implications treatment of older adults at risk of becoming physically disabled.
   a. Onder G, Penninx BW, Balkrishnan R, Fried LP, Chaves PH, Williamson J, **Carter CS**, Di Bari 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 Mar 16;359(9310):926-30. **PubMed PMID: 11918911.**
   b. **Carter CS**, Onder G, Kritchevsky SB, Pahor M. Angiotensin-converting enzyme inhibition intervention in elderly persons: effects on body composition and physical performance. *J Gerontol A Biol Sci Med Sci*. 2005 Nov;60(11):1437-46. **PubMed PMID: 16339331.**
   c. 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. *J Am Geriatr Soc*. 2012 Jul;60(7):1244-52. **PubMed PMID: 22726232; PubMed Central PMCID: PMC3625953.**
   d. Buford TW, Hsu FC, Brinkley TE, **Carter CS**, Church TS, Dodson JA, Goodpaster BH, McDermott MM, Nicklas BJ, Yank V, Johnson JA, Pahor M. Genetic influence on exercise-induced changes in physical function among mobility-limited older adults. *Physiol Genomics*. 2014 Mar 1;46(5):149-58. **PubMed PMID: 24423970; PubMed Central PMCID: PMC3949106.**

4. We have shown that physical function is predictive of longevity and that life-long CR improves function in rodent models of aging. Whether mimetics that purport to increase life span necessarily translate into mimetics of increased functional performance and health span is questionable. There may in fact be overt dissociations between the two such that life span may be enhanced at the expense of overall function. This is especially relevant to assessing late-life interventions, for which there is a growing need in the context of the world's rapidly aging population and for which very little clinical data exist.
   a. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, Nadon NL, Wilkinson JE, Frenkel K, **Carter CS**, Pahor M, Javors MA, Fernandez E, Miller RA. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature*. 2009 Jul 16;460(7253):392-5. **PubMed PMID: 19587680; PubMed Central PMCID: PMC2786175.**
   b. **Carter CS**, Leeuwenburgh C, Daniels M, Foster TC. Influence of calorie restriction on measures of age-related cognitive decline: role of increased physical activity. *J Gerontol A Biol Sci Med Sci*. 2009 Aug;64(8):850-9. **PubMed PMID: 19420296; PubMed Central PMCID: PMC2709546.**
   c. **Carter CS**, Khamiss D, Matheny M, Toklu HZ, Kirichenko N, Strehler KY, Tümer N, Scarpace PJ, Morgan D. Rapamycin Versus Intermittent Feeding: Dissociable Effects on Physiological and Behavioral Outcomes When Initiated Early and Late in Life. *J Gerontol A Biol Sci Med Sci*. 2015 Jan 23; **PubMed PMID: 25617380. PMC [in process]**
   d. Scarpace PJ, Matheny M, Strehler KY, Toklu HZ, Kirichenko N, Carter CS, Morgan D, Tümer N. Rapamycin Normalizes Serum Leptin by Alleviating Obesity and Reducing Leptin Synthesis in Aged Rats. *J Gerontol A Biol Sci Med Sci*. 2015 Jan 23; **PubMed PMID: 25617379. PMC [in process]**

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/collections/48621908/

D. Research Support

Ongoing Research Support

2012/06/01-2017/03/31
1P30AG028740-01, NIH/NIA
CARTER, CHRISTY S.
Claude D. Pepper Older Americans Independence Center
The major goals of this program are to assess the mechanisms leading to sarcopenia and functional decline, and to develop and test interventions for the treatment and prevention of physical disability in older adults. Role: Leader of the Pilot and Exploratory Core, Co-Leader of the Preclinical Core, Co-Leader of Development Projects in the Preclinical and Biostatistics Core, and Leader of a Small Exploratory Study.
Role: *Co-Investigator*

2015/07/01-2016/06/31
Proposal 96436, Sanofi
CARTER, CHRISTY S.
Rodent model of frailty and pharmaceutical interventions
The major goal of this program is to test a variety of mitochondrial enhancing interventions supplied by Sanofi for the prevention of frailty.
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 FIVE PAGES.***

NAME: Huaihou Chen

eRA COMMONS USER NAME: chenh13

POSITION TITLE: Assistant Professor

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Anhui University, Hefei, CHINA	B.S.	06/2004	Statistics
University of Science and Technology of China, Hefei, CHINA	M.S.	06/2007	Statistics
Columbia University, New York, NY	Ph.D.	05/2012	Biostatistics
New York University, New York, NY	Postdoctoral	06/2014	Biostatistics

A. Personal Statement

I have a broad background in biostatistics and neuroimaging, with specific training and expertise in longitudinal and functional data analysis, predictive modelling and functional connectivity analysis. As a postdoctoral fellow in the Department of Child and Adolescent Psychiatry, at New York University Medical Center, I carried out statistical methodological research on functional connectivity analysis, obtaining individual connectivity quantities and correlating the individual brain quantities with clinical outcomes. Besides statistical methodological research, I have broad collaborative research experience in the areas of neuroimaging, aging, psychiatry, neurology, chronic pain and etc. I apply standard and cutting edge statistical methods to solve scientific problems in collaborative research. I have a demonstrated record of accomplished and productive research projects on developing novel statistical methods as well as collaborative research, and my expertise and experience have prepared me for the proposed project "Brain Network Communication and Normal Aging".

B. Positions and Honors

Positions and Employment

2012-2014 Post-Doctoral Fellow, Department of Child and Adolescent Psychiatry, New York University School of Medicine, New York, NY

2014- Assistant Professor, Department of Biostatistics, Colleges of Medicine and Public Health & Health Professions, University of Florida, Gainesville, FL

Other Experience and Professional Memberships

2010- American Statistical Association

2013- ASA Mental Health Statistics Section

Honors

2007-2009 Fellowship, Columbia University

2012 ASA Biometrics Section Travel Award

C. Contribution to Science

1. My research has focused primarily on longitudinal and functional data analysis, and predictive modelling. 1) I develop novel statistical methods for flexible modelling the nonlinear time trends, which may be misspecified by a polynomial model. 2) Classification and clustering of functional data. 3) Novel predictive model that account for the complex structure of the data. Those developed methods can reduce estimation bias, increase power in testing group difference, and improve prediction accuracy. Developed methods are useful for characterizing biomarkers' changes over time, disease dynamic progression, treatment response, and have been applied to neuroimaging, psychiatric, and neurological studies. The developed methods are published in top statistical journals.

a. **Chen, H.**, Wang, Y. (2011). A penalized spline approach to functional mixed effects model analysis. *Biometrics*. 67, 861-870.
b. **Chen, H.**, Wang, Y., Paik, M. C., Choi, H. (2013). A marginal approach to reduced-rank penalized spline smoothing for multilevel data. *Journal of the American Statistical Association*. 108, 1216-1229.
c. **Chen, H.**, Reiss, P. T., Tarpey, T. (2014). Optimally Weighted L2 Distance for Functional Data. *Biometrics*. 70, 516-525.
d. Wang, Y., **Chen, H.**, Zeng, D., Mauro, C., Duan, N., & Shear, M. K. (2013). Auxiliary marker-assisted classification in the absence of class identifiers. *Journal of the American Statistical Association*. 108, 553-565.

2. As a biostatistician, I conduct collaborative research in the areas of neuroimaging, psychiatry, neurological, chronic pain and etc. I develop and apply cutting edge or standard statistical methods to neuroimaging, psychiatric, neurological studies. Applying the appropriate model and methods, I help my collaborators to predict food intake in anorexia nervosa patients, discover acute effects of Nimodpine for subarachnoid hemorrhage patients, building screening tools for psychosis in low-income minority. I develop methods for obtaining individual neurodevelopmental quantities and correlating the individual brain quantities with clinical outcomes.
   a. Steinglass, J., Sysko, R., Mayer, L., Berner, L., Schebendach, J., Wang, Y., **Chen, H.**, Albano, A., Simpson, B., and Walsh, T. (2010). Pre-meal anxiety and food intake in Anorexia Nervosa. *Appetite*. 55, 214-218.
   b. **Chen, H.**, Paik, M., Dhamoon, M.S., Moon, Y.P., Willey, J., Sacco, R.L. and Elkind, M. (2012). Semiparametric model for the dichotomized functional outcome after stroke: The Northern Manhattan Study. *Computational Statistics & Data Analysis*. 56(8), 2598-2608.
   c. Choi, H. A., Ko, S. B., **Chen, H.**, Gilmore, E., Carpenter, A. M., Lee, D., Claassen, J., Mayer, S. A., Schmidt, J. M., Lee, K., Connelly, E. S., Paik, M., Badjatia, N. (2012). Acute Effects of Nimodipine on Cerebral Vasculature and Brain Metabolism in High Grade Subarachnoid Hemorrhage Patients. *Neurocritical Care*. 2012 Jun;16(3): 363-367.
   d. **Chen, H.**, Kelly, C., F. Xavier Castellanosa, Xi-Nian Zuo, Ye He, Reiss, P. T. (2015). Quantile rank maps: a new tool for understanding individual brain development. *NeuroImage*.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=Huaihou+Chen

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: Cohen, Ronald

eRA COMMONS USER NAME rcohen1

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Tulane University	BS	05/1976	Psychology
Louisiana State University	PHD	12/1982	Clinical Psychology, Neuropsychology
UCLA Neuropsychiatric Institute, Westwood, CA	Resident	07/1982	Clinical Psychology Internship
University of Florida, Gainesville, FI	Postdoctoral Fellow	09/1983	Neuropsychology

A. Personal Statement

I am the director of the Center for Cognitive Aging and Memory (CAM) which is part of the Institute on Aging of the University of Florida. The CAM, which is funded by an endowment from the McKnight Brain Research Foundation, is focused on clinical-translational studies of age-associated changes in cognitive, behavioral and brain structure and function. Specifically, the center focuses on successful cognitive aging in the absence of neurodegenerative disease, though in the context of this mission we do studies that often compare elderly participants with and without evidence of early MCI. More broadly, our research focuses on a variety of age-associated comorbidities including vascular disease and cerebral hemodynamic function, the effects of obesity and metabolic disturbances on the aging brain, and also various medical disorders and etiological factors that may contribute to accelerated brain aging and cognitive decline. I am the Evelyn McKnight Chair for Cognitive and Memory at UF and have developed a multidisciplinary research program directed at study factors that influence cognitive aging that will integrate neurocognitive, neuroimaging, and laboratory biomarker methods. A primary goal of this center is clinical translational in nature with a focus on translating neuroscience findings from the laboratory to clinical application for both improvement assessment and intervention. I have an extensive background in neuroimaging and the neuroscience of attention-executive functions, and strong record of research involving the use of functional and structural neuroimaging methods in studies of age-associated brain disorders and neurodegenerative brain disorders. I have published over 250 peer-reviewed articles, and numerous book chapters on topics of relevance to this project. Besides co-editing several books on topics related to areas of clinical neuropsychological research, I authored "Neuropsychology of Attention" in 1993 which was the first book on this topic in the field, which I just updated and published as a second edition this year. I am authored a book "Brain Imaging in Behavioral Medicine and Clinical Neuroscience", which will be the first to address the use of neuroimaging methods for studying various problems in clinical neuroscience and to lead the current project. Specifically, my laboratory has been conducting human studies employing multimodal neuroimaging in conjunction with MRS to examine pathophysiological changes occurring in normal and pathological brain aging, and also secondary to risk factors including obesity, diabetes, heart disease, viral infections (e.g., HIV), and neurodegenerative disease such as AD.

B. Positions and Honors

Positions and Employment

1983 - 1990 Assistant Professor, Department of Neurology, University of Massachusetts Medical School
1990 - 1993 Associate Professor, Department of Neurology, University of Massachusetts Medical School
1993 - 1996 Assistant Professor, Department of Psychiatry-Human Behavior, Brown University
1993 - 2008 Director of Neuropsychology, The Miriam Hospital, Warren Alpert School of Medicine, Brown University
2004 - 2012 Professor, Department of Psychiatry-Human Behavior, Brown University
2004 - 2012 Professor, Brain Sciences Program, Brown University
2012 - Professor, Departments of Aging, Neurology and Psychiatry, University of Florida
2012 - Director, Center for Cognitive Aging and Memory, University of Florida

Other Experience and Professional Memberships

1983 - Member, International Neuropsychological Society

Honors

2012 Endowment in Support of the Center for Cognitive Aging and Memory, McKnight Brain Research Foundation
2015 Evelyn McKnight Chair, Cognitive Aging and Memory

C. Contribution to Science

1. My research was an outgrowth of interest and expertise in neuropsychology and cognitive neuroscience. My early research focused on attentional influences on cognitive functions, including studies of the effects of particular neurological brain disorders and psychiatric disturbances on effort and attentional control. This led to a number of publications focusing on the cingulate cortex, intentional behavior and also emotional processing, with much of this work culminating in the publication of his book "Neuropsychology of Attention. These studies present major contributions to neuropsychology and cognitive neuroscience. A few examples of these studies are listed above.

   My early clinical research focused on neurodegenerative disease in the elderly (AD). This evolved into investigations focusing on vascular dementia, as shown in a sample of my publications below, which employed neuroimaging methods to examine white matter abnormalities (FLAIR), cortical and subcortical morphometry, and functional imaging.
   a. **Cohen RA**, O'Donnell BF, Meadows ME, Moonis M, Stone WF, Drachman DA. ERP indices and neuropsychological performance as predictors of functional outcome in dementia. *J Geriatr Psychiatry Neurol*. 1995 Oct;8(4):217-25. **PubMed PMID: 8561835.**
   b. **Cohen RA**, Paul RH, Zawacki TM, Sethi M, Ott BR, Moser DJ, Stone W, Noto R, Gordon N. Single photon emission computed tomography, magnetic resonance imaging hyperintensity, and cognitive impairments in patients with vascular dementia. *J Neuroimaging*. 2001 Jul;11(3):253-60. **PubMed PMID: 11462291.**
   c. **Cohen RA**, Paul RH, Ott BR, Moser DJ, Zawacki TM, Stone W, Gordon N. The relationship of subcortical MRI hyperintensities and brain volume to cognitive function in vascular dementia. *J Int Neuropsychol Soc*. 2002 Sep;8(6):743-52. **PubMed PMID: 12240738.**
   d. Sweet LH, Paul RH, **Cohen RA**, Moser D, Ott BR, Gordon N, Browndyke JN, Shah P, Garrett KD. Neuroimaging correlates of dementia rating scale performance at baseline and 12-month follow-up among patients with vascular dementia. *J Geriatr Psychiatry Neurol*. 2003 Dec;16(4):240-4. **PubMed PMID: 14653434.**

2. As my work on VaD progressed, it became clear that it was necessary to examine patients with vascular disease and risk factors before they developed dementia. This led to R01 funded studies focusing on cognitive and neuroimaging abnormalities associated with cardiovascular disease, including heart failure. This work incorporated systemic vascular indices in conjunction with structural and functional measures. We also began to exam vessel and blood-barrier disturbances that might linked vascular factors with AD (Stopa et al.). To address these questions my research began to employ other neuroimaging methods, including ASL to assess CBF disturbances in relationship to FMRI alterations in HF and vascular cognitive impairment. My laboratory made significant contributions to characterizing the interaction between systolic problems linked to cardiac output and microvascular disease in the brain causing hemodynamic dysregulation and vulnerability to neuronal and white matter injury.
   a. Haley AP, Sweet LH, Gunstad J, Forman DE, Poppas A, Paul RH, Tate DF, **Cohen RA**. Verbal working memory and atherosclerosis in patients with cardiovascular disease: an fMRI study. *J Neuroimaging*. 2007 Jul;17(3):227-33. **PubMed PMID: 17608908.**
   b. Jefferson AL, Tate DF, Poppas A, Brickman AM, Paul RH, Gunstad J, **Cohen RA**. Lower cardiac output is associated with greater white matter hyperintensities in older adults with cardiovascular disease. *J Am Geriatr Soc*. 2007 Jul;55(7):1044-8. **PubMed PMID: 17608877; PubMed Central PMCID: PMC2721459.**
   c. Stopa EG, Butala P, Salloway S, Johanson CE, Gonzalez L, Tavares R, Hovanesian V, Hulette CM, Vitek MP, **Cohen RA**. Cerebral cortical arteriolar angiopathy, vascular beta-amyloid, smooth muscle actin, Braak stage, and APOE genotype. *Stroke*. 2008 Mar;39(3):814-21. **PubMed PMID: 18258839.**
   d. **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 Jan;31(1):96-110. **PubMed PMID: 18608677; PubMed Central PMCID: PMC2739675.**

3. My research on vascular and metabolic factors affecting the aging brain led to R01 funding focusing on HIV. I was a co-PI of HIV Neuroimaging Initiative to investigated longitudinal changes in brain function, structure and cerebral metabolite abnormalities. This work employed MRS, DTI, and more recently FMRI. Subsequent R01 grants awarded to me examined HIV and aging, and HIV in the context of alcohol and other drug use. Neuroimaging methods continue to play a major role in this area of my research, with current funded projects employing FMRI to examine functional connectivity in relationship to white matter connectivity and regional cerebral metabolite disturbance.

a. Paul RH, Ernst T, Brickman AM, Yiannoutsos CT, Tate DF, **Cohen RA**, Navia BA. Relative sensitivity of magnetic resonance spectroscopy and quantitative magnetic resonance imaging to cognitive function among nondemented individuals infected with HIV. *J Int Neuropsychol Soc*. 2008 Sep;14(5):725-33. **PubMed PMID: 18764968.**
b. Bunea F, She Y, Ombao H, Gongvatana A, Devlin K, **Cohen RA**. Penalized least squares regression methods and applications to neuroimaging. *Neuroimage*. 2011 Apr 15;55(4):1519-27. **PubMed PMID: 21167288.**
c. Gongvatana A, Harezlak J, Buchthal S, Daar E, Schifitto G, Campbell T, Taylor M, Singer E, Algers J, Zhong J, Brown M, McMahon D, So YT, Mi D, Heaton R, Robertson K, Yiannoutsos C, **Cohen RA**, Navia B. Progressive cerebral injury in the setting of chronic HIV infection and antiretroviral therapy. *J Neurovirol*. 2013 Jun;19(3):209-18. **PubMed PMID: 23613008; PubMed Central PMCID: PMC3740160.**
d. Caldwell JZ, Gongvatana A, Navia BA, Sweet LH, Tashima K, Ding M, **Cohen RA**. Neural dysregulation during a working memory task in human immunodeficiency virus-seropositive and hepatitis C coinfected individuals. *J Neurovirol*. 2014 Aug;20(4):398-411. **PubMed PMID: 24867610; PubMed Central PMCID: PMC4351737.**

4. In addition, to these specific areas of clinical focus, my laboratory continues to conduct studies that address more basic cognitive and behavioral neuroscience questions using neuroimaging as a core component. Some examples are listed below. Studies with Wing, McCaffery, Sweet and me focused on the role of brain reward and inhibitory control systems in obesity. This related to other work on obesity and metabolic effects on the brain and recent R01 funding to use use neuroimaging to study bariatric surgery and weight loss effects on the brain. We continue to also conduct studies to better understand the neural bases of functional neuroimaging responses, including the temporal dynamics of the BOLD response of specific tasks (e.g., Paskavitz et al). I also continue to conduct studies that examine older adults with and with out evidence of cognitive decline. For example, Ott et al. showed the relationship between ventricular volume increases and CSF biomarkers in AD, MCI and healthy controls. This represents a small sample of the areas of research that my center continues to explore.
   a. McCaffery JM, Haley AP, Sweet LH, Phelan S, Raynor HA, Del Parigi A, **Cohen RA**, Wing RR. Differential functional magnetic resonance imaging response to food pictures in successful weight-loss maintainers relative to normal-weight and obese controls. *Am J Clin Nutr*. 2009 Oct;90(4):928-34. **PubMed PMID: 19675107; PubMed Central PMCID: PMC2744621.**
   b. Ott BR, **Cohen RA**, Gongvatana A, Okonkwo OC, Johanson CE, Stopa EG, Donahue JE, Silverberg GD, Alzheimer's Disease Neuroimaging Initiative. Brain ventricular volume and cerebrospinal fluid biomarkers of Alzheimer's disease. *J Alzheimers Dis*. 2010;20(2):647-57. **PubMed PMID: 20182051; PubMed Central PMCID: PMC3078034.**
   c. Paskavitz JF, Sweet LH, Wellen J, Helmer KG, Rao SM, **Cohen RA**. Recruitment and stabilization of brain activation within a working memory task; an FMRI study. *Brain Imaging Behav*. 2010 Mar;4(1):5-21. **PubMed PMID: 20503110.**
   d. Daiello LA, Gongvatana A, Dunsiger S, **Cohen RA**, Ott BR. Association of fish oil supplement use with preservation of brain volume and cognitive function. *Alzheimers Dement*. 2015 Feb;11(2):226-35. **PubMed PMID: 24954371.**

5. A major emphasis on my work over the past decade has been clinical translational research focused at factors that affect the brain and cognition in in the context of normal aging. We have been conducting studies within the the CAM-CTRP of the UF Institute on Aging directed at the influence of systemic and neuroinflammation, endocrine changes, and other factors occurring with aging that may accelerate cognitive decline as people reach advanced age.
   a. Woods AJ, **Cohen RA**, Pahor M. Cognitive frailty: frontiers and challenges. *J Nutr Health Aging*. 2013 Sep;17(9):741-3. **PubMed PMID: 24154645; PubMed Central PMCID: PMC4471842.**
   b. Szabo AJ, Alosco ML, Miller LA, McGeary JE, Poppas A, **Cohen RA**, Gunstad J. Brain-derived neurotrophic factor Val66Met polymorphism and cognitive function in persons with cardiovascular disease. *Psychogeriatrics*. 2013 Dec;13(4):206-12. **PubMed PMID: 24289461; PubMed Central PMCID: PMC3847660.**
   c. **Cohen RA**, Seider TR, Navia B. HIV effects on age-associated neurocognitive dysfunction: premature cognitive aging or neurodegenerative disease? *Alzheimers Res Ther*. 2015;7(1):37. **PubMed PMID: 25848401; PubMed Central PMCID: PMC4386102.**
   d. Hawkins MA, Alosco ML, Spitznagel MB, Strain G, Devlin M, **Cohen RA**, Crosby RD, Mitchell JE, Gunstad J. The Association Between Reduced Inflammation and Cognitive Gains After Bariatric Surgery. *Psychosom Med*. 2015 Jul-Aug;77(6):688-96. **PubMed PMID: 25478707; PubMed Central PMCID: PMC4456339.**

D. Research Support

Ongoing Research Support

1R01DK09933401A1 **(Ronald Cohen, PI)** 09/30/14-8/30/19
NIDDK
"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**

2 P01 AA019072 (Monti) 9/1/15-5/31/20
NIAAA $893,352
Alcohol and HIV: Biobehavioral Interactions and Intervention
The goals of this program project are to study the effects of alcohol use on HIV disease progression, the effects of interventions to reduce alcohol use in HIV-infected populations, and the effects of alcohol on sexual decision making. The project also fosters multidisciplinary collaborations and training in research on alcohol and HIV and dissemination of research findings to clinicians treating addictions and HIV. Research Component 1 (Cohen, PI) is a continuation of the study being conducted in the parent ARCH, but will now examine the effects of reducing alcohol consumption via a motivational interviewing approach in HIV-infected heavy drinkers, with a specific focus on changes in cognitive performance, functional brain response on FMRI, and cerebral metabolite abnormalities (MRS).
Role: **Co-1; Research Component-1: PI (20% effort)**

U24 AA022002 Cook (PI) 09/01/13-08/31/16
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-I**

P01 AA019072 Monti (PI) 09/30/10 - 08/31/16
NIAAA
Alcohol and HIV: Biobehavioral Interactions and Intervention (ARCH)
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 the R01 type project (RC1) overseeing all aspects of the study.
Role: **Co-Investigator; PI: Research Component 1**

P01 AA019072 Monti (PI) 08/30/10 - 08/31/16
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 the R01 type project (RC1) overseeing all aspects of the study.
Role: **Co-Investigator; PI: Research Component 1**

RO1 NS080655 Thompson (PI) 8/1/2012-7/31/2016
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 by 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**

1U54EB020403-01 Thompson (PI) 9/29/14-9/30/18
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. 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, creating new algorithms to handle Big Data from (1) Imaging Genomics, (2) Connectomics, and (3) Machine Learning & Clinical Prediction

Dr. Cohen is a co-I (10% effort) and director of HIV data initiative

Completed Research Support

R01 HL089311 Gunstad (PI) 09/15/08 - 05/31/12
NHLBI/Subcontract from Kent State
Cognitive Benefits of Cardiac Rehabilitation in Heart Failure
The main goal of this project will be to study CVD and its effects on the brain, and particularly how cardiac rehabilitation and the effects of vascular conditioning are influenced by the vascular CVD and systemic vascular disease factors.
Role: **PI of Subcontract**

R01 HL084178 Sweet (PI) 01/25/07 - 11/30/12
NHLBI/Subcontract from Butler Hospital
Hemodynamic and Cognitive Function in Cardiovascular Disease
This study aims at characterizing the relationship between cerebral hypoperfusion and abnormalities of BOLD on FMRI in association with working memory and attention performance among patients with heart failure.
Role: **PI of Subcontract**

R01 MH074368 Cohen (PI) 09/30/06 - 08/31/12
Age Effects on HIV-Associated Brain Dysfunction
The goal of this project was to achieve greater understanding of how HIV infection interacts with aging to cause brain abnormalities that affect neurocognitive functioning.
Dr. Cohen oversees this entire project.

BIOGRAPHICAL SKETCH

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

NAME: Robert Lewis Cook, MD, MPH

eRA COMMONS USER NAME: cookrl

POSITION TITLE: Professor of Epidemiology and Medicine

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of North Carolina at Chapel Hill, NC	BSPH	/1986	Biostatistics
University of North Carolina at Chapel Hill, NC	MD, MPH	1991	Epidemiology
University of Virginia, Charlottesville, VA	Residency	1996	Internal Medicine
University of North Carolina at Chapel Hill, NC	Residency	1996	Preventive Medicine
University of North Carolina at Chapel Hill, NC	Fellowship	1994-96	RWJ Clinical Scholars

A. Personal Statement

Dr. Robert Cook is Professor of Epidemiology with a joint appointment in a division of Internal Medicine at the University of Florida. He has been working in the field of clinical epidemiology related to HIV infection for over 20 years and most of this work has been related to the connection between alcohol consumption and HIV infection. He is the PI of an NIH-funded study to conduct a randomized clinical trial of a pharmacologic intervention (oral naltrexone) for harmful alcohol consumption among women with HIV infection. In addition, he has continued to be a primary care physician in an outpatient medical clinic, and have built new research collaborations with clinicians and health services researches throughout Florida. He is also the Director of the Southern HIV & Alcohol Research Consortium (SHARC).

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. Contribution to Science

1. Much of my work has focused around the role of alcohol in the prevention, transmission, and outcomes related to HIV infection and other STDs. In 1999, I received a K-23 award from the National Institute on Alcohol Abuse and Alcoholism, to learn more about alcohol consumption in persons attending a large STD clinic. We learned that alcohol abuse was common, was associated with increased risk for STDs, and we identified screening questions that best correlated with alcohol use disorder.
   a. **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.**
   b. **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.**
   c. **Cook RL**, Chung T, Kelly TM, Clark DB. Alcohol screening in young persons attending a sexually transmitted disease clinic: comparison of AUDIT, CRAFFT, and CAGE instruments. *J Gen Intern Med* 2005; 20:1-6. **PMID: 15693920. PMC1490040.**

2. Over the next several years, I identified the associations of alcohol consumption with other behavioral outcomes in persons living with HIV. I was among the first to report a strong association of alcohol consumption to HIV medication adherence, and to identify longitudinal patterns of alcohol consumption in persons living with HIV. Within this research, I have sought to identify the subsets of persons with greatest need for intervention, and to better define problem drinking within specific population subgroups (e.g. women, men who have sex with men). During the past 3 years, I have been leading the NIH-funded Southern HIV Alcohol Research Consortium, which supports a range of alcohol-HIV research and training, and I lead a randomized clinical trial of naltrexone vs. placebo to reduce alcohol consumption in women with HIV.
   a. **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.**
   b. **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.**
   c. **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.**
   d. McGinnis KA, Fiellin DA, Tate JP, **Cook RL**, Braithwaite RS, Bryant KJ, Edelman EJ, Gordon AJ, Kraemer KL, Maisto S, Justice AC. Number of drinks to "Feel a Buzz" varies by HIV status and viral load in men. (In press), *AIDS and Behavior*, 2015.

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**, 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.**

4. **Cook RL**, Clark DB. Is there an association between alcohol consumption and sexually transmitted diseases? A systematic review. S*ex Transm Dis* 2005: 32:156-64. **PMID: 15729152.**

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. **Cook RL**, Xu X, Yablonsky EJ, Sakata N, Tripp JH, Sejvar JJ, Hess R, Piazza P, Rinaldo CR. Demographic and clinical factors associated with persistent symptoms after West Nile virus infection. *Am J Tropical Medicine and Hygiene*, 2010 Nov; 83(5):1133-6.

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. 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. (In Press, 2013)

9. **Cook RL**, Østergaard, L, Hillier SL, Murray PJ, Chang CH, Comer DM, Ness RB for the DAISY study team. Home screening for sexually transmitted diseases in high-risk young women: randomized controlled trial. *Sex Transm Infect* 2007 Jul;83(4):286-91. **PMID: 17301105. PMC2598665.**

10. **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.**

11. **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.**

12. **Cook RL**, Hutchison SL, Ostergaard L, Braithwaite RS, Ness RB. Non-invasive testing for chlamydia and gonorrhea: A systematic review. *Annals of Internal Medicine* 2005: 142: 914-25. **PMID: 15941699.**

13. Braithwaite RS, McGinnis KA, Conigliaro J, Maisto SA, Crystal S, Day N, **Cook RL**, Gordon A, Bridges MW, Seiler JFS, Justice AC. A temporal and dose-response association between alcohol consumption and medication adherence among veterans in care. *Alcohol Clin Exp Res* 2005: 29: 1190-1197. **PMID: 16046874.**

14. McMurtrey C , Lelic A, Piazza P, Chakrabarti AK, Yablonsky EJ, Wahl A, Bardet W, Fleshman A, **Cook RL**, Hess R, Buchli R, Loeb M, Rinaldo CR, Bramson J, and Hildebrand WH. Epitope discovery in West Nile Virus infection: Identification and effective immune recognition of unique viral epitopes. *Proc Nat Acad Sci* 2008 Feb 26;105(8):2981-6. **PMID: 18299564. PMC2268571.**

15 Akrim, M, Lemrabet S, Elharti E, Gray R, Tardy JC, **Cook, RL**, Salemi M, Andre P, El Aouad R. HIV-1 Molecular epidemiology in Morocco from the sentinel surveillance survey data 2004-2005. *AIDS Res Ther* 2012, Feb 14;9(1):5. **PMID 22333070. PMC3308925.**

D. Research Support

Ongoing Research Support

Miami Women's Interagency HIV Study (WIHS)
Role: Co-investigator (Fischl PI)
Funding: NIAID
Period: 2013-2018
Amount: $25,522
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.

Southern HIV & Alcohol Research Consortium (SHARC)
Role: Principal Investigator
Funding: NIAAA U24 AA022002
Period: 2012 – 2017
Amount: $2,493,604
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.

Pharmacotherapy for alcohol consumption in HIV-infected women: Randomized trial
Role: Principal Investigator
Funding: National Institute of Alcohol Abuse and Alcoholism 1 U01 AA020797-01
Period: September 25, 2011 – September 24, 2016
Amount: $2,776,000
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. This award also 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.

Rural South Public Health Training Center
Role: Co-investigator (Peoples-Sheps PI)
Funding: HRSA 1UB6HP2282
Period: 2011-2015
Amount: $2,593,537
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.

University of Florida Clinical and Translational Science Institute CTS K Award
Role: Primary Mentor (Whitehead PI)
Funding: CTSI Unnumbered
Period: 01/30/2015-12/31/2016
Amount: 75% salary support for junior investigator
Title: Substance Use Intervention for Older Underserved HIV+ Adults in the Primary Care Setting
This competitive institutional grant provides 75% salary support for junior investigators to aid in the transition to an independent research career. The goal of the current study is to pilot the implementation of an evidence-based substance use intervention for older HIV positive adults.

Completed Research Support (most relevant to current submission
Pharmacotherapy to reduce hazardous drinking in HIV-infected women.
Role: Primary Investigator
Funding: R01 Supplement, AA018934
Period: 2009-2012
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.

Home Screening for Bacterial Vaginosis to Prevent STD: A Study of the STI Clinical Trials Group
Role: Protocol Chair
Funding: NIAID, HHSN2662 00400074C
Period: 2007-2010
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 and for study, which began recruitment in the May, 2008.

Alcohol Use Disorders and Infectious Diseases among Youth
Role: Primary Investigator
Funding: K23 AA000303-01
Period: 1999-2003
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: Ding, Mingzhou

eRA COMMONS USER NAME: mingzhou_ding

POSITION TITLE: Pruitt Family Professor

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Peking University, China	BS	1982	Astrophysics
Institute of Theoretical Physics, China	--	1982-86	Theoretical Physics
University of Maryland, College Park, MD	PhD	1990	Physics

A. Personal Statement

The long-term objective of my laboratory is to understand the neural basis of cognition and its impairments in neurological and psychiatric disorders. Trained as a theoretical physicist/applied mathematician, my initial encounters with cognitive neuroscience occurred in the early 1990s. 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. Currently, 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/magnetoencephalogram (EEG/MEG), electrocorticogram (ECOG), functional magnetic resonance imaging (fMRI), and simultaneous EEG-fMRI, we investigate basic and clinical neuroscience questions in attention, working memory, emotion, and cognitive control. Over the past three years, through my collaboration with Drs. Cohen and Woods, I have become increasingly interested in the phenomenology and neuronal mechanisms of age-related cognitive decline and its therapeutic interventions. In this project I will work with the PI to implement the MRI imaging protocols as well as associated analysis and cognitive interpretation.

B. Positions and Honors

Positions

1990-2004	Assistant, associate and full Professor, Center for Complex Systems and Brain Sciences and Department of Mathematical Sciences, Florida Atlantic University, Boca Raton, Florida
2004-present	Professor, J. Crayton Pruitt Family Department of Biomedical Engineering, University of Florida
2008-present	J. Crayton Pruitt Family Professor, J. Crayton Pruitt Family Department of Biomedical Engineering, University of Florida

Honors

1989	University of Maryland Dissertation Fellowship
1992	First Prize for Natural Sciences, Chinese Academy of Sciences, China
1993	State Award of Second Rank in Natural Sciences, State Council, China
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	Fellow, American Institute for Medical and Biological Engineering (AIMBE)
2008-2012	Member, NIH Study Section on Cognitive Neuroscience (COG)
1995-2015	ad hoc member, numerous NIH study sections

2012-2015 ad hoc member, numerous NSF panels
2013-present University of Florida Research Foundation Professorship
2015-present Editor, Scientific Reports
2015-present Guest Associate Editor, Frontiers in Human Neuroscience and Frontiers in Physics

C. Contribution to Science

My complete publication (>140 journal papers) and citation record (>11000) can be found at: http://scholar.google.com/citations?user=4QTe24cAAAAJ&hl=en

1. *Analyzing information flow in neural networks:* Neural interactions, being mediated by the synaptic transmission of action potentials, are directional. Our ability to assess the directionality of neural interactions and information flow in brain networks holds the key to understanding the cooperative nature of neural computation and its breakdown in disease. Research over the last few years has proven that Granger causality is a statistical technique that furnishes this capability. My lab has pioneered the application of Granger causality to neuroscience by demonstrating its effectiveness in recordings from multiple species and experimental paradigms and developing the software package used by hundreds of labs around the world.
   a. Wen, X., Liu, Y., Yao, L., & **Ding, M**. (2013). Top-down regulation of default mode activity in spatial visual attention. *Journal of Neuroscience*, 33(15), 6444-6453. **PMCID: PMC3670184.**
   b. Dhamala, M., Rangarajan, G. & **Ding, M**. (2008). Analyzing information flow in brain networks with nonparametric Granger causality. *NeuroImage*, 41(2), 354-362. **PMCID: PMC2685256.**
   c. Brovelli, A., **Ding, M**, Ledberg, A., Chen, Y., Nakamura, R., & Bressler, S.L. (2004). Beta oscillations in a large-scale sensorimotor cortical network: Directional influences revealed by Granger causality. *Proceedings of the National Academy of Sciences of the United States of America*, 101(26), 9849-9854. **PMCID: PMC470781.**

2. *Single trial analysis of event-related signals:* Neural data following the onset of a stimulus is comprised of an event-related component that is relatively time-locked to stimulus onset and ongoing brain activity. These two types of signals, generated by possibly different neural mechanisms, may reflect different aspects of cognitive information processing. Estimation of the two, however, remains a major challenge. My lab has developed methods that are capable of separating the two signals on a trial-by-trial basis and demonstrated their effectiveness in numerous experimental preparations and paradigms. These methods are currently being used to answer questions in areas ranging from network basis of decision-making to improved target detection in cognitive brain machine interface to determination of the time course of emotional conditioning.
   a. Knuth, K.H., Shah, A.S., Truccolo, W.A., **Ding, M.,** Bressler, S.L., & Schroeder, C.E. (2006). Differentially Variable Component Analysis (dVCA): Identifying Multiple Evoked Components Using Trial-to-Trial Variability. *Journal of Neurophysiology*, 95, 3257-3276.
   b. Xu, L., Stoica, P., Li, J., Bressler, S.L., Shao, X., & **Ding, M**. (2009). ASEO: A Method for the Simultaneous Estimation of Single-trial Event-Related Potentials and Ongoing Brain Activities. I*EEE Transactions on Biomedical Engineering*, 56, 111-121.
   c. Liu, Y., Keil, A., and **Ding, M**. (2012). Effects of emotional conditioning on early visual processing: Temporal dynamics revealed by ERP single-trial analysis. *Human Brain Mapping*, 33, 909-919.

3. Neuronal oscillations: Electrophysiological recordings of neural activity are replete with oscillatory components. Characterizing the function of these neuronal oscillations is important for understanding both normal brain function and its impairments in brain disorders. My lab has contributed significantly to this field. We are the first to provide a thorough laminar analysis of alpha oscillations in multiple visual areas in awake-behaving macaque monkeys. We are also the first to demonstrate that theta oscillations mediate the interaction between prefrontal cortex and medial temporal lobe in human memory.
   a. Bollimunta, A., Chen, Y., Schroeder, C.E., & **Ding, M**. (2008). Neuronal Mechanisms of Cortical Alpha Oscillations in Awake-behaving Macaques. *Journal of Neuroscience*, 28, 9976-9988.
   b. Anderson, K.L., Rajagovindan, R., Ghacibeh, G.A., Meador, K.J., & **Ding, M**. (2010). Theta Oscillations Mediate Interaction Between Prefrontal Cortex and Medial Temporal Lobe in Human Memory. *Cerebral Cortex*, 20, 1604-1612.
   c. Rajagovindan, R. & **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.

4. *Simultaneous recording of EEG and fMRI:* EEG and fMRI are the two major methods for imaging human brain function. EEG is known for its excellent temporal resolution (millisecond) but poor spatial resolution (centimeter) whereas fMRI is known for its good spatial resolution (millimeter) but poor temporal resolution (second). Simultaneous EEG-fMRI, in which EEG is recorded together with fMRI inside the MRI scanner, is an emerging technique that promises to combine the strengths of the two methods and overcome their shortcomings. My lab is at the forefront of applying this cutting-edge technology to address important neuroscience problems.
   a. Liu, Y., Huang, H., McGinnis, M., Keil, A., & **Ding, M**. (2012). Neural substrate of the late positive potential in emotional processing. *Journal of Neuroscience*, 32, 14563–14572.

b. Mo, J., Liu, Y., Huang, H., & **Ding, M**. (2013). Coupling Between Visual Alpha Oscillations and Default Mode Activity. *NeuroImage*, 68,112-118.
c. Liu, Y., Bengson, J., Huang, H., Mangun, G.R., & **Ding, M**. (2015). Top-down Modulation of Neural Activity in Anticipatory Visual Attention: Control Mechanisms Revealed by Simultaneous EEG-fMRI. *Cerebral Cortex*, in press.

5. Cognitive fatigue and fatigability: Fatigue is the primary reason community-dwelling older adults restrict their activities and is associated with disability, diminished quality of life and increased mortality. Our understanding of the causes of fatigue in older adults is quite limited and we have no proven treatments. The construct of fatigue can be divided into perceived fatigue and performance fatigability with the former referring to subjective perceptions of exhaustion and the latter objective decrements in performance associated with prolonged exertion. My lab has made original contributions to the measurement of cognitive fatigability, its relation to perceived fatigue and the underlying neuronal mechanisms.
   a. Wang, C., **Ding, M.**, & Kluger, B.M. (2014). Change in Intraindividual Variability over Time as a Key Metric for Defining Performance-Based Cognitive Fatigability. *Brain and Cognition* 85, 251-258.

D. Research Support

R01 MH097320 **Ding**/Keil (PI) 04/02/12-02/28/17 NIMH
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.
Overlap: None

R01 MH100820 Kocsis/**Ding (PI)** 04/01/14-03/31/19 NIMH
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.
Overlap: None

R21 AG044862 **Ding**/Kluger (PI) 09/15/14-04/30/16 NIA
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.
Overlap: None.

BCS-1439188 **Ding (PI)** 09/01/14–08/31/17 NSF
Mechanisms of anticipatory attention
Objective: To study the neural basis of anticipatory attention in both humans and monkeys using electrophysiology and advanced computational methods.
Overlap: None

R01 MH094386 Lang (PI) 04/04/12-03/31/17 NIMH
Anxiety, comorbidity, negative affect, and fear circuit activation
Objective: To identify the pathophysiology underlying anxiety, fear and emotional dysregulation using multimodal brain imaging.
Overlap: none

R01 MH098078 Lang (PI) 09/12/12-05/31/17 NIMH
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.
Overlap: None

R01 NR014181 Price (PI) 09/26/12-05/31/17 NINR
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.
Overlap: None

R01 NS076665 Marino (PI) 09/27/12-06/30/17 NINDS
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.
Overlap: None

R01 NS082386 Price (PI) 09/25/13-08/31/18 NINDS
White Matter Connectivity and PD Cognitive Phenotypes
Objective: To examine white matter connectivity in PD patients and develop biomarkers for different cognitive phenotypes.
Overlap: None

BCS-1344285 Poeppel (PI) 09/15/13-08/31/16 NSF
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.
Overlap: None

N/A Neubert (PI) 02/01/15-01/31/16 Facial Pain Research Foundation
Mapping Towards a Cure – Identification of Neurophysiologic Signatures of Trigeminal Neuralgia Pain
Objective: To study the cause of trigeminal neuralgia pain using a translational approach by combining both humans and animals models.
Overlap: None

Completed Research Support

RX4235406 Wu (PI) 09/07/13-02/06/15 NSF
Brain activity maps of novelty detection
Objective: To study the neural basis of novelty detection using multi-modal neuroimaging and advanced computational approaches.

R01 MH060358 Schroeder (PI) 09/29/09-05/31/14 NIMH
Neuronal Oscillations as Instruments for Sensory Selection
Objective: To identify the mechanistic contributions of neuronal oscillations to sensory processing.

R01 MH079388 Ding (PI) 07/01/07-06/30/13 NIMH
Top-down Control of Attention
Objective: To investigate the role of oscillatory neural activity in implementing attentional control in the absence of sensory stimulation.

R21 MH087777 Kocsis (PI 07/01/10-05/31/13 NIMH
Information Flow in the Limbic Theta Circuit Revealed by Granger Causality
Objective: To investigate the mechanisms of theta oscillations in the rat limbic system.

R21 MH087275 Schroeder/Ding (PI) 04/01/10-12/31/12 NIMH
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. Positions 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
2012-2015 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. 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:10.1080/13825585.2012.736469.

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. Bryant, V.E., Whitehead, N.E., Burrell, L.E., **Dotson, V.M.**, Cook, R.L., Malloy, P., Devlin, K., & Cohen, R.A. (2014). Depression and apathy among people living with HIV: Implications for treatment of HIV associated neurocognitive disorders. *AIDS and Behavior*. doi: 10.1007/s10461-014-0970-1

20. McLaren, M.E., Szymkowicz, S.M., Kirton, J.W., & **Dotson, V.M**. (2015). Impact of education on memory deficits in subclinical depression. *Archives of Clinical Neuropsychology*, 30, 387–393. doi: 10.1093/arclin/acv038

21. Szymkowicz, S.M., McLaren, M.E., Kirton, J.W., O'Shea, A., Woods, A.J., Manini, T.M., Anton, S.D., & **Dotson, V.M**. (2015). Depressive symptom severity is associated with increased cortical thickness in older adults. *International Journal of Geriatric Psychiatry*. doi: 10.1002/gps.4324

22. Kirton, J.W. & **Dotson, V.M**. (2015). The interactive effects of age, education, and BMI on cognitive functions in community dwelling adults. *Aging, Neuropsychology and Cognition*. doi: 10.1080/13825585.2015.1082531

23. **Dotson, V.M.**, Hsu, F.C., Langaee, T.Y., McDonough, C.W., King, A.C., Cohen, R.A., Newman, A.B., Kritchevsky, S.B., Myers, V., Manini, T.M., Pahor, M., & LIFE Study Group (in press). Genetic moderators of the impact of physical activity on depressive symptoms. *Journal of Frailty and Aging*

24. Anton, S.D., Woods, A.J., Ashizawa, T., Barb, D., Buford, T.W., Carter, C.S., Clark, D.J., Cohen, R.A., Corbett, D.B., Cruz-Almeida, Y., **Dotson, V.M.**, et al. (in press). Successful aging: Advancing the science of physical independence in older adults. *Ageing Research Reviews*

25. O'Shea, D.M., **Dotson, V.M.**, Fieo, R.A., Angeliki, T., Zahodne, L. & Stern, Y. (in press). Older adults with poor self-rated memory have less depressive symptoms and better delayed memory performance when perceived self-efficacy is high. *International Journal of Geriatric Psychiatry*

D. Research Support

Ongoing Research Support

R03 MH109336-01A1 **Dotson (PI)** 8/14/15-4/30/17 National Institute of Mental Health
Dissociating Components of Anhedonia: Pilot Behavioral and fMRI Data for the Effort Expenditure for Rewards Task
The study purpose is to dissociate functional brain activity underlying anticipatory and consummatory components of anhedonia in young and older adults.
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.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Ebner, Natalie C

eRA COMMONS USER NAME (agency login): NATALIE.EBNER

POSITION TITLE: Assistant Professor

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

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Free University Berlin, Berlin	BA	04/1998	Psychology
Free University Berlin, Berlin	MA	03/2001	Psychology
Free University Berlin, Berlin	PHD	05/2005	Psychology

A. Personal Statement

My laboratory focuses on social-cognitive and affective experimental aging research. 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 using cognitive-behavioral measures. As a postdoctoral fellow and later as Associate Research Scientist at Yale University and as faculty at University of Florida (UF), I expanded my research to examine neuropsychological changes associated with cognition-emotion interactions in adulthood using neuroimaging 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 hold a joint appointment as faculty in the Center for Cognitive Aging and Memory (CAM) in the Aging Department at the College of Medicine at UF. My work has been funded by the NIH-sponsored Scientific Research Network on Decision Neuroscience and Aging, the National Science Foundation, the UF Pepper Center, and the UF Clinical and Translational Science Institute. I have received awards such as the Young Research Scientist Award from the German Psychological Association and the International Max Planck Research School on the Life Course Outstanding Alumni Award sponsored by the APA Board of Educational Affairs Award to Advance Interdisciplinary Education and Training in Psychology.

Representative Publications

1. **Ebner NC**, Johnson MK, Fischer H. Neural mechanisms of reading facial emotions in young and older adults. *Front Psychol*. 2012;3:223. **PubMed PMID: 22798953; PubMed Central PMCID: PMC3394436.**
2. **Ebner NC**, Johnson MR, Rieckmann A, Durbin KA, Johnson MK, Fischer H. Processing own-age vs. other-age faces: neuro-behavioral correlates and effects of emotion. *Neuroimage*. 2013 Sep;78:363-71. **PubMed PMID: 23602923; PubMed Central PMCID: PMC3684564.**

B. Positions and Honors

Positions and Employment

2001 - 2005 Predoctoral Fellow, Free University Berlin & Max Planck Institute for Human Development, Berlin
2005 - 2007 Postdoctoral Fellow, Max Planck Institute for Human Development, Berlin
2007 - 2010 Postdoctoral Fellow, Yale University, Department of Psychology, New Haven, FL
2010 - 2011 Associate Research Scientist, Yale University, Department of Psychology, New Haven, CT
2011 - Assistant Professor, University of Florida, Department of Psychology, Gainesville, FL
2013 - Adjunct Faculty, at Cognitive Aging and Memory Clinical Translational Research Program; CAM-CTRP, University of Florida, Gainesville, FL

Other Experience and Professional Memberships

2000 - 2011 Member, German Psychological Association
2003 - Member, Society for Personality and Social Psychology
2003 - 2009 Member, American Psychological Association
2008 - Member, Association for Psychological Science
2009 - 2009 Reviewer, 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, Swiss National Fund
2012 - Early Career Reviewer (ECR), National Institute ofHealth, Center for Scientific Review (CSR)
2014 - Member, Society for Affective Science

Honors

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, APA Board of Educational Affairs Award to Advance Interdisciplinary Education and Training in Psychology
2015 Kavli Fellow National Academy of Sciences

C. Contribution to Science

1. **Full List of Published Work**
   https://scholar.google.com/citations?user=z9g4mYIAAAAJ&hl=en
   My expertise in experimental behavioral aging research coupled with my background in affective, social, and cognitive neuroscience allows for a comprehensive view of brain-behavior relationships in the study of emotion, motivation, and social cognition in aging (Ebner & Fischer, 2014a, 2014b). I use a multi-methods approach in my research that combines convergent measures, including self-report, cognitive-behavioral measures, eye tracking, functional neuroimaging (fMRI, ERP), and neurobiological techniques (e.g., oxytocin administration), with the aim to integrate introspective, behavioral, and neuropsychological data.

   Representative Publications

   a. **Ebner, N. C.**, Horta, M., Lin, T., Feifel, D., Fischer, H., & Cohen, R. A. (2015). Oxytocin modulates meta-mood as a function of age and sex. *Frontiers in Aging Neuroscience*, 7, 175. DOI: 10.3389/fnagi.2015.00175 **PMCID: PMC4565056.**
   b. **Ebner NC**, Johnson MK. Young and older emotional faces: are there age group differences in expression identification and memory? *Emotion*. 2009 Jun;9(3):329-39. **PubMed PMID: 19485610; PubMed Central PMCID: PMC2859895.**
   c. **Ebner NC**, Fischer H. Studying the various facets of emotional aging. *Front Psychol*. 2014a;5:1007. **PubMed PMID: 25250008; PubMed Central PMCID: PMC4158868.**
   d. **Ebner NC**, Fischer H. Emotion and aging: evidence from brain and behavior. *Front Psychol*. 2014b;5:996. **PubMed PMID: 25250002; PubMed Central PMCID: PMC4158975.**

2. **Own-Age Bias in Attention, Memory, and Emotion Perception**
   One line of my research builds on the fact that our environment is complex and our cognitive system limited so that not all stimuli can be fully and simultaneously analyzed. There is evidence that emotional and self-relevant information is preferentially processed, possibly due to the highly practiced and elaborate knowledge-structures associated with it and the greater personal and social costs of inattention or inaccurate memory. My research findings open new insights into how faces of different ages are processed and how they bias attention and memory, under some conditions in interaction with the emotional content of the faces and with consequences for memory related to goals and agendas. My results challenge and inform interpretations of face and emotion processing and age-related differences therein as older participants may be at a disadvantage relative to young participants when stimuli are faces of only young individuals. My findings are not only important from a developmental perspective but they also place constraints of general theories of attention and memory and have various important implications for social interactions, emotional regulation, self-perceptions, psychological well-being, and health in adults of different ages.

   Representative Publications

   a. **Ebner NC**, He Y, Johnson MK. Age and emotion affect how we look at a face: visual scan patterns differ for own-age versus other-age emotional faces. *Cogn Emot*. 2011 Sep;25(6):983-97. **PubMed PMID: 21614704; PubMed Central PMCID: PMC3339265.**
   b. **Ebner NC**, He Y, Fichtenholtz HM, McCarthy G, Johnson MK. Electrophysiological correlates of processing faces of younger and older individuals. *Soc Cogn Affect Neurosci*. 2011 Sep;6(4):526-35. **PubMed PMID: 21030480; PubMed Central PMCID: PMC3150862.**
   c. **Ebner NC**, Johnson MK, Fischer H. Neural mechanisms of reading facial emotions in young and older adults. *Front Psychol*. 2012;3:223. **PubMed PMID: 22798953; PubMed Central PMCID: PMC3394436.**
   d. **Ebner NC**, Johnson MR, Rieckmann A, Durbin KA, Johnson MK, Fischer H. Processing own-age vs. other-age faces: neuro-behavioral correlates and effects of emotion. *Neuroimage*. 2013 Sep;78:363-71. **PubMed PMID: 23602923; PubMed Central PMCID: PMC3684564**.

3. **Oxytocin and Socioemotional Aging**

As summarized recent theoretical papers (Ebner, Diaz, Kamin, MacDonald, & Cohen, 2015; Ebner, Maura, MacDonald, Westberg, & Fischer, 2013), oxytocin is a neuropeptide with beneficial effects in social and emotional domains, mostly studied in young adults, schizophrenia, and autism. Our group is the first to comprehensively study acute and chronic oxytocin effects in the context of emotional, motivational, and social-cognitive aging. We have developed a theoretical framework that allows us to examine the extent to which the neuropeptide oxytocin is associated with improved functioning in aging, considering gene-brain-behavior relationships using behavioral, (epi)genetic, pharmacological, and neuroimaging techniques.

Representative Publications

a. **Ebner NC**, Maura GM, Macdonald K, Westberg L, Fischer H. Oxytocin and socioemotional aging: Current knowledge and future trends. *Front Hum Neurosci*. 2013;7:487. **PubMed PMID: 24009568; PubMed Central PMCID: PMC3755210.**

b. **Ebner NC**, Kamin H, Diaz V, Cohen RA, MacDonald K. Hormones as "difference makers" in cognitive and socioemotional aging processes. *Front Psychol*. 2014;5:1595. **PubMed PMID: 25657633; PubMed Central PMCID: PMC4302708.**

D. Research Support

Ongoing Research Support

2013/01/01-2017/12/31
Swedish Research Council
Ebner, Natalie C. (PI)
Effects of Oxytocin on Physical and Cognitive Functioning in the Elders
The goal of this project is to examine acute effects of intranasal oxytocin administration on cognition and social functioning in aging.
Role: **PI**

2013/10/01-2017/09/01
1R01AA022456-01, NIH/NIAAA
Nixon, Sara Jo (PI)
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.
Role: **Co-Investigator**

2014/09/01-2016/08/31
SaTC EAGERs NSF 13-037, National Science Foundation
Ebner, Natalie C (PI)
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.
Role: **PI**

2013/08/01-2016/03/31
P30AG028740, University of Florida Center for Cognitive Aging and Memory & Claude D. Pepper Older Americans Independence Center (sponsor: NIH/NIA)
Ebner, Natalie C. (PI)
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.
Role: **PI**

Completed Research Support

2014/09/01-2015/03/31
Scientific Research Network on Decision Neuroscience and Aging (SRNDNA; sponsored by NIH/NIA)
Ebner, Natalie C. (PI)
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.
Role: **PI**

2013/01/01-2013/12/31
UL1 TR000064, 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)
Ebner, Natalie C. (PI)
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.
Role: **PI**

2011/08/15-2013/06/01
N/A, Department of Psychology 2011 Michael L. & Judith D. Woodruff Research Competition Grant
Ebner, Natalie C. (PI)
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.
Role: **PI**

2007/07/01-2010/06/30
DFG EB 436/1-1, German Science Foundation
Ebner, Natalie C. (PI)
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.
Role: **PI**

Thomas Foster, PhD

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: Thomas Foster

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

POSITION TITLE: Professor of Neuroscience

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of 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 the relationship of brain aging and age-related cognitive decline and neurodegenerative disease of aging. My long-term goal is the amelioration of cognitive deficits associated with aging. 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 aging, from the molecular to the behavioral level. I have been continuously funded through NIH as a principle investigator since 1992 and my work includes over 100 publications on mechanisms for brain aging. Recent examples of this work are provided below.

a) **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. **PMCID: PMC22307057.**

b) Kumar A and **Foster TC**. Linking redox regulation of NMDAR synaptic function to cognitive decline during aging. *J Neurosci*, 2013; 33: 15710-15715. **PMCID: PMC24089479.**

c) Guidi, M., Kumar, A., and **Foster T.C.**, Impaired attention and synaptic senescence of the prefrontal cortex involves redox regulation of NMDA receptors. *J Neurosci*, 2015, 35(9) 3966-3977. **PMCID: PMC25740525.**

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 (2001-2015)
Member NIH IFCN-7 Study Section 1999-2004
Member NIH Learning and Memory study section (7/2014-6/2018)
Shannon Investigators Award, 1992

C. Contribution to Science

1. In general, my research is focused on understanding mechanisms for modifying synaptic transmission and their relationship to memory, particularly in the context of cognitive decline during aging. My early work employed in vivo recording and showed

that neuronal discharge activity in the hippocampus, a brain structure involved in memory, could represent the history of experience and the association of sensory-motor information.

a) **Foster, T.C.**, Christian, E.P., Hampson, R.E., Campbell, K.A. and Deadwyler, S.A. (1986) Sequential dependencies regulate sensory evoked responses of single units in the rat hippocampus. *Brain Research* 408:86-96. **PMCID: PMC3594233**

b) **Foster, T.C.**, West, M.O., Hampson, R.E. and Deadwyler, S.A. (1988) Control of sensory activation of granule cells in the fascia dentata by extrinsic afferents: Septal and entorhinal inputs. *Journal of Neuroscience* 8:3869-3878. **PMCID: PMC3193182**

c) **Foster, T.C.**, Castro, C.A. and McNaughton, B.L. (1989) Spatial selectivity of rat hippocampal neurons: Dependence on preparedness for movement. *Science* 244: 1580-1582. **PMCID: PMC2740902**

2. Synaptic plasticity is thought to mediate the associative and information storage properties of neurons; however, the mechanisms that regulate the induction and expression of synaptic plasticity remained to be elucidated. Therefore, I developed in vitro quantal analysis techniques to determine presynaptic and post synaptic mechanisms for expression changes in synaptic strength due to long-term potentiation (LTP), aging, or due to differential experience. The results provided a frame work for the cellular basis of memory.

a) **Foster, T.C.** and McNaughton, B.L. (1991) Long-term enhancement of synaptic transmission is due to increased quantal size, not quantal content. *Hippocampus* 1:79-91. **PMCID: PMC166934**4

b) **Foster, T.C.**, Barnes, C.A., Rao, G. and McNaughton, B.L. (1991) Increase in perforant path quantal size in aged F-344 rats. *Neurobiology of Aging* 12:441-448.**PMCID: PMC1776764**

c) **Foster, T.C.** and Dumas, T.C. (2001) Mechanisms for increased hippocampal synaptic strength following differential experience. *Journal of Neurophysiology* 85: 1377-1383. **PMCID: PMC11287462**

d) McNaughton, B.L. and **Foster, T.C**. (1990) The cellular basis of memory. *Science* 249:1487. **PMCID: PMC2271062**

3. Intracellular calcium (Ca2+) levels occupy a pivotal position in regulating the induction of synaptic plasticity and Ca2+ regulation is disrupted during aging, providing a possible link between age-related cognitive decline and senescent synaptic function. My work established this linked, showing that altered synaptic plasticity in region CA1 of the hippocampus is related to a specific age-related decline in episodic spatial memory and revealed the mechanisms for dysregulation of Ca2+ sources due to an oxidized redox state.

a) Norris, C.M., Korol, D.L. and **Foster, T.C**. (1996) Increased susceptibility to induction of long-term depression and long-term potentiation reversal during aging. *Journal of Neuroscience* 16: 5382-5392. **PMCID: PMC8757251**

b) Norris, C.M., Halpain, S. and **Foster, T.C**. (1998) Reversal of age-related alterations in synaptic plasticity by blockade of L-type Ca2+ channels. *Journal of Neurosciences*, 18: 3171-3179. **PMCID: PMC9547225**

c) Bodhinathan, K., Kumar A., **Foster, T.C**. Intracellular redox state alters NMDA receptor response during aging through Ca2+/calmodulin-dependent protein kinase II. *Journal of Neurosciences* 2010; 30(5):1914-1924.**PM: PMC20130200**

d) Kumar, A. and **Foster, T.C**. Linking redox regulation of NMDAR synaptic function to cognitive decline during aging. *Journal of Neuroscience* 2013; 33: 15710-15715. **PMCID: PMC24089479**

4. Questions remain as to the factors that contribute to the aging mechanisms we have described and could determine the well characterized variability in cognitive decline. For example, gender differences have been describe for the rate of cognitive decline during aging suggesting a possible role of sex steroids (e.g. estrogen) in preserving cognitive function. My work has examined rapid synaptic effects and long-term gene regulation effects of estradiol. Moreover, we demonstrated a critical window for effective estrogen treatment in aging female rats, and reveals differential role for various estrogen receptors in regulating estrogen effects on cognition and the maintenance of neuronal health.

a. **Foster, T.C.**, Sharrow, K.M., Kumar, A. and Masse, J. (2003) Interaction of age and chronic estradiol replacement on memory and markers of brain aging. *Neurobiology of Aging*, 24: 839-852, **PMCID: PMC12927766.**

b) **Foster, T.C.**, Rani, A., Kumar, A., Cui, L. and Semple-Rowland, S.L. (2008) Viral vector mediated delivery of estrogen receptor-alpha to the hippocampus improves spatial learning in adult estrogen receptor-alpha knockout mice. *Molecular Therapy* ,16: 1587-1593, **PMCID: PMC18594506.**

c) Aenlle, K.K., Kumar, A., Cui, L., Jackson, T.C., **Foster, T.C**. (2009) Estrogen effects on cognition and hippocampal transcription in middle-aged mice. *Neurobiol Aging* 30(6):932-945.**PM: PMC17950954**

d) Han, X., Aenlle, K.K., Bean, L.A., Rani, A., Semple-Rowland, S.L., Kumar, A., and **Foster, T.C**. Role of estrogen receptor alpha and beta in preserving hippocampal function during aging. *Journal of Neuroscience* 2013, 33: 2671-2683. **PMCID: PMC23392694**

e) Bean, L.A., Kumar, A., Rani, A., Guidi, M., Rosario, A., Cruz, P., Golde, T., **Foster, T.C**. Re-opening the critical window for estrogen therapy. *Journal of Neuroscience* 2015, 35 16077-1693.

Complete List of Published Work in MyBibliography
http://www.ncbi.nlm.nih.gov/sites/myncbi/thomas.foster.1/bibliograpahy/40906731/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

R37 AG036800 **Foster (PI)** 09/01/2014 to 08/31/19

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**

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.

Role: **advice on animals models of aging and age-related cognitive decline**

NIH/NS R01NS04389 Ranum (PI) 8/1/2015 – 7/31/2019

This proposal examines the molecular genetic characterization of SCA8.

Role: **advice on electrophysiological studies.**

NIH/NINDS R21NS091435 Notterpek (PI) 4/15-3/17

This project examines therapeutic targeting of the chaperone pathway for myelin repair in hereditary neuropathies.

Role: **involves statistical expertise for repeated measures of behavior.**

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**

R01AG029421-07A1 Bizon (PI) 4/1/2014-3/31/2015

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**

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: Heilman, Kenneth M.

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

POSITION TITLE: Distinguished Professor of Neurology, University of Florida; Neurologist, NF/SG VAMC

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Virginia, Charlottesville VA		05/1959	Chemistry
University of Virginia, College of Medicine, Charlottesville VA	MD	06/1963	Medicine
Cornell Medical Div. Bellevue Hospital, NY	Intern and Assistant Resident (PGY 1,2)	06/1965	Internal Medicine
Harvard Neurological Unit, Boston City Hospital, Boston MA	Resident, Chief Resident and Fellow (PGY 3,4,5)	06/1970	Neurology

A. Personal Statement

I am a Behavioral Neurologist who has a strong interest in training, clinical care and research. In regard to research, since joining the faculty at the University of Florida in 1970, and the Malcom Randall VAMC in 1977, I have established and maintained a productive research program. Research in my laboratory includes studies on the neurological basis and disorders of emotion, language, skilled purposeful movements (praxis), frontal-action-intentional systems, episodic memory, attention and neglect, and creativity.

B. Positions and Honors

Positions and Employment

1965-1967 Captain, Air Force, and Chief of Medicine, NATO Hospital, Izmir, Turkey
1970-1973 Assistant Professor of Medicine, Division of Neurology, University of Florida College of Medicine
1973-1975 Associate Professor of Neurology, University of Florida College of Medicine
1973-1977 Associate Professor of Clinical Psychology, University of Florida College of Medicine
1975-1998 Professor, Department of Neurology, University of Florida, Gainesville, Florida
1977-present Professor, Department of Clinical Psychology, University of Florida Gainesville, Florida
1977-1996 Staff Physician, Malcom Randall VA Medical Center, Gainesville, Florida
1984-present Director, Center for Neuropsychological Studies, University of Florida College of Medicine
1988-present Director, Cognitive and Memory Disorder Clinic, University of Florida
1990-2008 James E. Rooks Jr., Professor of Neurology, University of Florida
1996-2008 Chief of Neurology, Malcom Randall Veterans Affairs Medical Center
1998-present Distinguished Professor, University of Florida College Medicine, Gainesville, Florida
2009-present James E. Rooks Jr., Professor of Neurology
2009-present Staff Physician and Member of GRECC, Malcom Randall VA Medical Center

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

1976	Presentation to the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research – Psychosurgery
1976-1977	University of Florida Senate
1981-1984	National Institutes of Health: Study Sections: Neurobiology Review Group (Study Section)
1984-1985	University of Florida Senate
1986-1992	American Board of Psychiatry and Neurology, Part I Neurology Committee (Minor Subcommittee)

Memberships and Honors

	Association of University Professors
1970-present	Alachua County Medical Society
1970-present	American Academy of Neurology (Fellow from 1975-present)
1974-1977	International Neuropsychology Society (Member, Executive Committee)
1976-2008	American Neurological Association Active Member
1982	Alpha Omega Alpha
1982	Sigma Xi
1982-1983	Society for Behavioral and Cognitive Neurology; President
1982-1983	International Neuropsychology Society (President)
1984	International Society for Research of Emotion; Board of Directors, Phi Kappa Phi
1987-1990	American Academy of Aphasia (Governing Board)
1997-1999	University of Florida Research Foundation Professorship (Award)
1989	National Aphasia Association; Advisory Board
1993	Faculty Research Award in Clinical Science, College of Medicine, University of Florida
1994-2004	American Society of Neurorehabilitation
1996	Society for Behavioral and Cognitive Neurology; Outstanding Achievement Award Aphasia Research Group of the World Federation of Neurology
2003	The Dana Foundation Alliance
2003	The American Speech and Hearing Association, Distinguished Service Award for Scientific and Educational Contributions
2005-2007	University of Florida Research Foundation Professorship (Award)
2008-present	American Neurological Association Honorary Member
2008	University of Florida, College of Medicine, Lifetime Achievement Award
2009	International Neuropsychology Society Lifetime Achievement Award
2009	American VA Speech and Language Pathologists' President's Award
2009	American Academy of Neurology, Wartenberg Award and Keynote Lecture

C. Contribution to Science

1. New Disorders and Diseases: Throughout my career I have identified previously unrecognized neurological diseases, creating new opportunities for research and treatment. The following are four examples of new neurological diseases that my coworkers and I have characterized:
   a. Orthostatic Tremor: **Heilman, KM**. "Orthostatic tremor." *Archives of neurology* 41, no. 8 (1984): 880-881.
   b. Hyperlipidemic Dementia: Heilman, Kenneth M., and Waldo R. Fisher. "Hyperlipidemic dementia." *Archives of neurology* 31, no. 1 (1974): 67-68.
   c. Primary Progressive Speech Abulia: Milano, NJ, and **Heilman, KM**. "Primary Progressive Speech Abulia." *Journal of Alzheimer's Disease* (2015) [Epub ahead of print] **PMID: 25854928.**
   d. Progressive affective aprosodia and prosoplegia. Ghacibeh, GA, and **Heilman, KM**. "Progressive affective aprosodia and prosoplegia." *Neurology* 60, no. 7 (2003): 1192-1194.

2. Unilateral Spatial Neglect: Patients with primarily right-sided strokes and some patients with degenerative diseases present with a very disabling disorder called unilateral neglect, where they are unaware of items or parts of their body in the contra-lesional portion of space. Spatial neglect has been a primary research interest throughout my career, and I have published more than 150 peer-reviewed papers on this topic. For example, while it had been known that neglect was often induced

by parietal lesions, we reported that neglect could also be induced by injury to the lateral and medial frontal lobes including the cingulate gyrus (Heilman, KM, Valenstein, E. "Frontal lobe neglect in man." Neurology, 22 (1972): 660-664) as well as the thalamic and mesencephalic reticular formation (Watson, RT, Heilman, KM. "Thalamic neglect." Neurology, 29 (1979): 690-694). Based on this, we proposed an attention network model and demonstrated that the right hemisphere is dominant in mediating attention (Heilman, KM, Van den Abell, R. "Right hemisphere dominance for attention: The mechanism underlying hemispheric asymmetries of inattention." Neurology, 30 (1980): 327-330) We also showed that neglect could be caused by a failure to initiate actions in and/or toward contralateral space, called intentional neglect (Heilman KM, "Intentional neglect." Frontiers in Bioscience 9:694-705).

3) Emotional Communication: Since the time of Paul Broca, it has been known that the left hemisphere mediates propositional speech, reading and writing. We were one of the first laboratories to reveal that the right hemisphere mediates emotional communication, and that disorders of the right hemisphere can impair both the expression and comprehension of emotional prosody or emotional facial expressions. We have written more than 65 papers on the neuropsychology of emotions and the following are 4 of the earlier papers we had written on this topic: a) Bowers, D., Coslett, HB, Speedie, LJ, Heilman, KM. "Comprehension of emotional prosody following unilateral hemispheric lesions; Processing defects vs. distraction defects." Neuropsychologia, 25 (1987): 317-328; b) Harciarek M, Heilman KM. "Contribution of anterior and posterior regions of the right hemisphere to the recognition of emotional faces." J Clin Exp Neuropsychol. 31(3) (2009): 322-30; c) Blonder, LX, Bowers, D, Heilman, KM. "The role of the right hemisphere on emotional communication." Brain, 114 (1991): 1115-1127. d) Bowers, D, Bauer, RM, Coslett, HB, Heilman, KM. "Processing of faces by patients with unilateral hemispheric lesions. I. Dissociation between judgments of facial affect and facial identity." Brain and Cognition, 4 (1985): 258-272.

4) Anosognosia: One hundred years ago, unawareness of hemiplegia was first called anosognosia by Babinski. This lack of awareness interferes with both rehabilitation and compensation for the deficit. We have written more than 30 papers that attempt to elucidate the brain mechanism that may account for this disorder. Weinstein and Kahn posited that anosognosia was a psychological defense mechanism; however, clinical reports as well as studies using transient hemispheric anesthesia reveal anosognosia for hemiplegia is more commonly associated with right than left hemisphere dysfunction, which is not entirely compatible with this denial hypothesis. Some patients with anosognosia will recognize their hemiparesis when their paretic hand is placed into ipsilesional hemispace, suggesting that de-afferentation and inattention-neglect may be important mechanisms. Some patients with anosognosia have asomatognosia, and since they are unaware that their paretic arm belongs to them, they do not recognize that they have a deficit. Other patients have phantom movements, and may confabulate these movements because they have a hemispheric disconnection. The feed-forward hypothesis posits that, without an attempt to move, there is no expectation of movement. Thus, in the absence of arm movement there will be no discord that leads to discovery. Thus, motor neglect may be another cause of anosognosia. A defect in a theoretical comparator, where expectations are compared to feedback, may also be a cause of anosognosia, but further evidence is needed to support this postulate. Based on the studies of anosognosia for hemiplegia, it appears that normal self-awareness depends on several modular systems (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). Anosognosia with stroke is not limited to hemiplegia and can also be seen with cognitive deficits such as aphasia (Shuren, J.E., Hammond, C., Maher, LM., Rothi, LJG., Heilman, KM. "Attention and anosognosia: The case of an aphasic with unawareness of language deficit." Neurology, 45 (1995): 376-378] as well as in patients with movement disorders Shenker JI, Wylie SA, Fuchs K, Manning CA, Heilman KM. "On-line anosognosia: Unawarenes for chorea in real time but not on videotape delay." Neurology. 63(1) (2004): 159-160] and degenerative dementia (Barrett AM, Eslinger PJ, Ballentine NH, Heilman KM. "Unawareness of cognitive deficit (cognitive anosognosia) in probable AD and control subjects." Neurology. 64(4) (2005): 693-9).

5) Disorders of Purposeful Skilled Movements—Apraxia: In order to perform activities of daily living and instrumental activities, people have to be able to use their upper limbs to perform skilled purposeful movements. A loss of these skills is called apraxia. There are several forms of apraxia, and we have published more than 70 papers that have attempted to understand the pathophysiology of these disorders. For example, we have determined that the spatial and temporal components of skilled movements are mediated by a left hemisphere network that includes the parietal and premotor portions of the cerebral cortex (Heilman KM, Rothi LJ, Valenstein E. "Two forms of ideomotor apraxia." Neurology. 32(4) (1982): 342-6). We have also reported that callosal lesions can induce ideomotor apraxia of the left upper limb (Watson RT, Heilman KM. "Callosal apraxia." Brain. Jun;106 (Pt 2) (1983): 391-403). A loss of finger deftness is called limb-kinetic apraxia. We have found that the left hemisphere also appears to be dominant for mediating hand and finger deftness (i.e., precise independent but coordinated finger movements) (Hanna-Pladdy B, Mendoza JE, Apostolos GT, Heilman KM. "Lateralised motor control: hemispheric damage and the loss of deftness." J Neurol Neurosurg Psychiatry. 73(5) (2002): 574-7). Furthermore, we call a loss of knowledge about the mechanical advantage of tools "conceptual apraxia" and have revealed that the left hemisphere is also

dominant in storing this knowledge ([Heilman KM, Maher LM, Greenwald ML, Rothi LJ. "Conceptual apraxia from lateralized lesions." Neurology. 49(2) (1997): 457-64).

Bibliography of papers available within PubMed (Note: it was infeasible to cross-reference papers and books published before the advent of PubMed-indexed journals or in those that have not been subsequently indexed):
http://www.ncbi.nlm.nih.gov/sites/myncbi/1PgQ2XC8Hg55o/bibliography/44852418/public

D. Research Support

I01 CX000744 VA Clinical Science Research & Development - Merit Review 10/1/2012 – 9/30/2016
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.'
Role: **PI**

XZ302 DOEA State of Florida, Department of Elder Affairs Memory Disorder Clinics 7/1/88 – 6/30/15
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.
Role: **PI**

R21 AG044449 National Institute of Health/National Institute on Aging 9/30/13 – 6/30/15
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.
Role: **PI**

IK2 RX000707 VA Rehabilitation Research & Development - Career Development 2 4/1/2012 – 3/31/2017
White Matter Changes and Mild TBI: Emotional and Autonomic Consequences
Research on the brain mechanisms that may induce the behavioral deficits caused by mild TBI is important for several reasons. Perhaps the most important reason is the frequency of these injuries and the disability and suffering caused by TBI. Understanding the pathophysiology of a disorder is often an important initial step in finding a successful treatment.
Role: **Mentor** (PI: John B. Williamson, PhD)

IK1 RX000961 VA Rehabilitation Research & Development - Career Development 1 7/1/2013 – 6/30/2015
Motor Impairments in Traumatic Brain Injury:Effects of Callosal Disconnection
The expected outcome of this study is a greater understanding of the pathophysiology of motor dysfunction in TBI and particularly those effects caused by callosal disconnection.
Role: **Mentor** (PI: Adam Falchook, MD)

IK1 RX000958 VA Rehabilitation Research & Development - Career Development 1 10/1/2013 – 9/30/2015
Treatment of Emotional Prosodic Disorders in Parkinson's Disease
The primary goal of this research is to compare a treatment protocol shown to be effective in treating emotional prosodic deficit in stroke and TBI (Leon et al., 2005; Rosenbek et al., 2006) to a standard clinical treatment for prosody deficit that does not target the emotional aspect of the disorder in individuals with PD.
Role: **Mentor** (PI: Susan Leon, PhD)

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: **JOHNSON, SARAH ANNE**

eRA COMMONS USER NAME (agency login): sj56.nyu

POSITION TITLE: Postdoctoral Associate

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

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Dalhousie University, Halifax, NS, Canada	BSc	5/2004	Neuroscience
University of Toronto, Toronto, ON, Canada	MSc	6/2007	Neuroscience
University of Toronto, Toronto, ON, Canada	PhD	10/2013	Psychology
New York University, New York, NY, USA (postdoc)	n/a	8/2014	Neuroscience
McKnight Brain Institute / University of Florida, FL, USA (postdoc)	n/a	Present	Neuroscience

A. Personal Statement

The goal of my proposed postdoctoral research to be conducted in Dr. Sara Burke's laboratory is to determine the neural mechanisms underlying high-order perceptual deficits in aging, as they relate to impairments of memory encoding and maintenance. As Key Personnel on this application, I will employ my expertise in behavioral and molecular biological techniques acquired through my graduate and previous postdoctoral training.

My postdoctoral training in the Department of Neuroscience at the University of Florida will allow me to continue on the path to becoming an independent investigator. I will broaden my technical expertise to include in vivo recordings of neuronal physiological activity and analysis of single-unit and EEG data from hippocampal and cortical regions. Combined with my prior experience in behavioral and molecular approaches, outlined below, this will allow me to develop an independent research program aimed at understanding processes underlying the formation of stable, accurate long-term memories at three levels of analysis. Further, I will gain deeper knowledge of the neurobiology of aging based on supervision from Dr. Burke, who has over ten years of experience in this area of research, and through close collaborations with colleagues at the McKnight Brain Institute. This will allow me to focus my independent research program on the central question of how aging impacts memory function, one that is of significant public health and clinical interest.

Collectively, my graduate training provided a solid grounding in the use of animal models to study learning and memory, and modulation of these processes under the influence of stress hormones and drug exposure. During this period I was continuously funded by competitive research fellowships, and also received a number of academic and teaching awards. I chose to complete a first period of postdoctoral training in Dr. Cristina Alberini's laboratory at New York University to pursue my interest in long-term memory from a mechanistic standpoint. Dr. Alberini is recognized as a leader in the field of molecular and cellular memory consolidation. As a postdoctoral trainee in her laboratory, I mastered skills in intracerebral cannulation for targeted delivery of drugs, and in the preparation of total and synaptic tissue fractions for assessment of protein expression critical to memory consolidation. During my two and a half-year period in her laboratory, I took on a new line of investigation assessing the effects of aging on memory consolidation and the role of insulin-like growth factor 2 (IGF-2) in age-related long-term memory deficits. I capitalized on the molecular techniques available to determine that aged rats show loss of mature IGF-II protein localized to hippocampal synapses. Combining molecular interventions with my training in behavioral methods, I went on to demonstrate that localized administration of mature IGF-II protein in the dorsal hippocampus prevents age-related impairment of both contextual fear memory and object location memory.

B. Positions and Honors

Positions and Employment

2002-2004 Undergraduate Research Assistant in Dr. Lisa Kalynchuk's Molecular Psychiatry laboratory

Department of Neuroscience & Psychology, Dalhousie University, Halifax, NS, Canada
2004-2007 Graduate Research Associate in Dr. L. Trevor Young's Molecular Psychiatry laboratory
Centre for Addiction and Mental Health / University of Toronto, Toronto, ON, Canada
2007-2012 Graduate Research Associate in Dr. Suzanne Erb's Neurobiology of Relapse laboratory
Department of Psychology, University of Toronto, Toronto, ON, Canada
2007-2011 Laboratory Instructor for NROB60: Neuroscience I Cell Anatomy and Physiology
Department of Psychology, University of Toronto, Toronto, ON, Canada
2010-2012 Laboratory Instructor for NROD63: Advanced Behavioral Neuroscience Laboratory
Department of Psychology, University of Toronto, Toronto, ON, Canada
2012-2013 Junior Research Scientist, Laboratory of Dr. Cristina Alberini
Center for Neural Science, New York University, New York, NY

Academic and Professional Honors

2000 University of Toronto National Book Award
2000-2004 Dean's List, Faculty of Science, Dalhousie University
2003 NSERC Undergraduate Student Research Award (National)
2004 Departmental Honors in Neuroscience, Dalhousie University
2004 NSERC Postgraduate Training Grant, University of Toronto (National)
2006 International Behavioral Neuroscience Society Travel Award
2006 Peterborough K.M. Hunter Graduate Studentship, University of Toronto
2007 Ontario Graduate Scholarship (Provincial)
2008 NSERC Canada Graduate Training Grant, University of Toronto (National)
2010 Canadian Association for Neuroscience Travel Award
2010 Ontario Mental Health Foundation Research Studentship (Provincial)
2012 Principal's Graduate Student Teaching Award, University of Toronto
2013 Honorable Mention, Poster Competition, NYU Center on Brain Aging Research Day
2015 North Central Florida Chapter of the Society for Neuroscience Travel Award

Memberships in Professional Societies and Other Activities

2004- Member, Society for Neuroscience
2004- Member, International Behavioral Neuroscience Society (IBNS)
2005-2007 Member of IBNS Program Committee
2007-2008 Elected Trainee Councilor to IBNS Council
2008-2010 Member of IBNS Education and Training Committee
2005-2008 Facilitator, Society for Neuroscience Southern Ontario Chapter Local Brain Bee
2007-2009 Judge for poster competition, Annual Toronto High School Science & Technology Fair
2007-2011 Member, Canadian College of Neuropsychopharmacology
2007-2012 Mentor, Undergraduate Neuroscience Honors Research Program, University of Toronto
2008-2009 Member, Search Committee for Position in Vertebrate Physiology, University of Toronto
2009-2010 Member, Project Planning Committee for Instructional Centre, University of Toronto
2009-2010 Co-Chair, Brain & Behavior Seminar Series, Dept of Psychology, University of Toronto
2010- Member, Canadian Association for Neuroscience
2010-2011 Co-Chair, Graduate Student Seminar Series, Dept of Psychology, University of Toronto
2011- Member, Molecular and Cellular Cognition Society
2014 Mentor, Summer Undergraduate Research Program, Center for Neural Science, NYU
2015 Judge for poster competition, Annual Meeting of the North Central Florida SfN Chapter
2015- Member, North Central Florida Chapter of the Society for Neuroscience
2015- Member, Faculty for Undergraduate Neuroscience

C. Contributions to Science

My Contributions to Science are organized into three time periods: I. Early Career; II. Graduate Career; and III. Postdoctoral Career.

I. **Early Career:** My early career contributions were focused on identifying the relationship of chronic stress to pathophysiology of mental illness. Specifically, my undergraduate Honors thesis at Dalhousie University examined the link between stress hormone exposure and depression. I led a project that demonstrated chronic exposure to glucocorticoids results in a dose-dependent emergence of depression-like behavior and blunting of HPA axis activation in rats, and published this work as first author. This paper has been cited over 100 times in 9 years. My Masters' thesis at the University of Toronto determined the

effects of chronic stress on neural plasticity in the amygdala as it relates to hypertrophy and excitability of this region in bipolar disorder. This work also led to a first author publication that demonstrated lithium treatment prevents the emergence of amygdalar hypertrophy and aberrant gene expression resulting from chronic stress in rats.

Research papers

Johnson SA, Fournier NM, Kalynchuk LE. Effect of different doses of corticosterone on depression-like behavior and HPA axis responses to a novel stressor. *Behav Brain Res*. 2006 Apr 3; 168(2):280-8. **PubMed PMID: 16386319.**

Johnson SA, Wang JF, Sun X, McEwen BS, Chattarji S, et al. 2009. Lithium treatment prevents stress-induced dendritic remodeling in the rodent amygdala. *Neuroscience*. 2009 Sep 29; 163(1):34-9. **PubMed PMID: 19501634.**

Published abstracts

Johnson SA, Stamp JA, and Kalynchuk LE. Repeated corticosterone injections facilitate depression-like behavior and suppress hypothalamic-pituitary-adrenal axis activation in a dose-dependent manner. Abstract for poster presentation 762.7, *Society for Neuroscience*, San Diego, CA, October 2004

Johnson SA, Barlow K, Wang JF, Nobrega J, Chattarji S, et al. Lithium protects the rodent amygdala against stress-induced dendritic remodeling and down-regulation of BDNF mRNA expression. Abstract for poster presentation 298.3, *Society for Neuroscience*, San Diego, CA, November 2007.

II. **Graduate Career:** My graduate research contributions focused on the role of long-term memory for drug experience in predisposition to relapse. Using an animal model in which rats received multiple exposures to cocaine in distinct environments, I demonstrated that conditioned behavioral responses to drug-associated contexts persist for months even when individuals have no control over initial drug administration. These results indicated that strong Pavlovian associations are formed between psychostimulant reward and drug-associated stimuli, and that extinction therapies could be crucial to reducing risk of relapse.

Research papers

Johnson SA, Sediqzadah S, Erb S. Expression and resilience of a conditioned locomotor response after brief and extended drug-free periods. *Behav Brain Res*. 2012 Apr 21; 230(1):69-77. **PubMed PMID: 22326371.**

Published abstracts

Erb S, **Johnson SA**, Sediqzadah S, and Placenza FM. Conditioned locomotion and structural plasticity in the amygdala after repeated cocaine administration: assessment after brief and extended drug-free periods. Abstract for poster presentation 649.7, *Society for Neuroscience*, Chicago, IL, October 2009.

Johnson SA, Sediqzadah S, Grella SL, Nobrega JN, and Erb S. Cocaine-associated contextual cues increase c-fos mRNA expression in the basolateral amygdala and prefrontal cortex after extended drug-free periods. Abstract for poster presentation 575.21, *Society for Neuroscience*, San Diego, CA, November 2010.

Johnson SA, Sediqzadah S, and Erb S. The conditioned locomotor response to a cocaine-paired context is not susceptible to reinstatement or spontaneous recovery after brief or extended withdrawal. Abstract for poster presentation 473.20, *Society for Neuroscience*, Washington, DC, November 2011.

III. **Postdoctoral Career:** As a postdoctoral fellow, my research activities have centered on identifying molecular and physiological mechanisms that subserve formation of accurate long-term memories, as well as how these mechanisms are affected by aging. In my first postdoctoral position, I showed that levels of the biologically active mature form of insulin-like growth factor 2 (IGF-2) are reduced in the hippocampus of aged rats. Given that IGF-2 plays a critical role in memory consolidation, I went on to show that administration of the mature IGF-2 peptide to the hippocampus of aged rats prevents deficits in long-term memory. This work was recently submitted for publication. In my second postdoctoral position, I am focused on determining how physiological changes within the aged hippocampus impact memory function. Theoretical models and recent experimental results suggest the hippocampal dentate gyrus and CA3 support storage of distinct representations of similar events in memory. Given that this ability is critical to the formation of lasting, accurate long-term memories, and that these hippocampal regions are both adversely affected by aging, I am investigating changes in neuronal physiological activity that occur in the aged dentate gyrus and CA3 during behavioral tasks that require discrimination of similar stimuli and events. I have now shown that aged rats are impaired in performing difficult spatial and object discriminations when stimuli share many overlapping features. Ongoing experiments have two aims: (1) to identify the effects of aging on activation of local and distributed hippocampal networks during difficult discrimination tasks with a molecular gene expression imaging approach; and (2) to determine the effects of aging on neuronal physiological activity during discrimination tasks using simultaneous multi-channel in vivo recordings from the dentate gyrus and CA3.

Research papers

Steinmetz A*, **Johnson SA***, Iannitelli D, Pollonini G, Alberini CM. Insulin-like growth factor 2 rescues aging-related memory loss in rats. Submitted Dec 25 2015 to *Neurobiology of Aging*. *authors contributed equally.

Johnson SA, Sacks PK, Turner SM, Gaynor LS, Ormerod BK, AP Maurer, JL Bizon, SN Burke. Spatial discrimination performance is modulated by difficulty, age, and cumulative interference. Submitted Dec 7 2015 to Learning & Memory.

Published abstracts

Johnson SA and Alberini CM. Rescue of age-related memory deficits by insulin-like growth factor 2. Abstract for poster presentation 391.07, Society for Neuroscience, San Diego, CA, November 2013.

Johnson SA, Gaynor LS, Sacks PK, Turner SM, Yoder WM, Ormerod BK, Maurer AP, Bizon JL, Burke SN. Age-related decline of spatial discrimination performance based on difficulty may reflect pattern separation deficits. Abstract for poster presentation 84.01, Society for Neuroscience, Chicago, IL, October 2015.

Gaynor LS, **Johnson SA**, Sacks PK, Maurer AP, Bizon JL, Burke SN. Cholinergic modulation of spatial discrimination performance in young and aged rats. Abstract for poster presentation 84.10, Society for Neuroscience, Chicago, IL, October 2015.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1xepxf-OPS2/bibliography/43445388/public/?sort=date&direction=descending

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: Ashok Kumar

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

POSITION TITLE: Assistant Professor of Neuroscience

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Lucknow, Lucknow	BS	1984	Life Sciences
University of Lucknow, Lucknow	MS	1986	Zoology
Central Drug Research Institute, Lucknow	Ph.D.	1992	Pharmacology
Yale University, New Haven,	Postdoctoral Fellowship	1998	Neuroscience/Neurobiology of Aging

A. Personal Statement

My research is directed towards understanding the influence of age-related changes in cognition over the life span. Toward this goal, a central focus of my research involves the role of various interventions such as environmental enrichment and exercise in restoring/improving age-associated impaired cognition, synaptic plasticity, and cell excitability. Currently, I am a Co-I on three on ongoing research project (R01, PI: Dr. Tom Foster) examining estrogen and NMDA receptors, systemic inflammation and age-related cognitive decline, where I oversee surgery/viral injections, behavior and molecular analyses, and electrophysiology.

My recent work examined N-methyl-D-aspartate receptor (NMDAR) hypofunction during aging and its relationship with cognitive impairment; this work highlights a link between age-associated oxidative stress and a decline in NMDAR function. In addition to my expertise in electrophysiology, I helped to develop the 5-choice serial reaction time task in the lab; this task is employed to assess executive function, including attention. Furthermore, I have extensive experience with the water maze task, to characterize hippocampal-dependent spatial memory function. Finally, I have extensive experience in surgeries for viral vector mediated gene delivery/expression.

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

Editorial Service

Associate Editor: Frontiers in Neuroscience
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. Contribution to Science

Overall, my research is focused on understanding the influence of age-related changes in cognition over the life span. Towards this goal, my research focus is to delineate the possible mechanisms that contribute to memory deficits associated with advanced age and develop possible therapeutic interventions that could possibly restore/ameliorate age-induced impaired cognition.

1. I have considerable expertise employing an in vitro slice electrophysiology to examine age-related changes in synaptic function and senescent neural physiology. My work helped to characterize age-related changes in synaptic plasticity; long-term potentiation (LTP) and long-term depression (LTD) in the hippocampus. This body of work highlights that age-related differences in these two major forms of synaptic plasticity are largely due to a shift in the threshold synaptic activity required for induction rather than a difference in asymptotic levels of LTP and LTD. As part of this research I have examined the effects of receptors (metabotropic and muscarinic) that modulate cell signaling to influence synaptic plasticity thresholds.
   i) **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.**
   ii) **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.**
   iii) **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.**
   iv) **Ashok Kumar** and T.C. Foster, Interaction of DHPG-LTD and synaptic-LTD at senescent CA3-CA1 hippocampal synapses, *Hippocampus*, 24 466-475 (2014), **PMID: 24390964.**

2. In addition, I have gone on to demonstrate that the mechanism for altered synaptic plasticity thresholds during aging is due to calcium dysregulation (i.e. the calcium dysregulation hypothesis for senescent synapses). The mechanisms involve a decrease in calcium influx through NMDA receptors and increased calcium release from internal calcium stores (see below). My work on NMDA receptor function indicates that oxidative stress during aging underlies a redox-mediated NMDAR hypofunction. Furthermore, the decline in NMDAR function begins in middle-age and correlates with cognitive impairments. These results challenge the current clinical concept of using NMDA receptor antagonists for therapeutic intervention for memory decline.
   i) **Ashok Kumar**, K. Bodhinathan, and T.C. Foster, Susceptibility to calcium dysregulation during brain aging, *Frontiers in Aging Neuroscience*, 1 1-13 (2009), **PMID: 20552053.**
   ii) **Ashok Kumar** and T.C. Foster, Linking redox regulation of NMDAR synaptic function to cognitive decline during aging, *Journal of Neuroscience*, 40, 15710-15715 (2013), **PMID: 24089479.**
   iii) 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.**
   iv) M. Guidi, **Ashok Kumar**, and T.C. Foster, Impaired attention and synaptic senescence of the prefrontal cortex involves redox regulation of NMDA receptors, *Journal of Neuroscience*, 35 (9), 3966-3977 (2015), **PMID: 25740525.**

3. The age-related increase in calcium released from internal stores contributes to a decrease in hippocampal cell excitability. I have employed in vitro single cell recording techniques to demonstrate that aging is associated with an increase in the calcium-dependent potassium-mediated afterhyperpolarization in male and female rats. The afterhyperpolarization limits the cell excitability and NMDAR activation, which normally depends on depolarization of the cell. My work provides evidence that the age-associated increase in the afterhyperpolarization influences the threshold for synaptic plasticity and could contribute to impaired cognitive performance.
   i) **Ashok Kumar** and T.C. Foster, 17β-estradiol benzoate decreases AHP in CA1 pyramidal neurons, *Journal of Neurophysiology*, 88, 621-626 (2002), **PMID: 12163515.**
   ii) **Ashok Kumar** and T.C. Foster, Enhanced long-term potentiation during aging is masked by processes involving intracellular calcium stores, *Journal of Neurophysiology*, 91, 2437-2444 (2004), **PMID: 14762159.**

iii) **Ashok Kumar** and T.C. Foster, Intracellular calcium stores contribute to increased susceptibility to LTD induction during aging, *Brain Research*, 1031, 125-128 (2005), **PMID: 15621020.**

iv) **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.**

4. It is hypothesized that the shift in synaptic plasticity mediates a decline in hippocampal-dependent episodic memory. Therefore, I initiated a number of studies examining the effect of various treatments on relationship between synaptic plasticity and cognition during aging. Our results demonstrate that social interaction, exercise, and expression of antioxidant enzymes could improve the synaptic function and ameliorate the cognitive performance.

   i) **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.**

   ii) **Ashok Kumar**, A. Rani, O. Tchigranova, W.H. Lee, and T.C. Foster, Influence of late-life exposure to environmental enrichment or exercise on hippocampal function and CA1 senescent physiology, *Neurobiology of Aging*, 33, 828.e1-828. e17 (2012), **PMID: 21820213.**

   iii) 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.**

   iv) R.B. Speisman, **Ashok Kumar**, A. Rani, T.C. Foster and B. 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.**

URL LINK to a full published work: *http://www.ncbi.nlm.nih.gov/sites/myncbi/1ncRuN720ry5h/bibliography/47719056/public/?sort=date&direction=ascending*

D. Research Support

Ongoing Research Support

1. NIH/NIA, AG037984 (Dr Tom Foster PI, **Kumar Co-I**) 9/15/10 - 7/31/16
   Estrogen signaling and cognition over the life span
   Examines estrogen effects on memory function and delaying brain aging through regulation of transcription via the estrogen receptor alpha.
   Overlap: None.

2. NIH/NIA, R37AG036800 (Dr. Tom Foster PI, **Kumar Faculty/Co-I**) 10/05/10 - 04/30/19
   Signaling cascades and memory deficits during aging
   The major goals of this project are to examine the hypothesis that age-related changes in NMDAR signaling mediate memory deficits and changes in hippocampal synaptic plasticity.
   Overlap: None.

3. NIH/NIA, R01AG049711 (Dr. Tom Foster PI, **Kumar Co-I**) 4/01/15 - 3/31/20
   Systemic inflammation in regulating the onset and progression of brain aging
   The goal of this project is to determine the contribution of central and peripheral inflammation on the onset of age-related cognitive decline.
   Overlap: None.

4. NIH/NS, R37NS040389 (Dr. Ranum PI, **Kumar Senior Personnel**) 07/01/15 - 3/31/20
   Molecular Genetic Characterization of SCA8
   Overlap: None.

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: Lamb, Damon Geoffrey

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

POSITION TITLE: Research Health Science Specialist (VAMC); Research Assistant Professor (UF)

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of 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

My long term goal is to bridge cutting edge basic science and clinical/treatment focused research. I apply my computational and mathematical skills to create and develop models of complex phenomena, from subcellular neuronal processes through network and systems scales. These models both test our current understanding of neurophysiology as well as provide insights and hypotheses for future research. I also develop research tools and apparatus to meet complex demands.

B. Positions and Honors

Positions

2001 Product Engineer, Hughes Network Systems
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
2007-2013 Graduate Student, Neuroscience Program, Emory University
2013-pres Research Health Science Specialist, U.S. Dept. of Veterans Affairs
2013-pres Research Assistant Professor, University of Florida

Honors

2005 Computer Science Faculty Commendation, University of Chicago
2007-2009 IGERT:Hybrid Neural Microsystems Fellow, NSF
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. Contribution to Science

1. **Correlated ionic conductances and interactions underlie coordinated neuronal activity**

Neurons can have widely differing intrinsic membrane properties, in particular the density of specific conductances (or resistance to ionic flow through ion channels), but how these contribute to characteristic neuronal activity or pattern formation is not well understood. My biophysical modeling work on a small neuronal network investigated how these ionic conductances contribute to the coordinated motor output. Previous work had elucidated some correlational relationships between pairs of conductances, but they were generally required to be similar in their time courses, although of opposing polarity. My work showed that much more complex correlational relationships contribute to the output of neuronal networks,

as well as providing an explanation of the basis for these relationships. Outside of the novel modeling approaches and the combination of algorithmic optimization approaches, computational tools, and biological data I used, this work has implications for the variability of individual response to psychoactive medication. The primary publication from this large, multi-year modeling work has already been cited 5 time over the past year and a half since its publication.

a. **Lamb, Damon G.**, and Ronald L. Calabrese. "Neural circuits controlling behavior and autonomic functions in medicinal leeches." *Neural systems & circuits* 1, no. 1 (2011): 1-10.
b. **Lamb, Damon G.**, and Ronald L. Calabrese. "Small is beautiful: models of small neuronal networks." *Current opinion in neurobiology* 22, no. 4 (2012): 670-675.
c. **Lamb, Damon G.**, and Ronald L. Calabrese. "Correlated conductance parameters in leech heart motor neurons contribute to motor pattern formation." *PloS one* 8, no. 11 (2013): e79267.

2. **Scientific experimental and data analysis software & hardware**
Throughout my scientific career I have applied my technical skills to the design, development, and deployment of computer software and hardware to improve and enable research. An example of the data processing tools I have developed is CardioEdit/CardioBatch, which allows efficient raw data processing and analysis of electrocardiogram signals for the extraction of heart rate variability measures, which are an index of autonomic nervous system function. I used these tools to conduct collaborative research with both animal and human biological psychology researchers, but they were also made freely available to the research community. As a testament to the utility of this software, over 65 papers cite using my software to process and analyze their data. In 2000, I developed a multi-center data collection and aggregation tool that enabled distributed, offline collection of child abuse and maltreatment information collected by social workers, police, and researchers. This tool has been a critical tool for at least 18 papers, and the ideas about aggregating multi-site data have led to subsequent tools developed by other scientific programmers. More applicable to the proposed investigation, I also developed the Dynamic Affect Recognition Experiment software and initial hardware, a test which presents subjects with a morphing emotional face whose emotion they identify.

a. Grippo, Angela J., **Damon G. Lamb**, C. Sue Carter, and Stephen W. Porges. "Social isolation disrupts autonomic regulation of the heart and influences negative affective behaviors." *Biological psychiatry* 62, no. 10 (2007): 1162-1170.
b. Grippo, Angela J., **Damon G. Lamb**, C. Sue Carter, and Stephen W. Porges. "Cardiac regulation in the socially monogamous prairie vole." *Physiology & behavior* 90, no. 2 (2007): 386-393.
c. Van Hecke, Amy Vaughan, Jocelyn Lebow, Elgiz Bal, **Damon Lamb**, Emily Harden, Alexis Kramer, John Denver, Olga Bazhenova, and Stephen W. Porges. "Electroencephalogram and heart rate regulation to familiar and unfamiliar people in children with autism spectrum disorders." Child development 80, no. 4 (2009): 1118-1133.
d. Bal, Elgiz, Emily Harden, **Damon Lamb**, Amy Vaughan Van Hecke, John W. Denver, and Stephen W. Porges. "Emotion recognition in children with autism spectrum disorders: Relations to eye gaze and autonomic state." *Journal of autism and developmental disorders* 40, no. 3 (2010): 358-370.

3. **Time-resolved particle-beam emittance measurement**
Early in my research career, I gathered the first time-resolved particle-beam emittance data. This experiment looked into how a 100ns charged particle-beam was different along its length. Such a measurement was technically challenging at many levels, and the success of this experiment relied on two key control systems I programmed: one controlling the electro-magnetic focusing and bending optics, and the other an adaptive control system for the beam-measurement apparatus. The data and the functional measurement system that resulted from this work directly contributed to journal papers and referred conference papers, and enabled other researchers to investigate otherwise inaccessible research questions.

a. Bernal, S., B. Beaudoin, Y. Cui, M. Glanzer, T. F. Godlove, J. Harris, M. Holloway et al. "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, no. 1 (2004): 380-387.
b. Walter, Mark, B. Quinn, **D. Lamb**, S. Bernal, T. Godlove, I. Haber, M. Holloway et al. "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, no. 1 (2005): 374-377.

My NCBI bibliography is available at: *http://www.ncbi.nlm.nih.gov/sites/myncbi/1j9Hg8t4ygtkW/bibliography/47495904/public/?sort=date&direction=descending*

A citation report is available on google scholar:
http://scholar.google.com/citations?user=X49GAQkAAAAJ&hl

D. Research Support

IK2 RX000707 VA Rehabilitation Research & Development 4/1/2012 -3/31/2017
White matter changes and mild TBI: Emotional and autonomic consequences
Principal Investigator: John B. Williamson
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 (8/26/2013 – present)**

I01 CX000744 VA Clinical Science Research & Development - Merit Review 10/1/2012 - 9/30/2016
Vertical Neglect
Principal Investigator: Kenneth M. Heilman
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 (8/26/2013 – present)**

R01 NS024072 1/7/1984 – 1/5/2013
Neuromodulatory influences on motor systems
Principal Investigator: Ronald L. Calabrese
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 (5/1/2009 – 8/23/2013)**

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: Christiaan Leeuwenburgh

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

POSITION TITLE: Professor and Chief

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Florida, Gainesville	BS	05/88	Applied Physiology
University of Florida, Gainesville	MS	05/90	Applied Physiology
University of Illinois, Urbana-Champaign	PhD	10/95	Biochemistry and Aging
University of Wisconsin, Madison	Pre-Fellow	10/95	Biochemistry and Aging
Washington Univ. School of Medicine, St Louis	Post-Fellow	12/98	Geriatrics & Gerontology

A. Personal Statement

The objective of this project is to test the feasibility and efficacy of an ischemic pre-conditioning protocol, which can be readily translated into clinical practice as well as transferred to similar patient populations at risk of losing function, strength and therefore, independence. We will perform the biochemical analysis in skeletal muscle biopsy samples which will facilitate the identification of potential biologic pathways related to atrophy and hepertrophy. We will analyze mammalian target of rapamycin complex 1 (mTORC1) signaling pathway as well as the expression of anabolic genes (MyoD and Myogenin) and catabolic genes (MuRF1 and Atrogin1). I received my PhD from the University of Illinois, Urbana-Champagne in 1995 which focused on the regulation of glutathione (major intracellular antioxidant) and antioxidant enzymes in young and old animals. I completed my 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 John Holloszy (MD) and Jay Heinecke (MD) as primary mentors. My major research focus is to better understand the molecular mechanisms of mitochondrial dysfunction, autophagy, inflammation, oxidative stress and programmed cell death (apoptosis) with age and age-related diseases. I have participated in various NIH study sections, NIH workshops focused on the biology of aging, mitochondrial biology and geriatric research and have published papers in Cell, Science, Aging Cell, The Journal of Biological Chemistry, American Journal of Physiology, PLoS One, Journal of Gerontology, FASEB Journal, Experimental Gerontology, Neurobiology of Aging, Rejuvenation Research, Journal of Clinical Investigation and PNAS. Our work on the assessment of muscle biology, oxidative stress, inflammation, mitochondrial dysfunction, autophagy, mitochondrial mediated apoptosis, and oxidative damage in aging and disease has been increasingly recognized and appreciated by scientists worldwide. In summary, as a basic and translational scientist, my goal is to bridge the gap between basic and clinical sciences, focusing on biological mechanisms of aging, infections and disease and testing translational interventions.

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; Mentors: John O. Holloszy, MD and Jay W. Heinecke, MD
1998-2002	Assistant Professor, Director of the Biochemistry of Aging Laboratory, University of Florida
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, Metabolism and Translational Science Core of the University of Florida Institute on Aging
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

1995-2008	Society for Free Radical Biology and Medicine
1995-2008	International Society for Free Radical Research
2004-2012	NIH Peer Review Committees; Special Emphasis Panels
1997-present	The American Physiological Society
2003-present	Member, American Aging Association
2003-present	Member, Gerontological Society of America
2008-present	Editor, Experimental Gerontology

Honors

1993-1995	American Heart Association, Pre-doctoral Fellowship, Illinois Affiliate
1996	Young Investigator Award, Oxygen Society, Intern. Soc. Free Rad. Res., Miami, FL
1997-1998	National Research Service Award, NRSA-NIH, National Institute of Aging
1999-2000	Merck Geriatric Cardiology Research Award, Society of Geriatric Cardiology
2000-2002	American Heart Association, Young Investigator Award, FL
2004-2005	University of Florida Research Foundation, Professor Award
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)
2010	Exemplary Teacher Award, College of Medicine
2011-2013	University of Florida Research Foundation Professor

C. Contribution to Science

1. In 2005 we published a publication in Science (Kujoth, Science 2005; cited 1095 times) using transgenic mice to show that for the first time an accumulation of mtDNA mutations can promote apoptosis and is a central mechanism driving mammalian aging. At that time it was unknown if mutations in mitochondrial DNA (mtDNA) accumulate in tissues of mammalian species drive aging, although it was shown that they were associated with aging no causal relationship was established. We showed experimentally that mice expressing a proofreading-deficient version of the mitochondrial DNA polymerase g (POLG) accumulate mtDNA mutations also displayed significant features of accelerated aging. Accumulation of mtDNA mutations was also causal to the induction of apoptosis, particularly in tissues characterized by rapid cellular turnover. The levels of apoptotic markers were also found to increase during aging in normally aging mice.
   a. 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.

   In 2010, we published a paper in the journal Cell "Sirt3 mediates reduction of oxidative damage and prevention of age-related hearing loss under caloric restriction" (Someya, Cell 2010; cited over 400 times) to demonstrate for the first time that one of the sirtuins (Sir3) had an important role in maintaining an important physiological function (hearing loss) with aging. It was already known that caloric restriction (CR) extends the life span and health span of a variety of species and slows the progression of age-related hearing loss (AHL), a common age-related disorder associated with oxidative stress. However, in this report we showed that CR reduces oxidative DNA damage in multiple tissues and prevents AHL in wild-type mice but fails to modify these phenotypes in mice lacking the –mitochondrial- deacetylase Sirt3, a member of the sirtuin family. In response to CR, Sirt3 also directly deacetylates and activates mitochondrial isocitrate dehydrogenase 2 (Idh2), leading to increased NADPH levels and an increased ratio of reduced-to-oxidized glutathione in mitochondria. In addition using cultured cells, overexpression of Sirt3 and/or Idh2 increases NADPH levels protects cells from oxidative stress-induced cell death. Therefore, these findings identify for the first time that Sirt3 is an essential player in enhancing the mitochondrial glutathione antioxidant defense system during CR and shows that Sirt3-dependent mitochondrial adaptations are a central mechanism of aging retardation in mammals.
   a. 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. **PMCID : PMC3018849**

   In 1997 two papers where published in the Journal of Biological Chemistry documenting specific free radical reactions in human disease (atherosclerosis in human intima). "Reactive nitrogen intermediates promote low density lipoprotein oxidation in human atherosclerotic intima" (Leeuwenburgh et al 1997; JBC; cited 470 times). This publication was the first to show that reactive nitrogen species such as peroxynitrite (ONOO-) form in the human artery wall and I provided direct evidence for a specific reaction pathway that promotes LDL oxidation in vivo. The detection of 3-nitrotyrosine in LDL isolated from vascular lesions raised the possibility that NO, by virtue of its ability to form reactive nitrogen intermediates (ONOO-), promotes atherogenesis, counteracting the well-established anti-atherogenic effects of NO. The second paper in 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" (Leeuwenburgh et al, JBC 1997; cited 373 times) I was the first to elucidate additional free radical pathways in human disease. During this time lipoprotein oxidation had been implicated in the pathogenesis of atherosclerosis. However, the physiologically relevant pathways mediating oxidative damage thought to be causal in human disease were not yet identified. To explore the involvement of tyrosyl radical, hydroxyl radical, and metal ions in atherosclerosis, I developed a highly sensitive and quantitative method for measuring levels of o, o'-dityrosine, o-tyrosine, and m-tyrosine in proteins, lipoproteins, and tissue, using stable isotope dilution gas chromatography-mass spectrometry. By this time it was though that three potential mechanisms for oxidative damage where thorugh tyrosyl radical, hydroxyl radical, and redox active metal ions. I found that tyrosyl radicals form o,o'-dityrosine cross-links in proteins and this was evident in human intima's. The highly reactive hydroxyl radical oxidizes phenylalanine residues to o-tyrosine and m-tyrosine and pathways of metal ions oxidize low density lipoprotein (LDL) was poorly understood during this time and also measured in human atherosclerosis. The detection of a selective increase of o,o'-dityrosine in LDL isolated from vascular lesions was consistent with the hypothesis that oxidative damage in human atherosclerosis is mediated by tyrosyl radical. In contrast, for the first time, my observations did not support a role for free metal ions as catalysts of LDL oxidation in the human artery wall.

a. **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.
b. **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.

The Publication "Aging and exercise training in skeletal muscle: responses of glutathione and antioxidant enzyme systems" Leeuwenburgh et al (AJP 1994; cited 312 times) was the first to show that in skeletal muscle aging causes an overall elevation of antioxidant enzyme activities in contrast to what was shown in many other tissues. In addition, there was also a fiber specific adaptation of the glutathione (GSH) system in skeletal muscle. Exercise training, although increasing selective antioxidant enzymes in the young rats, did not offer additional protection against oxidative stress in senescent muscle.

a. **Leeuwenburgh, C.**, Fiebig, R., Chandwaney, R., and Ji, L.L. 1994. Aging and exercise training in skeletal muscle: responses of glutathione and antioxidant enzyme systems. *The American journal of physiology* 267:R439-445.

Complete list of published works in My Bibliography.
http://www.ncbi.nlm.nih.gov/sites/myncbi/christiaan.leeuwenburgh.1/bibliography/41138731/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

R01 DK090115 NIH (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**

Osato Research Institute (Anton-**Leeuwenburgh**)
7/1/2013 – 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**

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**

1 P30 AG028740-01 NIH/NIA (Pahor)
4/1/2012-3/31/2017
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.
Genomics and Biomarkers Core: **PI**
Research Career Dev. Core: **Co-L**

1R01DC012552 NIH (Someya)
7/1/2013-6/30/2018
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 NIH (Manini)
7/15/2013-6/30/2018
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**

R01 AT007564-01 NIH (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**

R01 HL122846 NIH (McDermott)
4/1/2014-3/31/2018
Low Intensity Exercise Intervention in Peripheral Artery Disease: the LITE Trial
This proposed study will determine whether an alternative exercise intervention that employs remote monitoring by a coach and avoids exercise-related ischemic-pain improves functional performance at 52-week follow-up in people with PAD.
Role: **Co-I**

R21 AG047510 NIH (McDermott)
5/15/2014-4/30/2016
Resveratrol to improve outcomes in older people with PAD: The RESTORE Trial
The goal is to test our hypotheses that resveratrol significantly improves calf skeletal muscle oxidative metabolism, increases calf skeletal muscle mitochondrial biogenesis, and improves systemic endothelial function, thereby improving lower extremity functioning in older people with PAD.
Role: **PI**

P50 GM111152 NIH (Moore)
9/1/2014-5/31/2019
PICS: A New Horizon for Surgical Critical Care
The overall product of this P50 Center is a better understanding of the causes and consequences of CCI in the surgery or trauma ICU patients who experience sepsis. Driven by an innovative observation of PICS, the program will determine the magnitude and clinical implications of this new syndrome, test several mechanistic hypotheses about its cause, and develop potential and novel therapeutic interventions.
Role: **PI Core C; Co-I Project 2; Co-PI Project 4**

R01 DK079879 NIH (Kim)
9/22/2014-8/31/2019
Autophagy in Liver injury
The goal of this study is to develop novel therapeutic strategies to improve liver function after ischemia/reperfusion injury occurring during liver resection and transplantation surgery.
Role: **Co-I**

1R01DK099334 NIH (Cohen)
6/25/2014-5/31/2019
Obesity and type-2 diabetes: Bariatric surgery effects of brain function
The proposed prospective longitudinal study will examine whether cerebral metabolic and vascular dysfunction, including glucose/insulin disturbances (co-morbid diabetes) underlie obesity-associated cognitive dysfunction, and whether significant weight loss and diabetes remission following bariatric surgery reduces these disturbances.
Role: **Co-I**

NIH R01 DC014437 (Someya)
4/1/2015-3/31/2020
Cochlear detoxification system
The overall goal of our research proposal is to provide new basic knowledge of the molecular basis for the cochlear detoxification system and its role in the elimination of foreign chemicals throughout the lifespan.
Role: **Co-I**

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Long, Joanna R.	Associate Professor of Biochemistry & Molecular Biology
eRA COMMONS USER NAME	
jrlong	

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 Arkansas; Fayetteville, Ark.	B.S.	1990	Chemistry
Massachusetts Institute of Technology	Ph.D.	1997	Physical Chemistry
University of Washington; Seattle, Wash	postdoc	1997-2000	Molec. Bioengineering

A. Personal Statement

Overall, my research objectives are to characterize biomolecular structure, dynamics and interactions in vivo and in complex (i.e. native-like) environments to determine biophysical relationships and how they can be manipulated. My research group focuses on specific systems of importance to understanding and remediating disease states. We utilize NMR spectroscopy as a primary tool for characterizing biomolecular structure and dynamics coupled with other biophysical techniques, particularly dynamic nuclear polarization (DNP) to enhance NMR sensitivity and enable in vivo MRS.

For this proposal, I will be serving on the Internal Advisory Board. I am the director of the AMRIS facility where the MRI systems supporting this center are installed and maintained for users. I manage a staff of eight scientists and technicians who support users with operations of the instruments, maintain the equipment, and assist with experiment design and data handling. I also oversee fiscal administration of the facility and procurement of new equipment in addition to directing the NHMFL user program.

B. Positions and Honors

Positions and Employment

1990-1991	Graduate Teaching Assistant, Dept. of Chemistry, MIT; Cambridge, Mass.
1991-1996	Graduate Research Assistant, Dept. of Chemistry, MIT; Cambridge, Mass.
1997-2000	Postdoctoral Research Associate, Dept. of Bioengineering, Univ. of Washington; Seattle, Wash.
2000-2002	Staff Scientist, Dept. of Chemistry, Univ. of Washington; Seattle, Wash.
2002-2009	Asst Professor, Dept. of Biochemistry and Molecular Biology, Univ. of Florida; Gainesville, Fla.
2009-	Assoc Professor, Dept. of Biochemistry and Molecular Biology, Univ. of Florida; Gainesville, Fla.
2009-	Director of the Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) Facility and NSF-funded National High Magnetic Field Laboratory (NHFML) user program at AMRIS
2013-	Associate Laboratory Directory, NHMFL

Service

NHMFL User Collaboration Grants Program, Executive Committee, Diversity Committee, Science Council
Organizer Southeast Magnetic Resonance Conference (2006 and 2015); Rocky Mountain Conference (2016)
Interdisciplinary Sciences PhD Program Admissions Committee (2007-2009)
Ad hoc reviewer for NIH, NSF, DoE, Alzheimer's Association; NIH SIG panel; NSF MRI panel; NIH P41 panel

Honors

1986-1990	Sturgis Fellow, Summa cum laude, Alumni Award, University of Arkansas
1990-1993	National Science Foundation Predoctoral Fellowship, MIT

C. Contributions to Science

I have a broad background in physical chemistry and biochemistry, with specific training and proficiency in NMR spectroscopy, NMR probe and technique development, organic synthesis, characterizing biomolecular structure and dynamics, and protein expression and purification.

1. **Development of NMR techniques and hardware for increasing sensitivity and resolution**

NMR is an exquisitely sensitive technique for obtaining atomic level information on biomolecular structure, dynamics and question. Nonetheless, its inherently low signal-to-noise relative to other spectroscopies constrains its application in biological systems. Part of the mission of NHMFL is to provide state-of-the-art facilities and to develop new technologies enabling the

use of NMR to solve complex problems. I have been involved for many years in a three-pronged approach to enhancing NMR signals: a) progressing to ever higher magnetic fields, b) developing probe technology for ssNMR applications and c) pursuing methods for increasing polarization.

a. Smith AS and **Long JR** (2016) Dynamic Nuclear Polarization as an Enabling Technology for Solid State Nuclear Magnetic Resonance Spectroscopy. *Anal. Chem*., DOI: 10.1021/acs.analchem.5b04376 (In Press).
b. Smith AS, Caporini M, Fanucci GE, **Long JR** (2015) A Method for Dynamic Nuclear Polarization Enhancement of Membrane Proteins. Angew. Chemie, 54(5):1542–1546. **[PMID 25504310]**
c. Gor'kov PL, Brey WW, **Long JR** (2010) *Probe developments for biosolids NMR spectroscopy. in Solid-State NMR Studies of Biopolymers*, McDermott, A.E and Polenova, T. (eds). John Wiley & Sons Ltd, Chichester, UK, pp 141-158.
d. McNeill SA, Brey WW, Gor'kov PL **Long JR** (2009) A low-E magic angle spinning probe for biological solid state NMR at 750 MHz. *J. Magn Reson*, 197(2):135-44. **[PMID 19138870]**
e. Fu, R et al. (2005) Ultra-wide bore 900 MHz high-resolution NMR at the National High Magnetic Field Laboratory. *J Magn. Resonance*, 177(1):1-8. **[PMID 16125429]**

2. **Molecular mechanisms of lipid trafficking in pulmonary surfactant**

Lung surfactant protein B (SP-B) is a highly hydrophobic membrane protein essential to pulmonary surfactant (PS) function. SP-B is responsible for lipid trafficking and unique lipid morphologies in the aqueous PS subphase and ultimately respiration. Much of its activity can be recaptured by amphiphilic pep-tides based on the N- and C-termini; KL4, an analog of the C-terminus, was recently approved as the first synthetic, peptide-based therapy for the prevention of respiratory distress in at-risk infants. Using ssNMR and EPR spectroscopies, we have characterized the molecular mechanisms of lipid binding, transfer and specificity for pulmonary surfactant peptides to provide guidance for the development of synthetic pulmonary surfactant (PS) therapies.

a. Farver S, Smith AN, Mills FD, Egri AG, **Long JR** (2015) Delineation of the dynamic properties of individual lipid species in native and synthetic pulmonary surfactants. *BBA-Biomembranes* 1848(1B):203–210. **[PMID 24853659]**
b. Turner AL, Mills FD, Fanucci GE, **Long JR** (2014) Residue specific partitioning of KL4 into phospholipids bilayers. *BBA-Biomembranes* 1838(12): 3212-3219. **[PMID 25251362]**
c. Farver RS, Mills FE, Antharam VD, Chebukati JN, Fanucci GE, **Long JR** (2010) Lipid Polymorphism Induced by Surfactant Peptide SP-B(1-25). *Biophys J*, 99(6):177-82. **[PMID 20858421]**
d. **Long JR**, Mills FD, Ganesh OK, Farver RS (2009) Partitioning, dynamics, and orientation of lung surfactant peptide KL4 in phospholipid bilayers. *BBA-Biomembranes*, 1798(2):216-22. **[PMID 19735643]**

3. **Developing and applying NMR techniques to understand complex processes**

The organization and assembly of biomolecular complexes such as lipid bilayers, biofilms and biominerals are intractable to standard high resolution techniques such as x-ray crystallography or solution NMR. Through collaborations with a number of research groups, we develop tailored NMR experiments to answer specific questions regarding structure, dynamics and assembly.

a. Bewernitz MA, Gebauer D, D, **Long JR**, Colfen H, H, Gower LB (2012) A metastable liquid precursor phase of calcium carbonate and its interactions with polyaspartate. *Faraday Discussions*, 159:291-312
b. Frederick TE, Goff PC, Mair CE, Farver RS, **Long JR**, Fanucci GE (2010) Effects of the Endosomal Lipid bis(monoacylglycero) phosphate on the thermotropic properties of DPPC: A 2H NMR and spin-label EPR study. *Chem Phys Lipids*, 163(7):703-11. **[PMID 20599855]**
c. Mehta MA, Eddy MT, McNeill SA, Mills FD, **Long JR** (2008) Determination of peptide backbone torsion angles using double-quantum dipolar recoupling solid-state NMR. *J. Am. Chem. Soc*. 130(7):2202-12. **[PMID 18220389]**
d. Drobny GP, **Long JR**, Karlsson T, Shaw W., Popham J, Oyler N, Bower P, Stringer J, Gregory D, Mehta M, Stayton PS (2003) Structure studies of biomaterials using double quantum solid state NMR spectroscopy. *Ann. Rev. Phys. Chem*. 54:531-71. **[PMID 12709513]**

4. **Developing and applying NMR techniques to understand complex processes**

I have recently begun collaborating with Jeannine Brady to characterize the assembly of extracellular cell wall-associated adhesin P1 in Streptococcus mutans which facilitates bacterial attachment to the acquired pellicle on teeth. Her previous work showed that P1 self-proteolyzes, with fragments attaching to intact P1 on the cell surface as well as self-aggregating to form fibrils that possess common biophysical properties ascribed to amyloids. This project focuses on characterizing the structures of intact P1 and its fragments important to biofilm formation to understand the roles of self-assembly and amyloid formation underlying this process and to develop inhibitors of biofilm formation.

a. Heim KP, Crowley PJ, **Long JR**, Kailasan S, McKenna R, Brady LJ (2014) A novel intramolecular lock facilitates folding and stabilizes the tertiary structure of Streptococcus mutans adhesion P1. *P. Natl. Acad. Sci*., 111(44):15746-15751. **[PMID 25331888]**

b. Tang W, Bhatt A., Heim KP, Crowley PJ, Brady LJ (2015) Specific Interactions of amyloidogenic regions of Streptococcus mutans adhesin P1 with intact P1 on the cell surface by solid state NMR. Manuscript in revision.

Full list of citations:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40856477/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

NSF **Long (Co-I)** 01/01/13-12/31/17
Division of Materials Research
"National High Magnetic Field Laboratory"
The goal of this research is to develop high field magnets and their applications to scientific problems
No overlap.

U24 DK 097209 **Long (Co-I)** 9/01/13 – 8/31/18
NIH/NIDDK
"Southeast Resource Center for Integrated Metabolomics (SECIM)"
The Southeast Resource Center for Integrated Metabolomics (SECIM) integrates existing strengths to create a comprehensive resource for basic and clinical scientists to obtain state-of-the-art metabolomics data and analyses
No overlap.

NIH R01-DE021789 **Long (Co-I)** 03/05/12-02/28/16
NIH/NIDCR
"Functional amyloid formation in streptococcus mutans"
This grant is to characterize the structure and amyloid properties of S. mutans cell surface-localized adhesin called P1 and to identify and characterize additional amyloid forming proteins of S. mutans.
No overlap.

S10 OD 018519 **Long (Co-I)** 7/15/2014 – 7/14/2015
NIH
"14.1 T magnet with +/-1280 G Field Regulation and Integrated MAS Cryogenic System"
The goal of this research is to enable the development and application of high field dynamic nuclear polarization in biological solid state NMR.
No overlap.

NHMFL-UCGP **Long (Co-I)** 10/01/2014-9/30/2016
NSF/DMR
"1H detected solid state NMR with ultrafast magic-angle spinning and high fields"
This proposal is to develop 100 kHz magic angle spinning capabilities for biosolids NMR.
No overlap.

Completed

NIH S10-RR031637 **Long (PI)** 3/15/11-3/14/12
Shared Instrumentation Grant
"Console upgrade for microimaging and solid state NMR spectroscopy at 600 MHz"
This grant is to replace a 12 year old NMR console for a 600 MHz NMR spectrometer located in the Advanced Magnetic Resonance Imaging and Spectroscopy Facility at the University of Florida

NSF **Long (Co-I)** 09/15/10-09/14/12
Division of Materials Research – Academic Research Infrastructure
"Revitalization of University of Florida Helium Liquefaction and Recovery System"
This grant is to update the helium liquefaction and recovery system at the University of Florida

Gates Foundation
Long (PI) 11/01/10-04/30/12
Initiative to Create New Technologies to Improve the Health of Mothers and Newborns
"Creation of a highly stable pulmonary surfactant replacement"
The goal of this research is to develop chemically stable peptidomimetic/lipid formulations as pulmonary surfactant replacement therapies to treat acute respiratory distress syndrome

BIOGRAPHICAL SKETCH

NAME: Manini, Todd

eRA COMMONS USER NAME (agency login): TMANINI

POSITION TITLE: Associate Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Ohio University, Athens, OH	BS	06/1997	Biology
Syracuse University, Syracuse, NY	MS	12/2000	Exercise Science
Syracuse University, Syracuse, NY	PHD	12/2004	Exercise Science and Science Education
National Institute on Aging, Bethesda, MD	Fellow	12/2006	Epidemiology

A. Personal Statement

I am expert in conducting interventions to prevent mobility impairments in older adults (example publications below). Additionally, I have specific interest in understanding biological adaptations that occur in both behavioral and medication/ nutraceutical interventions. I am actively leading several intervention government sponsored trials in older persons and I serve as a co-site PI on the ENRGISE project. As such I feel qualified to serve as a Co-site PI on "ENRGISE-COG". Additionally, I am conducting and have conducted trials on neutraceuticals akin to products being tested in the ENRGISE project (e.g. Resveratrol for Improved Performance in Elders – RIPE trial - NCT01126229). I currently lead the Florida LIFE field center and thus have the experience to recruit and intervene upon high risk older adults with mobility impairment. Additionally, I have two active R01s evaluating (1) Metabolic cost of daily activities in older adults, and (2) Mitochondrial DNA variant modifiers of cardiopulmonary responsiveness to physical activity in older adults that are closely linked to the proposed research. My formal education also makes me well suited for this project. I have well-rounded background in Physiology, Epidemiology and Gerontology that provides me the necessary expertise to be a valuable team member on the project. In 2012, I became a Fellow of the American College of Sports Medicine and I currently serve as a member of the Strategic Health Initiative on Aging in Exercise Science and Sports Medicine. I am also on the editorial board of the Journals of Gerontology: Medical Sciences and the Journal of Frailty & Aging. Furthermore, Dr. Woods and I have a strong collaborative relationship already in place, working together on two funded projects investigating mobility impaired older adults. This existing relationship will facilitate our continued success as collaborators on ENRGISE-COG. I look forward to implementing my expertise in this exciting proposal on anti-inflammatory inventions to prevent and/or enhance cognition in older adults.

1. Higgins TJ, Janelle CM, **Manini TM**. Diving below the surface of progressive disability: considering compensatory strategies as evidence of sub-clinical disability. *J Gerontol B Psychol Sci Soc Sci*. 2014 Mar;69(2):263-74. **PubMed PMID: 24170713; PubMed Central PMCID: PMC3968860.**

2. Bann D, Hire D, **Manini TM**, Cooper R, Botoseneanu A, McDermott MM, Pahor M, Glynn NW, Fielding R, King AC, Church T, Ambrosius WT, Gill T; LIFE Study Group. Light Intensity physical activity and sedentary behavior in relation to body mass index and grip strength in older adults: cross-sectional findings from the Lifestyle Interventions and Independence for Elders (LIFE) study. *PLoS One*. 2015 Feb 3;10(2). **PubMed PMID: 25647685; PubMed Central PMCID: PMC4315494.**

3. Fitzgerald JD, Johnson L, Hire DG, Ambrosius WT, Anton SD, Dodson JA, Marsh AP, McDermott MM, Nocera JR, Tudor-Locke C, White DK, Yank V, Pahor M, **Manini TM**, Buford TW; LIFE Study Research Group. Association of objectively measured physical activity with cardiovascular risk in mobility-limited older adults. *J Am Heart Assoc*. 2015 Feb 18;4(2). **PubMed PMID: 25696062; PubMed Central PMCID: PMC4345863.**

4. **Manini TM**, Lamonte MJ, Seguin RA, Manson JE, Hingle M, Garcia L, Stefanick ML, Rodriguez B, Sims S, Song Y, Limacher M. Modifying effect of obesity on the association between sitting and incident diabetes in post-menopausal women. *Obesity* (Silver Spring). 2014 Apr;22(4):1133-41. **PubMed PMID: 24123945; PubMed Central PMCID: PMC3968183.**

B. Positions and Honors

Positions and Employment

1997 - 2001 Graduate Assistant, Syracuse University, Syracuse, NY
2004 - 2006 Post-Doctoral Fellow, National Institute on Aging, Bethesda, MD
2006 - 2007 Research Asst Professor, University of Florida, Department of Aging & Geriatric Research, Gainesville, FL
2007 - 2014 Assistant Professor, University of Florida, Department of Aging & Geriatric Research, Gainesville, FL

2008 - Adjunct Professor, Department of Applied Physiology & Kinesiology and Department of Epidemiology, University of Florida, Gainesville, FL

2014 - Associate Professor, University of Florida, Department of Aging & Geriatric Research, Gainesville, FL

Other Experience and Professional Memberships

Study section: NSF/Cyber-Physical Systems Program (NSF 15-541), (2015) Neurological, Aging and Musculoskeletal Epidemiology (NAME-2013/14/15), NIA/National Institute on Aging Grants for Early Medical/Surgical Specialists Transition to Aging Research (GEMSSTAR - 2013), ZAG1 ZIJ-7 NIA Thrombosis RFA review, ZAG1 ZIJ-M1 Special Emphasis Panel SRG (2008)

DSMB Researching the Effectiveness of Lumbar Interventions for Enhancing Function Study (RELIEF study) and Health Outcomes of Tai Chi in Subsidized Senior Housing, DSMB membership

Referee Journal of the American Medical Association (JAMA), Journal of Physiology, Journals of Gerontology: Biological & Medical Science, Journal of the American Geriatrics Society, Biomed Central: Geriatrics, British Medical Journal, Aging Clinical and Experimental Research, Medicine Science in Sports and Exercise

Recent Honors

2010 Assistant Professor Excellence Award, University of Florida

2011 Keynote speaker for Quebec network for research on aging, Sarcopenia ≠ Dynapenia

2011 Exemplary Teachers Award, UF College of Medicine

2011 Fellowship status, American College of Sports Medicine

2012 Director of the Office of Disease Prevention (ODP), Invitation to contribute panel on, Physical Activity and Disease Prevention Research Gaps and Goal-Setting: How Do We Get More People Moving More?

2013 Associate Editor (Editorial board), The Journal of Frailty & Aging

2014 Associate Editor (Editorial board), The Journals of Gerontology: Medical Sciences

C. Contributions to Science

Twenty-three percent of the United States population, 65+ years of age report having serious difficulty walking or climbing stairs and 3.6 million older adults report having difficulty with very basic activities like dressing and bathing. My overall research program has contributed to understanding modifiable factors that cause losses in physical function like muscle weakness and physical inactivity. I use these discoveries for steering new data science and applied technologies to prevent and rehabilitate mobility impairment in older adults.

1. My research is focused on determinates of age-related changes in muscle performance to prevent and rehabilitate losses in physical function among older adults. At the beginning of my career, I spearheaded efforts to identify signs of early declines in physical function and operationalize a pre-clinical stage of disability. Such an approach is ideal for identifying and intervening on physical disability prior to its development. This work suggests that performing physical interventions in a manner that are closely connected to the activity of daily living yield optimal effects. I continue to pursue this area of research as one of the PIs on the Lifestyle Interventions and Independence for Elders Study (The LIFE study) – a Phase 3 randomized controlled trial (RCT) to understand the role of exercise for reducing the incidence of major mobility disability in at risk older adults.
    a. **Manini T**, Marko M, VanArnam T, Cook S, Fernhall B, Burke J, Ploutz-Snyder L. Efficacy of resistance and task-specific exercise in older adults who modify tasks of everyday life. *J Gerontol A Biol Sci Med Sci*. 2007 Jun;62(6):616-23. **PubMed PMID: 17595417.**
    b. **Manini TM**, Newman AB, Fielding R, Blair SN, Perri MG, Anton SD, Goodpaster BC, Katula JA, Rejeski WJ, Kritchevsky SB, Hsu FC, Pahor M, King AC. Effects of exercise on mobility in obese and nonobese older adults. *Obesity* (Silver Spring). 2010 Jun;18(6):1168-75. **PubMed PMID: 19834467; PubMed Central PMCID: PMC3114403.**
    c. 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. *J Am Geriatr Soc*. 2012 Jul;60(7):1244-52. **PubMed PMID: 22726232; PubMed Central PMCID: PMC3625953.**
    d. Pahor M, Guralnik JM, Ambrosius WT, Blair S, Bonds DE, Church TS, Espeland MA, Fielding RA, Gill TM, Groessl EJ, King AC, Kritchevsky SB, **Manini TM**, McDermott MM, Miller ME, Newman AB, Rejeski WJ, Sink KM, Williamson JD. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. *JAMA*. 2014 Jun 18;311(23):2387-96. **PubMed PMID: 24866862; PubMed Central PMCID: PMC4266388.**

2. One of the highlights of my research program came in 2008. My colleague and I published a paper that became a seminal article in the literature on aging and sarcopenia (defined as the age-related loss in muscle size). The paper argued that there was a disproportionate amount of effort placed into understanding why humans lose muscle size as they age. This is certainly

an important area of research, but from our perspective the size of muscle played a relatively small role in age-related decreases in muscle performance (i.e. maximal muscle strength). We provided abundant evidence indicating other physiological factors function to regulate muscle performance beyond muscle mass. We suggested that the term dynapenia be applied to describe the age-related loss of strength. The paper made an impact on the field because it increased focus on uncovering new origins for the loss in muscle performance with aging. Additionally, this article and the articles that followed on this topic helped contribute to national (National Institute on Aging and Federal Drug Association— Sarcopenia Consensus Summit) and international (the E.U / U.S Task Force on Designing Drug Trials for Sarcopenia in Frail Older Adults) efforts to define sarcopenia for targeting older adults with muscle weakness.

a. **Manini TM**, Visser M, Won-Park S, Patel KV, Strotmeyer ES, Chen H, Goodpaster B, De Rekeneire N, Newman AB, Simonsick EM, Kritchevsky SB, Ryder K, Schwartz AV, Harris TB. Knee extension strength cutpoints for maintaining mobility. *J Am Geriatr Soc*. 2007 Mar;55(3):451-7. **PubMed PMID: 17341251.**
b. Clark BC, **Manini TM**. Functional consequences of sarcopenia and dynapenia in the elderly. *Curr Opin Clin Nutr Metab Care*. 2010 May;13(3):271-6. **PubMed PMID: 20154609; PubMed Central PMCID: PMC2895460.**
c. **Manini TM**, Clark BC. Dynapenia and aging: an update. *J Gerontol A Biol Sci Med Sci*. 2012 Jan;67(1):28-40. **PubMed PMID: 21444359; PubMed Central PMCID: PMC3260480.**
d. Clark BC, **Manini TM**. What is dynapenia? *Nutrition*. 2012 May;28(5):495-503. **PubMed PMID: 22469110; PubMed Central PMCID: PMC3571692.**

3. In another line of research, we are learning the role of activity energy expenditure and metabolic costs of movement for predicting healthspan of older adults. First, we demonstrated that daily activity energy expenditure is a critical component to preserving lifespan and independent living among older adults. I used this work to springboard additional laboratory studies that led to an important publication demonstrating aging is associated with a large difference in the metabolic cost of daily activities. Additionally, lower physical function further increases metabolic costs of movement. These data were instrumental for successfully obtaining R01 AG04525 entitled, "Metabolic costs of daily activities in older adults" that represents a key foundation for my future contribution to research. This work has also branched into an interesting and complementary line of research with my colleague Greg Tranah aimed at understanding the role of mitochondrial genetic variants for explaining the variability in activity energy expenditure and other health outcomes in older adults. This work has also led to recent funding on the MtDNA variant modifiers of cardiopulmonary responsiveness to physical activity (#HL121023).
   a. **Manini TM**, Everhart JE, Patel KV, Schoeller DA, Colbert LH, Visser M, Tylavsky F, Bauer DC, Goodpaster BH, Harris TB. Daily activity energy expenditure and mortality among older adults. *JAMA*. 2006 Jul 12;296(2):171-9. **PubMed PMID: 16835422.**
   b. **Manini TM**, Everhart JE, Anton SD, Schoeller DA, Cummings SR, Mackey DC, Delmonico MJ, Bauer DC, Simonsick EM, Colbert LH, Visser M, Tylavsky F, Newman AB, Harris TB. Activity energy expenditure and change in body composition in late life. Am *J Clin Nutr*. 2009 Nov;90(5):1336-42. **PubMed PMID: 19740971; PubMed Central PMCID: PMC2762160.**
   c. **Manini TM**. Energy expenditure and aging. *Ageing Res Rev*. 2010 Jan;9(1):1-11. **PubMed PMID: 19698803; PubMed Central PMCID: PMC2818133.**
   d. Knaggs JD, Larkin KA, **Manini TM**. Metabolic cost of daily activities and effect of mobility impairment in older adults. *J Am Geriatr Soc*. 2011 Nov;59(11):2118-23. **PubMed PMID: 22091979; PubMed Central PMCID: PMC3874461.**

A complete list of publications can be found here:
http://www.ncbi.nlm.nih.gov/sites/myncbi/todd.manini.1/bibliography/40192556/public/?sort=date&direction= descending

D. Research Support

Ongoing Research Support as Principal Investigator

2013/07/15-2018/06/30
R01 AG042525-03, National Institute on Aging (NIA)
Metabolic Costs of Daily Activities in Older Adults
This study will determine the age-related differences in metabolic cost of common daily activities. The study will provide a new understanding of the true metabolic intensity of performing daily tasks in older adults.
Role: **PI**

2014/01/15-2018/12/31
R01 HL121023-02, National Heart, Lung and Blood Institute (NHLBI)
MtDNA variant modifiers of cardiopulmonary responsiveness to physical activity
This project will identify mtDNA variants that predispose older individuals to a high or low cardiopulmonary response to chronic exercise.
Role: **Administrative PI** (Co-PI: Tranah)

2009/09/01-2016/12/01
1 UO1 AG022376-05, NIA
The LIFE Study
This is a multi-site Phase III randomized controlled trial of physical activity to prevent major mobility disability and cognitive decline in older adults.
Role: **Principal Investigator of the Florida Field Center** (PI: Pahor)

2013/01/01-2016/01/01
P30AG028740-Pilot, NIA
A pilot study to evaluate the role of brain integrity on post-hospital sarcopenia (Strong Brain Study)
Neuroimaging biomarkers will be used to predict physical function recovery following hospitalization.
Role: **PI**

2012/01/01-2017/01/01
P30AG028740-R6, NIA
OAIC Data Science and Applied Technology Core
The Data Science and Applied Technology (DSAT) Core is as an interactive data ecosystem that meets the accelerated demand for data-driven approaches and new interactive technology.
Role: **Co-Leader of core** (PI: Pahor)

Ongoing Research Support as Co-Investigator
2010/01/01-2015/01/01
N01WH22110, NHLBI
Women's Health Initiative Extension Study
The primary goal of this project is to continue follow-up of the original cohort of the Women's health Initiative that began in 1994. A secondary goal is to conduct a second wave data collection surveys.
Role: **Co-Investigator** (PI: Limacher)

2013/01/01-2018/01/01
RFA-AG-14-009, Patient-Centered Outcomes Research Institute (PCORI)
STRIDE: Randomized Trial of a Multifactorial Fall Injury Prevention Strategy
The trial will compare the effects of a multifactorial or standard care intervention for preventing serious fall injuries using a cluster randomization strategy of clinical practices.
Role: **Co-Investigator** (PIs: Bhasin, Gill and Reuben)

Completed Research
2013/08/01-2015/12/01
NA, Sanofi Pharmaceuticals
Database analyses for Sarcopenia research
The goal of the proposed work is to examine the natural history of sarcopenia (loss of muscle mass) and other contributing factors (e.g. muscle strength and comorbid conditions).
Role: **PI**

2014/01/01-2015/09/01
UF Informatics Institute Seed Fund
Informatics of actigraphy for preventing mobility incidents in older adults
Informatics will be performed on actigraphy data collected from a tri-axial accelerometer to estimate associations with mobility incidents in older adults
Role: **PI**

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: MARSISKE, MICHAEL

eRA COMMONS USER NAME (agency login): mmarsiske

POSITION TITLE: Associate Professor and Associate Chair

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

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Toronto, Toronto, Ontario	BS	06/1987	Psychology
The Pennsylvania State University, University Park, PA	MS	12/1990	Human Development and Family Studies
The Pennsylvania State University, University Park, PA	PHD	12/1992	Human Development and Family Studies
Max Planck Institut fuer Bildungsforschung, Berlin	Postdoctoral Fellow	07/1995	Psychology and Human Development

A. Personal Statement

In this grant, I bring (a) a general expertise in cognitive aging and cognitive interventions, (b) a specific research history of conducting research on cognitive sequelae, and (c) expertise in data analysis/statistics and research design having served as a statistical team member on numerous externally funded grants. I will assist this project in three ways: (1) substantively and operationally, given my history in conducting cognitive outcome studies; (2) with recruitment, given my role as Recruitment core leader for the NIA-funded Claude Denson Pepper Older Americans' Independence Center at University of Florida; and (3) with data analysis, given my role as core leader for the data analysis & management core of the NIA-funded Florida Alzheimer's Consortium, an ADRC comprised of University of Florida, Florida International University, University of Miami and Mt. Sinai Medical Center.

1. **Marsiske M**, Margrett JA. *Handbook of the Psychology of Aging*. 6th Edition ed. Birren JE, Schaie KW, editors. New York: Academic Press; 2006. Everday problem solving and decision making; p.315-342.

2. Cook SE, Sisco SM, **Marsiske M**. Dual-task effects of simulated lane navigation and story recall in older adults with and without memory impairment. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2013;20(4):383-404. **PubMed PMID: 23043546; PubMed Central PMCID: PMC3823673.**

3. Belchior P, **Marsiske M**, Sisco SM, Yam A, Bavelier D, Ball K, Mann WC. Video game training to improve selective visual attention in older adults. *Comput Human Behav*. 2013 Jul 1;29(4):1318-1324. **PubMed PMID: 24003265; PubMed Central PMCID: PMC3758751.**

4. Yam A, **Marsiske M**. Cognitive longitudinal predictors of older adults' self-reported IADL function. *J Aging Health*. 2013 Dec;25(8 Suppl):163S-85S. **PubMed PMID: 24385635; PubMed Central PMCID: PMC3882335.**

B. Positions and Honors

Positions and Employment

1992 - 1995 Postdoctoral Fellow, Max Planck Institut fuer Bildungsforschung, Berlin
1995 - 2000 Assistant Professor, Wayne State University, Detroit, MI
2000 - Associate Professor and Associate Chair, University of Florida, Gainesville, FL

Other Experience and Professional Memberships

1987 - Member, American Psychological Association
1992 - Member, American Psychological Society
1992 - 2010 Member, International Society for the Study of Behavioral Development
1995 - 2014 Executive Member, Division on Adult Development and Aging, American Psychological Association
1998 - Fellow, Gerontological Society of America

2001 - 2003 Member, NIH Peer Review, NIA-S (Behavioral and Social Science of Aging)
2003 - 2003 Member, NIH Peer Review, Special Emphasis Panel (Roybal Centers)
2003 - 2005 Chair, NIH Peer Review, NIA-S (Behavioral and Social Science of Aging)
2003 - 2008 Member, Editorial Board, Journal of Gerontology: Psychological Sciences
2004 - Member, Member, Editorial Board, Aging, Neuropsychology and Cognition
2005 - 2005 Member, NIH Peer Review, Special Emphasis Panel (HRS/AHEAD)
2007 - 2007 Member, NIH Peer Review, Special Emphasis Panel (Program Project), NIA
2008 - 2008 Member, NIH Peer Review, Special Emphasis Panel (P50 Supplement), NIA
2009 - 2009 Member, NIH Peer Review, Special Emphasis Panel (Roybal Centers)
2009 - 2009 Member, NIH Peer Review, Special Emphasis Panel, Recovery Act Career Awards, RC2-SEP1 review
2009 - 2009 Member, Member, NIH Peer Review, Special Emphasis Panel, Research and Research Infrastructure "Grand Opportunities" (RC2).
2009 - 2009 Member, Member, NIH Peer Review, Special Emphasis Panel (Alzheimer's Disease Clinical Trials Special Emphasis Panel (BBBP-N[52]), National Institute on Aging, SBIR/STTR
2010 - 2010 Member, NIH Peer Review, Special Emphasis Panel (P50 Supplement), NIA
2012 - 2015 Chair-Elect/Chair, Membership Committee, Gerontological Society of America

Honors

1994 Fellowship for Summer Institute on Successful Midlife Development, MacArthur Foundation Research Network on Successful Midlife Development
1997 Springer Award for Early Career Achievement in Research on Adult Development and Aging, Division on Adult Development and Aging, American Psychological Association
2002 Fellowship status, Gerontological Society of America
2008 Research Mentorship Award, Graduate Student Organization, Univ. of Fla Dept. Clinical/Health Psychology
2009 Research Mentorship Award, Graduate Student Organization, Univ. of Fla Dept. Clinical/Health Psychology
2011 Audrey Schumacher Award for Teaching Excellence (2003, 2005, 2006, 2009, 2011), Graduate Student Organization, Univ. of Fla Dept. Clinical/Health Psychology
2011 University of Florida Research Foundation Professorship, University of Florida
2013 University of Florida Doctoral Mentoring Award, University of Florida

C. Contribution to Science

1. A key focus of my work has been on cognitive interventions with older adults. I had the privilege of training with Sherry Willis and Warner Schaie (PhD, Penn State) and Paul Baltes (Max Planck Institute) on some of the earliest NIH- and other funded research on cognitive training with older adults. This evolved to my role as a PI on the multi-site NIA-funded ACTIVE trial, where (in over 2,800 older adults) we showed that cognitive training in memory/reasoning/processing speed could yield improvements in trained domains that lasted at least ten years. Moreover, while transfer of training was narrow, self-reported everyday functioning showed attenuated age-related decline in adults who received training. A Robert Wood Johnson funded trial showed that off-the-shelf video games could also boost visual attention in older adults, and more recent work has focused on combinations of physical exercise, game play and cognitive training.
   a. Margrett JA, **Marsiske M**. Gender differences in older adults' everyday cognitive collaboration. *Int J Behav Dev*. 2002 Jan;26(1):45-59. **PubMed PMID: 20657668; PubMed Central PMCID: PMC2909137.**
   b. Willis SL, Tennstedt SL, **Marsiske M**, Ball K, Elias J, Koepke KM, Morris JN, Rebok GW, Unverzagt FW, Stoddard AM, Wright E. Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA*. 2006 Dec 20;296(23):2805-14. **PubMed PMID: 17179457; PubMed Central PMCID: PMC2910591.**
   c. Belchior P, **Marsiske M**, Sisco S, Yam A, Mann W. Older adults' engagement with a video game training program. *Act Adapt Aging*. 2012 Dec 19;36(4):269-279. **PubMed PMID: 23504652; PubMed Central PMCID: PMC3596832.**
   d. Thomas KR, **Marsiske M**. Verbal prompting to improve everyday cognition in MCI and unimpaired older adults. *Neuropsychology*. 2014 Jan;28(1):123-34. **PubMed PMID: 24219613; PubMed Central PMCID: PMC3935329.**

2. Much of my work has examined the measurement of "everyday cognition" or "everyday problem solving" in older adults. This work, which started with my dissertation, aims to answer the "so what" question in cognitive aging. How do we reconcile that apparent declines in the underlying cognitive process often seem to have little functional impact on elders' maintenance of everyday independence. Theoretical speculation has argued that older adults may invoke compensatory domain-specific knowledge built up through years of experience. But our work (with Sherry Willis, Jason Allaire, Manfred Diehl and, recently, Kelsey Thomas) suggests that the rate of decline in everyday cognition may parallel that seen for traditional measures of cognition. As such, there may be a growing vulnerability in the ability to perform novel but important tasks (like medication

use), even before clinically significant declines are observed.

a. **Marsiske M**, Willis SL. Dimensionality of everyday problem solving in older adults. *Psychol Aging*. 1995 Jun;10(2):269-83. **PubMed PMID: 7662186; PubMed Central PMCID: PMC2923471.**
b. Allaire JC, **Marsiske M**. Well- and ill-defined measures of everyday cognition: relationship to older adults' intellectual ability and functional status. *Psychol Aging*. 2002 Mar;17(1):101-15. **PubMed PMID: 11931279; PubMed Central PMCID: PMC2909873.**
c. Diehl M, **Marsiske M**, Horgas AL, Rosenberg A, Saczynski JS, Willis SL. The Revised Observed Tasks of Daily Living: A Performance-Based Assessment of Everyday Problem Solving in Older Adults. *J Appl Gerontol*. 2005;24(3):211-230. **PubMed PMID: 18160968; PubMed Central PMCID: PMC2153442.**
d. Yam A, Gross AL, Prindle JJ, **Marsiske M**. Ten-year longitudinal trajectories of older adults' basic and everyday cognitive abilities. *Neuropsychology*. 2014 Nov;28(6):819-28. **PubMed PMID: 24885451; PubMed Central PMCID: PMC4227959.**

3. Race-related disparities in cognition, the resulting differences in trajectories of cognitive aging as a function of disparities, and the underlying health antecedents of these disparities have been consistent through-lines in my research. The interest in race stemmed from opportunities (my site in the ACTIVE clinical trial included approximately 75% African American participants), collaborators (most notably Adrienne Aiken Morgan, now at Duke University, and Carolyn Tucker, a close colleague here at the University of Florida). Moreover, the lifetime opportunity structures associated with race-related disparities are a clear demonstration of developmental contextualism (as Paul Baltes called it), the role of environmental factors in shaping age-related change.
   a. Morgan AA, **Marsiske M**, Whitfield KE. Characterizing and explaining differences in cognitive test performance between african american and European American older adults. *Exp Aging Res*. 2008 Jan-Mar;34(1):80-100. **PubMed PMID: 18189169; PubMed Central PMCID: PMC2211729.**
   b. Aiken Morgan AT, **Marsiske M**, Dzierzewski JM, Jones RN, Whitfield KE, Johnson KE, Cresci MK. Race-related cognitive test bias in the active study: a mimic model approach. *Exp Aging Res*. 2010 Oct;36(4):426-52. **PubMed PMID: 20845121; PubMed Central PMCID: PMC2941916.**
   c. Tucker CM, **Marsiske M**, Rice KG, Nielson JJ, Herman K. Patient-centered culturally sensitive health care: model testing and refinement. *Health Psychol*. 2011 May;30(3):342-50. **PubMed PMID: 21553978; PubMed Central PMCID: PMC3092156.**
   d. **Marsiske M**, Dzierzewski JM, Thomas KR, Kasten L, Jones RN, Johnson KE, Willis SL, Whitfield KE, Ball KK, Rebok GW. Race-related disparities in 5-year cognitive level and change in untrained ACTIVE participants. *J Aging Health*. 2013 Dec;25(8 Suppl):103S-27S. **PubMed PMID: 24385632; PubMed Central PMCID: PMC3882334.**

4. Methodological and statistical consultation, especially in multivariate and longitudinal contexts, has been a through line in my research. Owing to early training with Warner Schaie, John Nesselroade and Paul Baltes at Penn State and Max Planck Berlin, I have leveraged my training to teach advanced graduate statistics (from regression and ANOVA through mixed effects, structural equation analysis and survival analysis) since 1996. I serve as methods/statistics co-investigator on several grants, and I direct the Data Analysis/Management Core for the NIA-funded Florida Alzheimer's Consortium (alzfl.org).
   a. Jones RN, Rosenberg AL, Morris JN, Allaire JC, McCoy KJ, **Marsiske M**, Kleinman KP, Rebok GW, Malloy PF. A growth curve model of learning acquisition among cognitively normal older adults. *Exp Aging Res*. 2005 Jul-Sep;31(3):291-312. **PubMed PMID: 16036723; PubMed Central PMCID: PMC2908897.**
   b. Aiken Morgan AT, **Marsiske M**, Dzierzewski JM, Jones RN, Whitfield KE, Johnson KE, Cresci MK. Race-related cognitive test bias in the active study: a mimic model approach. *Exp Aging Res*. 2010 Oct;36(4):426-52. **PubMed PMID: 20845121; PubMed Central PMCID: PMC2941916.**
   c. Zahodne LB, **Marsiske M**, Okun MS, Rodriguez RL, Malaty I, Bowers D. Mood and motor trajectories in Parkinson's disease: multivariate latent growth curve modeling. *Neuropsychology*. 2012 Jan;26(1):71-80. **PubMed PMID: 22142359; PubMed Central PMCID: PMC3296901.**
   d. Zahodne LB, **Marsiske M**, Bowers D. A latent class analysis of psychological disturbance in Parkinson's disease. *Int J Geriatr Psychiatry*. 2013 Oct;28(10):1054-60. **PubMed PMID: 23307695; PubMed Central PMCID: PMC3656148.**

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/michael.marsiske.1/bibliography/40338977/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support (omits two awards for space)

2002/07/01-2018/04/30
T32 AG020499-14, National Institute on Aging (NIA)
MARSISKE, MICHAEL (PI)
Physical, Cognitive and Mental Health in Social Context
Role: **PI**

2014/07/01-2016/06/30
no number assigned, American Psychological Association
THOMAS, KELSEY (PI)
Characterization Of Elderly On Daily Activities In The Real-World
The goal of this study is to develop and pilot a new measure of everyday cognition for older adults
Role: **Faculty**

2013/05/01-2016/04/30
RX000339, Veterans Administration Rehabilitation Research and Development Service
Levy, Charles (PI)
Virtual Environments for Therapuetic Solutions (VETS) mTBI/PTSD Phase II
The goal of this study is to develop and test a virtual therapeutic environment (supermarket) in which cognitive and emotionally challenging situations can be presented; both assessment and intervention modules are being developed.
Role: **Co-Investigator**

2014/09/15-2016/04/30
R21 AG044862, National Institute on Aging
DING, MINGZHOU (PI)
Measuring Cognitive Fatigability In Older Adults
The goal of this study is to investigate induction, covariates, and neural signatures, of cognitive fatigability in older adults.
Role: **Co-Investigator**

2006/07/01-2016/03/31
P30 AG028740, National Institute on Aging
PAHOR, MARCO (PI)
Claude D. Pepper Older Americans Independence Center (OAIC) RC1
The goal of this center grant is to provide support to investigators conducting research on sarcopenia and the preservation of function in older adults. Marsiske directs the recruitment operation of the Clinical Core.
Role: **PI**

2014/03/01-2016/02/28
no number assigned, The Village of Gainesville
BOWERS, DAWN (PI)
Re-VITALIZE, VITAL and CEDAR
The goal of this study is to support pilot studies in cognitive intervention, mindfulness, and everyday cognitive assessment in older adults
Role: **PI**

2011/09/01-2015/11/30
U01 AG022376, National Institute on Aging
PAHOR, MARCO (PI)
The LIFE Study
The goal of this study is to investigate the long-term effects of a physical exercise/walking intervention on the functional health of older adults.
Role: **Co-Investigator**

Completed Research Support
1996/09/30-2013/04/30
U01 AG014276-11, National Institute on Aging (NIA)
MARSISKE, MICHAEL (PI)
ACTIVE Phase III: UF/WSU Field Site
Role: **PI**

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: MAURER, ANDREW

eRA COMMONS USER NAME (agency login): DREWMAURER

POSITION TITLE: Research Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Pittsburgh, Pittsburgh, PA	BS	12/2003	Neuroscience
University of Arizona, Tucson, AZ	PHD	12/2009	Neuroscience
University of Arizona, Tucson, AZ	Postdoctoral Fellow	06/2014	Neurobiology of Aging

A. Personal Statement

Throughout my scientific career, I have been focused on trying to understand the mechanisms that govern information propagation and communication across the neural networks of the brain. 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. 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 age-related cognitive decline, in which I continued to develop and implement high-level analyses to reveal novel computations of the CA1 subregion of the hippocampus. Moreover, in collaboration with my spouse, Dr. Sara Burke, we have developed novel neuroanatomical methods that will enable us to visualize which neurons are active during behavior (see proposal). These methodological approaches are central to the current application. Dr. Burke and I have collaborated for over a decade. Although we have recently moved to the University of Florida, we have already published multiple papers since establishing research independence. My current research is an innovative extension of my previous research experience, combining high-density recording methods, the analysis of large datasets and aging with a novel examination of the cross-regional brain interactions that support decision-making as well as learning and memory.

B. Positions and Honors

Positions and Employment

2002 – 2004 Undergraduate Research Assistant, Dr. Bill Yates' Vestibular Research laboratory (U of Pitt), Pittsburgh, PA
2004 – 2008 Graduate Research Associate , Dr. Bruce McNaughton's Neural Systems, Memory and Aging Laboratory (U of Arizona), Tucson, AZ
2005 – 2006 Graduate Teaching Assistant, Course- "Memory mechanisms & Neural Computation", Tucson, AZ
2009 – 2014 Postdoctoral Research Fellow, Evelyn F. McKnight Brain Institute with Dr. Carol Barnes, Tucson, AZ
2014 - Affiliate faculty member, Department of Biomedical Engineering, University of Florida, Gainesville, FL
2014 - Assistant Professor, Department of Neuroscience, University of Florida, Gainesville , FL

Other Experience and Professional Memberships

2002 - Member, Society for Neuroscience
2014 - North Central Florida Chapter of the Society for Neuroscience

Honors

2003 Cum Laude, Unviersity of Pittsburgh
2007 Recipient of Conference Travel Award, Society for Neuroscience
2008 Recipient of the D.B. Marquis Behavioral Neuroscience Award, Behavioral Neuroscience Journal
2011 Recipient of the Ruth L. Kirschstein National Research Service Award, National Institute of Health

C. Contribution to Science

1. Prior to my thesis research, only two studies investigated the hippocampal dynamics in the posterior/ventral region of the hippocampus. Therefore, I sought out to determine the firing rate characteristics of neurons in the intermediate portion of the hippocampus compared to the dorsal. We found that place field size was larger in more posterior regions, associated with a decreased rate of phase precession and a decreased sensitivity to velocity.

a. **Maurer AP**, Vanrhoads SR, Sutherland GR, Lipa P, McNaughton BL. Self-motion and the origin of differential spatial scaling along the septo-temporal axis of the hippocampus. *Hippocampus*. 2005;15(7):841-52. **PubMed PMID: 16145692.**
b. **Maurer AP**, Cowen SL, Burke SN, Barnes CA, McNaughton BL. Organization of hippocampal cell assemblies based on theta phase precession. *Hippocampus*. 2006;16(9):785-94. **PubMed PMID: 16921501.**
c. **Maurer AP**, Cowen SL, Burke SN, Barnes CA, McNaughton BL. Phase precession in hippocampal interneurons showing strong functional coupling to individual pyramidal cells. *J Neurosci*. 2006 Dec 27;26(52):13485-92. **PubMed PMID: 17192431.**

2. Theta phase precession has long been thought to be a mechanism by which the brain temporally organizes events in order to facilitate learning and memory. The basic neuronal mechanisms, from ion channels to network dynamics governing this phenomenon, however, are not well understood. In order to elaborate and test the models of theta phase precession, I designed an experiment in which we trained rats to ambulate backwards, thereby, dissociating self-motion from head direction. These data support a view that head-direction input in not critical for theta phase precession.
   a. **Maurer AP**, McNaughton BL. Network and intrinsic cellular mechanisms underlying theta phase precession of hippocampal neurons. *Trends Neurosci*. 2007 Jul;30(7):325-33. **PubMed PMID: 17532482.**
   b. **Maurer AP**, Lester AW, Burke SN, Ferng JJ, Barnes CA. Back to the future: preserved hippocampal network activity during reverse ambulation. *J Neurosci*. 2014 Nov 5;34(45):15022-31. **PubMed PMID: 25378167; PubMed Central PMCID: PMC4220031.**

3. One of the prominent characteristics of hippocampal pyramidal cell activity is their firing correlates with short-term predictions of future locations. Of course ambulatory characteristics will modulate both the future location and the distance covered. We have determined how ambulation alters firing patterns as well as tested models of hippocampal updating by training rodents to walk backwards on a linear track and found that when rodents walk backwards, hippocampal activity patterns continue to predict future locations regardless of head direction.
   a. **Maurer AP**, Burke SN, Lipa P, Skaggs WE, Barnes CA. Greater running speeds result in altered hippocampal phase sequence dynamics. *Hippocampus*. 2012 Apr;22(4):737-47. **PubMed PMID: 21538659; PubMed Central PMCID: PMC3367321.**
   b. **Maurer AP**, Lester AW, Burke SN, Ferng JJ, Barnes CA. Back to the future: preserved hippocampal network activity during reverse ambulation. *J Neurosci*. 2014 Nov 5;34(45):15022-31. **PubMed PMID: 25378167; PubMed Central PMCID: PMC4220031.**

4. While The size of hippocampal spatial receptive fields increases along the dorsal to ventral longitudinal axis, we asked the additional question on whether non-spatial factors could influence the firing rate charachteristics. By placing objects on the track, we showed that the spatial metric of hippocampal receptive fields can be reduced. This work produced new insights regarding the impact of sensory information along the hippocampal longitudinal axis and highlights the productive collaborative efforts of Dr. Burke and myself.
   a. Burke SN, **Maurer AP**, Nematollahi S, Uprety AR, Wallace JL, et al. The influence of objects on place field expression and size in distal hippocampal CA1. *Hippocampus*. 2011 Jul;21(7):783-801. **PubMed PMID: 21365714; PubMed Central PMCID: PMC3314262.**
   b. Burke SN, **Maurer AP**, Hartzell AL, Nematollahi S, Uprety A, et al. Representation of three-dimensional objects by the rat perirhinal cortex. *Hippocampus*. 2012 Oct;22(10):2032-44. **PubMed PMID: 22987680; PubMed Central PMCID: PMC3447635.**
   c. Burke SN, **Maurer AP**, Nematollahi S, Uprety A, Wallace JL, et al. Advanced age dissociates dual functions of the perirhinal cortex. *J Neurosci*. 2014 Jan 8;34(2):467-80. **PubMed PMID: 24403147; PubMed Central PMCID: PMC3870932.**

5. Interneurons have been hypothesized to provide the "scaffold" by which neuronal activity is structured within neural networks. In this sense, they can both govern the rate that information propagates through neural circuits as well as perform computational operations on the information. In light of these theories, we were enthusiastic to discover that putative basket cells exhibted theta phase precession, plausibly inherited from afferent pyramidal cell activity.
   a. **Maurer AP**, Cowen SL, Burke SN, Barnes CA, McNaughton BL. Phase precession in hippocampal interneurons showing strong functional coupling to individual pyramidal cells. *J Neurosci*. 2006 Dec 27;26(52):13485-92. **PubMed PMID: 17192431.**

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/andrew.maurer.1/bibliography/43942059/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

2015/04/01-2015/03/31
1R21DA03970, NIH - National Institute on Drug Abuse
MAURER, ANDREW (M-PI), Setlow, Barry (M-PI)
Development of a rat model of cannabis smoke self-administration
In conjunction with Dr. Barry Setlow (a leading expert in drug addiction), we designed an apparatus that will allow precisely-calibrated, response-contingent delivery of cannabis smoke using experimental designs similar to those employed with other drugs of abuse. We will use this apparatus to determine whether rats will reliably show operant responding for cannabis smoke delivery. Successful development of a rodent cannabis smoke self-administration model will lay the groundwork for a larger research program on neurobehavioral mechanisms of cannabis smoking as well as allow us to bridge animal and human research.
15% effort

2015/08/15-2017/05/31
1R03AG049411, NIH - National Institute on Aging
MAURER, ANDREW (M-PI), Burke, Sara (M-PI), Ormerod, Brandi (M-PI)
Neurogenesis and Memory Network Dynamics during Normal Aging.
This collaborative R03 is designed to develop preliminary data aimed at understanding of the role of neurogenesis in memory and learning. Simply, there has yet to be a high-density electrophysiological investigation of dentate gyrus neural dynamics in aged, freely-behaving animals. As this region appears to be highly vulnerable to the aging process, we are in the process of relating functional change to alteration in neurogenesis.
5% effort

2016/01/01-2020/12/31
1R01AG049722-01A1, NIH - National Institute on Aging
Burke, Sara N (PI), **MAURER, ANDREW (co-I)**
Contribution of Declines in Functional Connectivity to Cognitive Aging
5% effort

BIOGRAPHICAL SKETCH

NAME: McQuail, Joseph Aloysius

eRA COMMONS USER NAME: JAMCQUAIL

POSITION TITLE: Postdoctoral Fellow

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
College of William and Mary	B.S.	05/2004	Neuroscience
Wake Forest University	Ph.D.	05/2013	Neuroscience
University of Florida	Postdoctoral	Current	Neuroscience

A. Personal Statement

I am a neuroscientist-in-training with more than 10 years of research experience in the area of neurocognitive aging. The fundamental and enduring goal of my work is to determine the neural basis of age-related cognitive decline and to use this insight in the design of new therapeutics that can protect and optimize cognitive function across the lifespan. As a predoctoral student and NIH F31 recipient, I examined age-related changes to modulatory G-protein coupled receptors that mediate reference memory. Specifically, I discovered that the constitutive activity of a particular G-protein subtype, Gαq/11, is increased in the hippocampus of older rats, but this persistent action likely recruits a compensatory desensitization of downstream effectors that impairs normal synaptic function. Now a postdoctoral fellow supported by a NIH F32 award, I am working to determine how alterations in neural excitation and inhibition contribute to age-related impairments in executive function. Specifically, my work examines the role of prefrontal NMDA and GABA(B) receptors in normal working memory and their decline with age. Further work will harness this emerging data to develop new therapeutic strategies that can prevent or reverse cognitive decline associated with aging. In all, my present position provides exceptional opportunities for new scientific discovery as well as additional training that will expand the range of questions that I can address in my future independent research program.

B. Positions and Honors

Positions and Employment

2003-2004 Honors Research Student, Dept. of Psychology, College of William and Mary, Williamsburg, VA
2004-2006 Research Technician, Dept. of Psychological and Brain Sciences, Johns Hopkins University, Baltimore, MD
2006-2007 Research Associate, Dept. of Pharmacology and Experimental Therapeutics, University of Maryland School of Medicine, Baltimore, MD
2007-2013 Graduate Research Assistant, Program in Neuroscience, Wake Forest University, Winston-Salem, NC
2013- Postdoctoral Fellow, Dept. of Neuroscience, University of Florida, Gainesville, FL

Other Experience and Professional Memberships

2004- Society for Neuroscience
2015- International Behavioral Neuroscience Society
2015- Molecular and Cellular Cognition Society

Honors

2004 Highest Honors in Neuroscience, College of William and Mary, Williamsburg, VA
2007 Appointed to the Wake Forest University NIH T32 Predoctoral Training Program in Neuroscience
2008 Alumni Travel Award, Wake Forest University, Winston-Salem, NC
2011 Predoctoral National Research Service Award (F31) from the National Institute on Aging
2013 Gordon A. Melson Outstanding Doctoral Student Award, Wake Forest University, Winston-Salem, NC

2013 SfN Travel Award, North Central Florida Chapter of Society for Neuroscience
2015 1st Place, Robert Levitt Research Award, Institute for Learning in Retirement of Oak Hammock of the University of Florida
2015 Travel Award given by the International Behavioral Neuroscience Society
2015 3rd Place, Poster Competition, International Behavioral Neuroscience Society
2015 Postdoctoral National Research Service Award (F32) from the National Institute on Aging
2015 Trainee Professional Development Award, Society for Neuroscience
2015 1st Place, McKnight Poster Competition, McKnight Brain Research Foundation

C. Contribution to Science

My early research sought to clarify the role of cholinergic neurotransmission in normal cognition as well as in age-related cognitive decline. Indeed, loss of cholinergic neurons is well-established in age-related neurodegenerative conditions such as Alzheimer's disease, but its role in normal aging remains poorly understood. My first publication utilized behavioral pharmacology methods to determine that muscarinic, but not nicotinic, cholinergic receptors are essential for intact attention and working memory. Next, I utilized a naturally occurring model of age-related cognitive decline to determine that neither presence of behaviorally verified memory impairment nor changes in the local basal inflammatory state are associated with loss of cholinergic neurons in the basal forebrain. This insight directed my next investigation to use this same model of cognitive aging to examine the functionality of hippocampal muscarinic receptors. This study revealed that constitutive activity of Gαq/11, a G-protein affiliated with postsynaptic M1 muscarinic receptors, is enhanced in the aged hippocampus. However, greater basal G-protein activity in the aged brain was discovered to associate with reduced downstream intracellular signaling when muscarinic receptor-mediated Ca2+ mobilization was evaluated in hippocampal slices. Collectively, my earliest research endeavors were important to establish that age-related cognitive decline is not due to loss of cholinergic neurons, but rather, dysfunction associated with intracellular signaling mediated by postsynaptic M1 receptors and their cognate G-protein.

McQuail JA, Burk JA (2006) Evaluation of muscarinic and nicotinic receptor antagonists on attention and working memory. *Pharmacology, Biochemistry and Behavior*. 85(4):796-803. **PMID: 17196638.**
McQuail JA, Riddle DR, Nicolle MM (2011) Neuroinflammation not associated with cholinergic degeneration in aged-impaired brain. *Neurobiology of Aging*. 32(12):2322.e1–2322.e4. **PMID: 20561717.**
McQuail JA, Davis KN, Miller F, Hampson RE, Deadwyler SA, Howlett AC, Nicolle MM (2013) Hippocampal Gαq/11 but not Gαo-coupled receptors are altered in aging. *Neuropharmacology*. 70:63-73. **PMID: 23347951.**
McQuail JA, Nicolle MM (2015) Spatial reference memory in normal aging Fischer 344 × Brown Norway F1 hybrid rats. *Neurobiology Aging*. 36(1):323-33. **PMID: 25086838.**

In addition to my work on cholinergic neurotransmission in the aged brain, I also collaborate with team of researchers to investigate the role of GABA(B) receptors in working memory and their decline with age. The inspiration for this work began with a study where I demonstrated that GABA(B) receptor function and expression was reduced in the aged prefrontal cortex (PFC), but not in the hippocampus. Compared to the hippocampus, far less is known about the neural basis of cognitive functions supported by the PFC and their changes with age. Our next study revealed that reduced GABA(B) receptor expression in the PFC is an adaptive phenotype that protects working memory, a form of short term memory. However, as GABA signaling may differentially contribute to various forms of PFC-dependent behaviors, we more recently discovered that loss of GABA(B) receptors in the aged PFC is detrimental to set-shifting, an assay of cognitive flexibility. Collectively, these studies reveal that diverse shifts in GABA signaling within the aged PFC are affiliated with specific cognitive outcomes. Importantly, each study also determined that cognition can be rescued in aging provided its neural basis is effectively understood; in the context of working memory, a GABA(B) receptor antagonist improves cognition whereas in the case of impaired cognitive flexibility, a GABA(B) receptor agonist restores set-shifting. More broadly, these new findings bring important attention the status of GABA signaling in the aged PFC, an area that is not well investigated at present.

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. *Neurobiology of Aging*, 33(6):1124.e1–1124.e12. **PMID: 22169202.**
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. Journal of Neuroscience, 34(10): 3457-3466. **PMID: 24599447.**
McQuail JA, Frazier CJ, Bizon JL (2015) Molecular aspects of age-related cognitive decline: the role of GABA signaling. *Trends in Molecular Medicine*, 21(7):450-60. **PMID: 26070271.**
Beas, BS, **McQuail JA**, Bañuelos C, Setlow B, Bizon JL (In revision) Prefrontal cortical GABAergic signaling and impaired behavioral flexibility in aged F344 rats. *Neuroscience*.

Although age-related changes to neural function and cognition are the focus of my work, I am also interested to study insults and interventions across the lifespan that can either contribute to or protect against cognitive decline. In this capacity I have collaborated with a variety of scientists to study the detrimental effects of maternal of nicotine and hypoxia (a model of maternal smoking during pregnancy) on brain development and the effects of whole-brain irradiation on neuroinflammation across the lifespan (as the majority of secondary brain metastases occur in the mature, post-adolescent brain). Further, I have also collaborated with other researchers to investigate the efficacy of dietary manipulations to reduce peripheral and central indices of inflammation and determine whether they provide protection against cognitive decline later in life.

Sergeant S, **McQuail JA**, Riddle DR, Chilton FH, Ortmeier S, Jessup JA, Groban L, Nicolle MM (2011) Dietary fish oil modestly attenuates the effect of age on diastolic dysfunction but has no effect on memory or brain inflammation in aged rats. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 66(5):521-33. **PMID: 21393424.**

Blutstein T, Castello MA, Viechweg SS, Hadjimarkou MM, **McQuail JA**, Holder M, Thompson LP, Mong JA (2013) Differential responses of hippocampal neurons and astrocytes to nicotine and hypoxia in the fetal guinea pig. *Neurotoxicity Research*. 24(1):80-93. **PMID: 23192463.**

Hua K, Schindler MK, **McQuail JA**, Forbes ME, Riddle DR (2012) Regionally distinct responses of microglia and glial progenitor cells to whole brain irradiation in adult and aging rats. *PLoS ONE* 7(12): e52728. **PMID: 23300752.**

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1HcEbBqAHk7/bibliography/40131215/public/?sort=date&direction=a scending

D. Research Support

Ongoing Research Support

F32 AG051371 **McQuail (PI)** 08/14/15-08/13/18
Molecular and physiological determinants of age-related working memory decline
This individual National Research Scholar Award supports postdoctoral training to examine interactions of normal aging and psychogenic stress on excitatory and inhibitory signaling in the prefrontal cortex and to assess the impact of such processes on working memory.
Role: **PI/Fellow**

Completed Research Support

McKnight Brain Institute Fellowship 01/01/14-03/13/15
The role of prefrontal cortical NMDA receptors in age-related cognitive decline
This competitive, institutional fellowship supported postdoctoral training to examine NMDA receptor signaling on distinct neuron populations in the prefrontal cortex of aged rats and determine relationships to executive function
Role: **PI/Fellow**

F31 AG038266 **McQuail (PI)** 08/01/11-04/31/13
Oxidative damage to receptor:G-protein coupling in the aged hippocampus
This individual National Research Scholar Award supported pre-doctoral training to evaluate the relationship between G-protein coupled receptors and spatial reference memory impairment in aged rats
Role: **PI/Fellow**

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: **Okun, Michael S.**

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

POSITION TITLE: **Professor of Neurology**

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Florida State University, Tallahassee, FL	BS	1993	History
University of Florida, Gainesville, FL	MD	1993-1996	Medicine
University of Florida, Gainesville, FL		1996-	Internship
University of Florida, Gainesville, FL		1997-2000	Neurology Residency
Emory University, Atlanta, GA		2000-2002	Movement Disorders Fellowship

A. Personal Statement

Michael S. Okun, M.D. is currently the Chair of Neurology and the Administrative Director, and the Co-Director of the Center for Movement Disorders and Neurorestoration, as well as the Adelaide Lackner Professor of Neurology. Dr. Okun is considered an international expert in Parkinson's Disease and is the current National Medical Director of the National Parkinson Foundation (NPF). He is PI of the Bachmann-Strauss Parkinson and Dystonia Center of Excellennce, and he runs the NPF Ask the Doctor International web-forum, and has been on the steering committee for the worldwide NPF quality improvement clinical-research database (every Parkinson's patient at each center has one page of data collected every year). He has administered many national studies. His expertise has included many physiology and brain imaging projects as well as many device related projects. Dr. Okun is an established Movement Disorders researcher with over 300 peer-reviewed publications and he has been PI, co-PI, or co-I on multiple NIH Parkinson's Disease intervention studies including the PI of a recently completed and published randomized controlled study of cognition and mood with deep brain stimulation (The NIH COMPARE study). Dr. Okun's research efforts have focused on the motor and non-motor aspects of deep brain stimulation as applied to basal ganglia disorders. He is currently Multi-PI of a R01 on mobile computing platforms. Dr. Okun has been working with Dr. Vaillancourt for over 5 years, and together they have published 14 papers, including the recent progression marker in Brain. Finally, Dr. Okun has trained more than 30 M.D. fellows in movement disorders and many with an emphasis on imaging. He has the administrative experience and also the resources as the Chair of Neurology and Medical Director of NPF to run and to ensure the success of the Udall center proposed in this application.

1. **Okun MS**. Deep-brain stimulation--entering the era of human neural-network modulation. *N Engl J Med*. 2014 Oct 9;371(15):1369-73. **PMID: 25197963.**
2. Ofori, E., Pasternak, O., Planetta, P.J., Li, H., Burciu, R., Snyder, A., Lai, S., **Okun, M.S.**, Vaillancourt D.E. (2015). Longitudinal changes in free-water within the substantia nigra of Parkinson's disease. *Brain* 138(Pt 8) 2322-2331. **PMID: 25981960.**
3. Ofori, E., Pasternak, O., Planetta, P.J., Burciu, R., Snyder, A., Febo, M., Golde, T.E, **Okun, M.S.**, Vaillancourt D.E. (2015). Increased extracellular free-water in the substantia nigra of Parkinson's disease: a single-site and multi-site study. *Neurobiology of Aging* 36(2):1097-1104. **PMID: 25467638.**
4. Neely, K.A., Kurani, A., Shukla, P., Shukla, A.W., Planetta, P.J., Goldman, J.G., Corcos, D.M., **Okun, M.S.**, Vaillancourt, D.E. (2015) Functional brain activity related to 0-3 Hz and 3-8 Hz force oscillations in essential tremor. *Cerebral Cortex*. EPub Ahead of Print. **PMID: 24962992.**
5. Planetta, P.J., Ofori, E., Pasternak, O., Burciu, R., Shukla, P., DeSimone, J.C., **Okun, M.S.**, McFarland, N., Vaillancourt D.E. (In Press). Free water imaging in Parkinson's disease and atypical Parkinsonism. *Brain.*

B. Positions and Honors

Positions and Employment

2000-2001	Fellowship, Emory University Movement Disorders
2001-2002	Fellowship, Emory University Stereotactic Neurosurgery for Movement Disorders
2002-2006	Assistant Professor, Co-Director Movement Disorders Center University of Florida Department of Neurology
2003-present	Director, National Parkinson Foundation Center of Excellenc
2006-present	National Medical Director, National Parkinson Foundation
2006-present	Adelaide Lackner Endowed Professor
2007-2012	Associate Professor of Neurology
2012-present	Professor of Neurology (with tenure)
2013- present	Associate Chair of Neurology

Professional Positions

1998-present	Executive Co-Director of the University of Florida Society for the History of Medicine
1999-2000	Chief Resident, University of Florida Department of Neurology
2001-present	Diplomate, American Board of Psychiatry and Neurology
Member:	American Academy of Neurology (AAN)
	American Neurological Association (ANA)
	Movement Disorders Society
	Alpha Omega Alpha Honor Society
	Phi Beta Kappa

C. Contribution to Science

Google Scholar Publicly Available Database of Research Papers: *https://scholar.google.com/citations?user=YXrkisUAAAAJ&hl=en*

1. **Historical Background:** Deep Brain Stimulation for Parkinson's disease has evolved as an important treatment for patients, however there existed an important knowledge gap in choosing the appropriate brain target for symptom specific and personalized therapy. Scientific Problem: There was a major controversy about using the subthalamic nucleus (STN) versus the globus pallidus internus (GPi) for treatment of medication refractory Parkinson's disease. Central Finding: We conducted a randomized NIH study comparing the STN target to the GPi DBS target in Parkinson's disease. This was the first adequately powered randomized target comparison, and it was also the first randomized comparison to show that there was no difference in motor outcomes between targets. A year after publication of our study (in the Annals of Neurology), the large bilateral VA study was published and the results were consistent with our findings. We were able to elucidate target specific differences between STN and GPi and advantages and disadvantages of a unilateral approach. Our team has been instrumental over many years in the development of DBS screening tools and the development and implementation of multidisciplinary DBS screening teams. Influence of the Finding: Today, targets and approaches (unilateral versus bilateral) to DBS are tailored to the individual needs of patients through the use of multidisciplinary screening teams and this approach was influenced by our many publications in this area. Today groups are more likely to use unilateral implants for select patients, and to carefully choose targets based on symptom profiles. Specific Role: PI on the NIH grant (The COMPARE Trial).

Relevant Papers:

1. Taba HA, Wu SS, Foote KD, Hass CJ, Fernandez HH, Malaty IA, Rodriguez RL, Dai Y, Zeilman PR, Jacobson CE, **Okun MS**. A closer look at unilateral versus bilateral deep brain stimulation: results of the National Institutes of Health COMPARE cohort. *J Neurosurg*. 2010 Dec;113(6):1224-9. doi: 10.3171/2010.8.JNS10312. Epub 2010 Sep 17. Erratum in: *J Neurosurg*. 2013 Oct;119(4):1086. **PubMed PMID: 20849215.**

2. Zahodne LB, **Okun MS**, Foote KD, Fernandez HH, Rodriguez RL, Wu SS, Kirsch-Darrow L, Jacobson CE 4th, Rosado C, Bowers D. Greater improvement in quality of life following unilateral deep brain stimulation surgery in the globus pallidus as compared to the subthalamic nucleus. *J Neurol*. 2009 Aug;256(8):1321-9. doi: 10.1007/s00415-009-5121-7. Epub 2009 Apr 12. **PubMed PMID: 19363633; PubMed Central PMCID: PMC3045861.**

3. **Okun MS**, Fernandez HH, Wu SS, Kirsch-Darrow L, Bowers D, Bova F, Suelter M, Jacobson CE 4th, Wang X, Gordon CW Jr, Zeilman P, Romrell J, Martin P, Ward H, Rodriguez RL, Foote KD. Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial. *Ann Neurol*. 2009 May;65(5):586-95. doi: 10.1002/ana.21596. **PubMed PMID: 19288469; PubMed Central PMCID: PMC2692580.**

4. **Okun MS**, Wu SS, Fayad S, Ward H, Bowers D, Rosado C, Bowen L, Jacobson C, Butson C, Foote KD. Acute and Chronic Mood and Apathy Outcomes from a randomized study of unilateral STN and GPi DBS. *PLoS One*. 2014 Dec 3;9(12):e114140. doi: 10.1371/journal.pone.0114140. eCollection 2014. **PubMed PMID: 25469706; PubMed Central PMCID: PMC4254912.**

2. **Historical Background:** Cognitive and mood issues following DBS surgery can limit the overall success of this procedure, and there was a need for a better analysis of this issue. Scientific Problem: Issues such as verbal fluency declines were emerging as potentially limiting factors in deep brain stimulation surgery. Central Finding: Our studies revealed that verbal fluency was the most common cognitive side effect of DBS and it is now recognized as the most common cognitive side effect of DBS for Parkinson's disease. Our NIH COMPARE trial revealed that there was no difference in verbal fluency overall outcome whether blindly on or off stimulation, though outcome could be changed by target and by location of the stimulation field. We were the also the lead authors on the St. Jude randomized constant current DBS trial that led to FDA approval of a new DBS device. This trial had a randomized group with implants but no activation of the DBS, and it corroborated the findings of the initial NIH COMPARE trial. It also added to our previous decade of publications on the microlesional effects of DBS therapy. Influence of Finding: Our group contributed much of the basic understanding of the most common cognitive effect of deep brain stimulation and we demonstrated that the effect was more surgical (traumatic) than stimulation induced. The effect could be modulated somewhat within the target by altering the stimulation field. Patients and clinicians now use this information in pre-operative discussions and post-operative management. Additionaly, much of our early work has helped to define lesion and placebo effects of DBS. Specific Role: PI of the NIH grant, and lead author on the randomized St. Jude trial.

Relevant Papers:

1. **Okun MS**, Foote KD, Wu SS, Ward HE, Bowers D, Rodriguez RL, Malaty IA, Goodman WK, Gilbert DM, Walker HC, Mink JW, Merritt S, Morishita T, Sanchez JC. A trial of scheduled deep brain stimulation for Tourette syndrome: moving away from continuous deep brain stimulation paradigms. *JAMA Neurol*. 2013 Jan;70(1):85-94. doi: 10.1001/jamaneurol.2013.580. **PubMed PMID: 23044532.**

2. Dietz J, Noecker AM, McIntyre CC, Mikos A, Bowers D, Foote KD, **Okun MS**. Stimulation region within the globus pallidus does not affect verbal fluency performance. *Brain Stimul*. 2013 May;6(3):248-53. doi: 10.1016/j.brs.2012.05.011. Epub 2012 Jun 16. **PubMed PMID: 22766102; PubMed Central PMCID: PMC3491090.**

3. Mikos A, Bowers D, Noecker AM, McIntyre CC, Won M, Chaturvedi A, Foote KD, **Okun MS**. Patient-specific analysis of the relationship between the volume of tissue activated during DBS and verbal fluency. *Neuroimage*. 2011 Jan;54 Suppl 1:S238-46. doi: 10.1016/j.neuroimage.2010.03.068. Epub 2010 Mar 31. **PubMed PMID: 20362061; PubMed Central PMCID: PMC2908727.**

4. Zahodne LB, **Okun MS**, Foote KD, Fernandez HH, Rodriguez RL, Kirsch-Darrow L, Bowers D. Cognitive declines one year after unilateral deep brain stimulation surgery in Parkinson's disease: a controlled study using reliable change. *Clin Neuropsychol*. 2009 Apr;23(3):385-405. doi: 10.1080/13854040802360582. Epub 2008 Sep 23. **PubMed PMID: 18821180; PubMed Central PMCID: PMC3045862.**

3. **Historical Background:** There are many neuropsychiatric diseases and symptoms that may possibly be addressed by DBS. Scientific Problem: Understanding targets and symptoms as well as developing a safety profile and outcome predictors for DBS in Obsessive Compulsive Disease and Tourette syndrome has been a challenge. Additionally, the development of non-continuous stimulation strategies (scheduled and responsive) will be important to the future of the field. Central Finding: We performed the first NIH funded trial of OCD DBS and we have performed two other studies in Tourette DBS showing the potential for scheduled rather than continuous stimulation. We are also developing outcome predictors for DBS in neuropsychiatric disorders inclusive of clinical (e.g. the smile response) and physiological measures (e.g. oscillation changes). We have also performed the first human closed loop DBS experiments on Tourette patients. Our laboratory runs the Tourette Syndrome Association International DBS registry, Influence of Finding: Our data was pooled and used for the FDA HDE approval for OCD and we plan to submit our data to the FDA for Tourette syndrome. We are helping to pioneer the necessary database monitoring for DBS in neuropsychiatric diseases. We also hold the DBS think tank each year at UF and there is an associated published proceedings. The think tank is designed to create cutting edge DBS collaboration for neurological and neuropsychiatric diseases. We have recently led the publication for the updated recommendations for Tourette DBS in Movement Disorders. Closed loop smart DBS may provide an important alternative to standard DBS and may be used to modulate individual symptoms in real-time. Our lab has ongoing closed loop experiments. Specific Role: Co-I on NIH OCD grant, PI on two NIH Tourette DBS grants.

Relevant Papers:

1. Haq IU, Foote KD, Goodman WG, Wu SS, Sudhyadhom A, Ricciuti N, Siddiqui MS, Bowers D, Jacobson CE, Ward H, **Okun MS**. Smile and laughter induction and intraoperative predictors of response to deep brain stimulation for obsessive-compulsive disorder. *Neuroimage*. 2011 Jan;54 Suppl 1:S247-55. doi: 10.1016/j.neuroimage.2010.03.009. Epub 2010 Mar 10. **PubMed PMID: 20226259; PubMed Central PMCID: PMC2907450.**

2. Goodman WK, Foote KD, Greenberg BD, Ricciuti N, Bauer R, Ward H, Shapira NA, Wu SS, Hill CL, Rasmussen SA, **Okun MS**. Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design. *Biol Psychiatry*. 2010 Mar 15;67(6):535-42. doi: 10.1016/j.biopsych.2009.11.028. Epub 2010 Feb 8. **PubMed PMID: 20116047.**

3. Almeida L, Martinez-Ramirez D, Rossi PJ, Peng Z, Gunduz A, **Okun MS**. Chasing tics in the human brain: development of open, scheduled and closed loop responsive approaches to deep brain stimulation for tourette syndrome. *J Clin Neurol*. 2015 Apr;11(2):122-31. doi: 10.3988/jcn.2015.11.2.122. Review. **PubMed PMID: 25851890; PubMed Central PMCID: PMC4387477.**

4. Gunduz A, Morita H, Rossi PJ, …, **Okun MS**. Proceedings of the Second Annual Deep Brain Stimulation Think Tank: What's in the Pipeline. *Int J Neurosci*. 2014 Dec 19:1-31. [Epub ahead of print] **PubMed PMID: 25526555.**

D. Research Support

Current Research Support

NIH R01 **Okun** and Butson **(multi-PI)** 09/01/14-08/31/19

Mobile Decision Support System for Nurse Management of Neuromodulation Therapy

The major goal of this study is to assess improvements in DBS patient outcomes from use of mobile computing platform. The UF site will use an iPad mobile computing platform and measure outcomes compared to standard of care DBS programming. We will identify anatomical regions where stimulation provides the most effective symptomatic relief or most significant side effects.

Role: **PI**

R01 NS052318 Vaillancourt (PI) 11/01/11-07/31/15 NIH

Scaling and Sequencing Motor Output in Humans: fMRI study

The major goal of this project is use fMRI and DTI to understand how structural and functional deficits in the basal ganglia and cortex change longitudinally in early stage PD.

Role: **Co-Investigator**

1R01 NS082386-01A1 Price (PI) 04/01/14-03/31/18 NIH

White Matter Connectivity and PD Cognitive Phenotypes

The major goal of this grant is to define white matter connectivity and changes associated with Parkinson's disease and to develop a technique to better define the cognitive phenotypes of Parkinson's disease.

Role: **Co-Investigator**

The Bachmann-Strauss Dystonia & Parkinson's Disease COE **Okun (PI)** 07/16/13-07/01/16

Bachmann-Strauss FDN & Tyler's' Hope FND

The major goal of this grant is to develop a clinical research center for dystonia and Parkinson's disease. The center projects include translational animal models, biomarker and and drug discovery paradigms.

Role: **PI**

C-11-07 3004369.005 **Okun (PI)** 07/01/11-06/30/16

St. Jude Medical/Advanced Neuro Systems

Brain Bank for subjects implanted with the LibraTM Deep Brain Stimulation System

The goal of this project is to pair well standardized clinical data from major DBS trials to collection of post-mortem tissue. The project aims to uncover tissue based changes results from DBS.

Role: **PI**

R01NS075012-01A1 Vaillancourt (PI) 07/16/12-07/15/17 NIH

Non-Invasive Markers of Neurodegeneration in Movement Disorders

The Major Goal of this project is to examine the imaging aspects of neurodegenerative disorders such as Parkinson's disease and no examine imaging changes that may serve as markers of disease.

Role: **Co-Investigator**

TSA International Data Base **Okun (PI)** 11/01/12-06/3019

TSA International Database of deep Brain Stimulation Studies in Tourette Syndrome

The Major Goal of this project is to create an international registry of Tourette DBS procedures. The database contains DBS procedure parameters, scale measurements, and more information on an individual's deep brain stimulation surgery for the treatment of Tourette Syndrome.

Role: **PI**

NEUROMODULATION 2014 **Okun (PI)** 01/16/15-01/15/17 Michael J Fox Foundation (MJFF)
A Responsive Closed-Loop Approach to Treat Freezing of Gait in Parkinson's Disease
The major goal of this study is to provide a rapid, automated closed-loop algorithm prototyping. Our approach will identify the local field potentials (LFP) occurring in GPi and PPN during normal walking and during maneuvers known to instigate freezing episodes. We will use an algorithm to facilitate a responsive train of stimulation to break freezing episodes.
Role: **PI**

NIH CTSI KL2 Gunduz (PI) 01/15/15-01/14/17
The Human Tic Detector: A Responsive Deep Brain Stimulator for the Treatment of Tourette Syndrome
The goal of this study is to detect the neural signatures of Tourette Syndrome to initiate and terminate deep brain stimulation.
Role: Mentor

UF Research Foundation Gunduz (PI) 06/01/15-05/31/17
Uncovering an Electrical Biomarker for Freezing of Gait in Parkinson's Disease
The goal of this study is to investigate biomarkers of freezing of gait in Parkinson's Disease during ambulation using wireless EEG systems.
Role: **Co-PI**

Pending (Submitted and Scored)
NIH R01 **Okun (Admin-PI)** PENDING (NINDS, Score 15%)
The Human Thalamocortical Network in Tourette Syndrome
The major goal of this study is to understand the thalamcortical network in Tourette syndrome and develop a closed loop neuromodulatory treatment strategy.

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: Caitlin Orsini

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

POSITION TITLE: Postdoctoral Fellow

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Washington College, Chestertown, MD	B.S.	05/2007	Behavioral Neuroscience
University of Michigan, Ann Arbor, MI	M.S., Ph.D.	07/2012	Biopsychology
University of Florida, Gainesville, FL	Postdoc	present	Neuroscience/Psychiatry

A. Personal Statement

During my graduate training with Dr. Stephen Maren at University of Michigan, my research focused on elucidating the neural circuitry that mediates the persistence of fear memories after extinction learning. After I received my Ph.D., I began post-doctoral training at the University of Florida under the supervision of Drs. Barry Setlow and Jennifer Bizon, whose research involves investigating the neurobiology of addiction and risky decision-making. Stemming from my graduate work, one line of research that I am pursuing in this grant proposal is how the basolateral amygdala and its interactions with other limbic brain structures (e.g. nucleus accumbens) contribute to risky decision-making behavior. In addition to understanding the neural circuitry mediating risk-taking in a drug naïve state, my research focuses on how it becomes compromised after chronic drug use. In a broader therapeutic context, results from these projects have implications for understanding how the brain balances rewards and punishments in order to arrive at optimal decisions, and how this balance is dysregulated in addiction. During my post-doctoral training, I am learning several new techniques to answer these research questions, providing me with new skill sets (e.g., intravenous drug self-administration in rodents, in vivo electrophysiology, and in vivo optogenetics) that I will be able to incorporate into my own independent research program. My long-term goal is to lead my own laboratory, which will focus on identifying brain circuits that are vulnerable to psychiatric diseases and ways in which to intervene to prevent the development of these conditions.

1. **Orsini, C.A.**, Kim, J.H., Knapska, E. & Maren, S. (2011). Hippocampal and prefrontal projections to the basal amygdala mediate contextual regulation of fear after extinction. *The Journal of Neuroscience*, 23, 17269-77. **PMCID: 3241946.**
2. **Orsini, C.A.** & Maren, S. (2012). Neural and Cellular Mechanisms of Fear and Extinction Memory Formation. *Neuroscience and Biobehavioral Reviews*, 36, 1773-1802. **PMCID: 3345303.**
3. **Orsini, C.A.**, Trotta, R.T., Bizon, J.L. Setlow, B. (2015). Dissociable Roles for the Basolateral Amygdala and Orbitofrontal Cortex in Decision-Making under Risk of Punishment, *The Journal of Neuroscience*, 35, 1368-1379. **PMCID: 4308589.**

B. Positions and Honors

ACTIVITY/OCCUPATION	BEGINNING DATE (mm/yy)	ENDING DATE (mm/yy)	FIELD	INSTITUTION/COMPANY	SUPERVISOR/ EMPLOYER
Research Intern	05/06	08/06	Psychology	University College London	Dr. Celia Heyes
Graduate Student Instructor	01/09	05/09	Biopsychology	University of Michigan	Dr. Stephen Maren
Graduate Student Instructor	01/10	05/10	Biospychology	University of Michigan	Dr. Kent Berridge

Other Experience and Professional Memberships

2007-	Member, Society for Neuroscience
2007-	Member, Molecular, Cellular and Cognition Society
2013-	Member, International Behavioral Neuroscience Society
2011-2013	Associate Chair, Gordon Research Seminar on Amygdala in Health and Disease
2013-	Chair, Gordon Research Seminar on Amygdala in Health and Disease
2014-	Annual Chapter Conference Coordinator, North Central Florida Society for Neuroscience

Invited Reviewer for the following journals: *The Journal of Neuroscience, Brain Structure and Function, Learning and Memory, Behavioral Brain Research, Behavioral Neuroscience, PloS One, British Journal of Pharmacology, Neuropsychopharmacology*

Honors/Awards

Intramural

2007	Graduated summa cum laude from Washington College
2007	George Washington Medal, Washington College (highest academic honor awarded to one graduating senior)
2008-2012	University of Michigan Rackham Travel Award
2013	North Central Florida Society for Neuroscience Chapter Travel Award
2014	North Central Florida Society for Neuroscience Chapter Travel Award

Extramural

2012	Travel Award, American College of Neuropsychopharmacology Annual Meeting
2013	Travel Award, Cold Spring Harbor Cellular Biology of Addiction course
2014	Travel Award, International Behavioral Neuroscience Society Annual Meeting
2015	Travel Award, Winter Conference on Brain Research

C. Contributions to Science (in chronological order)

1. Previous work has shown that the unconscious imitation (mimicry) of others in social interactions creates stronger relationships and better rapport between individuals. My first publication investigated whether the reverse was true: do social attitudes affect how individuals unconsciously imitate one another? The data in this publication demonstrated a small but significant difference between individuals receiving positive and negative words on their imitation response; specifically, individuals who were primed with words with a positive connotation showed a better imitation response than those who were primed with negative words. Based on the data reported in this publication, we concluded that there is a causal relationship between social/emotional attitudes and mimicry of behavior, and that the effect of these attitudes on mimicry is unconscious. In a broader context, this work demonstrates that social attitudes can directly affect behavior without conscious knowledge of these attitudes or intention of imitation. I served as a co-investigator in this study.
   a. Leighton, J., Bird, G., **Orsini, C.A.** & Heyes, C. (2009). Social attitudes modulate automatic imitation. *Journal of Experimental Social Psychology*, 46, 905-910.

2. Pathological fear memories are at the heart of several disorders of fear and anxiety, including post-traumatic stress disorder (PTSD). Extinction is a form of learning that is central to behavioral interventions that reduce fear, such as exposure therapy. Thus, it is critical to identify the neural substrates of extinction in order to develop targeted therapeutic interventions that will promote long-lasting reductions in fear. To this end, in my first two years of graduate school, I demonstrated that glutamate receptors within the auditory thalamus (medial geniculate nucleus) are necessary for extinction of conditioned fear, but that this structure is not a crucial site of plasticity underlying extinction memory formation. This information is useful as it reinforces the notion that plasticity underlying fear and extinction learning occurs in structures downstream of the thalamus, such as the basolateral amygdala.
   a. Chang, C., Knapska, E., **Orsini, C.A.**, Rabinak, C., Zimmerman, J. & Maren, S. (2009). Fear Extinction in Rodents. *Current Protocols*. **PMCID: 2756523.**
   b. **Orsini, C.A.** & Maren, S. (2009). Glutamate receptors in the medial geniculate nucleus are necessary for expression and extinction of conditioned fear in rats. *Neurobiology of Learning and Memory*, 92, 581589. **PMCID: 2745571.**

3. As is evident in both preclinical and clinical research, extinction memories are considered to be fragile, as they can dissipate with the passage of time or changes in context. In particular, the mechanisms by which the brain processes contextual cues that signal whether an environment is "safe" or "unsafe" are relatively unknown. To address this question, I led research focusing on how the hippocampus and prelimbic portion of the medial prefrontal cortex communicate with the amygdala during the renewal, or relapse, of learned fear after extinction. Through the use of lesions, immunohistochemistry and anatomical tracing, these experiments demonstrated that the renewal of fear requires convergent input in the amygdala

from the ventral hippocampus and prelimbic cortex. These results did not demonstrate, however, how cell assemblies in these regions use contextual information to organize behavioral selection. As such, in the second part of this body of work, I used cellular compartment analysis of fluorescent in situ hybridization (catFISH, a method that allows visualization of neuronal activation during two different behavioral experiences) to determine whether the same or different populations of neurons in the prefrontal cortex and ventral hippocampus are recruited during fear extinction and renewal. The results of these experiments demonstrated that fear and extinction learning result in the segregation of unique neuronal populations that represent fear and extinction memories, respectively, in an orthogonal manner across multiple brain regions. More broadly, these findings provide a more refined understanding of how the brain represents different cues in the environment that may signal danger or safety, and further inform scientists and clinicians about how these representations may become altered after major trauma.

a. **Orsini, C.A.**, Kim, J.H., Knapska, E. & Maren, S. (2011). Hippocampal and prefrontal projections to the basal amygdala mediate contextual regulation of fear after extinction. *The Journal of Neuroscience*, 23, p. 17269-77. **PMCID: 3241946.**
b. **Orsini, C.A.** & Maren, S. (2012). Neural and Cellular Mechanisms of Fear and Extinction Memory Formation. *Neuroscience and Biobehavioral Reviews*, **PMCID: 3345303.**
c. **Orsini, C.A.**, Yan, C. & Maren, S. (2013). Ensemble coding of context-dependent fear memory in the amygdala. *Frontiers in Behavioral Neuroscience*, 7:199, **PMCID: 3861741.**

4. Many of the brain regions implicated in fear and anxiety behavior also play a role in decision-making. In particular, the integrity of the amygdala and prefrontal cortex are critical for adaptive risk-based decision-making. However, most laboratory assessments of risky decision-making use paradigms in which the "risk" is reward omission rather than actual adverse consequences as would be encountered in the real-world. To address the roles of the amygdala and prefrontal cortex in this type of "real-world" risky decision-making, I employed a behavioral task developed in the Setlow and Bizon laboratories, in which rats choose between a small, "safe" reward and a large, "risky" reward that is accompanied by variable probabilities of punishment. My research showed that the basolateral amygdala and orbitofrontal cortex play dissociable roles in risky decision-making, with the former being critical for moderating risk-taking in the face of punishment, and the latter being critical for using information about punishment probability to adjust risk-taking strategy. These data are the first to show this functional distinction between these structures in risk-taking behavior and suggest that modulation of these structures may be a potential approach for treating psychiatric diseases that are characterized by pathological risk-taking behavior (e.g. addiction, anorexia nervosa, and bipolar disorder).
   a. **Orsini, C.A.**, Trotta, R.T., Bizon, J.L. & Setlow, B. (2015). Dissociable Roles for the Basolateral Amygdala and Orbitofrontal Cortex in Decision-Making under Risk of Punishment, *The Journal of Neuroscience*, 35:1368-1379. **PMCID: 4308589.**
   b. **Orsini, C.A.**, Moorman, D.E., Young, J.W., Setlow, B. & Floresco, S.B. (2015). Neural mechanisms regulating different forms of risk-related decision-making: Insights from animal models, *Neuroscience and Biobehavioral Reviews*, 58:147-167. **PMID: 26072028.**
   c. **Orsini, C.A.**, Willis, M., Gilbert, R.J. Bizon, J.L., & Setlow, B. (in press).Sex differences in risky decision-making in rodents, *Behavioral Neuroscience*, **PMID: 26653713.**

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1bsByWdCvvhAb/bibliography/43040309/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

K99 DA041493 (NIH-NIDA) Impact Score = 24 (pending admin. review)
"Neural circuits and mechanisms underlying maladaptive risk-taking following cocaine self-administration"
The goal of this project is to determine how prefrontal and amygdala connections with the nucleus accumbens mediate risk-taking and how chronic cocaine exposure alters these circuits to promote maladaptive risk-taking.
Role: **PI**

Thomas H. Maren Junior Investigator Postdoctoral Fellowship 03/01/2015-02/28/2017
"Risk-taking and the nucleus accumbens: neural circuitry and the impact of cocaine"
The goal of this study is to determine how connections between the nucleus accumbens and afferent brain regions mediate risk-taking behavior and how this communication becomes compromised after chronic cocaine use.
Role: **PI**

Completed Research Support

American Psychological Association Dissertation Award 11/01/2010-10/31/2011

F31 MH091822-01 07/10/2010-06/31/2012

"Interactions between the ventral hippocampus and amygdala during renewal of fear"

The goal of this project was to delineate the neural circuitry underlying the renewal of fear with a specific focus on connectivity between the ventral hippocampus and basolateral amygdala.

Role: **PI**

National Center for Responsible Gambling 08/01/2013-09/30/2014

"The Effects of PTSD on risky decision-making"

The goal of this project focused on investigating the relationship between post-traumatic stress disorder and pathological gambling using animal models.

Role: **PI**

McKnight Brain Institute Fellowship 01/01/2014-12/31/2015

"Risk-taking and the Amygdala: Neural Circuitry and Impact of Chronic Cocaine"

The goal of this study is to determine how the amygdala and its connections with other brain structures become compromised after chronic cocaine use and how these alterations contribute to maladaptive risk-taking.

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
Pahor, Marco	Professor and Chair Institute Director
eRA COMMONS USER NAME (credential, e.g., agency login) mpahor	

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
Lycee Chateaubriand, Rome, Italy	B.A.	06/74	Physics/Natural Sciences
Catholic University, Rome, Italy	M.D.	11/80	Medicine and Surgery
Catholic University, Rome Italy	Specialty Thesis	11/84	Internal Medicine, Geriatrics

A. Personal Statement

Dr. Marco Pahor has demonstrated long-term academic excellence, productivity and commitment to multidisciplinary clinical research, education and patient care. Dr. Pahor holds over 34 years of outstanding academic career and 16 years of expertise in key senior leadership roles as Institute/Center director. Dr. Pahor is a nationally and internationally known thought leader in the areas of aging, disability and function in population-based studies, clinical trials and translational research. He has an outstanding NIH and federal funding record. He has authored or co-authored 327 publications in peer reviewed journals, which have resulted in over 16,000 citations. He has extensive expertise in leading multidisciplinary research teams, such as the Claude Pepper Older Americans Independence Center, the University of Florida Clinical Translational Sciences Institute KL2 mentoring program, and multicenter clinical trials. Dr. Pahor has special expertise in randomized controlled trials in older adults involving both pharmacological and behavioral interventions. He is the principal investigator and director of the Administrative Coordinating Center of The LIFE Study, a large (n=1,635) long-term multicenter trial to assess whether physical activity prevents major mobility disability and health related outcomes in older adults funded by the NIA. The LIFE study has demonstrated outstanding recruitment, retention and adherence yields, and timely provision of all study deliverables and benchmarks. Dr. Pahor is the field center PI of the TTrial of testosterone in older persons to assess effects on mobility, vitality and sexual function. Dr. Pahor was the PI of the Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors (TRAIN) study randomized controlled trial funded by the NHLBI to assess the effect of the ACE inhibitor fosinopril on inflammatory and other biomarkers. Dr. Pahor has also long-term experience in the studying low-grade chronic inflammation on mobility in older persons. He has published over 40 papers on the health effects of low-grade inflammation in older cohorts. He was the principal investigator of the American Heart Association grant (9970066N) to measure cytokines in the Health ABC cohort, which resulted in seminal publications regarding the impact of low-grade chronic inflammation on mobility impairments in older populations.

B. Positions and Honors

Positions and Employment

1980-1985	Residency, Internal Medicine and Geriatrics, Catholic University, Rome, Italy
1993	Consultant European Economic Community Pharmacoepidemiology
1992-1995	Visiting Scientist for a total of 12 months, Epidemiology, Demography and Biometry Program, National Institute on Aging, Bethesda, MD
1986-1996	Assistant Professor, tenured in 1991, Int. Med. and Geriatrics, Catholic University, Rome
1994-1999	Contract Professor of Pharmacoepidemiology, University of Florence, Italy
1996-1999	Associate Professor, Dept of Preventive Medicine, University of Tennessee, Memphis, TN
1999	Professor with tenure, Dept of Preventive Medicine, University of Tennessee, Memphis, TN
1999-2005	Professor with tenure, Dept of Internal Medicine, Wake Forest University, Winston-Salem, NC
1999-2005	Head Section on Gerontology and Geriatrics, Wake Forest University, Winston-Salem, NC
1999-2005	Director Sticht Center on Aging, Wake Forest University, Winston-Salem, NC
2002-2004	Deputy Associate Dean, Office of Research, Wake Forest University, Winston-Salem, NC
2005-present	Director Institute on Aging, University of Florida, Gainesville, FL
2005-present	Professor and Founding Chair, Department of Aging and Geriatric Research, University of Florida, Gainesville, FL

Other Experience and Professional Memberships

1994	Award recognition for the contributions to the Women's Health and Aging Study, NIH
1996-2000	Associate Editor / Section Editor for International Affairs, J. Am. Geriatr. Soc.
2003	Board of Scientific Counselors – Intramural Program NIA
2001-2004	Research Committee, American Geriatrics Society
2008	National Institute on Aging, National Advisory Council on Aging, review roster of the Division of Behavioral and Social Research
2007-2010	National Institute on Aging, Physical Exercise Task Force
2010	Review roster of the Geriatrics and Clinical Gerontology Program, National Institute on Aging
1997-present	Contributor to several NIH peer review study sections
2000-present	Consulting Editor, Aging, Clinical and Experimental Research
2002-present	Editorial Board: Nutrition, Health and Aging
2004-present	Associate Editor Journal of Gerontology Medical Sciences
2008-present	National Institute on Aging Clinical Trials Advisory Panel

C. Selected Peer-reviewed Publications (Selected from 327 peer-reviewed publications)

Most relevant to the current application

1. Ferrucci L, Harris TB, Guralnik JM, Wacholder S, Tracy RP, Corti MC, Penninx BWJH, **Pahor M**, Wallace RB, Havlik RJ. Serum IL-6 and the development of disability in older persons. *J Am Geriatr Soc* 1999; 47(6):639-646. **PMID: 10366160**

2. Onder G, Penninx BW, Balkrishnan R, Fried LP, Chaves PH, Carter CS, Williamson JD, Di Bari M, Guralnik JM, **Pahor M**. Relation between use of angiotensin-converting inhibitors and muscle strength and physical function in older women: an observational study. *Lancet* 2002; 359(9310):926-930. **PMID: 11918911**

3. Kritchevsky SB, Nicklas BJ, Visser M, Simonsick EM, Newman AB, Harris TB, Lange EM, Penninx BW, Goodpaster BH, Satterfield S, Colbert LH, Rubin SM, **Pahor M**. Angiotensin-converting enzyme insertion/deletion genotype, exercise, and physical decline. *JAMA* 2005; 294(6):691-698. **PMID: 16091571**

4. Penninx BW, Kritchevsky SB, Newman AB, Nicklas BJ, Simonsick EM, Rubin S, Nevitt M, Visser M, Harris T, **Pahor M**. Inflammatory markers and incident mobility limitation in the elderly. *J Am Geriatr Soc* 2004; 52(7):1105-1113. **PMID 15209648**

5. Penninx BW, Abbas H, Ambrosius W, Nicklas BJ, Davis C, Messier SP, **Pahor M**. Inflammatory Markers and Physical Function Among Older Adults with Knee Osteoarthritis. *J Rheumatol* 2004; 31(10):2027-2031. **PMID 15468370**

6. Kritchevsky SB, Nicklas BJ, Visser M, Simonsick EM, Newman AB, Harris TB, Lange EM, Penninx BW, Goodpaster BH, Satterfield S, Colbert LH, Rubin SM, **Pahor M**. Angiotensin-converting enzyme insertion/deletion genotype, exercise, and physical decline. *JAMA*. 2005;294(6): 691-698. **PMID: 16091571**

7. Cesari M, Kritchevsky SB, Baumgartner RN, Atkinson H, Penninx BWJH, Lenchik L, Palla S, Ambrosius WT, Tracy RP, P**ahor M**. Sarcopenia, obesity and inflammation – Results from the Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors study. *Am J Clin Nutr* 2005; 82(2):428-434. **PMID 16087989**

8. Newman AB, Simonsick EM, Naydeck EM, Kritchevsky SB, Nevitt M, **Pahor M**, Satterfield S, Brach JS, Studenski SA, Harris TB. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. *JAMA* 2006;295(17):2018-26. **PMID: 16670410**

9. **Pahor M**. The LIFE study investigators. Effects of a physical activity intervention on measures of physical performance: Results of the lifestyle interventions and independence for Elders Pilot (LIFE-P) study. J *Gerontol A Biol Sci Med Sci* 2006; 66(11): 1157-65. **PMID: 17167156**

10. Nicklas BJ, Hsu FC, Brinkley TJ, Church T, Goodpaster BH, Kritchevsky SB, **Pahor M**. Exercise training and plasma C-reactive protein and interleukin-6 in elderly people. *J Am Geriatr Soc* 2008; 56(11):2045-2052. **PMCID: PMC2683336**

11. Cesari M, Kritchevsky SB, Atkinson HH, Penninx BW, Bari MD, Tracy RP, **Pahor M**. Angiotensin-converting enzyme inhibition and novel cardiovascular risk biomarkers: results from the Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors (TRAIN) study. *Am Heart J* 2009; 157(2):334.e1-8. **PMID 19185642**

12. Fielding RA, Rejeski WJ, Blair SN, Church T, Espeland MA, Guralnik JM, Gill TM, Hsu FC, Katula JA, King AC, Kritchevsky SB, McDermott MM, Miller ME, Nayfield S, Newman AB, Williamson JD, Bonds DE, Romashkan S, Hadley E, **Pahor M**. The Lifestyle Interventions and Independence for Elders (LIFE) Study: design and methods. *J Gerontol A Biol Sci Med Sci* 2011:66(11):1226-1237. **PMCID: PMC3193523**

13. Marsh AP, Lovato LC, Glynn NW, Kennedy K, Castro C, Domanchuk K, McDavitt E, Rodate R, Marsiske M, McGloin J, Groessl EJ, **Pahor M**, Guralnik JM. Lifestyle Interventions and Independence for Elders Study: Recruitment and Baseline Characteristics. *J Gerontol A Biol Sci Med Sci* 2013; 68(12):1549-1558. **PMCID: PMC3814232**

14. 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. *J Am Geriatr Soc* 2012; 60(7):1244-1252. **PMCID: PMC3625953**

15. **Pahor M**, Guralnik JM, Ambrosius WT, Blair S, Bonds DE, Church TS, Espeland MA, Fielding RA, Gill TM, Groessl EJ, King AC, Kritchevsky SB, Manini TM, McDermott MM, Miller ME, Newman AB, Rejeski WJ, Sink KM, Williamson JD. 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. **PMCID: 24866862**

C. Research Support

Ongoing Research Support

NIH-NIA 1UO1 AG022376-01 **Pahor (PI)** 09/01/09-08/31/15
The LIFE study
The major goal of this project is to determine by conducting a Phase 3 randomized, controlled trial whether physical exercise prevents major mobility disability in older persons.

NIH-NIA U01AG022376. **Pahor (PI)** 09/01/09-08/31/15
The LIFE Study – NHLBI Supplement
The major goal of this project is to assess sleep disturbances and cardiopulmonary outcomes.

NIH-NIA 1P30 AG028740-01 **Pahor (PI)** 04/01/12-03/31/17
Claude D. Pepper Older Americans Independence Centers
The major goals of this project are the developing, testing and dissemination of effective therapies for the treatment and prevention of physical disability.

NIH-NCRR 1C06RR029852-01 **Pahor (PI)** 01/14/10-01/13/15
Institute on Aging Clinical Translational Research Building
Goal: to construct a 40,000 GSF building to host the University of Florida Clinical Translational Research Building.

NIH-NIA 1U01AG030644-01A1 Snyder (PI) 05/05/09-04/30/15
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: **Site PI**

NIH-NCRR 1UL1RR029890 Nelson (PI) 07/14/09-07/13/15
UF Clinical and Translational Science Award
This project focuses on the ability of the University of Florida to transform the manner by which it conducts multi-and interdisciplinary clinical and translational research and training.
Role: **Co-Investigator**

Completed Research Support

NIH-NIA 1 R01 AG026556-01 **Pahor (PI)** 12/01/06-06/30/12
Oxidative damage, disability and mortality in elders
Ancillary study to the Health, Aging and Body Composition study to evaluate the predictive value of oxidative damage, platelet activation and inflammation for incident mobility disability and mortality in older persons.

NIH-NIA 1 P30 AG028740 **Pahor (PI)** 04/01/07-03/31/12
Claude D. Pepper Older Americans Independence Centers
The major goals of this project are the developing, testing and dissemination of effective therapies for the treatment and prevention of physical disability.

NIH-NIA 1 R01 AG027529 Nicklas (PI) 09/15/06-08/31/11
Exercise training and inflammatory risk factors for disability
The goal is to measure plasma concentrations of inflammatory biomarkers in blood samples collected from LIFE participants following randomization to the interventions to test our primary hypothesis that: 1) compared to a non-exercise health education

intervention, a 12-month exercise training intervention will decrease concentrations of inflammatory biomarkers in elderly men and women at high risk for physical disability.
Role: **Co-Investigator**

NIH-NIA 1 P30 AG028740-03S1 **Pahor (PI)** 09/20/09-08/31/11
Claude D. Pepper Older Americans Independence Centers Supplement
Goal: to assess the impact of mitochondrial function and fatigue on physical function and disability.

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: Porges, Eric

eRA COMMONS USER NAME (agency login): eporges

POSITION TITLE: Postdoctoral Associate

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

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Hampshire College, Amherst, MA	BA	01/2004	Cognitive Science
University of Chicago, Chicago, IL	MA	09/2012	Neuroscience
University of Chicago, Chicago, Illinois	PHD	08/2013	Neuroscience

A. Personal Statement

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 transitioning to a Research Assistant Professor at the Center for Cognitive Aging and Memory (CAM) in the Institute on Aging, at the University of Florida from my position as Postdoctoral Associate in the same institution. My primary mentor is Dr. Ron Cohen. Under Dr. Cohen's mentorship I have and will continue to work 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. As an adjunct to this line of research, my work has extended into a second area, involving the study of cognitive, affective and autonomic modulation via transcutaneous vagal nerve stimulation (tVNS). 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.

1. Yoder KJ, **Porges EC**, Decety J. Amygdala subnuclei connectivity in response to violence reveals unique influences of individual differences in psychopathic traits in a nonforensic sample. *Hum Brain Mapp*. 2015 Apr;36(4):1417-28. **PubMed PMID: 25557777.**

2. **Porges EC**, Smith KE, Decety J. Individual differences in vagal regulation are related to testosterone responses to observed violence. *Front Psychol*. 2015;6:19. **PubMed PMID: 25759673; PubMed Central PMCID: PMC4338751.**

3. Smith KE, **Porges EC**, Norman GJ, Connelly JJ, Decety J. Oxytocin receptor gene variation predicts empathic concern and autonomic arousal while perceiving harm to others. *Soc Neurosci*. 2014 Feb;9(1):1-9. **PubMed PMID: 24295535; PubMed Central PMCID: PMC3923324.**

4. Clark DJ, Rose DK, Ring SA, **Porges EC**. Utilization of central nervous system resources for preparation and performance of complex walking tasks in older adults. *Front Aging Neurosci*. 2014;6:217. **PubMed PMID: 25202270; PubMed Central PMCID: PMC4142860.**

B. Positions and Honors

Positions and Employment

1999 - 2002 Emergency Medical Technician, Hampshire College Emergency Medical Services, Amherst, MA
2001 - 2002 Director of Hampshire College Emergency Medical Services, Hampshire College Emergency Medical Services, Amherst, MA
2002 - 2002 Project Manager, Greenleaf Medical, Palo Alto, CA
2003 - 2003 Intern, Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, Urbana, IL
2004 - 2005 Research Coordinator , University of Illinois at Chicago, Chicago, IL
2006 - 2008 Lab Manager, Social Cognitive Neuroscience Lab, University of Chicago, Chicago, IL
2008 - 2013 Graduate Student, Integrative Neuroscience program, Department of Psychology, University of Chicago, Chicago, IL

2013 - Postdoctoral Associate, Department of Aging and Geriatric Research, Institute on Aging, Center for Cognitive Aging and Memory, University of Florida, Gainesville, FL

Other Experience and Professional Memberships

2010 - Member, Society for Neuroscience
2011 - Member, Society for Social Neuroscience
2011 - Ad Hoc Reviewer, International Journal Psychophysiology
2012 - Member, Cognitive Neuroscience Society
2012 - Member, Society for Psychophysiological Research
2012 - Social Neuroscience, Ad Hoc Reviewer
2013 - Ad Hoc Reviewer, Developmental Review
2014 - Review Editorial Board, Frontiers in Psychology; Emotion Science
2015 - Review Editorial Board, Frontiers in Psychology, section Psychology for Clinical Settings

Honors

2010 Norman Henry Anderson Award, Department of Psychology at the University of Chicago
2011 Research Award, University of Chicago Psychology graduate student organization
2011 Norman Henry Anderson Award, Department of Psychology at the University of Chicago
2012 Student Poster Award, Society for Psychophysiological Research
2012 Travel Award, University of Chicago Psychology graduate student organization
2012 Norman Henry Anderson Award, Department of Psychology at the University of Chicago

C. Contribution to Science

1. Violence is an incredibly salient stimulus and an important environmental signal with survival consequences, conveying information about potential threats to personal health and safety. The primary aim of this branch of my research was to employ a multilevel approach to characterize factors that contribute to individual differences in peripheral and central physiological responses to observed violence. Study one employs measures of peripheral physiology and demonstrates an inverse relationship between parasympathetic tone and testosterone release. Study two employs measures of genetic polymorphisms and reports that participants with the genotype GG for OXTR (SNP) rs53576 respond to violent entertainment with increased sympathetic and self-reported arousal and increased dispositional empathic concern. Study three employs functional connectivity analyses of brain imaging data and demonstrates that the modulation of neurophysiological recruitment of specific brain areas is related to individual differences in subjective appraisals. The work presented here demonstrated that across diverse methods, individual responses to observed violence can be predicted by preexisting traits. Most relevant to the proposed research, higher resting parasympathetic tone predicted a lower testosterone response to observed violence, demonstrating the influence of autonomic regulation of physiological response to external stimuli.
    a. **Porges EC**, Decety J. Violence as a source of pleasure or displeasure is associated with specific functional connectivity with the nucleus accumbens. *Front Hum Neurosci*. 2013;7:447. **PubMed PMID: 23964226; PubMed Central PMCID: PMC3741555.**
    b. Clark DJ, Rose DK, Ring SA, **Porges EC**. Utilization of central nervous system resources for preparation and performance of complex walking tasks in older adults. *Front Aging Neurosci*. 2014;6:217. **PubMed PMID: 25202270; PubMed Central PMCID: PMC4142860.**
    c. Smith KE, **Porges EC**, Norman GJ, Connelly JJ, Decety J. Oxytocin receptor gene variation predicts empathic concern and autonomic arousal while perceiving harm to others. *Soc Neurosci*. 2014 Feb;9(1):1-9. **PubMed PMID: 24295535; PubMed Central PMCID: PMC3923324.**
    d. **Porges EC**, Smith KE, Decety J. Individual differences in vagal regulation are related to testosterone responses to observed violence. *Front Psychol.* 2015;6:19. **PubMed PMID: 25759673; PubMed Central PMCID: PMC4338751.**

Complete List of Published Work in My Bibliography:
http://1.usa.gov/1NCHRhe

D. Research Support

Ongoing Research Support

Internal Funding, University of Florida, Institute on Aging
Porges, Eric (PI)
09/01/13-09/01/16
postdoctoral fellowship
postdoctoral fellowship funded by the Center or Cognitive Aging and Memory.
Role: **PI**

IK2 RX000707, VA Rehabilitation Research & Development
John B. Williamson (PI)
01/08/13-03/31/17
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-Investigator**

Completed Research Support
internal, VA RR&D
John Williamson (PI)
06/01/14-12/01/14
Brain Rehabilitation Research Center Pilot Innovation
External autonomic nervous system modulation for the treatment of PTSD.
Role: **Co-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 FIVE PAGES.**

NAME: Barry Setlow

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

POSITION TITLE: Associate Professor of Psychiatry and Neuroscience

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Yale University, New Haven, CT	BA	1994	Psychology
University of California, Irvine, CA	PhD	1998	Neurobiology & Behavior
Johns Hopkins University, Baltimore, MD	Post-doc	1998-2002	Neuroscience

A. Personal Statement

The NIH-funded research in my lab uses animal models to address a range of questions concerning disordered risk-taking and decision-making processes, much of it in the context of drugs of abuse. One line of work is focused on the mechanisms by which acute and chronic exposure to drugs of abuse alter impulsive and risky decision-making. Another line of work is focused on the behavioral and neural bases of individual differences in these forms of decision-making, and how such individual differences are related to vulnerability to drug use. In addition, I collaborate with several MBI investigators on projects investigating behavioral and neural mechanisms of age-related cognitive decline.

Relevant peer-reviewed publications: + = postdoctoral fellow; * = graduate student; ** = undergraduate student

1. Mendez, I. A.*, Simon, N. W.*, Hart, N.*, Mitchell, M. R.*, Nation, J. R., Wellman, P. J., & **Setlow, B**. (2010). Self-administered cocaine causes lasting increases in impulsive choice in a delay discounting task. *Behavioral Neuroscience*. 124, 470-477. **PMC2976632**

2. Simon N. W.*, Montgomery, K. S.*, Beas, B. S.*, Mitchell, M. R.*, LaSarge, C. L.*, Mendez, I. A.*, Bañeulos, C.*, Vokes, C. M., Taylor, A. B., Haberman, R. P., Bizon, J. L., & **Setlow, B**. (2011). Dopaminergic modulation of risky decision-making. *The Journal of Neuroscience*. 31, 17460-17470. **PMC3307370**

3. Mitchell, M. R.*, Weiss, V. G.**, Beas, B. S.*, Morgan, D., Bizon, J. L., & **Setlow, B**. (2014). Adolescent risk taking, cocaine self-administration, and striatal dopamine signaling. *Neuropsychopharmacology*. 39, 955-962. **PMC3924529**

4. Orsini, C. A.+, Trotta, R.**, Bizon, J. L., & **Setlow, B**. (2015). Dissociable roles for the basolateral amygdala and orbitofrontal cortex in decision-making under risk of punishment. *The Journal of Neuroscience*. 35, 1368-1379. **PMC4308589**

B. Positions and Honors

Positions and Employment

2002-2003 Assistant Research Scientist, Dept. of Psychology, Johns Hopkins University
2004-2010 Assistant Professor of Psychology and Faculty of Neuroscience, Texas A&M University
2010-present Associate Professor of Psychiatry, Neuroscience, and Psychology, University of Florida

Other Experience and Professional Memberships

2004-present, Reviewer (ad hoc and panels) for NIH, NSF, and several international funding agencies
2007-present, Consulting Editor, Cognitive, Affective, and Behavioral Neuroscience
2012-present, Editorial Board, Neuroscience
2012-present, Editorial Board, Neurobiology of Learning and Memory
2013-present, Faculty of 1000 (Psychiatry)
2014-present, Editorial Board, Journal of the Experimental Analysis of Behavior

2015-present, Associate Editor, The Journal of Neuroscience
2015-present, Editorial Board, Behavioral Neuroscience
2009-present College on Problems in Drug Dependence (Regular Member)
2011-present American College of Neuropsychopharmacology (Fellow)

Honors

1994 Graduated magna cum laude with distinction in psychology, Yale University
1995-1998 NSF Graduate Fellowship
2000-2003 NIH Individual National Research Service Award (F32, NIMH)
2008 American College of Neuropsychopharmacology Young Investigator Memorial Travel Award
2010 Leadership and Service Award, Faculty of Neuroscience, Texas A&M University
2011 Distinguished Lecturer Award, Dept. of Psychology, University of North Carolina, Chapel Hill

C. Contribution to Science

URL for full list of published work in My Bibliography *http://www.ncbi.nlm.nih.gov/sites/myncbi/barry.setlow.1/bibliograpahy/40590719/public/?sort=date&direction=ascending*

1. Development and validation of a rat model of risky decision-making. The ability to decide adaptively among options that vary in both their risks and rewards is a critical element of everyday life. For example, when approaching a yellow traffic light, a driver must choose whether to brake and stop (not very rewarding but safe) or to speed up and attempt to beat the light (arguably more rewarding but with greater potential for adverse consequences). Similarly, an intravenous drug user must choose between the smaller (in the short term) but safer rewards of abstinence vs. the greater but more dangerous rewards of continued drug use. Inherent in such real-world decisions is the risk of truly adverse consequences (i.e., those that involve consequential loss or harm); however, most laboratory studies of risky decision-making do not tend to incorporate such consequential outcomes. For the last several years, we have been working with a rat decision-making task that incorporates a risk of adverse outcomes. In this task, rats make choices between small, ""safe" food rewards and large, "risky" food rewards that are accompanied by varying probabilities of a mild footshock. Using this task, we have found numerous parallels between rodent and human risky decision-making, including a) risky choices are attenuated by acute administration of indirect dopamine agonists; b) high levels of risk-taking behavior predict greater propensity for cocaine self-administration; c) chronic cocaine self-administration causes a long-lasting increase in risk-taking; d) higher levels of risk-taking are associated with lower striatal dopamine D2 receptor expression. In addition, we have begun to delineate the neural circuitry supporting risky decision-making (e.g., dissociable roles for basolateral amygdala and orbitofrontal cortex).

+ = postdoctoral fellow; * = graduate student; ** = undergraduate student

1. Simon, N. W.*, Gilbert, R. J.**, Mayse, J. D.**, Bizon, J. L., & **Setlow, B**. (2009). Balancing risk and reward: A rat model of risky decision-making. *Neuropsychopharmacology*. 34, 2208-2217. **PMC2726909**

2. Simon N. W.*, Montgomery, K. S.*, Beas, B. S.*, Mitchell, M. R.*, LaSarge, C. L.*, Mendez, I. A.*, Bañeulos, C.*, Vokes, C. M., Taylor, A. B., Haberman, R. P., Bizon, J. L., & **Setlow, B**. (2011). Dopaminergic modulation of risky decision-making. *The Journal of Neuroscience*. 31, 17460-17470. **PMC3307370**

3. Mitchell, M. R.*, Weiss, V. G.**, Beas, B. S.*, Morgan, D., Bizon, J. L., & **Setlow, B**. (2014). Adolescent risk taking, cocaine self-administration, and striatal dopamine signaling. *Neuropsychopharmacology*. 39, 955-962. **PMC3924529**

4. Orsini, C. A.+, Trotta, R.**, Bizon, J. L., & **Setlow, B**. (2015). Dissociable roles for the basolateral amygdala and orbitofrontal cortex in decision-making under risk of punishment. *The Journal of Neuroscience*. 35, 1368-1379. **PMC4308589**

2. Effects of chronic cocaine on impulsive decision-making. Elevated preference for immediate over delayed gratification, or "impulsive choice", is frequently observed in individuals addicted to a variety of drugs of abuse. It is less clear, however, whether such elevated impulsive choice is a pre-existing condition (which could predispose individuals to drug use) or instead a consequence of chronic drug use. In a series of publications, we showed that either experimenter- or self-administered cocaine causes increased preference for immediate over delayed gratification (increased impulsive choice) that persists through at least 3 months of abstinence. These results suggest that at least some portion of the increased impulsive choice in human cocaine users is due to lasting effects of cocaine itself. Additional gene expression data suggest that cocaine-induced increases in impulsive choice may be attributable to altered prefrontal cortical dopamine receptor expression.

1. Simon, N. W.*, Mendez, I. A.*, & **Setlow, B**. (2007). Cocaine exposure causes long-term increases in impulsive choice behavior. *Behavioral Neuroscience*. 121, 543-549. **PMC2581406**

2. Mendez, I. A.*, Simon, N. W.*, Hart, N.*, Mitchell, M. R.*, Nation, J. R., Wellman, P. J., & **Setlow, B**. (2010). Self-administered cocaine causes lasting increases in impulsive choice in a delay discounting task. *Behavioral Neuroscience*. 124, 470-477. **PMC2976632**

3. Simon N. W.*, Beas, B. S.*, Montgomery, K. S.*, Haberman, R. P., Bizon, J. L., & **Setlow, B**. (2013). Prefrontal cortical-striatal dopamine receptor mRNA expression predicts distinct forms of impulsivity. *European Journal of Neuroscience*. 37, 1779-1788. **PMC3973541**

4. Mitchell, M. R.*, Weiss, V. G.**, Ouimet, D. J., Fuchs, R. A., Morgan, D. & **Setlow, B**. (2014). Intake-dependent effects of cocaine self-administration on impulsive choice in a delay discounting task. Behavioral Neuroscience. 128, 419-429. **PMC4107092**

3. Behavioral and neural mechanisms of age-related cognitive decline. Advances in medicine and public health have enabled a greater number of people to live to old age. With this increased lifespan, however, comes growing concern regarding maintenance of cognitive abilities at advanced ages. As part of a long-standing collaboration with Dr. Jennifer Bizon, my laboratory has a strong interest in using rodent models to elucidate the neural processes responsible for successful and impaired cognitive aging. One goal of this work has been to establish reliable rat models that are sensitive to unique aspects of age-related cognitive decline in order to provide a strong rationale for regional evaluation of underlying, causal neural mechanisms. A second goal of this work has been to determine these mechanisms, and to develop novel therapies targeting these mechanisms to remediate age-related cognitive impairments.

1. Simon, N. W.*, LaSarge, C. L.*, Montgomery, K. S.*, Williams, M. T.**, Mendez, I. A.*, **Setlow, B.**, & Bizon, J. L. (2010). Good things come to those who wait; attenuated discounting of delayed rewards in aged Fischer 344 rats. *Neurobiology of Aging*. 31, 853-862. **PMC2866647**

2. Gilbert, R.J., Mitchell, M.R.*, Simon, N.W.*, Bañuelos, C.*, **Setlow, B.**, & Bizon J.L. (2012). Risk, reward, and decision-making in a rodent model of cognitive aging. *Frontiers in Neuroscience*. 5, 144. **PMC3250056**

3. Beas, B. S.*, **Setlow, B.**, & Bizon, J. L. (2013). Distinct manifestations of executive dysfunction in aged rats. *Neurobiology of Aging*. 34, 2164-2174. **PMC3679301**

4. Bañuelos, C.*, Beas, B. S.*, McQuail, J. A.+, Gilbert, R. J., Frazier, C. J., **Setlow, B.**, & Bizon, J. L. (2014). Prefrontal cortical GABAergic dysfunction contributes to age-related working memory impairment. *The Journal of Neuroscience*. 34, 3457-3466. **PMC3942567**

4. The role of the nucleus accumbens and related circuitry in goal-directed behavior. The nucleus accumbens is often characterized as providing an interface between brain systems that learn about and encode motivationally-salient information and brain systems that produce motor output. During my postdoctoral training with Drs. Michela Gallagher and Peter Holland, I investigated the neural basis of learning about predictive relationships between cues and rewarding or aversive outcomes, and how these predictive cues are used to guide behavior. The findings of this research (which employed both analysis of behavior in animals with specific neurotoxic brain lesions and single-unit electrophysiological recording in behaving animals) showed that the basolateral amygdala is critical for learning new cue-outcome relationships, but not for their expression. In contrast, different structures to which the basolateral amygdala projects (including the nucleus accumbens, orbitofrontal cortex, and lateral hypothalamus) are critical for expression of this type of learning to guide different aspects of motivated behavior. Importantly, many of the properties of these brain systems are similar regardless of whether the learning is about cues predictive of appetitive or aversive outcomes.

1. **Setlow, B.**, Gallagher, M., & Holland, P. C. (2002). The basolateral complex of the amygdala is necessary for acquisition but not expression of CS motivational value in appetitive Pavlovian second-order conditioning. *European Journal of Neuroscience*. 15, 1841-1853.

2. **Setlow, B.**, Holland, P. C., & Gallagher, M. (2002). Disconnection of the basolateral amygdala complex and nucleus accumbens impairs appetitive Pavlovian second-order conditioned responses. *Behavioral Neuroscience*. 116, 267-275.

3. **Setlow, B.**, Schoenbaum, G., & Gallagher, M. (2003). Neural encoding in ventral striatum during olfactory discrimination learning. *Neuron*. 38, 625-636.

4. Schoenbaum, G., **Setlow, B.**, Saddoris, M. P., & Gallagher, M. (2003). Encoding predicted outcome and acquired value in orbitofrontal cortex during cue sampling depends upon input from basolateral amygdala. *Neuron*. 39, 855-867.

5. Amygdala-accumbens circuitry and memory consolidation. When I began my graduate training with Dr. Jim McGaugh, research in his laboratory had largely focused on memory consolidation processes involving the basolateral amygdala and hippocampus; however, I became interested in the nucleus accumbens after reading that it is a site of convergence for numerous sources of limbic cortical and subcortical input, including both the basolateral amygdala and hippocampus. This

reading convinced me that the accumbens might be an important component of a memory consolidation system. My dissertation examined this hypothesis using a combination of lesion, pharmacological, and behavioral approaches. I found that like the hippocampus, the accumbens is specifically involved in consolidation of spatial/declarative memory, and that like the basolateral amygdala, the accumbens is critical for pharmacological modulation of memory consolidation.

1. **Setlow, B.** & McGaugh, J. L. (1998). Sulpiride infused into the nucleus accumbens post-training impairs memory of spatial water maze training. *Behavioral Neuroscience*. 112, 603-610.
2. **Setlow, B.** & McGaugh, J. L. (1999). Differential effects of immediate posttraining sulpiride microinfusions into the nucleus accumbens shell and core on Morris water maze retention. *Psychobiology*. 27, 248-255.
3. **Setlow, B.**, Roozendaal, B., & McGaugh, J. L. (2000). Involvement of a basolateral amygdala complex - nucleus accumbens pathway in glucocorticoid-induced modulation of memory storage. *European Journal of Neuroscience*. 12, 367-375.
4. Roozendaal, B., de Quervain, D. J.-F., Ferry, B., **Setlow, B.**, & McGaugh, J. L. (2001). Basolateral amygdala - nucleus accumbens interactions in mediating glucocorticoid effects on memory consolidation. *The Journal of Neuroscience*. 21, 2518-2525.

D. Research Support

Current Laboratory Funding

R01 DA036534 (NIH - NIDA) 4/1/15-3/31/20 **Setlow (PI)**
"Risk taking and cocaine use: interactions, mechanisms, and therapeutic targets"
The goal is to determine neural mechanisms underlying relationships between risk taking behavior and cocaine self-administration.

R21 DA039701 (NIH-NIDA) 4/1/15-3/31/17 **Setlow (MPI)**
"Development of a rat model of cannabis smoke self-administration"
The goal is to develop an apparatus and procedure for cannabis smoke self-administration in rats.

R21 DA039349 (NIH-NIDA) 7/1/15-6/30/17 **Setlow (MPI)**
"Lasting behavioral and neuroimaging consequences of adolescent exposure to cannabis smoke"
The goal is to determine how adolescent passive exposure to cannabis smoke affects long-term neurobehavioral outcomes in a rat model.

R21 DA038009 (NIH-NIDA) 4/1/15-3/31/17 **(Setlow co-I)**, M Febo (PI)
"Imaging in vivo neural mechanisms of synthetic cathinones (bath salts)"
The goal is to determine the behavioral and neural consequences of exposure to MDPV, a typical component of "bath salts" drugs.

R01 AG029421 (NIH-NIA) 5/15/14-3/31/19 **Setlow (co-I)**, J Bizon (PI)
"Neural mechanisms of cognitive decline in aging"
The goal is to determine how age-related alterations in GABAergic signaling mechanisms in prefrontal cortex contribute to impairments in executive functions.

R01 NS091542 (NINDS - NIH) 9/1/15-8/31/19 **Setlow (co-I)**, A. Martynyuk (PI)
"Role of the limbic-hypothalamic-pituitary-adrenal axis and GABA(A) receptor-mediated excitation in the developmental central and systemic effects of neonatal anesthesia"
The goal is to determine the mechanisms by which neonatal anesthesia causes lasting alterations in hippocampal function.

Current Trainee Funding

Thomas H. Maren Postdoctoral Fellowship 3/1/15-2/28/17 **Setlow (sponsor)**, C.A. Orsini (PI)
This fellowship provides partial salary support to Dr. Orsini while she conducts research in Dr. Setlow's lab on neural mechanisms of maladaptive risk-taking.

McKnight Brain Institute Postdoctoral Fellowship 1/1/14-12/31/16 **Setlow (sponsor)**, C.A. Orsini (PI)
This fellowship provides partial salary support to Dr. Orsini while she conducts research in Dr. Setlow's lab on neural mechanisms of maladaptive risk-taking.

F32 AG051371 (NIH-NIA) 8/15/15-8/14/18 **Setlow (co-sponsor)**, J. McQuail (PI)
"Molecular and physiological determinants of age-related working memory decline"
The goal of this project is to determine how GABA and NMDA receptor signaling in prefrontal cortex contribute to impaired working memory function in aging.

Completed Funding

R01 DA024671 (NIH - NIDA) 4/1/09-3/31/15 **Setlow (PI)**

"Neural mechanisms of enduring cocaine effects on impulsive choice"

The goal of this project is to determine neural mechanisms by which chronic cocaine use causes long-lasting elevations in impulsive decision-making.

R01 AG029421 (NIH - NIA) 7/1/07-6/30/13 **Setlow (co-I)**, J. L. Bizon (PI)

"Basal Forebrain and Cognitive Aging: Novel Experimental and Therapeutic Avenues"

The goal of this project is to determine the role of cholinergic and GABAergic basal forebrain system dysfunction in age-related cognitive decline.

F31 DA033074 (NIH - NIDA) 5/11/12-1/31/13 **Setlow (Sponsor)**, M. R. Mitchell (PI)

"Adolescent risk-taking, dopamine signaling, and cocaine: A vicious circle"

The goal of this project is to determine the relationships between adolescent risk-taking, cocaine self-administration, and dopamine signaling, using a rat model.

BIOGRAPHICAL SKETCH

NAME: Williamson, John B

eRA COMMONS USER NAME: wjohnb

POSITION TITLE: Research Psychologist, Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
The Florida State University, Tallahassee Florida	BA	04/1996	Psychology
Virginia Polytechnic Institute and State University, Blacksburg, VA	PHD	05/2004	Clinical Psychology, Neuropsychology
University of Chicago, Chicago IL	Resident	07/2004	Clinical Psychology Internship
University of Illinois, Chicago	Postdoctoral Fellow	07/2006	Neuropsychology
University of Illinois, Chicago	Postdoctoral Fellow	07/2008	Neuroscience

A. Personal Statement

Dr. Williamson is an assistant professor in the Department of Neurology with affiliate appointments in Aging and Geriatric Research, and Clinical and Health Psychology. He also has a joint appointment as a Research Health Scientist at the Malcom Randall VAMC. He has conducted clinical neuroscience research that has incorporated neuroimaging, cognitive and autonomic data in the study of cerebrovascular disease (vascular cognitive impairment and vascular dementia) and traumatic brain injury. He has been engaged in funded research focused on vascular cognitive impairment over the past 10 years. This research, which has been aimed in part at examining factors leading to the development of vascular cognitive impairment including interactions between heart and brain, has reinforced the need to study patients prior to the emergence of vascular dementia, and also the value of disorders such as heart failure that provide a window into particular pathophysiological mechanisms, such as reduced cardiac output. Dr. Williamson is currently PI on an R56 funded grant designed to characterize the brain changes occurring as a result of improving cardiac output and cerebral perfusion as a means to better elucidating factors contributing to the development of and possible remediation of vascular cognitive impairment. CRT provides a unique method for accomplishing this. In his current role at the VA, he is the PI on a CDA-2 examining factors influencing autonomic disruption in patients with TBI in the context of white matter changes and emotional cognitive deficits. Dr. Williamson has over 40 peer-reviewed research articles related to aging, cerebrovascular disease, and autonomic disruption. He has been the PI or Co-I on multiple funded grants from the federal government (NIH and VA) that employ multimodal neuroimaging, neuropsychological, and psychophysiological methods to examine cognitive impacts of the effects of autonomic and white matter interactions of neurologically active processes. e completed postdoctoral work (NIH F32 funded study) with Dr. Stephen Porges training in psychophysiological methods and applications to disease models. He currently has pilot funding from the VA to examine the impact of a device (external vagal nerve stimulation) that impacts cardiovascular and brain activity to improve emotional cognition.

B. Positions and Honors

Positions and Employment

2012- Research Psychologist, Dept of Veteran Affairs, Gainesville FL
2008-2012 Research Health Scientist. Dept of Veteran Affairs, Gainesville FL
2009-2012 Research Assistant Professor, Department of Neurology University of Florida
2012- Assistant Professor (tenure track), Department of Neurology, University of Florida
2013- Assistant Professor Departments of Aging and Geriatric Research, and Clinical and Health Psychology
2013- Cognitive and Memory Clinical Translations Research Program Scholar, University of Florida

Other Experience and Professional Memberships

2002- Member, International Neuropsychological Society
2008- Member, Florida Society of Neurology
2013- Member, American Academy of Clinical Neuropsychology

C. Contributions to Science

1. *Advanced understanding of neurophysiological and cognitive consequences of mood and personality trait differences.* Dr. Williamson's early research focused on the role of differences in fronto-subcortical brain systems and laterality as a function of subclinical individual differences in mood and personality states and traits in the manifestation of autonomic mobilization

to regional brain tasks. We demonstrated that, in a college aged population, that high trait hostility resulted in elevated autonomic responses to tasks that recruited right hemisphere resources and that performance on these right hemisphere tasks was also degraded compared to their low trait hostility peers. Further we showed motor asymmetries in children and men with symptoms of depression and hostility. This research has been replicated multiple times by other groups and lead to a capacity model for understanding the interaction of personality traits on psychophysiological profiles that have been correlated to cardiovascular and cerebrovascular diseases later in life.

a) **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.
b) Demaree HA, Higgins D, **Williamson JB**, Harrison DW. Asymmetry in handgrip strength and fatigue in low- and high-hostile men. *International Journal of Neuroscience* 2002; 112:415-428.
c) Everhart DE, Harrison DW, Shenal BV, **Williamson JB**, Wuensch KL. Grip-strength, fatigue and motor perseveration in anxious men without depression. *Neuropsychiatry, neuropsychology and behavioral neurology* 2002; 15:122-142.
d) Emerson CS, Harrison DW, Everhart D, **Williamson JB**. Hand fatigue asymmetry in motor performances of depressed boys. *Neuropsychiatry, neuropsychology, and behavioral neurology* 2001; 14:130-134.

2. *Furthered the knowledge base of factors relating to cognition, emotion and autonomic disturbance in cerebrovascular disease and neurological injury.* Because of relationships between autonomic disruptions in trait hostility and other mood related features to later development of cardiovascular and cerebrovascular disease, Dr. Williamson became interested in research aimed at achieving a greater understanding of the bases of vascular dementia, and the contributions of vascular factors to the development of cognitive and emotional dysfunction in the elderly. This led to numerous studies of vascular cognitive impairment (dementia precursor) resulting in evidence showing the contribution of WMHs in VCI to cognition and also Dr. Williamson's early work on the use of DTI as a sensitive tool for assessing the relationship of regional white matter disruption on cognitive and mood indicators. Further, Dr. Williamson was funded by an F32 mechanism to study the relationship of regional white matter disease in stroke patients on mobilization of autonomic resources to perform cognitive and motor tasks.

a) **Williamson JB**, Nyenhuis DL, Pedelty L, Byrd S, Jhaveri M, Wang C, deTeledo-Morrell L, Sripathirathan K, Gorelick P. Baseline differences between Vascular Cognitive Impairment No Dementia reverters and nonreverters. *Journal of Neurology, Neurosurgery, and Psychiatry* 2008;79:1208-1214.
b) **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.
c) **Williamson JB**, Lewis GF, Grippo A, Lamb D, Harden E, Handleman M, Lebow J, Carter CS, Porges SW. Autonomic predictors of recovery following surgery: A comparative study. *Autonomic Neuroscience* 2010:156, 60-66.
d) **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.

3. *Elucidated impact of chronic lateralized stroke on spatial cognition as well as normal perturbations of sensory performance on laterality of spatial cognition and autonomic support.* These efforts led to several related lines of investigation to examine risk factors contributing to the development of spatial performance deficits in patients with cerebrovascular disease.

a) **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; 36:787-793.
b) Finney G, **Williamson JB**, Burtis DB, Drago V, Mizuno T, Jeong Y, Crucian G, Haque S, Heilman KM. Effects of chronic right hemisphere damage on the allocation of spatial attention: Alterations of accuracy and reliability. *Journal of the International Neuropsychological Society* 2015; 21:1-5.
c) 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.
d) 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; 100:79-85.

4. Provided theoretical model to advance the understanding of traumatic brain injury on manifestation of emotional dysregulation and also the impact of chronic emotional dysregulation on accelerated aging. TBI and PTSD are both critical issues that affect today's veteran population. Understanding neurological mechanisms of emotional disruption in this population is critical to developing appropriate treatments. The presented models provide clear testable hypotheses that may lead to effective diagnosis and treatments for this population. This work is ongoing (Williamson's CDA-2) and we are developing several lines of inquiry from the project including a CDA-2 submission this cycle (Damon Lamb) on tVNS and its impact in the context of our model on GABA and fMRI shifts in the limbic system in patients with mTBI/PTSD and the proposed merit submission integrating my mechanistic work (CDA-2) and the impact of tVNS on emotional cognition/

autonomic behavior.

a) **Williamson JB**, Heilman KM, Porges EC, Lamb DG, Porges SW. A possible mechanism for PTSD symptoms in patients with traumatic brain injury: central autonomic disruption. *Frontiers in neuroengineering* 2013.
b) **Williamson JB**, Porges EC, Lamb DG, Porges SW. Maladaptive autonomic regulation in PTSD accelerates physiological aging. *Frontiers in psychology* 2015.

My bibliography is available at: *http://www.ncbi.nlm.nih.gov/sites/myncbi/john.williamson.2/bibliography/48036192/public/?sort=date&direction=ascending*

D. Research Support

Ongoing Research Support

NIH 1R56HL127175-01 10/01/2015-10/01/2016
Brain and cognition effects of cardio resychronization therapy in heart failure.
The goal of this funding is to characterize brain changes as a result of improved cardiac output in heart failure including hemodynamic, task dependent regional brain activation and brain metabolic changes associated with improved cognitive performance and brain health.

VAMC 1 LK2RX000707-09 CDA-2 4/01/2012 – 03/31/2017
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 to the development of emotional dysregulation in veterans with PTSD. Preliminary analyses demonstrate independent (of PTSD symptom severity) contributions of TBI to emotional cognition. White matter and fMRI post-processing is ongoing.
Role: **PI**

VAMC BRRC Pilot Award 2014
External Non-invasive vagal nerve stimulation for the treatment of post-traumatic stress disorder.
The goal of this funding was to provide pilot data for the effect of transcutaneous vagal nerve stimulation on emotional cognition and physiology in patients with TBI and PTSD. Preliminary data analyses demonstrate alleviation of anxiety (state) in patients with TBI/PTSD.
Role: **PI**

VAMC Merit Review 10/2012-10/2016
Vertical Neglect
The goal of this funding is to examine the impact of unilateral stroke and aging on dorsal and ventral streams in vertical attention.
Role: **Co-I** (PI = Kenneth M. Heilman, MD)

VAMC Career Development Award 1 2013-2015
Traumatic Brain Injury and Motor Disorders
This career developmental award was designed to assess lateralized motor disorder presentations in patients with TBI. The central hypothesis was that corpus callosal injury would result in different forms of apraxia at the left and right hand driven by the laterality of motor control and communication deficits induced by the injury preventing normal performance of motor activities. The primary findings of this study did demonstrate laterality differences and this work is currently under review at a high impact factor journal.
Role: **Co-I** (PI = Adam Falchook, MD).

McKnight Brain Research Foundation Cohen (PI) 10/15/13-10/15/16
The ACTIVE Brain Study
The goal of this funding is to provide neuroimaging biomarkers of successful aging. Methods include MRI based measures including DTI, MRS (GABA, NAA, Cho, etc. . .), resting state fMRI, task dependent fMRI (CVMT, N-Back), NIH Tool Box, indices of personality trait and mood state, etc. . .
Role: **Co-I**

Completed Research Support

VAMC Merit Review 2008-2012
Approach-Avoidance Spatial Neglect
The goal of this funding was to examine the contribution of unilateral stroke to neglect.
Role: **Co-I** (PI = Kenneth Heilman)

1 F32 AG027648-01A1 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.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Woods, Adam Joshua

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

POSITION TITLE: Assistant Professor of Aging and Geriatric Research

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Alabama at Birmingham	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 the Assistant Director of the Center for Cognitive Aging and Memory in the Institute of Aging an Assistant Professor in the Department of Aging and Geriatric Research at the University of Florida. Dr. Woods is a cognitive neuroscientist by training, with a specific focus on cognitive aging in the human brain. His active program of research investigates neuroimaging-based biomarkers of cognitive impairment in older adults and novel non-invasive intervention strategies for enhancing cognitive function in adults with and without neurodegenerative disease. Dr. Woods has a strong background using multi-disciplinary cognitive neuroscience methodologies (MRI/fMRI, electrophysiology, non-invasive brain stimulation), extensive experience with aging-related disorders, and past research with neurological diseases. Dr. Woods has established a multimodal semi-automated neuroimaging pipeline using 1000 cores of the HiperGator super-computer at the University of Florida, specifically dedicated to the Center for Cognitive Aging and Memory. Dr. Woods collaborates on numerous ongoing funded projects using this pipeline for BOLD fMRI, MRS, DTI, and other imaging methods (e.g., 1U54 EB020403 ENIGMA project; R01AG044424). He currently leads both the Stimulated Brain and UTRACK studies in the CAM, has a K01 pending council review, an industry contract pending FDA approval, 2 R01s in review as PI, and multiple collaborative R01s, R21s, and a U01 under review as a co-investigator.

B. Positions and Honors

Positions and Employment

2010-2013 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 Scholar, University of Florida, Gainesville, FL

Academic and Professional Honors

2006-2009 National Science Foundation (NSF) Graduate Research Fellowship
2008 Research Enhancement Fund grant award for advanced dissertation research, GWU
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
2013-2015 Pepper Center/CAM-CTRP Scholar, Cognitive Aging and Memory Clinical Translational Research Program, University of Florida, Gainesville, FL
2014 Appointed Assistant Director of the Center for Cognitive Aging and Memory
2014 KL2 Scholar, Clinical Translational Science Institute
2014 Junior Fellow of the World Academy of Arts and Sciences
2015 Young Investigator Award in Neuromodulation, NYC Neuromodulation 2015, New York, NY, USA

C. Contributions to Science

Much of my current and past work focuses on successful cognitive aging interventions, in a variety of populations. This work has evaluated not only the cognitive and functional consequences of aging and various disorders, but also improvement in these processes following intervention. This line of my research attempts to identify novel markers (e.g., neuroimaging, etc.) and methods for prevention (e.g,. anti-inflammatory intervention) of age and disease related cognitive. This line of research is directly relevant to the current project.

a. Mark, V.W., **Woods, A.J.**, Mennemeier, M., Abbas, S., Taub, E. (2006). Cognitive assessment for CI therapy in the outpatient clinic. *Neurorehabilitation*, 21, 139-46.
b. **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**
c. **Woods, A.J.**, Cohen, R.A., Pahor, M. (2013). Cognitive frailty: frontiers and challenges. *Journal of Nutrition, Health, and Aging*. 17, 741-743. **PMCID: PMC4471842**
d. Anton, S., **Woods, A.J.**, Ashizawa, T., Barb, D., Buford, T., et al., Successful aging: Advancing the science of physical independence in older adults. *Aging Research Reviews*. 24, 304-27. **PMCID: PMC4661112**

For over five years, my work in neuroimaging has focused on understanding what brain networks underlie cognitive processes and how these processes are altered by age and medical disorders exacerbating aging of the human brain. This work has primarily used structural and functional magnetic resonance imaging and diffusion weighted imaging, but now includes magnetic resonance spectroscopy. Through multimodal neuroimaging, this work aims to identify markers predictive of cognitive decline in older adults, as well as markers of intervention effectiveness.

a. **Woods, A.J.**, Hamilton, R.H., Kranjec, A., Bikson, M., Minhaus, P., Yu, J., Chatterjee, A. (2014). Space, time, and causal inference in the human brain. *NeuroImage*, 92, 285-297. **PMCID: PMC4008651**
b. Yamamoto, N., Philbeck, J.W., **Woods, A.J.**, Gajewski, D., Chichka, D., Potollochio, S., Caputy, A. Medial temporal lobe roles in human path integration. (2014). *PLoS ONE*, 9(5): e96583. **PMCID: PMC4011851**
c. Seider, T., Gongvatana, A., **Woods, A.J.**, Porges, E., Chen, H., Cummings, T., Kahler, C.W., Monti, P.M., Cohen, R.A. Age exacerbates HIV associated white matter abnormalities. *Journal of Neurovirology*. In press. **PMCID: In process.**
d. Szynkowicz, S.M., McLaren, M.E., Kirton, J.W., O'Shea, A., **Woods, A.J.**, et al. (2015). Depressive Symptom Severity Is Associated with Increased Cortical Thickness in Older Adults. I*nternational Journal of Geriatric Psychiatry*. In press. **PMCID: In process.**

Over the past ten years, I have studied attentional processes in the brain using a variety of attention research methods in spatial neglect following stroke and health cognitive populations to understand the relative contributions of frontal and parietal systems in attention. My prior work in the relative contribution of frontal vs. parietal brain systems to attentional processing will be an important factor facilitating my contribution to the current grant.

a. 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, 1194-1211.
b. **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, 1406-12.
c. **Woods, A.J.**, Lehet, M., Chatterjee, A. (2012). Context modulates the contribution of time and space in causal inference. *Frontiers in Psychology*, 3, 371. doi: 10.3389/fpsyg.2012.00371 **PMCID: PMC3498891**
d. **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, 115-122. **PMCID: PMC3266979**

One area of in my prior work investigated the impact of stroke and aging on visual search and executive function. This work has spanned investigation of early development of visual search processes (age 2-18 years) to effects in later life (ages 60+) and following focal lesions to frontal and parietal brain systems. My background in age-related executive decline will be germane to the current project and interpretation of improvement following anti-inflammatory intervention.

a. Mark, V.W., **Woods, A.J.**, Ball, K.K., Roth, D.L., Mennemeier, M. (2004). Disorganized search is not a consequence of neglect. *Neurology*, 63(1), 78-84.
b. **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. **PMCID: PMC3275913**
c. **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. doi: 10.1016/j.actpsy.2013.03.008 **PMCID: PMC3651801**

d. Piedimonte, A., **Woods, A.J.**, Chatterjee, A. (2015). Disambiguating ambiguous motion perception: what are the cues? *Frontiers in Psychology*. 6: 902. **PMCID: PMC4496557**

Over the past five years, I have focused one arm of my research program on the technical and basic science application of non-invasive brain stimulation techniques as novel interventions for enhancement of cognitive function. This work includes both transcranial direct current stimulation and transcranial magnetic stimulation. To further the field, I co-founding a practical training course in tDCS that has trained over 500 researchers and students to safely and consistently apply this method of non-invasive brain stimulation. I have published several papers aimed at enhancing replicability and safety for the method, in addition to exploring its impact on a variety of cognitive functions in the brain. In addition, I was awarded the 2015 NYC Neuromodulation Young Investigator Award for my technical and educational contributions to the field. While this work is not central to the current grant, my experience in clinical translational methodology will be of significant benefit to the project.

a. Minhas, P., Bikson, M., **Woods, A.J.**, Rosen, A., Kessler, S. (2012). Transcranial direct current stimulation in the pediatric versus adult brain: A computational modeling study. *IEEE Xplore*: EMBC, 63: 859-862. **PMCID: PMC3641645**
b. Kessler, S., Minhas, P., **Woods, A.J.**, Rosen, A., Bikson, M. (2013). Dose considerations for transcranial direct current stimulation in children: a computational modeling study. *PLoS ONE*, 8(9): e76112. **PMCID: PMC3785412**
c. **Woods, A.J.**, Bryant, V., Sacchetti, D., Gervits, F., Hamilton, R. (2015). Effects of electrode drift on transcranial direct current stimulation. *Brain Stimulation*, in press. **PMCID: PMC4461479**
d. **Woods, A.J.**, Antal, A., Bikson, M et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clinical Neurophysiology*. In press. **PMCID: in process.**

Complete List of Published Work in MyBibliography: *http://www.ncbi.nlm.nih.gov/sites/myncbi/adam.woods.1/bibliography/45511051/public/?sort=date&direction=descending*

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**

P01AA019072 Monti (PI); Cohen (UF Site PI); Renewal 09/1/15-08/31/20
NIAAA
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**

U54 EB020403 Thompson (PI) 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**

R01AG044424 Clark (PI) 9/1/14-8/31/18
NIA
Neural mechanisms of dynapenia (The UNCODE Study)
This translational physiology study seeks to determine the neurological mechanisms (or contributors) to muscle weakness (i.e., Dynapenia) classically observed in older adults.
Role: **Co-I**

R56HL127175 Williamson (PI) 09/08/15-08/31/16
NHLBI
Brain and cognition effects of cardio resynchronization therapy in heart failure
The goal of this study is to evaluate cognitive and brain consequences of cardiac resynchronization therapy in heart failure patients using functional neuroimaging, magnetic resonance spectroscopy, & arterial spin labeling.
Role: **Co-I**

P30AG028740-06 Pahor (PI) 04/15/12-03/31/17
NIA
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**

P30 AG028740-06 Pahor (PI) 04/15/12-03/31/17
NIA
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
The ACTIVE Brain Study
The goal of this funding is to provide neuroimaging biomarkers of successful aging.
Role: **Co-I**

McKnight Brain Research Foundation (Wright; PI) 05/01/15-05/01/17
Neuroimaging Consortium Grant
UF Neuroimaging Consortium Cohort (Site PI: Cohen)
The goal of this project is to develop a cohort of 200 adults 85 years and older across four sites using multimodal neuroimaging and cognitive assessment – including structure MRI, DTI, and MRS, in addition to the NIH toolbox.
Role: **Co-I**

McKnight Brain Research Foundation (Cohen; PI) 10/1/15-09/30/17
Cognitive Assessment Consortium Grant
UF Cognitive Assessment Consortium Cohort (Site PI: Cohen)
The goal of this project is to develop norms for the NIH toolbox for adults 85 years and older in a cohort of 200 older adults across four sites using comprehensive cognitive assessment – including the NIH Toolbox Cognitive Battery and a variety of common cognitive and sensory measures. Novel measures will also be developed at each site.
Role: **Co-I**

McKnight Brain Research Foundation **Woods (PI)** 12/1/13-12/1/15
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)** 1/1/14-1/1/16
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**

F31AA024060 Bryant (PI) 5/1/15-4/30/18
NIAAA
Working memory: a critical factor underlying alcohol reduction intervention response
The goal of this project is to evaluate the role of working memory function in response to an effective alcohol reduction intervention (Motivational Interviewing) in HIV and non-HIV older adults. The student will receive training in functional and structural magnetic resonance imaging methods.
Role: **Co-Mentor**

NIA K99AG048762 Fazeli (PI) 9/15/14-5/31/16
A novel neurorehabilitation approach for cognitive aging with HIV
The goal of this study is to investigate the efficacy of cognitive training paired with tDCS on remediation of cognitive deficits in HIV positive older adults. Dr. Fazeli will receive training in aging and tDCS research methods.
Role: **Co-mentor**

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: Wu, Samuel S

eRA COMMONS USER NAME: gatorwu

POSITION TITLE: Professor and Associate Chair, Department of Biostatistics

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	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

I have published numerous journal articles at the cutting edge of trial design, particularly in the area of adaptive experiment. Also, 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; 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 served as Director of Biostatistics Core at the VA Rehabilitation Outcome Research Center (2002-2012), the VA Brain Rehabilitation Research Center (2002-2014), and the UF Claude D. Pepper Older American Independence Center (2013-present). Thus, my training and experience have given me extensive practical knowledge of the issues faced by clinical researchers.

In addition, collaborating with Dr. Chen from computer science, we invented some privacy-preserving data collection 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. We have jointly published 5 papers, mainly in the area of data confidentiality and privacy protection.

Furthermore, I have strong experience to identify good treatment practices in tertiary clinical care centers through NPF's Quality Improvement Initiative. Also, I have a strong team who assists me in data management and analysis. Dr. Pei, Mr. Dai and Mr. Chen have worked with me as programmer and statistical research coordinator for several years. All of them have solid training in statistics and proficient skills in REDCap, SAS and R software.

In summary, my role in the project builds logically on my experience, my position, my interests and my proven abilities.

B. Positions and Honors

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, University of Florida
2008-2010	Tenured Associate Professor, Dept. of Epidemiology & Health Policy Research, 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, the VA RORC and the VA BRRC
2013-present	Director of Biostatistics Core, the UF Claude D. Pepper Older American Independence Center
2014-present	Professor and Associate Chair, Department of Biostatistics, University of Florida

Other Experience and Professional Memberships

Member, American Statistical Association, 1998 - present
Member, the Institute of Mathematical Statistics, 1998 - present

C. Contribution to Science

1. My primary research focus is on adaptive design of clinical trials and simultaneous statistical inference. Adaptive designs use continuously updated data to modify certain aspects of a trial without undermining its validity. Simultaneous inference techniques enable experimenters to answer many related questions efficiently while maintaining valid type I error control. Both topics are particularly relevant to medical research, where study information arrives incrementally and multiple cohorts often are compared on multiple outcomes across multiple time periods. I have published numerous journal articles at the cutting edge of clinical trial design. My accomplishments include developing methods for incorporating pilot study information into the testing procedure of a subsequent trial; establishing confidence limits for hypothesis tests commonly performed in two-stage, drop-the-losers clinical trials; deriving improved methods of estimating treatment effects in adaptive trial designs.
   a. **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)**
   b. 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 - 1220.
   c. 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), 2804-2814. **(PMID:21823142)**
   d. **Wu SS**, Wang W, Yang MCK. (2010). Interval estimation for drop-the-loser designs, *Biometrika*, 97, 405-418.

2. Collaborating with Dr. Chen from computer science, we invented technologies for privacy-preserving collection and analysis of confidential data (US Provisional Patent Application #1123). The method enables 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. Moreover, in contrast to previous work that performs masking at a central place after all data are collected, our masking procedure is performed in a distributed way at each participant's data-generating device: one subject (or a group of subjects) at a time, giving great flexibility for incremental data collection and processing. We believe these technologies will greatly increase people's willingness to reveal sensitive information in medical and social studies.
   a. **Wu SS**, Chen SG, Burr D, and Zhang L. A New Data Collection Technique for Preserving Privacy, to appear in *Journal of Privacy and Confidentiality*.
   b. **Wu SS**, Chen SG, Burr D, and Zhang L. *New Technologies for Full Privacy Protection in Data Collection and Analysis, in Proceedings of 2014 Joint Statistical Meetings*, Boston, Massachusetts, USA, August 2014.
   c. Pei QL, Chen SG, Xiao Y, and **Wu SS**. *Privacy-preserving Data Collection and Its Application in HIV Studies*, to appear in Current HIV Research.
   d. Tao L, **Wu SS**, Chen SG, Yang MCK. *Energy efficient algorithms for the RFID estimation problem*. Proc. IEEE INFOCOM10, pp. 1019-1027, San Diego, CA, US, March 2010.

3. In addition to methodological research, I have established as a productive collaborator for researchers on neurological disorders and stroke. I have acted as lead statistician and Co-director of the Data Management and Analysis Center for several randomized controlled clinical trials. Among them, Locomotor Experience Applied Post-Stroke (LEAPS) was the largest of its kind funded by the NIH's National Institute of Neurological Disorders and Stroke and National Center for Medical Rehabilitation Research.
   a. 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)**
   b. 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. N*ew England Journal of Medicine*. 364(21):2026-2036.
   c. Okun, M. S., Fernandez, H. H.,**Wu, S. S.**, Kirsh-Darrow, L., Bowers, D., Suelter, M., Jacobson, C. C., Wang, X., Gordon, C. W., Zeilman, P., Romrell, J., Martin, P., Rodriguez, R. L., Foote, k. D. (2009). Cognition and Mood in Parkinson disease STN versus GPi DBS. The COMPARE Trial. *Annals of Neurology*, 65(5): 586-595.
   d. Kluding P, Dunning K, O'Dell M, **Wu SS**, Ginosian J, Feld J, McBride K. (2013). Foot drop stimulation versus ankle foot orthosis following stroke: 30 week outcomes, *Stroke*, 44, 1660-1669.

4. I have applied adaptive theory to military and sports topics as well. Mo et al. (2001) considered a decision-making problem in defense in which a number of missiles will be fired sequentially to destroy as many targets as possible. We provided a

backward induction proof showing that the myopic strategy, defined as choosing the next target as the one with the highest intact posterior probability, is the optimal strategy. And in a series of papers on sports statistics, we provided more efficient designs for baseball, football and World Cup tournaments by scheduling matches using accumulated competition results. These papers showed that adaptive designs are often far superior to current methods, and these results have potential applications to clinical trials with pair-wise comparisons.

a. **Wu SS**, Yang MCK. (2008). An improved double-elimination tournament with application to the FIFA world cup. *The Mathematical Scientist*. 33: 79-92.
b. Annis D,**Wu SS**. (2007). Improved college football scheduling using a modified Swiss system. *Chance*. 20(1): 6-10.
c. Annis D, **Wu SS**. (2006). A comparison of potential playoff systems for NCAA I-A football. *The American Statistician*. 60(2):151-157.
d. Mo S,**Wu SS**, Chen R, Yang MCK. (2001). Optimal sequential allocation with imperfect feedback information. *J. Applied Probability*. Vol. 38, No.1: 248-254.

5. I have also contributed in genetic linkage analysis and statistical inference for orthogonal saturated designs, both involving simultaneous hypothesis tests. We developed a statistical method for linkage analysis of polymorphic markers; a statistical model for detecting major genes responsible for growth trajectories; and a hierarchical model for detecting major genes based on progeny tests of outcrossing species. Wu et al. (2006) introduced the so-called shrinkage tests that have the best average power for testing multivariate linear hypotheses. For the first time in the area, Wu and Wang (2007) derived step-up simultaneous testing procedures that control the experiment-wise error rate at a given level in the strong sense for orthogonal saturated designs.

a. **Wu SS**, Wang WZ. (2007). Step-up simultaneous tests for identifying active effects in orthogonal saturated designs, *Annals of Statistics*, 35(1), 449-463.
b. **Wu SS**, Li HY, Casella G. (2006). Tests with optimal average power in multivariate analysis, *Statistical Sinica*, 16(1), 255-266.
c. **Wu SS**, Wu RL, Ma CX, Zeng ZB, Yang MCK, Casella G. (2001). A multivalent pairing model of linkage analysis in autotetraploids, *Genetics*, 159(3), 2001, 1339-50.
d. Wu RL, Li BL, **Wu SS**, Casella G. (2001). A maximum likelihood-based method for mining major genes affecting a quantitative character, *Biometrics*, 57(3), 2001, 764-768.

Complete List of Published Work in MyBibliography: *http://www.ncbi.nlm.nih.gov/sites/myncbi/1lu1dogjq8GAv/bibliography/47276308/public/?sort=date&direction=ascending.*

D. Research Support

Ongoing Research Support

Project Number: U01AG050499 — Dates of Approved/Proposed Project
Source: NIH — 09/01/2015 to 07/31/2018
Title of Project: *The ENRGISE Study*
This project will assess whether lowering low-grade chronic inflammation improves mobility in older persons.
Role: **Co-I**

Project Number: 1R01DK099334 — Dates of Approved/Proposed Project
Source: NIH — 05/01/2015 to 03/31/2020
Title of Project: *Biopsychosocial Influence on Shoulder Pain (phase 2)*
This project will determine mechanisms and efficacy of personalized pharmaceutical and personalized psychological pain interventions designed to target the genetic and psychological factors that comprise the high risk subgroup.
Role: **Co-I**

Project Number: 1R01DK099334 — Dates of Approved/Proposed Project
Source: NIH — 06/25/2014 to 05/31/2019
Title of Project: *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**

Project Number: P30AG028740 — Dates of Approved/Proposed Project
Source: NIH — 4/1/2013 to 3/31/2017
Title of Project: *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**

Project Number: KK-G000790 Dates of Approved/Proposed
Source: APTA 1/29/2013 to 1/29/2016
Title of Project: *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**

Project Number: NA Dates of Approved/Proposed
Source: NPF 4/1/2012 to 6/30/2016
Title of Project: *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**

Project Number: NA Dates of Approved/Proposed
Source: NIDRR 10/1/2011 to 9/30/2016
Title of Project: *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**

Project Number: NA Dates of Approved/Proposed
Source: Dept of Veterans Affairs 10/1/2011/2011 to 9/30/2016
Title of Project: *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)

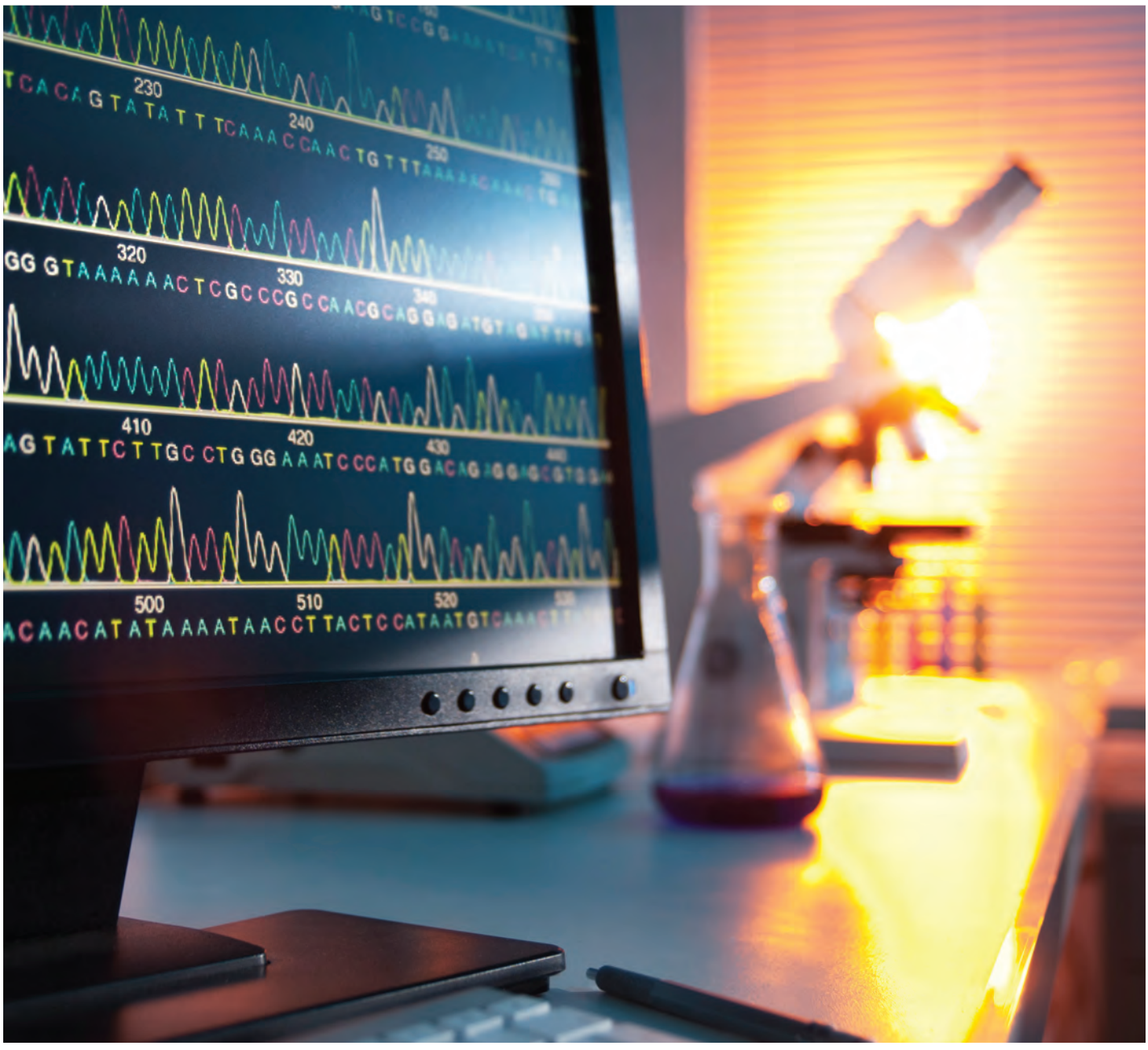
TSU Contracts Wu (PI) 10/01/2011 – 09/30/2013
Texas State University
Contract between Texas State University - San Marcos and UF
Provide statistical support in development of TSU's Air Force Medical Support Agency SG9S grant proposal titled *"Implications of Timing and Quality of Physical Therapy and Chiropractic Care on Low Back Pain Utilization and Costs in the Military Health System."*
Role: **PI**

1R01AR055899 George (PI) 07/01/2008 – 04/30/2013 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**

UF Award Wu (PI) 10/01/2011 – 07/30/2012 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**

R01 NS050506 Duncan (PI) 07/01/2005 - 06/30/2012 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



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0735-7044/15/$12.00 http://dx.doi.org/10.1037/bne0000093

Age-Related Impairments in Object-Place Associations Are Not Due to Hippocampal Dysfunction

Abigail R. Hernandez, Andrew P. Maurer, Jordan E. Reasor, Sean M. Turner, Sarah E. Barthle, Sarah A. Johnson, and Sara N. Burke
University of Florida

Age-associated cognitive decline can reduce an individual's quality of life. As no single neurobiological deficit can account for the wide spectrum of behavioral impairments observed in old age, it is critical to develop an understanding of how interactions between different brain regions change over the life span. The performance of young and aged animals on behaviors that require the hippocampus and cortical regions to interact, however, has not been well characterized. Specifically, the ability to link a spatial location with specific features of a stimulus, such as object identity, relies on the hippocampus, perirhinal and prefrontal cortices. Although aging is associated with dysfunction in each of these brain regions, behavioral measures of functional change within the hippocampus, perirhinal and prefrontal cortices in individual animals are often not correlated. Thus, how dysfunction of a single brain region within this circuit, such as the hippocampus, impacts behaviors that require communication with the perirhinal and prefrontal cortices remains unknown. To address this question, young and aged rats were tested on the interregion dependent object-place paired association task, as well as a hippocampal-dependent test of spatial reference memory. This particular cohort of aged rats did not show deficits on the hippocampal-dependent task, but were significantly impaired at acquiring object-place associations relative to young. These data suggest that behaviors requiring functional connectivity across different regions of the memory network may be particularly sensitive to aging, and can be used to develop models that will clarify the impact of systems-level dysfunction in the elderly.

Keywords: aging, functional connectivity, hippocampus, perirhinal cortex, prefrontal cortex

The majority of individuals over the age of 65 will experience cognitive decline that interferes with their quality of life and ability to maintain independence. Specifically, advanced age is accompanied by deficits in several distinct cognitive domains, such as spatial reference memory (Gallagher, Burwell, & Burchinal, 1993), executive function (Banuelos et al., 2014; Beas, Setlow, & Bizon, 2013; Bizon, Foster, Alexander, & Glisky, 2012), and object recognition (Burke, Ryan, & Barnes, 2012; Burke et al., 2011; Burke, Wallace, Nematollahi, Uprety, & Barnes, 2010). Importantly, age-associated cognitive dysfunction does not occur uniformly across these different domains, in part because there is profound variability amongst individuals in the behaviors that decline (Barense, Fox, & Baxter, 2002; Bizon et al., 2009; Burke et al., 2010; Davidson & Glisky, 2002; Gallagher et al., 1993; Morse, 1993).

Lesion studies have provided insights into the dissociable effects of functional loss within different brain regions on behavior, setting the foundation for hypotheses regarding the neural mechanisms of age-related cognitive decline. For example, the hippocampus (HPC) is critical for spatial reference memory (Morris, Garrud, Rawlins, & O'Keefe, 1982), but not necessary for object recognition memory (Forwood, Winters, & Bussey, 2005), or working memory at delays under 24 s, as measured by the delayed matching to position task (Sloan, Good, & Dunnett, 2006). The perirhinal cortex (PER) is integral to object recognition, but not involved in spatial reference memory (Norman & Eacott, 2005). Finally, the prefrontal cortex (PFC) supports working memory, but is not required for spatial reference memory (Sloan et al., 2006). In line with these lesion data, relationships between age-associated neurobiological alterations within the HPC (for review, see Burke & Barnes, 2010; Rosenzweig & Barnes, 2003; Samson & Barnes, 2013), PFC (Banuelos et al., 2014; Barense et al., 2002), and PER (Burke, Hartzell, Lister, Hoang, & Barnes, 2012; Burke et al., 2014) have been related to deficits in the specific cognitive function that is attributed to each of these brain regions.

Abigail R. Hernandez, McKnight Brain Institute, Department of Neuroscience, University of Florida; Andrew P. Maurer, McKnight Brain Institute, Department of Neuroscience, and Department of Biomedical Engineering, University of Florida; Jordan E. Reasor, Sean M. Turner, Sarah E. Barthle, and Sarah A. Johnson, McKnight Brain Institute, Department of Neuroscience, University of Florida; Sara N. Burke, McKnight Brain Institute, Department of Neuroscience, and Institute on Aging, University of Florida.

The first two authors contributed equally. This work was supported by the McKnight Brain Research Foundation, the University of Florida Research Seed Opportunity Fund, HHMI Science for Life Program, and the College of Medicine University Scholars Program. Additionally, we thank Amanda Schaerer, Nick Topper, Rodney Ndum, Joseph A. McQuail, and Jennifer L. Bizon for help with completing this article.

Correspondence concerning this article should be addressed to Sara N. Burke, Department of Neuroscience, College of Medicine, University of Florida, P.O. Box 100244, 1149 Newell Drive, McKnight Brain Institute, L1-100, Gainesville, FL 32610. E-mail: burkes@ufl.edu

Although biochemical and physiological changes within a single brain region correlate with behavioral deficits, no single neurobiological disruption can fully account for the wide spectrum of cognitive abnormalities observed in old age (Ash & Rapp, 2014). Moreover, localized disruptions within one structure plausibly affect higher-level interactions across neural systems either by impairing functional connectivity or provoking compensation. These systems-level interactions are particularly important in the context of age-related memory decline, as episodic and other explicit memories are among the most distributed processes in the brain (e.g., Nadel & Moscovitch, 1997; Squire & Alvarez, 1995). In fact, associating sensory stimuli with a spatial location or context is known to require dynamic interactions between the HPC, PER, and PFC (Barker, Bird, Alexander, & Warburton, 2007; Barker & Warburton, 2015; Jo & Lee, 2010a; Staresina & Davachi, 2008; Vilberg & Davachi, 2013). In this sense, dysfunction within a single locus of the memory network could impact the functional connectivity across brain areas. Thus, it is critical to develop behavioral models that can assay the integrity of the memory network on the systems level.

Recent research, using disconnection lesions, has emphasized the importance of interactions among the HPC, PER, and PFC for supporting the multimodal associations that are a hallmark of explicit memory. For example, in young animals, transient disconnection lesions of the HPC and PER impair the formation of object-place associations (Barker & Warburton, 2015; Jo & Lee, 2010a). Moreover, disconnecting the HPC and PFC leads to deficits in the encoding and retrieval of object-place associations (Barker & Warburton, 2015). These data suggest that quantifying an animal's ability to form and retain object-place associations across the life span could provide insight regarding memory network interactions in advanced age. In the current experiment, young and aged rats were monitored while they performed the object-place paired association task (OPPA; Jo & Lee, 2010a), which is believed to require HPC-PER-PFC interactions (Jo & Lee, 2010a, 2010b; Lee & Solivan, 2008). Individual aged rats with intact performance on the Morris water maze test of spatial reference memory (Morris, 1984) were significantly impaired on the OPPA task. HPC dysfunction, therefore, cannot fully account for performance declines on a task that requires HPC-PER-PFC interregion communication.

Method

Subjects

A total of 14 young (4–6 months old) and 18 aged (22–26 months old) male rats were cross-characterized on the Morris water maze test of spatial reference memory (Morris, 1984) and the object-place paired association task (OPPA; Jo & Lee, 2010b). Both Fischer 344 (F344; $n = 13$; four young, nine aged) and Fischer 344 x Brown Norway F1 hybrid (F344xBN; $n = 19$; ten young, nine aged) rats from the NIA colony at Taconic Farms were used. Each rat was housed individually and maintained on a 12-hr light/dark cycle with behavioral experiments performed exclusively during the dark phase of the cycle. During OPPA behavioral testing, rats were food-restricted on moist chow to 85% of their free-feeding weight, with access to water ad libitum. All experimental procedures were performed in accordance with National Institutes of Health guidelines and were approved by Institutional Animal Care and Use Committees at the University of Florida.

Apparatus and Testing Objects

A two-arm maze (see Figure 1), similar to the maze used by Jo and Lee (2010a, 2010b), was constructed from wood and sealed with waterproof black paint. A poster board was used to separate the two arms and ensure that the rat could not see the opposite arm. Distinct salient visual cues were affixed to the divider on each side in order to clearly differentiate the two arms of the maze. The arms radiated off a starting platform that was 48.3 cm in diameter. Each arm was 84 cm long and had a rectangular choice platform (31.75 cm × 24.13 cm) attached at the end. The choice platforms each contained two food wells (2.5 cm in diameter) that were recessed into the maze floor by 1 cm. The arms and choice platforms were contained within 6.4 cm raised walls to prevent the rat from exiting the testing apparatus. To dampen the influence of extraneous noise on behavior, a white noise machine was used during behavioral training and testing.

Two distinct objects were presented to individual rats during testing on the OPPA task; a plastic turtle and a ceramic baby figurine were used for one cohort, and an owl and a girl figurine were used for a second cohort (see Figure 2). There was no effect of cohort on OPPA task performance, $F(1,28) = 0.21$, $p = .65$; nor did cohort interact significantly with age group, $F(1,28) = 0.01$, $p = .98$. Both sets of object pairs were distinct in color, shape and texture. The entire maze and both objects were cleaned with 70% ethanol solution between each testing session. The same two-arm maze was used for testing animals on the control object discrimination and left-versus-right side discrimination conditions. For these control conditions, testing occurred within a single arm, while the opposing arm was blocked to prevent the rat from reaching the opposite choice platform (Figure 1B and C).

The Morris water maze task was carried out in a pool 1.83 m in diameter that contained a platform 12 cm in diameter. For training trials and probe tests of reference memory, the platform remained in one location, while for cued trials to assess visual function, the platform was moved to one of four different locations. The pool was filled with water at ~27 °C to a depth of 2 cm above the platform. White nontoxic tempera paint (Crayola, Easton, PA) was added to the water to obscure the platform location for reference memory trials. Visual cues were affixed to black curtains surrounding the pool. Water 2100 software (HVS Image, Buckingham, United Kingdom) was used to track the rats' position throughout training and testing.

Handling and Habituation

Upon arrival to the facility, rats were given 7–14 days acclimation with free access to food. Following this period, rats were handled daily for several days before being tested on the Morris water maze and Spontaneous Object Recognition Task (data not shown). Prior to water maze testing, F344 rats were dyed with ammonia-free black hair colorant (Revlon, New York, NY) to improve tracking in the water maze apparatus. Rats were then handled an additional 1–2 days in the water maze room for further habituation to the testing procedures. All animals were transported to and from testing rooms in ventilated plastic bins.

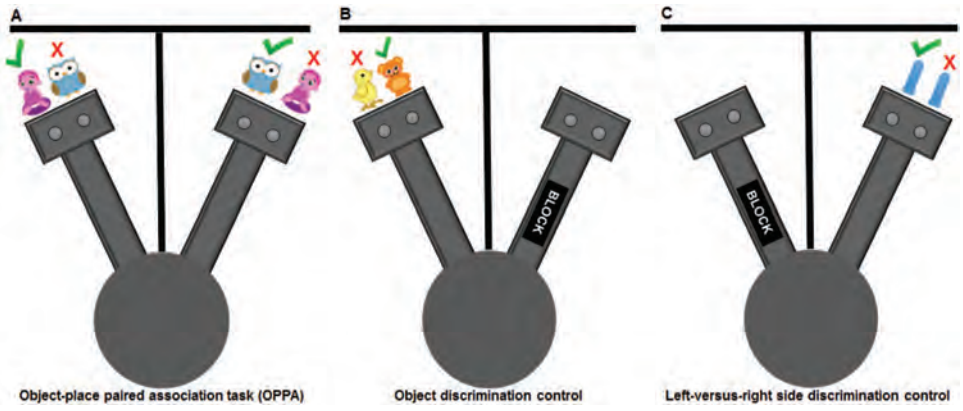

Figure 1. Schematic of the object-place paired association (OPPA) task and discrimination control conditions. A two-arm radial maze was used for all testing conditions. **(A)** During testing on the OPPA task, rats were required to discriminate between two distinct objects (e.g., girl figurine or owl); however, in the left arm the girl figurine was rewarded (green check mark) and not the owl (red X). In the right arm, the rats had to discriminate between the same two objects but the owl was the correct choice and the girl figurine was not rewarded, requiring rats to use an object-in-place rule. The placement of rewarded objects over the left or right food wells varied pseudorandomly across trials. **(B)** For the object discrimination control task, one arm of the maze was blocked and the rat shuttled between the central circle and choice platforms between discrimination trials. The same object was always rewarded (bear; green check mark). **(C)** The left-versus-right side discrimination control was carried out in the opposite arm of the maze than that used for object discrimination testing. For each trial, two identical objects covered both food wells and a single well on one side was always rewarded across trials (e.g., left well, green check mark). Whether the left or right well was the correct choice varied between rats. See the online article for the color version of this figure.

Morris Water Maze Test of Spatial Reference Memory and Visible Platform Task

Assessment of spatial reference memory followed the procedures of Bizon et al. (2009). Briefly, each rat received three trials a day for 8 consecutive days. For each trial, rats were placed into the water facing the wall of the maze at one of four equally spaced start positions (north, south, east, or west). The start positions were varied in a pseudorandom fashion such that all rats started from each of the locations the same number of times. Rats were allowed to swim for up to 90 s in order to locate the platform. If they failed to find the platform after 90 s, the trial would end, and the experimenter would guide the rat to the goal location where they would remain for 30 s. After each trial, rats were placed in the plastic holding bin for a 30-s intertrial interval. Every sixth trial was a probe test of retrieval in which the platform was lowered to the bottom of the maze for the first 30 s. These probe trials were used to quantify the proximity of the swim path to the target location (cumulative search error; Gallagher et al., 1993). A training block was considered the five trials conducted on 2 consecutive days (three trials and two trials, respectively). The probe trials that were conducted after each training block were used to calculate a Spatial Learning Index, which is a weighted sum of the cumulative search error during probe Trials 2–4 (Spatial Learning Index = probe $2^{*}1.25$ + probe $3^{*}1.6$ + probe $4^{*}1.7$) as previously described (Gallagher et al., 1993).

After completion of the reference memory task, rats were given a single session with six trials of cue training. In this session, rats were trained to escape to a visible platform that was moved to a different maze quadrant for each trial. Rats were given 90 s to reach the platform and were allowed to remain there briefly before a 30-s intertrial interval. These trials were used to control for sensorimotor impairments or poor motivation that could confound the data.

Object-Place Paired Association (OPPA) Task

Following water maze testing, rats were placed on a restricted feeding schedule. Once target weights were reached (over 1–2 weeks), animals were habituated to the OPPA testing maze for 10 min per day for 2 days. Froot Loop pieces (Kellogg Company, Battle Creek, MI) were scattered throughout the maze to encourage exploration of the entire apparatus. Rats were trained to visit alternate arms of the maze by placing a single cereal treat in one random food well on either the left or right arm. Each rat began the OPPA behavioral task once it could successfully alternate arms 32 times within 30 min.

Testing on the OPPA task was carried out as previously described (Jo & Lee, 2010a). The first trial was initiated by placing the two objects over the food wells of one of the radial arms while the rat was placed in the opposite arm. The starting arm was counterbalanced across testing sessions. The same two objects were always presented in both arms of the maze; however, the position of the rewarded object within the choice platform of an arm (left or right) pseudorandomly varied across trials (Figure 1A). Successful completion of the OPPA task required rats to develop an object-in-place rule by learning to associate the different arms with distinct rewarded objects. In other words, one object was always rewarded in one arm while the alternate object was rewarded in the opposite arm. The rat only received a cereal treat if they selected the correct object, which required the displacement of the figurine to access the hidden food well. If an incorrect

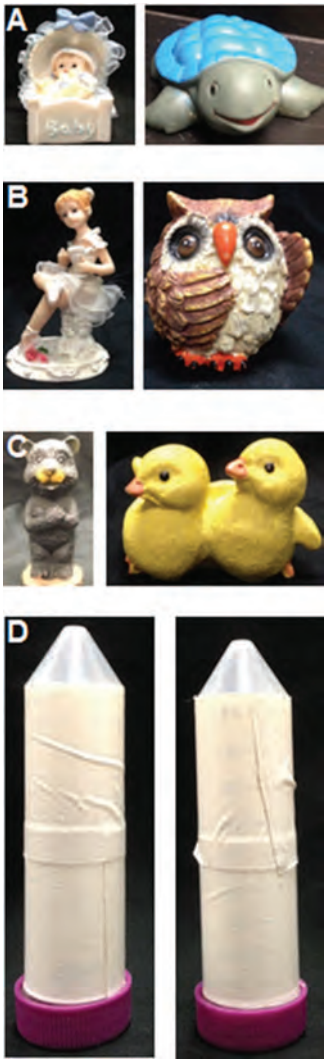

Figure 2. Stimulus sets. Object stimuli used for the **(A)** first and **(B)** second cohort of rats tested on the object-place paired association task (OPPA), **(C)** for control object discrimination, and **(D)** control left-versus-right side discrimination. See the online article for the color version of this figure.

choice was made, the objects and food reward were immediately removed from the platform preventing the rat from selecting the alternate figurine. Following the completion of a trial, the experimenter moved the objects to the opposite arm. Consecutive trials required alternation between the two arms. If a rat failed to alternate, returning to the previously tested arm, the trial was logged as a working memory error. Criterion performance was achieved once a rat was able to select the correct object for a minimum of 26 per 32 trials, with at least 13 correct choices in each arm on 2 consecutive days. Rats were tested 5 to 6 days a week until reaching criterion for the task. A retention test was administered 48 hr after each rat had successfully achieved criterion performance.

To ensure potential age effects were not confounded by sensorimotor impairments or differences in motivation, upon completion of the OPPA task, all rats were further screened in simple object discrimination (Figure 1B) and left-versus-right side discrimination tasks (Figure 1C). The control discrimination tasks were conducted in a single arm of the radial maze. Prior to testing, the rats were rehabituated to the arena and trained to shuttle back and forth between one choice platform and a reward placed adjacent to a blockade in the central circular platform of the maze. For the object discrimination, two nonidentical novel objects were placed over the food wells in the choice platform. One of the objects, independent of location, covered a rewarded food well. Following an incorrect selection, the objects and reward were removed and the rat was required to exit the testing arm prior to initiating the next trial. Once a correct choice was made for at least 26 out of 32 trials on 2 consecutive days, the rat began testing on the left-versus-right side discrimination task.

Left-versus-right discrimination testing was conducted in the arm not used for the control object discrimination task. In order to disambiguate the control tasks, two identical novel objects were used. The rewarded side was counterbalanced across rats, with approximately half the rats rewarded for selecting the left object while the rest were rewarded for right object selection. Criterion performance was correct selection of the appropriate side (left-vs.-right) 26 out of 32 times on 2 consecutive days.

Statistical Analyses

Prior to acquiring the object-in-place rule, rats often show a response bias for a particular side (Jo & Lee, 2010a, 2010b). Therefore, indices of a bias for choosing a single object (object bias) or a food well (left-vs.-right side bias) were calculated for each rat. The object bias was the absolute value of the (total number of Object 1 choices − total number of Object 2 choices)/(total number of trials), while the side bias was the absolute value of the (total number of left choices − total number of right choices)/(total number of trials). For the OPPA task, group means of five dependent variables (incorrect trials to criterion, object bias, side bias, working memory errors and percent correct responses during retention testing) were examined using analyses of variance (ANOVA) with the between subjects factors of rat strain (F344, F344xBN), age (young, aged), and task type (OPPA, object control, left-vs.-right side control). The group means of water maze data for the training trials (corrected integrated path length; CIPL), and the Spatial Learning Index (calculated from the cumulative search error; Gallagher et al., 1993) were also examined using ANOVAs. All analyses were performed with Statistical Package for the Social Sciences (SPSS) v22. Statistical significance was considered at p values less than 0.05. Individual group differences were assessed using either the Tukey's HSD test or planned orthogonal contrasts in cases where specific a priori hypotheses had been made regarding group differences. The relationship between OPPA task performance and spatial reference memory was examined using Pearson's correlation coefficients.

Results

Object-Place Paired Association (OPPA) Task Performance

The average number of days it took animals to reach criterion performance on the OPPA task was 11.1 for the young rats (95%

confidence interval [8.6, 13.6]) and 14.3 for the aged rats (95% confidence interval [10.8, 17.8]), which differed significantly $T_{(30)} = 2.93$, $p < .01$). The mean percent correct responses during the first 13 days of testing for the young (black) and aged (gray) rats is shown in Figure 3A. The mean numbers of incorrect trials made by each age group on the OPPA task, as well as the control object discrimination and left-versus-right side discrimination conditions are presented in Figure 3B. Age had a significant effect on the number of incorrect trials made during the OPPA task, $F(1, 28) = 12.17$, $p < .01$, but not during the object discrimination control, $F(1, 28) = 0.02$, $p = .89$, or the left versus right side control, $F(1, 28) = 0.59$, $p = .46$. Together, these data show that, while aged and young rats perform comparably at discriminating between a pair of objects and the left-versus-right food wells, aged animals are selectively impaired at acquiring the object-in-place rule that is necessary for OPPA task performance. Rat strain (F344 vs. F344xBN) did not significantly affect OPPA performance, $F(1, 28) = 0.21$, $p = .65$, nor did the interaction between strain and age reach statistical significance, $F(1, 28) = 0.01$, $p = .98$. These data indicate that aged animals of both F344 and F344xBN hybrid strains have similar deficits in forming object-place associations.

In order to determine if there was a subset of aged rats that were not impaired at acquiring object-place associations, aged rats that performed within 1 *SD* of young rat performance were identified (Figure 3C; hashed circles). Six of the 18 aged rats were in the normative range of young rat performance. Notably, two aged F344 and four aged F344xBN hybrid rats met this criterion for being aged-unimpaired. The stability of the estimated range of performances across the population of young animals was further validated by bootstrapping the sample of young rat data (randomly resampling the data with replacement) to generate a new sample ($n = 14$), from which descriptive statistics were recalculated. Aligned with standard Monte Carlo simulations for resampling, this process was repeated 2,000 times to generate a distribution of the estimated population confidence interval and standard deviation (DiCiccio & Efron, 1996; Efron, 1987), which is consistent with the application of this method to behavioral data (Kernan & Mullenix, 1991). Again, six of the 18 aged rats had performance

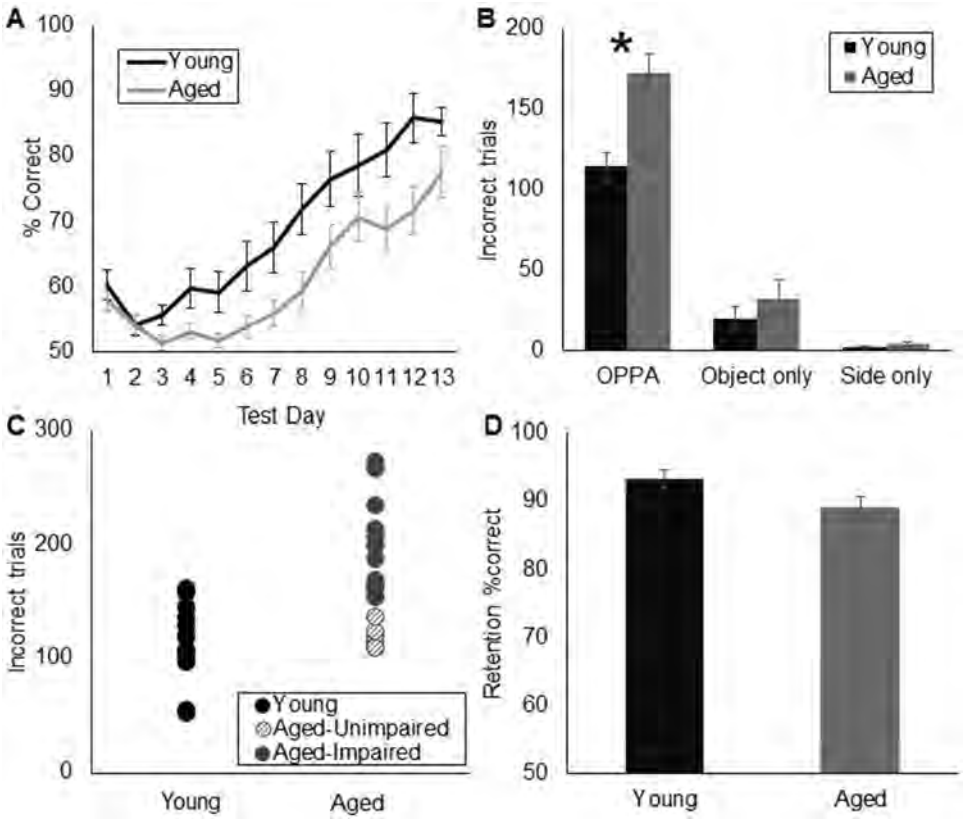

Figure 3. Object-place paired association (OPPA) task performance. **(A)** Percent of correct responses (Y-axis) on the OPPA task for each of the first 13 days of testing (X-axis) in young (black) and aged (gray) rats. **(B)** Mean number of incorrect trials made prior to reaching criterion performance (Y-axis) for young and aged rats on OPPA, object discrimination, and left-versus-right side discriminations tasks. Performance between age groups was significantly different for the OPPA task ($p < .01^{*}$), but not for the control object ($p = .89$) or left-versus-right side ($p = .46$) discrimination conditions. **(C)** Individual performance of young and aged rats on the OPPA task. Four aged rats performed within the normative range of young animals (unimpaired; hashed circles). **(D)** Percent of correct responses (Y-axis) on the 48-hr delay OPPA retention test was not significantly different between age groups ($p = .06$; X-axis). Error bars show +/−1 standard error of the mean.

values that fell within the estimated normative range of the young animal bootstrapped data. Importantly, the bootstrapped and raw sample data identified the same six rats as unimpaired.

Following the 48-hr delay, both young and aged rats were able to retain the object-in-place association with aged and young rats having a mean percent correct of 89% and 93%, respectively. Thus, for both age groups retention performance was above the criterion performance of 81.25%. Although there was a trend toward an effect of age on retention, the 4% difference in performances between the age groups did not reach statistical significance (Figure 3D; $T_{(31)} = 1.98$; $p = .06$; independent-samples). The observation that aged rats did not drop below criterion performance following a 48-hr delay is consistent with a previous report, which showed that aged animals retained information regarding reward-object stimulus associations similar to young even when acquisition rates are slower (Burke et al., 2011).

A potential contribution of distinct response biases between age groups to OPPA task performance was determined by examining the mean response index calculated from the left-versus-right side bias and the object bias (see Figure 4). A bias index of 1 would indicate an absolute preference for one stimulus over the other (e.g., the rat only chose the right side in each arm, or chose the same object for each trial), while 0 would be no bias. Both young and aged rats were significantly more likely to display a side bias relative to an object bias prior to learning the object-in-place rule, $F(1, 28) = 67.49$, $p < .001$; repeated-measures. The mean side bias as a function of test day for the young and aged rats for the first 13 days of testing in shown in Figure 4A. In both age groups, there was a tendency for the side bias to increase over the first 5 days of testing and then decrease as the animal got closer to reaching criterion. This pattern was not observed for the object bias (Figure 4B), in which a rat's tendency to select one object over another did not change over testing. Although both age groups were more likely to show a side bias, there was no significant effect of age on the response bias index, $F(1, 28) = 2.55$, $p = .12$. Moreover, there was no interaction between age and the type of bias (side vs. object; $F(1, 28) = 3.20$, $p = .1$). Together, these data indicate that the difference between young and aged rat OPPA task performance was not due to a perseveration of object or left-versus-right selection in the aged rats. Rather, it appears that aged rats were selectively impaired at forming object-place associations.

The number of working memory errors during the entire extent of OPPA testing also did not change as a function of age (Figure 4D). Most rats only made two to four of these errors in total before reaching criterion performance, and this did not differ significantly between young and old rats ($T_{(30)} = 0.92$, $p = .37$; equal variances not assumed). Thus, both age groups were able to track their

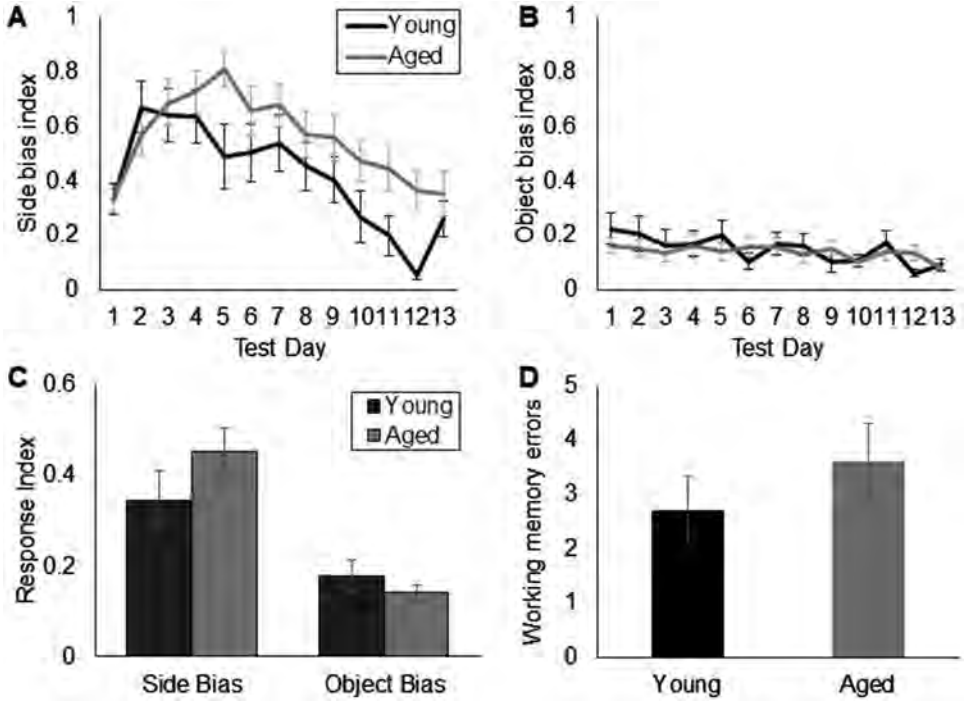

Figure 4. Response bias indices and working memory errors. **(A)** Mean left-versus-right side bias index (Y-axis) for young (black) and aged (gray) rats as a function of the first 13 test days (X-axis). **(B)** Mean object bias index (Y-axis) for young and aged rats for each of the first 13 test days (X-axis). **(C)** Mean response index across all test days (Y-axis) for the left-versus-right side and object biases. Prior to reaching criterion performance, all rats were significantly more likely to respond with a side bias than an object bias, $F(1,28) = 67.49$, $p < .001$; repeated-measures, but these response index values did not differ significantly with age, $F(1, 28) = 2.55$, $p = .12$. **(D)** Mean number of working memory errors (Y-axis) made by young (black) and aged (gray) rats before reaching criterion performance. The number of working memory errors did not differ significantly between age groups ($T_{(30)} = 0.92$, $p = .37$). Error bars show +/−1 standard error of the mean.

previous arm location in order to proceed to the correct arm on a subsequent trial, indicating that aged rats retained an ability to recognize their current location and use that information to guide appropriate behavior.

Morris Water Maze Test of Spatial Reference Memory

The performance of rats on the spatial reference memory version of the Morris swim task was similar across age groups. Cumulative search error during the four probe trials did not differ significantly between young and aged rats (Figure 5A); $F(1, 28) = 0.16$, $p = .69$. Critically, all rats were able to learn the platform location as evidenced by a significant decrease in cumulative search error across probe Trials 1–4, $F(1, 28) = 19.03$, $p < .001$, repeated-measures. This observation suggests that the lack of an age effect on water maze performance was not due to an overall inability of all rats to perform the task. In addition to age, the variable of strain did not have a significant effect on cumulative search error, $F(1, 28) = 0.67$, $p = .42$. Consistent with these findings, in this cohort of animals, the old rats did not have significantly longer mean corrected integral path length (CIPL) scores during the training trials compared with the young rats (Figure 5B); $F(1, 28) = 0.26$, $p = .87$. Moreover, there was a significant effect of testing block on the mean CIPL scores, $F(3,84) = 17.44$, $p < .001$ (repeated-measures), indicating that overall both the young and aged rats showed improved performance as a function of training. Planned comparisons revealed that this difference was due to significantly lower CIPL values across each subsequent testing block ($p < .05$ for all comparisons; repeated contrasts). There was not a significant interaction effect of testing block with age group, $F(1, 28) = 0.64$, $p = .43$ (repeated-measures) or with strain, $F(1, 28) = 0.02$, $p = .88$ (repeated-measures). Together, these data indicate that young and old rats of

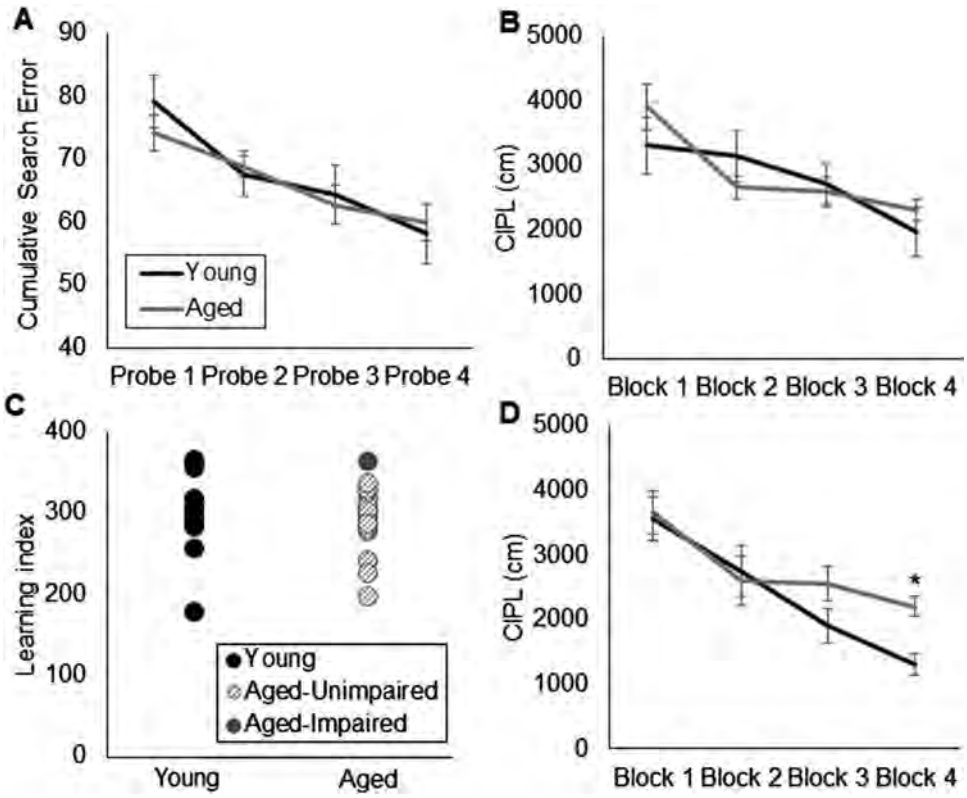

Figure 5. Morris water maze test of spatial reference memory. **(A)** Cumulative search error (Y-axis) across all probe trials (X-axis) in young (black) and aged rats (gray). Cumulative search error during the 4 probe trials did not differ significantly between age group, $F(1,28) = 0.16$, $p = .69$, and all rats showed significantly reduced search errors after training, $F(3,84) = 19.03$, $p < .001$; repeated-measures. **(B)** Mean corrected integrated path length (CIPL) values (Y-axis) for young (black) and (aged) rats across training blocks (X-axis). CIPL values decreased as a function of training block, $F(3,84) = 17.44$, $p < .001$ (repeated-measures), which did not differ significantly with age, $F(1,28) = 0.64$, $p = .43$. **(C)** Individual Spatial Learning Index values (Y-axis) for young and aged rats calculated from the cumulative search error on probe Trials 2–4. Learning index also did not significantly differ between age group, $F(1,28) = 0.34$, $p = .56$. Moreover, only one aged rat performed outside of the normative range of the young group (impaired, solid circle). **(D)** CIPL values (Y-axis) for a different cohort of young (black) and (aged) rats across training blocks (X-axis). In this group of rats, which were not tested on the OPPA task, there was a significant effect of age on CIPL values during training Block 4 ($T_{(24)} = 2.99$, $p < .01$). Error bars show +/−1 standard error of the mean.

both strains showed similar improvement in behavioral performance over the course of water maze training.

An additional means to evaluate water maze performance is to calculate a Spatial Learning Index (Gallagher et al., 1993). The learning indices of all individual rats are shown in Figure 5C. Only one aged rat performed outside of the normative range of the young animals (> 1 *SD*). Consistent with the lack of an age effect on CIPL and cumulative search error values, the Spatial Learning Index was also not significantly different between young and aged rats, $F(1, 28) = 0.34$, $p = .56$, or between strains, $F(1, 28) = 3.48$, $p = .08$. Finally, there was no significant interaction effect between age and rat strain on Spatial Learning Index values, $F(1, 28) = 0.10$, $p = .76$.

One prior study has shown that age-associated spatial reference memory deficits may not be evident in F344xBN hybrid rats even at 30 months of age (Hebda-Bauer, Morano & Therrien, 1999), while others show evidence of impairments by 24 months (Markowska & Savonenko, 2002; McQuail & Nicolle, 2015). Moreover, deficits are typically observed in F344 rats by 24 months of age (Shen & Barnes, 1996). The majority of rats in this particular cohort, however, maintained performance on the water maze task. Importantly, when a different cohort of rats were tested on the spatial reference version of the water maze task during the same time frame as the animals in the current study, a significant effect of age was detected for the CIPL score on Block 4 of testing (Figure 5D; $T_{(24)} = 2.99$, $p < .01$). These data suggest that the rats in the current study included a disproportionate number of animals that did not have hippocampal impairments.

The absence of an age effect on water maze performance for the rats tested on the OPPA task was not due to low internal reliability, as the CIPL scores were significantly correlated with the Spatial Learning Index (Figure 6A; $R_{(31)} = 0.41$, $p < .02$; Pearson's). The sensorimotor function of young and aged rats was also similar, as indicated by the lack of a significant difference in swim path length during the visually cued trials (Figure 6B; $T_{(30)} = 0.41$, $p = .68$). Collectively, these data indicate that the aged rats in this study did not display behavioral deficits on a HPC-dependent task,

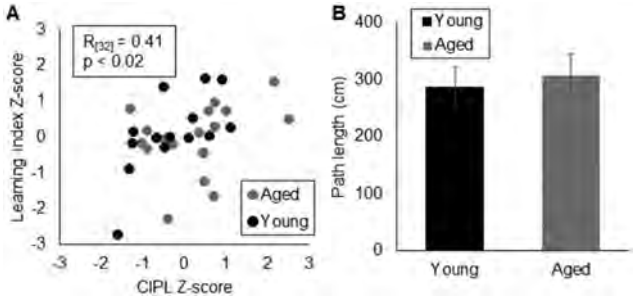

Figure 6. Validity of Morris water maze test data. **(A)** Relationship between normalized (Z-score transformed) CIPL values for training Block 4 (X-axis) and Spatial Learning Index (Y-axis). These two measures were significantly correlated ($R_{(31)} = 0.41$, $p < .02$; Pearson's), demonstrating the internal reliability of this water maze procedure. **(B)** Mean path length (Y-axis) of rats during the visually cued version of the water maze was not significantly different between age groups ($T_{(30)} = 0.41$, $p = .68$). This indicates that the aged rats did not suffer from gross sensorimotor impairments. Error bars show +/−1 standard error of the mean.

supporting the conclusion that dysfunction within the HPC cannot fully account for age-related impairments on the OPPA task.

Relationship Between Spatial Reference Memory and Object-Place Paired Association Task Performance

In order to further examine whether or not spatial reference memory was related to OPPA task performance, both of which rely on the HPC, the correlation coefficient between the normalized performance measures (z-scores) on these tasks was obtained. The mean CIPL values during Block 4 did not significantly correlate with the number of incorrect trials that rats made prior to reaching criterion performance on the OPPA task (Figure 7A; $R_{(31)} = -0.23$, $p = .20$; Pearson's). Similarly, the Spatial Learning Index did not significantly correlate with the number of incorrect trials that rats made prior to reaching OPPA criterion (Figure 7B; $R_{(31)} = 0.02$, $p = .91$; Pearson's). Thus, while both spatial reference memory and object-place associations require the HPC, dysfunction in this brain structure alone cannot account for age-associated impairments on the OPPA task.

The performance measures on the water maze and the OPPA task were further compared by calculating the effect size of age differences on each task. The effect size for the difference in means between young and aged rats was 0.043 (Cohen's *d*) for the Spatial Learning Index of water maze performance and 1.36 (Cohen's *d*) for the number of incorrect trials on the OPPA task. The large effect size of age group on the interregion dependent OPPA task, relative to the small effect size of the HPC-dependent water maze test of spatial reference memory suggests that behaviors requiring the HPC, PER, and PFC and functional connectivity among these structures may be more sensitive for detecting age-related cognitive deficits than tasks that assay behaviors more specifically reliant on the function of single brain regions.

Discussion

The current experiments demonstrate that aged animals with intact performance on the Morris water maze test of hippocampal (HPC)-dependent spatial reference memory are impaired in acquiring object-place associations (Figure 3). The dissociation of deficits in acquisition of object-place associations versus intact spatial reference memory in aged animals provides important insights with regards to aging. Lesion data have shown that the prefrontal cortex (PFC; Lee & Solivan, 2008) and the perirhinal cortex (PER; Jo & Lee, 2010a, 2010b) are both necessary for OPPA task, but not water maze, performance (Machin, Vann, Muir, & Aggleton, 2002; Sloan et al., 2006). Thus, these data support the hypothesis that age-associated disruptions in the PER (Burke et al., 2012; Burke et al., 2014) and/or PFC (Banuelos et al., 2014; Barense et al., 2002) are likely contributing to the performance deficits of aged animals on the OPPA task. Future experiments will need to cross-characterize rats on the OPPA task and PER/PFC-dependent behaviors in order to determine the extent to which the functional integrity of these structures contributes to an animal's ability to form object-place associations.

The current data provide additional insight regarding the ability of different behavioral assays to detect age-related dysfunction. Specifically, in this cohort of rats, age did not have a significant effect on HPC-dependent water maze performance,

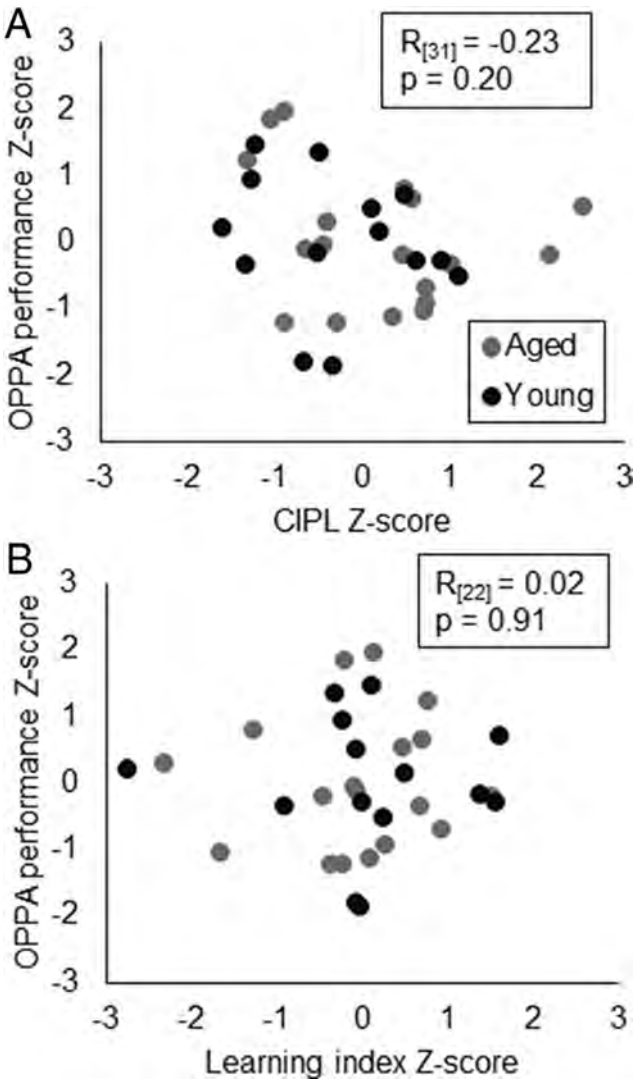

Figure 7. Spatial reference memory and object-place paired association (OPPA) task performance. **(A)** Z-scores of training block 4 CIPL values (Y-axis) did not significantly correlate with z-scores for the number of incorrect trials made on the OPPA task ($R_{(31)} = -0.23$, $p = .20$; Pearson's). **(B)** Z-score values of the Spatial Learning Index also did not significantly correlate with Z-score values for numbers of incorrect trials on the OPPA task ($R_{(31)} = 0.02$, $p = .91$; Pearson's).

and the effect size of the difference between means for the young and aged rats was small (0.043). In fact, the observation that only one of 18 aged rats tested in the current experiment performed 1 *SD* below the mean of the young animals is somewhat surprising. One prior study has shown that age-associated spatial reference memory deficits may not be evident in F344xBN hybrid rats even at 30 months of age (Hebda-Bauer, Morano, & Therrien, 1999). Moreover, it is well documented that aged rats exhibit a wide range of performances on the Morris water maze (e.g., Bizon et al., 2009; Gallagher et al., 1993). Thus, it is conceivable that within the cohort tested here, there was a disproportionate number of spatially unimpaired animals. In support of this idea, when data from a different cohort of rats that were Morris water maze tested in our laboratory during the time frame of the current experiments were analyzed, a significant age effect was detected in the cumulative search error during Block 4 (Figure 5D; $p < .01$).

In contrast to the Morris water maze test of HPC-dependent spatial reference memory, the effect size for the mean age difference in the number of incorrect trials prior to reaching criteria on the OPPA task was large (1.36). These data indicate that a task requiring interactions between the HPC-PER-PFC memory network may have enhanced sensitivity for identifying age-related impairments relative to a hippocampal-dependent task that does not require the PFC or PER. This observation is perhaps intuitive when one considers the neural circuitry that supports these two behaviors. Specifically, the Morris water maze task requires the HPC (Morris et al., 1982) and input from the medial entorhinal cortex (Brun et al., 2008; Steffenach, Witter, Moser, & Moser, 2005). Conversely, the integration of specific sensory features of an object with a spatial location, a requirement of the OPPA task, necessitates information in the medial entorhinal-HPC circuit to be associated with input from both the PER and the PFC. Thus, an age-associated disruption in any one of these nodes of the memory network, or their ability to interact, will affect behavioral output.

Although a deficit in sensory representations within the PER or PFC, or interactions across the HPC-PER-PFC network would explain the age-related OPPA task deficit, an alternate possibility is that the aged rats were impaired because they used a suboptimal response strategy more than the young animals. While PFC dysfunction in old age is associated with reduced behavioral flexibility (Beas et al., 2013; Moore, Killiany, Herndon, Rosene, & Moss, 2003), this possibility is unlikely. Specifically, in both age groups there was a tendency to develop a side bias over the course of testing, but the young and aged rats shifted their left-versus-right response bias over time to a similar degree (Figure 4).

While it cannot be unequivocally shown with the behavioral approach used in the current experiment, the possibility exists that impairments in OPPA performance arise from declines in the functional connectivity of the HPC-PER-PFC circuit. Such communication deficits could arise either from dysfunction in one or more of these brain areas, or from a reduced ability of these regions to transfer and update information across the memory network. Both of these ideas would be consistent with human imaging data that have used regional fluctuations in the BOLD signal (Cooper, Crow, Walter, & Winter, 1966) to understand functional connectivity in large-scale neural networks (Biswal, Yetkin, Haughton, & Hyde, 1995). Specifically, this experimental approach has established that PER-HPC interactions relate to cognitive performance in young subjects (O'Neil et al., 2012; Vilberg & Davachi, 2013) and that functional connectivity between the HPC and anterior temporal lobe during an associative memory task is reduced in advanced age (Tsukiura et al., 2011). Future research will be necessary to determine the origin of these reductions in interregion communication.

The use of a behavioral task that requires the HPC, PER, and PFC to test cognitive outcomes in old age could provide novel insights regarding the neurobiological explanation for high-performing older animals and the degree to which neural sys-

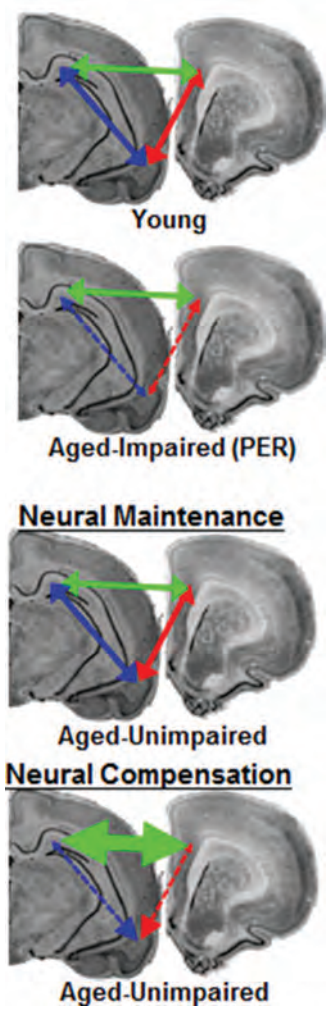

Figure 8. Two competing hypotheses of intact cognitive performance in old age: Neural Maintenance versus Neural Compensation. In the scenario presented here, compared to young, aged-impaired animals with perirhinal (PER) dysfunction would have reduced functional connectivity between this structure and adjacent regions. The Neural Maintenance view predicts that functional connectivity across the hippocampal (HPC)-PER-prefrontal cortical (PFC) network is conserved in aged-unimpaired rats, showing the same patterns of interregion communication as young animals. In contrast, the Neural Compensation view predicts that HPC-PER-PFC functional connectivity would change in the face of PER dysfunction to maintain behavior. See the online article for the color version of this figure.

tems reorganize across the life span. One theory contends that variations in cognitive performance among old individuals reflect differences in neural maintenance (Nyberg, Lövdén, Riklund, Lindenberger, & Backman, 2012). In this view, successfully aging animals have intact neural systems resembling those of young, with no dysfunction in any of the structures that comprise the network. Neural maintenance predicts that the four animals without an OPPA task impairment in the current experiment would have normal function across the brain (Neural Maintenance; Figure 8). A second theory proposes that the range of performance across aged individuals is due to differences in the ability to compensate on the network level when one brain area is compromised (Neural Compensation; Figure 8; Cabeza, Anderson, Locantore, & McIntosh, 2002; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008). This neural compensation view would predict that dysfunction in one brain region could initiate altered network connectivity in associated structures to promote better behavioral outcomes. To date, no neurobiological data are available to reconcile these two ideas. In the current study, the aged rats that had retained a normal ability to form object-place associations also had intact spatial reference memory. Although these data favor a neural maintenance view, future studies will need to cross-characterize animals on the OPPA task along with PFC- and PER-dependent behaviors. The extent to which network interactions reorganize to maintain behavioral output when the HPC, PER, and/or PFC are compromised in age or disease could then be determined. Understanding the relationship between functional connectivity and cognition across the life span will enable future interventional studies to promote memory network interactions that support successful aging.

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Original Investigation

Effect of a 24-Month Physical Activity Intervention vs Health Education on Cognitive Outcomes in Sedentary Older Adults
The LIFE Randomized Trial

Kaycee M. Sink, MD, MAS; Mark A. Espeland, PhD; Cynthia M. Castro, PhD; Timothy Church, MD, PhD, MPH; Ron Cohen, PhD; John A. Dodson, MD; Jack Guralnik, MD, PhD; Hugh C. Hendrie, MB, ChB, DSc; Janine Jennings, PhD; Jeffery Katula, PhD, MA; Oscar L. Lopez, MD; Mary M. McDermott, MD; Marco Pahor, MD; Kieran F. Reid, PhD, MPH; Julia Rushing, MS; Joe Verghese, MBBS; Stephen Rapp, PhD; Jeff D. Williamson, MD, MHS; for the LIFE Study Investigators

IMPORTANCE Epidemiological evidence suggests that physical activity benefits cognition, but results from randomized trials are limited and mixed.

OBJECTIVE To determine whether a 24-month physical activity program results in better cognitive function, lower risk of mild cognitive impairment (MCI) or dementia, or both, compared with a health education program.

DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial, the Lifestyle Interventions and Independence for Elders (LIFE) study, enrolled 1635 community-living participants at 8 US centers from February 2010 until December 2011. Participants were sedentary adults aged 70 to 89 years who were at risk for mobility disability but able to walk 400 m.

INTERVENTIONS A structured, moderate-intensity physical activity program (n = 818) that included walking, resistance training, and flexibility exercises or a health education program (n = 817) of educational workshops and upper-extremity stretching.

MAIN OUTCOMES AND MEASURES Prespecified secondary outcomes of the LIFE study included cognitive function measured by the Digit Symbol Coding (DSC) task subtest of the Wechsler Adult Intelligence Scale (score range: 0-133; higher scores indicate better function) and the revised Hopkins Verbal Learning Test (HVLT-R; 12-item word list recall task) assessed in 1476 participants (90.3%). Tertiary outcomes included global and executive cognitive function and incident MCI or dementia at 24 months.

RESULTS At 24 months, DSC task and HVLT-R scores (adjusted for clinic site, sex, and baseline values) were not different between groups. The mean DSC task scores were 46.26 points for the physical activity group vs 46.28 for the health education group (mean difference, −0.01 points [95% CI, −0.80 to 0.77 points], $P = .97$). The mean HVLT-R delayed recall scores were 7.22 for the physical activity group vs 7.25 for the health education group (mean difference, −0.03 words [95% CI, −0.29 to 0.24 words], $P = .84$). No differences for any other cognitive or composite measures were observed. Participants in the physical activity group who were 80 years or older (n = 307) and those with poorer baseline physical performance (n = 328) had better changes in executive function composite scores compared with the health education group ($P = .01$ for interaction for both comparisons). Incident MCI or dementia occurred in 98 participants (13.2%) in the physical activity group and 91 participants (12.1%) in the health education group (odds ratio, 1.08 [95% CI, 0.80 to 1.46]).

CONCLUSIONS AND RELEVANCE Among sedentary older adults, a 24-month moderate-intensity physical activity program compared with a health education program did not result in improvements in global or domain-specific cognitive function.

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The LIFE Study Investigators are listed at the end of the article.

Corresponding Author: Kaycee M. Sink, MD, MAS, Wake Forest University School of Medicine, Sticht Center on Aging, One Medical Center Boulevard, Winston-Salem, NC 27157 (kmsink@wakehealth.edu).

Epidemiological evidence suggests that physical activity is associated with lower rates of cognitive decline. Exercise is associated with improved cerebral blood flow and neuronal connectivity,[1] maintenance or improvement in brain volume,[2,3] and favorable changes in brain-derived neurotrophic factor and neurogenesis.[4,5] In transgenic Alzheimer mouse models, exercise reduces β-amyloid deposition.[6]

Randomized clinical trials (RCTs) assessing the effect of physical activity on cognitive function are equivocal,[7-9] perhaps due to small sample sizes, short intervention periods, and differences in cohorts and protocols, particularly intensity of physical activity.[7] Two small RCTs of physical activity[10,11] found no benefit from a structured physical activity program vs no intervention or cognitive training in older adults without dementia, but with cognitive complaints or at risk for cognitive decline. However, a 6-month RCT of a home-based physical activity program vs usual care in participants with memory complaints or mild cognitive impairment (MCI) found a modest cognitive benefit.[12] The Lifestyle Interventions and Independence for Elders (LIFE) pilot study showed a correlation between changes in physical and cognitive performance during a 12-month exercise intervention.[13]

We report the prespecified secondary cognitive outcomes of the LIFE study, the largest and longest RCT to assess the effect of a standardized physical activity intervention on cognitive function and impairment in sedentary older adults at risk for mobility disability.[14] We hypothesized that compared with health education, physical activity for 24 months would result in better cognitive function and lower risk of incident all-cause MCI or dementia.

Methods

Trial Design and Participants

The LIFE study was a single-blinded RCT of a physical activity intervention compared with a health education control conducted at 8 US field centers; participants were from rural and urban communities. Details of the LIFE study design and results have been published[14,15] and the trial protocol appears in the Supplement. The study included sedentary men and women aged 70 to 89 years who were at high risk for mobility disability based on objectively assessed lower-extremity functional limitations defined by a Short Physical Performance Battery[16] score of 9 or less (of 12 points), but who could walk 400 m (without assistance) within 15 minutes at baseline.

Eligible participants had no diagnosis of dementia or significant cognitive impairment on the Modified Mini-Mental State Examination[17] (3MSE) based on education- and race-specific norms. Participants with less than 9 years of education were excluded if the screening 3MSE score was less than 70 for black individuals and native Spanish speakers or less than 76 for English-speaking nonblack individuals. Participants with 9 or more years of education were excluded if their 3MSE score was less than 76 for black individuals and less than 80 for native Spanish speakers and English-speaking nonblack individuals. Race/ethnicity was self-reported and collected as required by the National Institutes of Health.

Recruitment was predominantly by mass mailing to age-eligible residents. Additional strategies included newspaper, radio, and television advertisements and presentations at health fairs, senior centers, medical clinics, and churches.

The LIFE study was approved by the institutional review boards at all 8 sites and monitored by a data and safety monitoring board appointed by the National Institute on Aging. Written informed consent was obtained from all participants.

Interventions

Participants were randomly assigned using a secure web-based data management system (permuted block algorithm with random block lengths) with equal probability to either a physical activity intervention or a successful aging health education program, stratifying by field center and sex. The physical activity intervention focused on walking, strength, flexibility, and balance training. Participants were expected to attended 2 center-based visits per week and perform home-based activity 3 to 4 times per week. The physical activity sessions progressed toward a goal of 30 minutes of walking at moderate intensity, 10 minutes of primarily lower-extremity strength training with ankle weights, and 10 minutes of balance training and large muscle group flexibility exercises.

The health education group attended weekly health education workshops during the first 26 weeks of the intervention and at least monthly sessions thereafter. Sessions lasted 60 to 90 minutes and consisted of interactive and didactic presentations, facilitator demonstrations, guest speakers, or field trips. Sessions included approximately 10 minutes of group discussion and interaction and 5 to 10 minutes of upper-extremity stretching and flexibility exercises. Example topics included travel safety, age-appropriate preventive services, legal and financial issues, and nutrition. The intervention committee ensured that health education activities were consistent across sites and unlikely to increase physical activity.

Measurements

Assessments were conducted every 6 months in person by staff masked to treatment group assignment. Home, telephone, and proxy assessments were attempted if participants could not attend clinic visits. Information on demographics, medical and hospitalization history, medication inventory, quality of well-being, and functional limitation was based on self-report.[18] Usual physical activity was assessed by self-report using the Community Healthy Activities Model Program for Seniors questionnaire[19] to measure total weekly minutes of walking and performing strength training exercises and objectively using an Actigraph accelerometer to measure total minutes of at least moderate activity (>760 counts/min) over 7 days.[14]

Cognitive Assessment

A previously described neuropsychological battery of tests was administered by trained and certified examiners at baseline and at 24 months after randomization.[20] Three computerized tasks were administered at baseline and at either 18 or 30 months, depending on when the participant was enrolled.[20]

Neuropsychological Battery

Cognitive tests at baseline included (1) the 3MSE,[17] which is a 100-point test of global cognitive function, (2) the Digit Symbol Coding (DSC) task subtest of the Wechsler Adult Intelligence Scale Third Edition,[21] which is a test of psychomotor speed, attention, and working memory, (3) the revised Hopkins Verbal Learning Test (HVLT-R),[22] which is a 12-item word list learning and recall task, and (4) a modified version of the Rey-Osterrieth Complex Figure, which assesses visuospatial function (copy) and figural memory (immediate recall). At 24 months, these measures were repeated along with (1) the Boston Naming Test, which is a measure of language,[23] (2) the Trail Making Test[24] part A, which is a measure of attention, concentration, and psychomotor speed, and part B, which is a measure of executive function, and (3) the category fluency test for animals, which is a measure of executive function. In all tests, except parts A and B of the Trail Making Test, higher scores indicate better performance.

Computerized Battery

Using a laptop computer, participants were administered 3 tasks that were chosen for added sensitivity in assessing speed of processing and executive function: the n-back task,[25] the Eriksen Flanker task,[26] and a task switching exercise.[27]

Outcome Determinations for MCI and Dementia

At baseline and 24 months after randomization, all participants were assigned 1 of the following cognitive classifications: no cognitive impairment, MCI, or dementia. Participants who scored 88 points or less on the 3MSE were sent for central adjudication by a panel (blinded to treatment assignment) of 8 clinical experts in the diagnosis of late-life cognitive impairment.[20] Each case was assigned to 2 independent adjudicators; disagreements were resolved by the full panel.

Adjudicators reviewed data from the neuropsychological battery, medical history, medications, discharge diagnoses for hospitalizations during the trial, Center for Epidemiology Studies-Depression scores,[28] self-reported disability, and informant-reported functional status (Functional Assessment Questionnaire; FAQ).[29] The FAQ is a 10-item interviewer-administered questionnaire assessing degree of dependence in cognitively challenging activities of daily living, such as preparing balanced meals, traveling outside the neighborhood, and managing finances. For all those who had a 3MSE score of 88 or less, the FAQ was administered either at baseline or at 24 months, or both, to the participant's proxy. Based on 2011 criteria from the National Institute on Aging and the Alzheimer's Association,[30,31] MCI and dementia were adjudicated.

Statistical Analyses

The LIFE protocol specified DSC (total score) and HVLT-R (immediate and delayed recall subscales mean) as the 2 primary cognitive outcomes for assessing cognitive decline. Outcomes were tested according to the intention-to-treat principle with analysis of covariance using 24-month data and covariate adjustment for field center, sex, and the baseline value. Additional prespecified cognitive outcomes were based on scores from the computerized battery. Raw scores from this battery were first winsorized to limit the influence of extreme values; this was done by replacing scores less than the first percentile of the cohortwide distribution with the value of the first percentile and replacing scores greater than the 99th percentile with the 99th percentile value. The *z* scores were formed for each cognitive test score by dividing their difference from the baseline mean by the baseline standard deviation.

Composite scores for the HVLT-R (immediate and delayed recall scores), n-back (1- and 2-back scores), task switching (no switch and switch reaction times), and Flanker tasks (congruent and incongruent reaction times) were formed by averaging the *z* scores for their 2 individual components. The global cognitive function score was the average of scores from these composites and the *z*-transformed DSC, renormalized to have a mean of 0 and an SD of 1 at baseline. The executive function composite score was the renormalized average of scores from the n-back, task switching, and Flanker tasks. In creating these composite scores, averages were taken of all available data (ie, missing data if participants did not complete the full battery were ignored). Supporting analyses were conducted using multiple imputation for which missing measures and examination scores were imputed to create 5 databases that were analyzed in parallel.[32]

Subgroup comparisons using interaction terms were prespecified for sex and baseline Short Physical Performance Battery score (<8 vs ≥8), 3MSE score (<90 vs ≥90), and age (70-79 years vs ≥80 years). Associations between changes in cognitive function and changes in objective and subjective physical activity level were assessed using linear regression and tests of interactions.

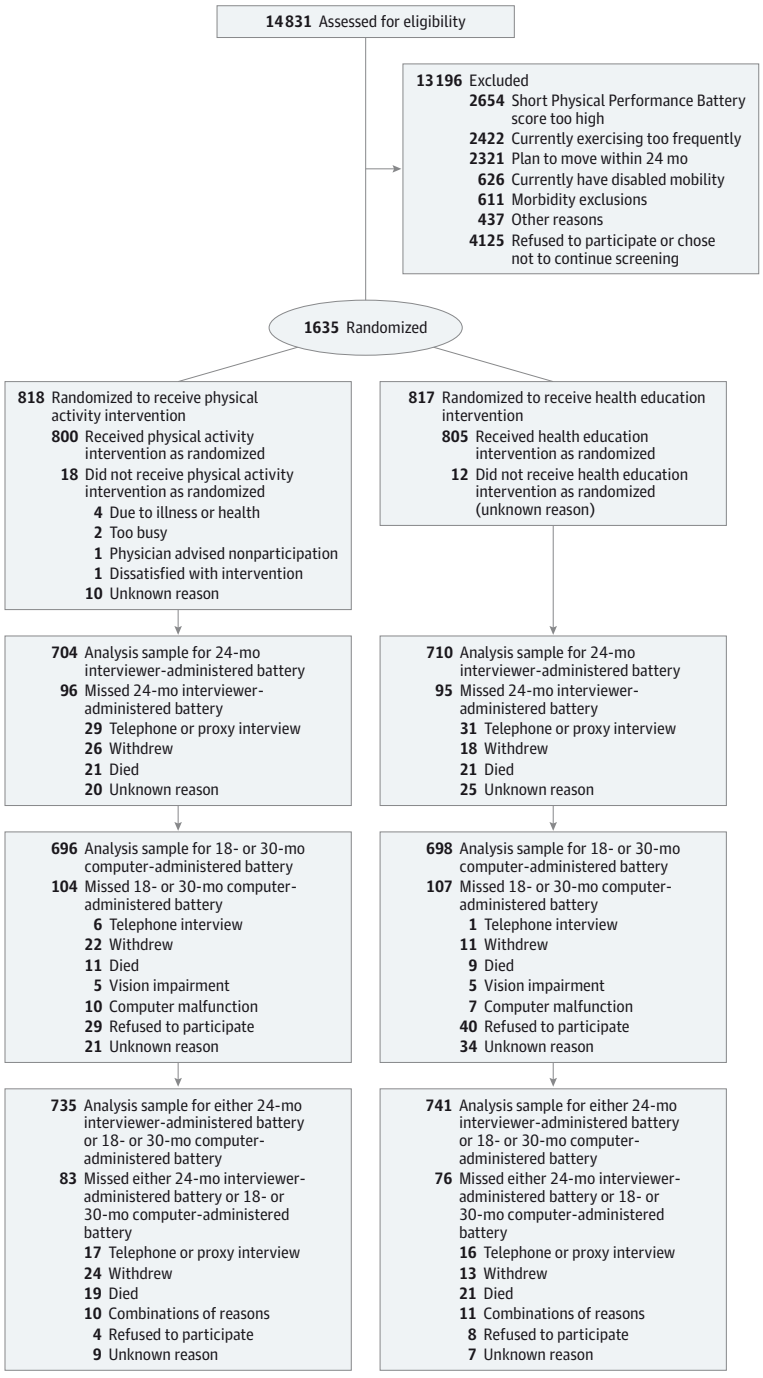
Progression in cognitive impairment (ie, from baseline normal cognitive function to either MCI or dementia or from baseline MCI to dementia) was a tertiary outcome. Logistic regression was used to compare progression rates between intervention groups. Participants with prevalent MCI (n = 141) at baseline were not included in the incidence of MCI, but were included in the incident dementia outcome if they progressed to dementia at 24 months. Seven participants were adjudicated to have dementia at the baseline visit (despite otherwise meeting LIFE study entry criteria). These participants were excluded from the incident dementia outcome analysis.

Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc). Two-sided inferences with $P < .05$ were considered statistically significant. The targeted sample size of 1600 was expected to provide 87% power to detect mean differences between groups of 0.15 SD for cognitive tests. This was projected to correspond to mean differences of 1.8 units for DSC scores and 0.8 units for HVLT-R immediate memory scores.

Results

From February 2010 until December 2011, 1635 participants were randomized (818 to physical activity group and 817 to health education group; **Figure 1**). Analyses are limited to 1476 participants (90.3%) with cognitive data during follow-up. Compared with participants without cognitive follow-up data, the participants included in the analyses had faster gait speeds

Figure 1. Flow of Participants in the Lifestyle Interventions and Independence for Elders (LIFE) Study



($P < .001$). The 24-month retention rates were 89.8% for the physical activity group and 90.7% for the health education group ($P = .56$).

Characteristics of the participants appear in **Table 1**. The mean (SD) age was 78.9 (5.2) years, 68% were women, and 67% had a college education. The mean (SD) 3MSE score was 91.7 (5.4) (range, 71-100). There were more black participants in the physical activity group vs the health education group.

Intervention Adherence

Based on accelerometry data, the physical activity group maintained moderate to vigorous physical activity levels between

Table 1. Baseline Characteristics of Participants in the Lifestyle Interventions and Independence for Elders (LIFE) Study[a]

	Physical Activity (n = 735)	Health Education (n = 741)
Age group, y		
70-79	428 (58.2)	413 (55.7)
80-89	307 (41.8)	328 (44.3)
Women	496 (67.5)	503 (67.9)
Education[b]		
≤High school	249 (33.9)	237 (32.1)
≥College	485 (66.1)	501 (67.9)
Race[b]		
Black	148 (20.2)	112 (15.2)
Non-Hispanic white	542 (73.9)	580 (78.5)
Other[c]	43 (5.9)	47 (6.4)
Short Physical Performance Battery score[d]		
<8	309 (42.0)	341 (46.0)
8-9	426 (58.0)	400 (54.0)
400-m walking speed, mean (SD), m/s	0.83 (0.16)	0.82 (0.16)
Body mass index, mean (SD)[e]	30.2 (5.8)	30.2 (6.1)
Walking and strength training, mean (SD), min/wk	75.1 (125.6)	86.7 (134.4)
History of hypertension	552 (75.1)	554 (74.8)
Diabetes status		
None	366 (49.8)	375 (50.6)
Impaired fasting glucose	173 (23.5)	154 (20.8)
Diabetes	196 (26.7)	212 (28.6)
History of cardiovascular disease	210 (28.6)	225 (30.4)
History of stroke	53 (7.2)	48 (6.5)
Apolipoprotein E ε4 allele		
0	525 (64.2)	529 (64.8)
1	146 (17.8)	153 (18.7)
2	10 (1.2)	9 (1.1)
Missing	137 (16.8)	126 (15.4)
Modified Mini-Mental State Examination score, mean (SD)[f]	91.61 (5.54)	91.71 (5.28)
Score <90	230 (31.3)	236 (31.8)
Digit Symbol Coding task score, mean (SD)[g]	45.99 (13.04)	47.01 (12.72)
No. correct on revised Hopkins Verbal Learning Test, mean (SD)		
Sum of 3 immediate word recall trials[h]	23.44 (5.12)	23.18 (5.44)
Delayed word recall[i]	7.79 (2.73)	7.70 (2.92)
Percentage correct on n-back task, mean (SD)[j]		
1-back	81.58 (17.85)	82.11 (16.30)
2-back	51.04 (19.84)	50.68 (21.47)
Reaction time on task switching, mean (SD), s[k]		
No switch	1.46 (0.73)	1.41 (0.69)
Switch	2.44 (1.04)	2.35 (1.01)
Reaction time on Eriksen Flanker task, mean (SD), s[k]		
Congruent	0.65 (0.19)	0.65 (0.20)
Incongruent	0.72 (0.22)	0.73 (0.24)

[a] Data are expressed as No. (%) unless otherwise indicated.

[b] Missing data for 4 participants.

[c] Included participants who self-identified as Asian, Native American, Alaskan Native, Pacific Islander, Hispanic white, other, or who refused to respond.

[d] Score range: 0-12 (higher scores indicate better performance).

[e] Calculated as weight in kilograms divided by height in meters squared.

[f] Score range: 0-100 (higher scores indicate better performance).

[g] Score range: 0-133 (higher scores indicate better performance).

[h] Score range: 0-36 (higher scores indicate better performance).

[i] Score range: 0-12 (higher scores indicate better performance).

[j] Score range: 0-100 (higher scores indicate better performance).

[k] Higher values indicate slower (worse) performance.

baseline and 24-month follow-up (mean difference, −2.1 min/wk [95% CI, −9.7 to 13.9 min/wk]) compared with the health education group (mean difference, −40.4 min/wk [95% CI, −29.4 to −51.4 min/wk]; $P < .001$). Based on data from the Community Healthy Activities Model Program for Seniors questionnaire, the physical activity group had a greater increase in self-reported physical activity level from baseline to 24 months (mean difference, 130.4 min/wk [95% CI, 116.7 to 144.1 min/wk]) compared with the health education group (mean difference, 30.5 min/wk [95% CI, 18.9 to 42.1 min/wk]; $P < .001$). The median attendance at physical activity sessions was 71%, excluding medical leave.

Table 2. Adjusted Raw and *z*-Transformed Follow-up Cognitive Function Scores

	Mean (95% CI)			
	Physical Activity (n = 735)[a]	Health Education (n = 741)[a]	Difference Between Groups	*P* Value
Digit Symbol Coding task				
Raw score	46.26 (45.75 to 46.82)	46.28 (45.72 to 46.83)	−0.01 (−0.80 to 0.77)	.97
z Score	−0.003 (−0.046 to 0.040)	−0.002 (−0.045 to 0.041)	−0.001 (−0.063 to 0.060)	
Revised Hopkins Verbal Learning Test				
Immediate word recall				
Raw score	22.83 (22.52 to 23.14)	22.97 (22.67 to 23.28)	−0.14 (−0.58 to 0.29)	.52
z Score	−0.073 (−0.132 to −0.014)	−0.046 (−0.105 to 0.013)	−0.027 (−0.110 to 0.055)	
Delayed word recall				
Raw score	7.22 (7.03 to 7.41)	7.25 (7.06 to 7.44)	−0.03 (−0.29 to 0.24)	.84
z Score	−0.167 (−0.234 to −0.100)	−0.157 (−0.224 to −0.090)	−0.010 (−0.103 to 0.084)	
Composite *z* score[b]	−0.130 (−0.187 to −0.073)	−0.106 (−0.163 to −0.049)	−0.024 (−0.105 to 0.057)	.56
Executive function				
Percentage correct on n-back task				
1-back	83.7 (82.5 to 84.9)	82.9 (81.8 to 84.1)	0.7 (−0.9 to 2.4)	.39
2-back	53.2 (51.6 to 54.8)	51.9 (50.4 to 53.5)	1.3 (−0.9 to 3.5)	.26
Reaction time on task switching, s				
No	1.47 (1.42 to 1.51)	1.46 (1.42 to 1.51)	0.01 (−0.06 to 0.07)	.86
Yes	2.43 (2.37 to 2.49)	2.39 (2.33 to 2.45)	0.04 (−0.05 to 0.13)	.37
Reaction time on Flanker task, s				
Congruent	0.65 (0.64 to 0.67)	0.67 (0.66 to 0.68)	−0.02 (−0.03 to −0.01)	.04
Incongruent	0.73 (0.72 to 0.74)	0.75 (0.73 to 0.76)	−0.02 (−0.04 to 0)	.07
Composite *z* score[b]	−0.003 (−0.060 to 0.054)	−0.025 (−0.080 to 0.030)	0.022 (−0.057 to 0.101)	.59
Mean global composite *z* score[b,c]	−0.052 (−0.099 to −0.005)	−0.081 (−0.128 to −0.034)	0.029 (−0.038 to 0.095)	.40

[a] Adjusted for sex, clinic site, and baseline values.

[b] Ordered so that positive values reflect better performance on tasks.

[c] Includes Digit Symbol Coding task, revised Hopkins Verbal Learning Test immediate and delayed recall, n-back task, and reaction time on task switching and Flanker tasks.

Cognitive Function Results

At baseline, interviewer-administered cognitive assessments were collected on all participants. Computer-based assessments were collected on 85.5% (2-back task) to 96.2% (Flanker task) of participants. There were no differences between groups on any cognitive tests at baseline.

Table 2 presents the raw scores and *z*-transformed cognitive outcomes, adjusting for clinic site, sex, and baseline values. The *z* scores are interpreted as the change from baseline in standard deviations. The adjusted mean raw DSC task scores (score range, 0-133) at follow-up were not different between the 2 groups (46.26 points [95% CI, 45.75 to 46.82 points] in the physical activity group vs 46.28 points [95% CI, 45.72 to 46.83 points] in the health education group; mean difference, −0.01 points [95% CI, −0.80 to 0.77 points]; *P* = .97). Similarly, the adjusted scores for mean HVLT-R delayed word recall (score range, 0-12) were not different between groups (7.22 words [95% CI, 7.03 to 7.41 words] for the physical activity group vs 7.25 words [95% CI, 7.06 to 7.44 words] for the health education group; mean difference, −0.03 words [95% CI, −0.29 to 0.24 words]; *P* = .84). There were no between-group differences in the executive function composite *z* score (*P* = .59) or the mean global composite *z* score (*P* = .40). Additional adjustment for race/ethnicity and education did not change the results.

The results of prespecified subgroup comparisons appear in **Figure 2**. Intervention effects did not vary by sex or baseline 3MSE score. However, for participants with a baseline Short Physical Performance Battery score of less than 8 or age of 80 years or older, there was heterogeneity in the intervention effects for the executive function composite, suggesting benefit in executive function associated with physical activity (*P* = .01 for interaction).

Relationships With Changes in Physical Activity

The 24-month changes in the 4 cognitive function measures were not correlated with changes in moderate physical activity as measured by accelerometry (*P* > .30) among the 697 participants with 24-month data. The 24-month changes in weekly walking and strength training from the Community Healthy Activities Model Program for Seniors questionnaire were modestly associated with global cognitive function (*r* = 0.07; *P* = .006) and executive function (*r* = 0.06; *P* = .04). These relationships were not different between the 2 groups (*P* > .70 for interaction). Results were unchanged when using 12-month change in level of physical activity.

Incident MCI or Dementia

There was no significant difference between groups in the incidence of MCI, dementia, or both combined; 13.2% of the physical

Figure 2. Intervention Effects on *z*-Transformed Scores From 4 Assessment Tools

A Digit Symbol Coding task

	Mean *z*-Transformed Score (95% CI)		Intervention Effect, Mean (95% CI)
	Physical Activity	Health Education	
Sex			
Female	0.004 (-0.050 to 0.057)	0.024 (-0.029 to 0.076)	-0.020 (-0.094 to 0.055)
Male	-0.018 (-0.093 to 0.058)	-0.055 (-0.133 to 0.029)	0.038 (-0.070 to 0.146)
Short Physical Performance Battery score			
<8	-0.060 (-0.127 to 0.008)	-0.027 (-0.091 to 0.036)	-0.032 (-0.125 to 0.061)
8-9	0.038 (-0.019 to 0.095)	0.021 (-0.039 to 0.080)	0.017 (-0.065 to 0.099)
Age group, y			
70-79	0.013 (-0.044 to 0.069)	0.047 (-0.011 to 0.105)	-0.034 (-0.115 to 0.047)
80-89	-0.026 (-0.095 to 0.042)	-0.064 (-0.130 to 0.002)	0.037 (-0.057 to 0.132)
Modified Mini-Mental State Examination score			
<90	-0.054 (-0.134 to 0.026)	-0.074 (-0.153 to 0.005)	0.020 (-0.090 to 0.130)
90-100	0.020 (-0.033 to 0.073)	0.032 (-0.021 to 0.086)	-0.013 (-0.087 to 0.061)

B Revised Hopkins Verbal Learning Test

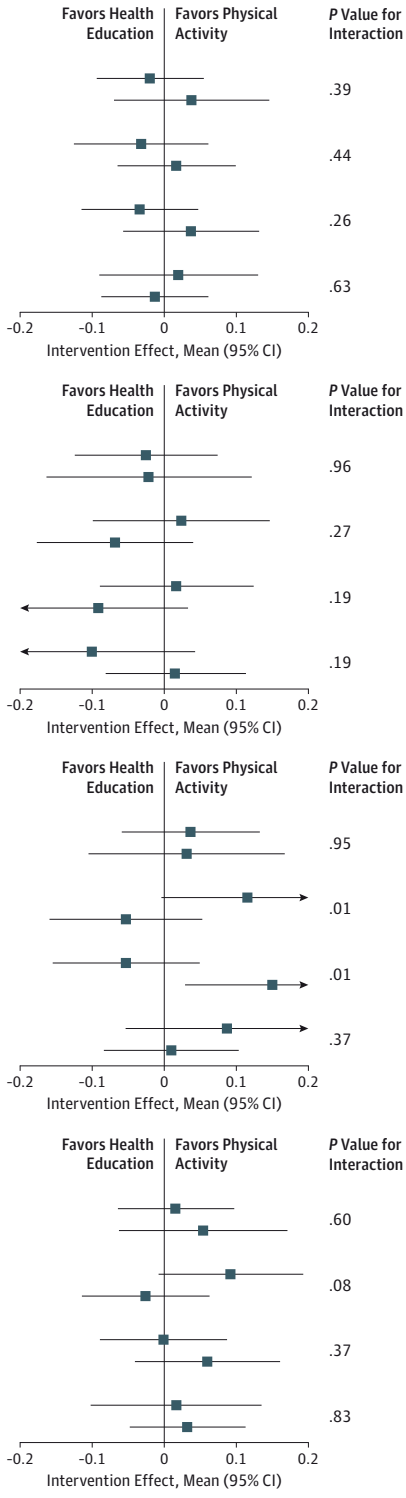
	Mean *z*-Transformed Score (95% CI)		Intervention Effect, Mean (95% CI)
	Physical Activity	Health Education	
Sex			
Female	-0.096 (-0.166 to -0.025)	-0.070 (-0.140 to -0.001)	-0.025 (-0.124 to 0.074)
Male	-0.199 (-0.300 to -0.099)	-0.178 (-0.281 to -0.076)	-0.021 (-0.163 to 0.121)
Short Physical Performance Battery score			
<8	-0.158 (-0.247 to -0.069)	-0.182 (-0.266 to -0.097)	0.024 (-0.099 to 0.146)
8-9	-0.109 (-0.184 to -0.033)	-0.040 (-0.118 to 0.037)	-0.068 (-0.177 to 0.040)
Age group, y			
70-79	-0.044 (-0.119 to 0.031)	-0.062 (-0.138 to 0.015)	0.017 (-0.089 to 0.124)
80-89	-0.253 (-0.343 to -0.163)	-0.161 (-0.248 to -0.075)	-0.091 (-0.216 to 0.033)
Modified Mini-Mental State Examination score			
<90	-0.354 (-0.460 to -0.248)	-0.254 (-0.361 to -0.148)	-0.100 (-0.244 to 0.043)
90-100	-0.023 (-0.094 to 0.047)	-0.039 (-0.109 to 0.031)	0.015 (-0.081 to 0.113)

C Executive function composite

	Mean *z*-Transformed Score (95% CI)		Intervention Effect, Mean (95% CI)
	Physical Activity	Health Education	
Sex			
Female	0.037 (-0.031 to 0.106)	0.001 (-0.066 to 0.068)	0.037 (-0.059 to 0.132)
Male	-0.017 (-0.113 to 0.080)	-0.048 (-0.145 to 0.049)	0.031 (-0.105 to 0.167)
Short Physical Performance Battery score			
<8	0.026 (-0.061 to 0.113)	-0.090 (-0.173 to -0.007)	0.116 (-0.004 to 0.236)
8-9	-0.023 (-0.098 to 0.051)	0.030 (-0.046 to 0.105)	-0.053 (-0.159 to 0.053)
Age group, y			
70-79	0.020 (-0.051 to 0.091)	0.073 (-0.000 to 0.146)	-0.053 (-0.155 to 0.049)
80-89	0.019 (-0.069 to 0.107)	-0.131 (-0.215 to -0.047)	0.150 (0.029 to 0.271)
Modified Mini-Mental State Examination score			
<90	-0.059 (-0.164 to 0.045)	-0.146 (-0.247 to -0.045)	0.087 (-0.054 to 0.228)
90-100	0.054 (-0.014 to 0.120)	0.044 (-0.023 to 0.111)	0.010 (-0.084 to 0.103)

D Global cognitive function composite

	Mean *z*-Transformed Score (95% CI)		Intervention Effect, Mean (95% CI)
	Physical Activity	Health Education	
Sex			
Female	-0.027 (-0.084 to 0.031)	-0.043 (-0.100 to 0.014)	0.016 (-0.064 to 0.097)
Male	-0.103 (-0.186 to -0.020)	-0.157 (-0.240 to -0.074)	0.054 (-0.063 to 0.171)
Short Physical Performance Battery score			
<8	-0.049 (-0.122 to 0.024)	-0.141 (-0.021 to -0.072)	0.092 (-0.008 to 0.193)
8-9	-0.054 (-0.116 to 0.008)	-0.029 (-0.093 to 0.035)	-0.026 (-0.114 to 0.063)
Age group, y			
70-79	-0.018 (-0.079 to 0.044)	-0.017 (-0.080 to 0.047)	-0.001 (-0.089 to 0.087)
80-89	-0.100 (-0.174 to -0.027)	-0.160 (-0.231 to -0.090)	0.060 (-0.041 to 0.161)
Modified Mini-Mental State Examination score			
<90	-0.115 (-0.205 to -0.025)	-0.132 (-0.219 to -0.044)	0.017 (-0.102 to 0.135)
90-100	-0.024 (-0.082 to 0.035)	-0.056 (-0.114 to 0.002)	0.032 (-0.048 to 0.113)



activity group developed MCI or dementia by 24 months compared with 12.1% of the health education group (unadjusted odds ratio, 1.08 [95% CI, 0.80-1.46]; $P = .61$; **Table 3**). There were no between-group differences within MCI subtypes (incident am-

Table 3. Incident Mild Cognitive Impairment or Dementia at 24 Months

	No./Total (%)		Odds Ratio (95% CI)[a]	*P* Value
	Physical Activity	Health Education		
Mild cognitive impairment[b]	70/686 (10.2)	62/682 (9.1)	1.14 (0.79-1.62)	.48
Dementia[c]	28/743 (3.8)[d]	29/747 (3.9)[d]	0.96 (0.57-1.63)	.88
Mild cognitive impairment or dementia	98/743 (13.2)[d]	91/747 (12.1)[d]	1.08 (0.80-1.46)	.61

[a] From unadjusted logistic regression.

[b] Of those free of mild cognitive impairment or dementia at baseline.

[c] Of those free of dementia at baseline.

[d] Denominator is slightly larger than in Table 1 because some participants were adjudicated but did not receive cognitive testing at 24 months (eg, those who died).

nestic MCI was 5.5% for the physical activity group vs 5.7% for the health education group [*P* = .85] and nonamnestic MCI was 4.6% and 3.2%, respectively [*P* = .16]).

Discussion

The LIFE study's structured, 24-month moderate-intensity physical activity intervention did not result in better global or domain-specific cognition compared with a health education program in older, sedentary adults. There was also no difference between groups in the incidence of MCI or dementia, although this was an exploratory outcome with limited statistical power. However, participants in the physical activity group who were 80 years or older and those with lower baseline physical functioning levels experienced benefits in executive functioning compared with participants in the health education group. Cognitive function remained stable over 2 years for all participants. We cannot rule out that both interventions were successful at maintaining cognitive function.

Despite epidemiological evidence supporting the benefits of exercise and physical activity on cognition, the results of the LIFE study are consistent with some other randomized trials.[7] In the Mental Activity and eXercise trial,[10] a structured aerobic physical activity intervention was not superior to a stretching exercise control or mental activity control in sedentary older adults. The Action for Health in Diabetes trial[33] found no benefit of diet plus physical activity on cognitive function over 8 years. A large trial of a multifactorial intervention including diet, physical activity, cognitive training, social activity, and management of metabolic and vascular risk factors showed a small, statistically significant benefit on global and executive cognitive function at 2 years.[34] However, it is difficult to compare this trial with the LIFE study because the population was 10 years younger, physically active at baseline, and had a multifactorial intervention.

Possible explanations for the lack of cognitive benefit of the physical activity intervention include (1) the assigned level of physical activity may have been insufficient to produce changes in the cognitive measures despite its effect on physical function[14]; (2) improvements in cognitive function in some shorter clinical trials, including the LIFE pilot study,[13] may dissipate by 24 months and thus may have been missed, especially if adherence to the physical activity intervention wanes over time[14]; (3) the study population was not specifically selected for cognitive vulnerability, although poor physical function, especially gait speed, has been shown to be a risk for cognitive decline[35,36]; (4) the participants were well educated (>two-thirds went to college), and high cognitive reserve may have protected against cognitive decline over 2 years[37]; and (5) the health education intervention may have benefited cognition.[10,38] The health education group attended interactive seminars providing both cognitive and social stimulation. Both cognitive and social stimulation have been shown to preserve cognition in older adults.[10,38]

The dose-response relationship between physical activity and cognition is not well understood.[7,39] The physical activity intervention was designed to provide moderate-intensity aerobic walking activity and was consistent with American College of Sports Medicine recommendations. However, we recruited a population with limited physical ability. Impaired lower-extremity functioning and the high prevalence of comorbidities may have limited participants' ability to exercise at sustained levels sufficient to improve cognition. Nonetheless, the physical activity group had significantly greater physical activity levels than the health education group, and a more intensive, sustained intervention that could be translatable at the population level would be difficult to achieve.

Despite the lack of overall benefit, our prespecified subgroup analyses of participants aged 80 years or older and those with lower baseline physical performance demonstrated that the physical activity group had better performance on executive function tasks than those in the health education group at 24 months. This finding is important because executive function is the most sensitive cognitive domain to exercise interventions,[40] and preserving it is required for independence in instrumental activities of daily living. Future physical activity interventions, particularly in vulnerable older adult groups (eg, ≥80 years of age and those with especially diminished physical functioning levels), may be warranted.

To our knowledge, the LIFE study is the largest, longest RCT of a physical activity intervention in sedentary older adults at increased risk for mobility disability. Other strengths include high retention rates, without differential loss to follow-up in the 2 groups; comprehensive standardized, well-validated cognitive assessments; and blinded adjudication of MCI and dementia.

However, there are several limitations. First, even though cognitive function and incident MCI and dementia were a priori outcomes for the LIFE study, our study was not specifically powered for these outcomes and may have been too short to affect incident events. Second, the intensity of the physical activity intervention was moderate by design. Although the physical activity intervention was sufficient to increase physi-

cal activity level and reduce incident mobility disability,[14] it may have been insufficient to produce cognitive effects. Third, the components of the health education intervention, including the cognitive and social components, may have improved or prevented cognitive decline. Fourth, we did not measure changes in mechanistic surrogate outcomes, such as brain volumes or cerebrospinal fluid β-amyloid levels.

Conclusions

Among sedentary older adults, a 24-month moderate-intensity physical activity program compared with a health education program did not result in improvements in global or domain-specific cognitive function.

ARTICLE INFORMATION

Author Affiliations: Section on Gerontology and Geriatric Medicine, Department of Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina (Sink, Williamson); Department of Biostatistical Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina (Espeland, Rushing); Stanford Prevention Research Center, Stanford University School of Medicine, Palo Alto, California (Castro); Pennington Biomedical Research Center, Baton Rouge, Louisiana (Church); College of Medicine, University of Florida, Gainesville (Cohen, Pahor); Leon H. Charney Division of Cardiology, Department of Medicine, New York University School of Medicine, New York, New York (Dodson); Division of Gerontology, Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore (Guralnik); Department of Psychiatry and Center for Aging Research, Indiana University, Indianapolis (Hendrie); Department of Psychology, Wake Forest University, Winston-Salem, North Carolina (Jennings); Department of Health and Exercise Sciences, Wake Forest University, Winston-Salem, North Carolina (Katula); Departments of Neurology and Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania (Lopez); Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois (McDermott); Senior Editor, *JAMA* (McDermott); Nutrition, Exercise Physiology and Sarcopenia Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts (Reid); Departments of Neurology and Medicine, Albert Einstein College of Medicine, Bronx, New York (Verghese); Department of Psychiatry, Wake Forest University School of Medicine, Winston-Salem, North Carolina (Rapp).

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Study concept and design: Sink, Espeland, Church, Guralnik, Hendrie, Jennings, Katula, McDermott, Pahor, Reid, Verghese, Rapp, Williamson.
Acquisition, analysis, or interpretation of data: Sink, Espeland, Castro, Church, Cohen, Dodson, Guralnik, Hendrie, Jennings, Katula, Lopez, McDermott, Pahor, Reid, Rushing, Verghese, Williamson.
Drafting of the manuscript: Sink, Espeland, Cohen, Hendrie, Katula, Lopez, Reid, Rushing, Williamson.
Critical revision of the manuscript for important intellectual content: Sink, Espeland, Castro, Church, Cohen, Dodson, Guralnik, Hendrie, Jennings, Katula, McDermott, Pahor, Reid, Verghese, Rapp, Williamson.
Statistical analysis: Espeland, Jennings, Rushing.
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Study supervision: Sink, Church, Guralnik, Hendrie, Katula, Lopez, McDermott, Pahor, Reid, Williamson.

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Group Information: The investigators for the LIFE study were Mary M. McDermott, MD (field center principal investigator), Bonnie Spring, PhD (field center co-principal investigator), Joshua Hauser, MD, Martha Gulati, MD, Sanjiv Shah, MD, Kathryn Domanchuk, Rex Graff, Kasia Kadela, and Alvito Rego (Northwestern University, Chicago, Illinois); Timothy Church, MD, PhD, MPH (field center principal investigator), Steven Blair, PED, Valerie Myers, PhD, Ron Monce, PA-C, Nathan Britt, NP, Melissa Nauta, BS, Ami Parks, MPA, BS, Ruben Rodarte, MBA, MS, BS, Heidi Millet, BS, Catrine Tudor-Locke, PhD, FACSM, Ben Butitta, BS, and Sheletta Donatto, MS, RD, LDN, CDE (Pennington Biomedical Research Center, Baton Rouge, Louisiana); Denise Bonds, MD (National Heart, Lung, and Blood Institute, Bethesda, Maryland); Evan C. Hadley, MD, Kushang V. Patel, PhD, and Sergei Romashkan, MD, PhD (National Institute on Aging, Bethesda, Maryland); Robert M. Kaplan, PhD (Office of Behavioral and Social Sciences Research, National Institutes of Health, Bethesda, Maryland); Abby C. King, PhD (field center principal investigator), Cynthia M. Castro, PhD, William L. Haskell, PhD, Randall S. Stafford, MD, PhD, Veronica Yank, MD, Leslie A. Pruitt, PhD, Kathy Berra, MSN, NP-C, FAAN, Carol Bell, NP, Rosita Thiessen, Kate P. Youngman, MA, Selene B. Virgen, BAS, Kristina N. Tarin, MS, CSCS, Heather Klaftenegger, Carolyn A. Prosak, RD, Ines Campero, BA, Dulce M. Garcia, José Soto, BA, Linda Chio, and David Hoskins, MS (Stanford University, Palo Alto, California); Roger Fielding, PhD (field center principal investigator), Miriam Nelson, PhD, Sara Folta, PhD, Edward Phillips, MD, Christine Liu, MD, Erica Cifarelli, MS, Kieran Reid, MSc, MPH, Paige Lacasse, BS, Dylan Kirn, BS, Evan Pasha, BS, Sonnly Ribourg, BS, Karen Ruais, NP, Won Kim, BS, and Gregory Cloutier, BS (Tufts University, Boston, Massachusetts); Todd Manini, PhD (field center principal investigator), Marco Pahor, MD (field center co-principal investigator), Stephen Anton, PhD, Thomas Buford, PhD, Susan Nayfield, MD, MSc, Joe Nocera, PhD, Michael Marsiske, PhD, Bhanu Sandesara, MD, Jocelyn Lee, PhD, Deborah Hiatt-Jensen, ARNP, MPH, Mieniecia Black, MS, Kimberly Case, PhD, Katherine Herring, BS, Amber Schwier-Delvisco, BS, Bill Burk, Brian Hoover, BS, Jeffrey Knaggs, BS, and Allison Martin, MS, RCEP (University of Florida, Gainesville); Chonglun Xie, MD, Holly Morris, RN, Flo Singletary, MS, CCC-SLP, Jackie Causer, Susan Yonce, RN, Christine Del Boccio, Charles Gay, DC, and Tangerica Peavy Alexander (Brooks Center for Rehabilitation Studies, satellite site); Marco Pahor, MD (principal investigator), Stephen Anton, PhD, Thomas Buford, PhD, Christiaan Leeuwenburgh, PhD, Susan Nayfield, MD, MSc, Todd Manini, PhD, Connie Caudle, Lauren Crump, MPH, Latonia Holmes, Jocelyn Lee, PhD, Ronald Lester, PhD, MBA, Ching-ju Lu, MPH, and Ryan O'Mara (Administrative Coordinating Center); Carl J. Pepine MD, MACC, Mario Ariet, PhD, Eileen Handberg, PhD, ARNP, Daniel Deluca, BS, and James Hill, MD, MS, FACC (Electrocardiogram Reading Center); Jack M. Guralnik, MD, PhD (co-principal investigator; University of Maryland School of Medicine, Baltimore); Anne B. Newman, MD, MPH (field center principal investigator), Stephanie A. Studenski, MD, MPH (field center co-principal investigator), Bret H. Goodpaster, PhD, Oscar Lopez, MD, Nancy W. Glynn, PhD, Janet T. Bonk, MPH, RN, Jennifer Rush, MPH, Piera Kost, BA, Allison Gerger, BS, Pamela Vincent, CMA, LaTisha Davis, BS, Mark A. Newman, PhD, George Grove, MS, and Kathy Williams, RN, BSEd, MHSA (University of Pittsburgh, Pittsburgh, Pennsylvania); Erik J. Groessl, PhD (VA San Diego Healthcare System and University of California,

San Diego); Stephen B. Kritchevsky, PhD (field center principal investigator), Anthony Marsh, PhD (field center co-principal investigator), Tina Brinkley, PhD, Jamehl Demons, MD, Kaycee Sink, MD, MAS, Kimberly Kennedy, BA, CCRC, Rachel Shertzer-Skinner, MA, CCRC, Abbie Wrights, MS, Rose Fries, RN, CCRC, and Deborah Barr, MA, RHEd, CHES (Wake Forest University, Winston-Salem, North Carolina); Jeff Williamson, MD, MHS (center principal investigator), Kaycee M. Sink, MD, MAS (center co-principal investigator), Hugh C. Hendrie, MB, ChB, DSc, Stephen R. Rapp, PhD, Joe Verghese, MBBS, Nancy Woolard, and Valerie K. Wilson, MD (Cognition Reading Center); Michael E. Miller, PhD (principal investigator), Mark Espeland, PhD (co-principal investigator), Walter Ambrosius, PhD, Don Babcock, BSEE, PE, Daniel Beavers, PhD, MS, Robert P. Byington, PhD, MPH, FAHA, Delilah Cook, Curt Furberg, MD, PhD, Candace Goode, Jason Griffin, BS, Lea Harvin, BS, Leora Henkin, MPH, Med, John Hepler, BFA, Fang-Chi Hsu, PhD, Kathy Joyce, Laura Lovato, MS, Wesley Roberson, BSBA, Julia Robertson, BS, Julia Rushing, BSPH, MStat, Scott Rushing, BS, Cynthia L. Stowe, MPM, Michael P. Walkup, MS, Don Hire, BS, Jack Rejeski, PhD, Jeff Katula, PhD, MA, Peter H. Brubaker, PhD, Shannon Mihalko, PhD, Janine M. Jennings, PhD, and Kathy Lane, BA (Data Management, Analysis and Quality Control Center); Thomas M. Gill, MD (field center principal investigator), Robert S. Axtell, PhD, FACSM (field center co-principal investigator), Susan S. Kashaf, MD, Nathalie de Renekeire, MD, Joanne M. McGloin, MDiv, MS, MBA, Raeleen Mautner, PhD, Sharon M. Huie-White, MPH, Luann Bianco, BA, Janice Zocher, Denise M. Shepard, RN, MBA, Barbara Fennelly, MA, RN, Sean Halpin, MA, Theresa Barnett, MS, APRN, Karen C. Wu, RN, Lynne P. Iannone, MS, Julie A. Bugaj, MS, and Christine Bailey, MA (Yale University, New Haven, Connecticut); and Geoffrey Chupp, MD, Gail Flynn, RCP, CRFT, Thomas M. Gill, MD, John Hankinson, PhD, and Carlos A. Vaz Fragoso, MD (Spirometry Reading Center).

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Hormones as "difference makers" in cognitive and socioemotional aging processes

Natalie C. Ebner[1,2]*, Hayley Kamin[1], Vanessa Diaz[1], Ronald A. Cohen[2] and Kai MacDonald[3]

[1] Department of Psychology, University of Florida, Gainesville, FL, USA
[2] Department of Aging and Geriatric Research, University of Florida, Gainesville, FL, USA
[3] Department of Psychiatry, University of California, San Diego, San Diego, CA, USA

Edited by:
Jean Decety, University of Chicago, USA

Reviewed by:
Gail A. Alvares, The University of Western Australia, Australia
Shawn Elizabeth Nielsen, University of Southern California, USA

***Correspondence:**
Natalie C. Ebner, Department of Psychology, University of Florida, PO. Box 112250, Gainesville, FL 32611, USA
e-mail: natalie.ebner@ufl.edu

Aging is associated with well-recognized alterations in brain function, some of which are reflected in cognitive decline. While less appreciated, there is also considerable evidence of socioemotional changes later in life, some of which are beneficial. In this review, we examine age-related changes and individual differences in four neuroendocrine systems—cortisol, estrogen, testosterone, and oxytocin—as "difference makers" in these processes. This suite of interrelated hormonal systems actively coordinates regulatory processes in brain and behavior throughout development, and their level and function fluctuate during the aging process. Despite these facts, their specific impact in cognitive and socioemotional aging has received relatively limited study. It is known that chronically elevated levels of the stress hormone cortisol exert neurotoxic effects on the aging brain with negative impacts on cognition and socioemotional functioning. In contrast, the sex hormones estrogen and testosterone appear to have neuroprotective effects in cognitive aging, but may decrease prosociality. Higher levels of the neuropeptide oxytocin benefit socioemotional functioning, but little is known about the effects of oxytocin on cognition or about age-related changes in the oxytocin system. In this paper, we will review the role of these hormones in the context of cognitive and socioemotional aging. In particular, we address the aforementioned gap in the literature by: (1) examining both singular actions and interrelations of these four hormonal systems; (2) exploring their correlations and causal relationships with aspects of cognitive and socioemotional aging; and (3) considering multilevel internal and external influences on these hormone systems within the framework of explanatory pluralism. We conclude with a discussion of promising future research directions.

Keywords: hormones, aging, cognitive functioning, socioemotional functioning, cortisol, estrogen, testosterone, oxytocin

INTRODUCTION

Advances in research and technology have extended the human lifespan. Consequently, old and very old individuals are a growing segment of society, and the question of how to maintain or augment cognitive and socioemotional functioning in older age has become an issue of great political, societal, and academic interest. This interest has been further spurred by evidence that some individuals fare better than others in their ability to remain cognitively, socially, and affectively engaged as they age (Tucker-Drob et al., 2014). These improved capacities are often associated with reduced morbidity and mortality (Amieva et al., 2010). An increased understanding of the interplay between the myriad factors that contribute to individual differences in aging trajectories has the potential to inform strategies toward amelioration of negative effects and promotion of life quality among older adults.

These considerations frame the current paper. In it, we review extant research that informs the role of four critical hormone systems—cortisol, estrogen, testosterone, and oxytocin—in age-related changes in brain function. In an attempt to advance research in this area, we focus both on singular and interaction effects of these systems in processes relevant to aging. Conceptually, we are mindful of research indicating that the function of each of these hormone systems is influenced by multiple overlapping and often recursive biopsychosocial factors. Among those are an individual's genes (Tost et al., 2010; Walum et al., 2012), early life experience (Carpenter et al., 2010; MacDonald, 2012), and current relationships (Schneiderman et al., 2012; Zilioli and Watson, 2012). Thus, our general approach to the neurobiology of the aging process is one of empirically based pluralism (Kendler, 2012). In particular, we propose to conceptualize hormones as "difference makers" worth studying in the context of cognitive and socioemotional aging.

AGE-RELATED CHANGE IN COGNITIVE AND SOCIOEMOTIONAL FUNCTIONING

As people age, they typically experience declines in various cognitive functions (Alexander et al., 2012; Tucker-Drob et al., 2014). Though there is notable heterogeneity in patterns of change in

cognitive function both across and within individuals (Albert et al., 1995; Ram et al., 2011; Schmiedek et al., 2013), studies consistently document age-related decreases in processing speed, reasoning ability, and various memory components (Bopp and Verhaeghen, 2005; Willis and Schaie, 2006; Salthouse, 2010). Alongside the broad cognitive aging literature, there is growing evidence of age-related change in socioemotional domains (Blanchard-Fields, 2007; Scheibe and Carstensen, 2010; Ebner and Fischer, 2014). While some of these changes are characterized by decline, other socioemotional functions remain stable or even improve with age. For example, older compared to young adults are worse in interpreting facial cues related to emotion or trust (Isaacowitz et al., 2007; Castle et al., 2012; Ruffman et al., 2012). Older adults also show increased difficulty with memory for social and emotional information such as names (Crook et al., 1993; Verhaeghen and Salthouse, 1997), faces (Bartlett et al., 1989; Grady et al., 1995), and negative emotional pictures or text (Reed et al., 2014). In contrast, the experience of positive affect increases with age (Charles et al., 2001; Teachman, 2006; English and Carstensen, 2014). Also, older adults become better at some aspects of emotion regulation and emotional problem solving (Kunzmann et al., 2005; Blanchard-Fields, 2007; Urry and Gross, 2010; Voelkle et al., 2013) and often show increased wisdom-related knowledge (Staudinger et al., 1992).

Previous studies have discussed possible mechanisms of cognitive and socioemotional age-related change from psychological, contextual, and biological perspectives (Li et al., 2001; Cabeza et al., 2002; Gazzaley et al., 2005; Ruffman et al., 2008; Ebner and Fischer, 2014). However, numerous open questions remain. In this paper, we propose that the level and function of an interrelated suite of hormones—cortisol, estrogen, testosterone, and oxytocin—operating throughout the body and brain have not been sufficiently addressed in their influence on cognition and socioemotional functioning in older adults.

Our focus on these particular hormones was guided by the conceptual consideration that they represent the discrete but overlapping actions of the hypothalamic–pituitary–adrenocortical (HPA) and the hypothalamic–pituitary–gonadal (HPG) axes. To reduce the number of hormones being discussed, we chose to limit this review to examination of a select set of hormones representative of these larger, interconnected systems. In particular, cortisol is released by the adrenal glands as the end product of a coordinated hormonal cascade. Estrogen is released in concert with progesterone by the ovaries and oxytocin and prolactin by the pituitary, with similar implications for behavior. Examination of these particular hormones provides an interesting contrast in that they mediate responses seen as being antithetical (i.e., cortisol and oxytocin) or important for differences between the sexes (i.e., estrogen and testosterone). Another reason to highlight cortisol, estrogen, testosterone, and oxytocin in the present context is that they constitute active regulators of domains important to the aging process (i.e., stress response, emotional support/bonding, biological transition to older age), as discussed below. Thus, as opposed to presenting an exhaustive review of the multitude of factors affecting cognitive and socioemotional development, we chose to describe four hormones representative of these broader psychological and physiological processes to provide a venue for looking at the interactive effects of hormones in aging.

INTERPLAY OF HORMONES, BRAIN, AND BEHAVIOR IN AGING

One useful way of conceptualizing the interplay between brain processes, hormonal activity, and behavior is to think of the brain as an endocrine organ. Within this model, the brain both regulates the production of hormones (through the hypothalamus and pituitary gland), and is itself a target for steroid and sex hormones that cross the blood–brain barrier and exert effects in the central nervous system and downstream regions (McEwen et al., 1979; Martignoni et al., 1992). As such, hormones play a central role in physiologic processes and initiation of signaling pathways responsible for development, aging, growth, immunity, reproduction, and behavior. In order to fully appreciate the multifaceted factors that impact cognition and socioemotional functioning it is crucial to have a clear understanding of the dynamics of age-related endocrine change.

Level and function of many hormones change with age (Weinert and Timiras, 2003; Conrad and Bimonte-Nelson, 2010) and, as a consequence, produce a number of psychological and physiological alterations. Typical changes are reduced secretion from peripheral glands and modifications in the central mechanisms controlling hormone release (Chahal and Drake, 2007). This includes reduction in inhibitory systems and dampening of circadian rhythms. These age-related changes in the endocrine system are complex and differ for specific hormones due to a variety of influences, some of which are concomitant with aging. Among those influences are sociodemographic (e.g., ethnicity, social status), lifestyle (e.g., level of physical activity, body mass index, smoking initiation or cessation, diet), and psychological factors (e.g., overall health status, perceived stress, supportive relationships, social integration; Seeman and McEwen, 1996; Uchino et al., 1996). For instance, in older adults, both physical and psychological changes brought about by body mass index, smoking, unemployment, and loss of a partner were associated with accelerations in individual declines in testosterone levels (Travison et al., 2007), while psychological factors like self-esteem and perceived stress contributed to individual differences in cortisol (Liu et al., 2014). Age-related hormonal change can also be a result of pathology associated with disease risk or decreased longevity.

Changes in brain and behavior are rarely attributable to the actions of a single hormone. Rather, they reflect aggregate and widespread changes across multiple hormonal systems, which themselves have recursive interactions with each other (Jankowska et al., 2006; Cappola et al., 2008). Therefore, examination of combined effects of multiple hormones that act simultaneously throughout body and brain is necessary. Based on this consideration we have structured our review in the following way. We first introduce the four hormones, and their physiological roles, with a particular eye toward their function in cognitive and socioemotional aging. We then continue with an integrative discussion of interdependent hormone effects. In this context, we also cover the modulatory role of sex on the relationship

between hormones and functional levels in aging. The current literature offers a knowledge base for the effects of cortisol, estrogen, and testosterone in aging. However, to date, very little is known about oxytocin's age-associated effects and the majority of what is known in this arena stems from animal work. For this reason, in discussing the effects of cortisol, estrogen, and testosterone on cognitive and socioemotional functioning, we leverage work from both young and older adults, while our discussion of oxytocin's effects is based more exclusively on evidence in young adults. Our discussion is aimed toward developing the central proposal of a multidimensional, systemic, complexity-embracing approach for application in future research.

CORTISOL: AGING, COGNITION, AND SOCIOEMOTIONAL FUNCTIONING

Cortisol is a steroid hormone released by the HPA axis in response to challenging situations. As the primary effector of the biological stress response in humans, it is implicated in a diverse array of physiologic, metabolic, immunologic, and psychological processes directed toward successful coping (Sapolsky et al., 2000; Kassel and Herrlich, 2007). Cortisol receptors are well-represented in limbic structures involved in affective response (i.e., hippocampus, hypothalamus, amygdala) and in regions central to executive function such as the prefrontal cortex and anterior cingulate cortex (Dedovic et al., 2009; Joëls and Baram, 2009). As a result, the effects of cortisol extend beyond the stress and threat response system to impact mood, attention, and memory (Lupien and McEwen, 1997; Sapolsky et al., 2000; de Kloet et al., 2005). Important also for this field of study is research demonstrating the long-term impact of adverse early experiences and their potential to have a canalizing or "programming" effect on stress hormone and inflammation-modulating systems (Glaesmer et al., 2010; Danese and McEwen, 2012; De Bellis and Zisk, 2014; Matthews et al., 2014).

Recent studies of humans showed negative associations between endogenous morning levels of cortisol and cognitive measures of processing speed (Reynolds et al., 2010) and executive function (Venero et al., 2013). In contrast, evidence indicated positive associations between cortisol levels that were acutely elevated by stress or hydrocortisone administration and inhibitory control (Schlosser et al., 2013) as well as spatial learning (Meyer et al., 2013). Regarding cortisol's effect on memory, the evidence is currently mixed (Schwabe et al., 2012; van Ast et al., 2013). While cortisol (as induced by stressful experience or acute administration) appears to enhance memory consolidation, it more often impairs memory retrieval. However, this association is not universal and can be modified by dispositional and situational factors such as testing context, emotional arousal, or previous experience.

There also is evidence that effects of cortisol on cognition vary in a dose-dependent fashion. In particular, there is evidence of cognitive improvements under conditions of moderate, time-limited cortisol elevation but evidence of cognitive impairments when cortisol concentrations are persistent or excessively high (Lupien et al., 1999; Abercrombie et al., 2003; Hupbach and Fieman, 2012; Schilling et al., 2013; Moriarty et al., 2014). It is possible that increased motivation for learning and improved coordination of brain regions involved in cognitive operations underlie the cognition-enhancing effects of moderate, short-term cortisol release (Buchanan and Lovallo, 2001; Cahill et al., 2003; Richter-Levin, 2004; Henckens et al., 2012). In contrast, adverse effects of persistent and high levels of cortisol may be a result of atrophy of brain structures critical to memory and reasoning (e.g., hippocampus; McEwan, 1995; Landfield et al., 2007).

A smaller, but growing body of work has addressed associations between cortisol level and socioemotional function. Socially challenging and emotionally evocative contexts such as social rejection and feelings of embarrassment and loneliness elicit cortisol release (Cacioppo et al., 2000; Gunnar et al., 2003; Gruenewald et al., 2004; Dickerson et al., 2008). Higher stress-reactive levels of cortisol have been associated with impaired social competence (Alink et al., 2012), greater withdrawal in social situations (Smider et al., 2002), reduced interpersonal trust (Takahashi et al., 2005), and less engagement in prosocial behaviors (Mathewson et al., 2012), but increased engagement in aggression (Murray-Close et al., 2008; Platje et al., 2013).

The impact of cortisol on key affective and cognitive processes and brain structures associated with those processes suggests that cortisol may play an important role in producing some of the cognitive and socioemotional changes observed in aging. This is particularly likely given evidence of age-associated changes in cortisol level and rhythm (Lupien et al., 1999; Ferrari et al., 2001). In particular, cortisol mean levels increase progressively with age (Laughlin and Barrett-Connor, 2000; Nater et al., 2013). In addition, the typical decline in cortisol across the course of the day is attenuated in aging (Yen and Laughlin, 1998; Heaney et al., 2010; but see Ice et al., 2004). At the same time, cortisol stress responses are often higher in older than young adults (Seeman et al., 2001; Kudielka et al., 2004; Neupert et al., 2006). A meta-analysis of 45 studies reported a significantly larger cortisol response to pharmacological and psychosocial challenge among older compared to young participants (Burke et al., 2005). This effect of aging on cortisol response was about three times greater in women than men. Of note, there were neither age nor sex differences in pre-challenge baseline cortisol levels. This is in line with other studies suggesting that baseline levels of cortisol may not differ between young and older adults (Wolf et al., 2002; Kukolja et al., 2008; but see Kudielka et al., 2004; Agrigoroaei et al., 2013). However, while current cross-sectional studies comparing basal levels of cortisol do not suggest differences between young and older adults, longitudinal studies measuring change in baseline cortisol level with age within individuals may offer a better predictor of risk for cognitive impairment.

Increased cortisol in response to stress has been identified as a feature of a well-functioning HPA axis. That is, some degree of cortisol rise is an adaptive response to stressful situations and also appears important to cognitive function. Evidence for this comes from a recent study that showed that low compared to high cortisol response to acute stress in older adults was associated with poorer declarative and working memory performance (Almela et al., 2014). These findings highlight the dynamic complexity of the study of hormonal stress-responses, as both the

dynamic reactivity of the system (hyperactive vs. hypoactive responses to challenges) and its intrinsic modulation (shorter vs. prolonged elevations) can impact outcomes (Lupien et al., 2009).

The negative impacts of cortisol among older adults have been proposed to occur, at least in part, as a result of the wear and tear body and brain experience from persistent activation of the biological stress system (McEwan, 2002; Juster et al., 2010). This allostatic load model appears particularly useful in explaining age-related cognitive decline. Chronic overexposure to cortisol damages brain structures and bodily systems. This in turn accelerates the physiological and cognitive aging process (Li et al., 2006; Lupien et al., 2009; Oitzl et al., 2010). This interpretation is supported by evidence that age-related elevations in endogenous cortisol levels were associated with declines in memory performance (Kalmijn et al., 1998; Lupien et al., 1998; Li et al., 2006; Lee et al., 2007; Huang et al., 2009) and executive function (Fonda et al., 2005; Lee et al., 2007). In addition, prolonged cortisol exposure contributed to hippocampal atrophy and cognitive impairments in aging (Lupien et al., 1998; McEwen et al., 1999).

Notably, the direction of the association between cortisol and functioning in aging is not consistent across all studies and a number of modulating psychosocial influences have been identified. One influence to consider is overall health status. Dysregulation of HPA axis activity is common in dementia and progressive cognitive impairment in aging (Csernansky et al., 2006; Lee et al., 2007; Peavy et al., 2009; but see Schrijvers et al., 2011). Alteration in HPA axis activity is also a hallmark of major depression (Holsboer, 2001; Blazer, 2003), although there are mixed results as to the direction of the cortisol-depression relationship (Fiocco et al., 2006; Wrosch et al., 2007; Chuia et al., 2014). Another modulator with high relevance in aging is supportive relationships and social integration (Seeman and McEwen, 1996; Uchino et al., 1996). There is evidence that chronic feelings of loneliness can strain the HPA system and accelerate the aging process (Hawkley and Cacioppo, 2007). Also, cortisol awakening response was higher among lonelier older individuals (Adam et al., 2006) and in those who reported low social status (Wright and Steptoe, 2005). Furthermore, older adults frequently exposed to negative age stereotypes may experience more stress and, as a consequence, a worse aging trajectory (Taylor et al., 2003; Liu et al., 2014; but see Sindi et al., 2012). This may be a result of the body becoming less resilient with age and less able to modulate the increased physiological arousal caused by adverse emotional states (Piazza et al., 2013). Supportive evidence comes from recent studies showing that subliminal exposure of older adults to negative age stereotype primes was associated with greater cardiovascular stress both before and after engagement in cognitive tasks and predicted worse task performance (Levy et al., 2000; Stein et al., 2002; Hess et al., 2003, 2004; O'Brien and Hummert, 2006). In addition, stereotype threat mediated the relation between age and memory recall performance (Chasteen et al., 2005). These findings suggest that negative age stereotypes may act to directly cause stress to older individuals, in that they exacerbate physiological responses when faced with stressors and negatively affect cognitive function.

ESTROGEN AND TESTOSTERONE: AGING, COGNITION, AND SOCIOEMOTIONAL FUNCTIONING

The role of the sex steroid hormones estrogen and testosterone in sexually dimorphic physiological characteristics is well-known. There is also increasing evidence that sex hormones influence cognitive and socioemotional functioning in aging. When controlling for factors such as disease status, weight, and alcohol consumption, increasing age was reliably associated with declines in estrogen and testosterone in humans (Ferrini and Barrett-Connor, 1998). In addition, age-associated estrogen and testosterone deficiencies were predictive of increased frailty and other forms of physical decline (Cappola et al., 2009; Horstman et al., 2012).

Steroid hormones act as trophic factors in brain development and plasticity (Peper et al., 2011). They are involved in neurite growth, myelination, and the organization of connections by augmenting synaptic growth and promoting the formation of dendritic branches and neural connections. As it pertains to the aging process, there is evidence of estrogen's long-term neuroprotective effects in hippocampal aging (Ha et al., 2007). Compared to post-menopausal women, young healthy women had smaller ventricles, less cerebrospinal fluid, and more gray matter. However, post-menopausal women on long-term estrogen supplementation showed a pattern better approximating that of young adults. That is, they showed smaller ventricles and greater white matter volume than post-menopausal women who were not on estrogen supplementation. Hormone exposure did not affect gray matter volumes. Furthermore, as reported in a comprehensive review, the ovarian hormones estrogen and progesterone appear to enhance cortical–cortical and cortical–subcortical connections in the human brain (Peper et al., 2011). For instance, estrogen infusion increased connectivity among the hippocampus and the frontal cortex, as well as the amygdala and the prefrontal cortex, all of which are structures associated with cognitive and emotional processes (Ottowitz et al., 2008).

In addition to these structural effects, the amount of circulating ovarian hormones influenced functional abilities in humans, specifically, verbal memory (Peper et al., 2011) and explicit memory recall (Gooren, 2007). Moreover, estrogen administration was found to protect against neurodegeneration only in cognitively intact women for whom degeneration had not yet started (Siegfried, 2007). A beneficial effect of ovarian hormones on cognitive ability was also shown in the context of Alzheimer's disease (AD), at least for younger women with no cellular damage (Vest and Pike, 2013). However, once the first signs of neurodegeneration were present, supplemental estrogen increased degeneration and accelerated disease progression (Siegfried, 2007). Thus, one potential reason for greater prevalence of AD in women than in men may be the relatively abrupt decrease of ovarian hormones upon menopause.

The relationship between testosterone levels and cognitive functions is mixed. Some studies document an association between decreasing levels of testosterone in old age and cognitive decline in men (Moffat et al., 2002). Other studies suggest that higher levels of testosterone do not contribute to enhanced cognitive ability (Emmelot-Vonk et al., 2008). Also, while some studies (Holland et al., 2011) suggest a neuroprotective effect of testosterone in older men, other studies do not (Gooren, 2007).

It is possible that there is an optimal level of testosterone, which, if surpassed, is not beneficial but rather has negative effects on cognition (Muller et al., 2010; Vest and Pike, 2013). Moreover, the neuroprotective effect reported for testosterone may be the result of its conversion to estrogen in the brain (Garcia-Segura et al., 2001). Or it may be due to direct binding of testosterone to sites with a high density of androgen receptors, such as the hippocampus, a brain structure that is crucial for memory formation (Holland et al., 2011). Notably, estrogen administration trials have failed to show therapeutic effects on present symptoms of AD in women (Henderson et al., 2000; Mulnard et al., 2000). In contrast, some success has been noted for testosterone administration in improving spatial memory (Cherrier et al., 2005) and overall life quality (Lu et al., 2006) in male patients.

In addition to their role in cognition, ovarian hormones have been shown to affect socioemotional functioning. For example, differences in levels of sex hormones may underlie the greater emotional expressivity and increased ability to recognize facial expressions in others seen in women compared to men (Hampson et al., 2006; Kret and De Gelder, 2012). In addition, specific periods of endogenous ovarian hormonal variability have been associated with greater negative mood symptomology in women, such as in premenstrual dysphoric disorder (Andréen et al., 2009; Bäckström et al., 2011). Also, women in the premenstrual phase of their cycles (associated with higher levels of estrogen and progesterone) showed increased activation in the anterior-medial orbitofrontal cortex but lower activation in the lateral orbitofrontal cortex to negative stimuli during an emotional go/no-go task compared to women in the post-menstrual phase (Protopopescu et al., 2005). Similarly, brain activity to positive vs. negative pictures was different in regions such as the medial prefrontal cortex and insula in post-menopausal women treated with estrogen compared to women treated with estrogen plus progestin and untreated women (Shafir et al., 2012). In particular, untreated compared to treated women showed greater activity in the medial prefrontal cortex, insula, and entorhinal cortex during naming of positive pictures.

In contrast with estrogen, high levels of testosterone appear to decrease empathy and increase aggression (Montoya et al., 2012). This is reason to think that, under certain conditions, testosterone may negatively affect aspects of socioemotional functioning. For example, levels of bioavailable testosterone have been associated with greater prevalence of depression as seen in hypogonandal men (Gooren, 2007). Notably, some of these effects of testosterone on socioemotional functioning were sex-specific. This may be due to reliably lower testosterone levels in women than men, which may render women more sensitive to variations in testosterone levels (Bancroft, 2009). For example, in a study conducted with young women, testosterone administration reduced cognitive empathy compared to placebo (van Honk et al., 2011). Similarly, while endogenous testosterone showed a positive association with sexual intimacy, it showed a negative association with nurturant intimacy in both men and women (van Anders et al., 2011). For men, there is further evidence of an association between biologically available testosterone and dominance and aggression (Gray et al., 1991), leading to the influential "challenge hypothesis" of testosterone function (Wingfield et al., 1990). More recent research suggests that the association may be less direct in women, such that an aggression-enhancing effect of naturally occurring high testosterone levels was seen only when cortisol levels were also high (Denson et al., 2013). The importance of recognizing such interaction effects among hormones in their role on cognitive and socioemotional functioning is a central premise of this review and will be discussed in more detail below, with reference to sex modulations and effects on aging.

OXYTOCIN: AGING, COGNITION, AND SOCIOEMOTIONAL FUNCTIONING

Oxytocin is a neuropeptide with both peripheral and central functions (Gimpl and Fahrenholz, 2001). In humans, though it has been traditionally associated with labor and lactation (Pedersen, 1997), oxytocin receptors have also been found in organs unrelated to reproduction (Gimpl and Fahrenholz, 2001). Behaviorally this is reflected in modulatory effects of oxytocin on a wide spectrum of processes related to cognition and socioemotional functioning (Bartz et al., 2011; Meyer-Lindenberg et al., 2011; Feifel et al., 2012; Szeto et al., 2013). These broad effects include a putative role in neurogenesis by which oxytocin administration stimulates adult neurogenesis in the rodent model (Jafarzadeh et al., 2014) even under conditions of stress and elevated glucocorticoids (Leuner et al., 2012).

Throughout this paper, though we emphasize the oxytocin system, we acknowledge the dynamic interplay between the oxytocin and the arginine vasopressin systems (Neumann and Landgraf, 2012). These two neuropeptides share a distant evolutionary ancestor, and differ by only two amino acids. Though their central actions are often contrasted (Legros, 2001; Neumann and Landgraf, 2012), there is also a potential functional overlap between the central effects of these hormones. In particular, oxytocin has an affinity for arginine vasopressin receptor 1A, the vasopressin receptor subtype found most commonly in the brain (Stoop, 2012). Animal experiments, in fact, indicate that arginine vasopressin receptors may play a role in some of oxytocin's central effects (Schorscher-Petcu et al., 2010; Sala et al., 2011; Mak et al., 2012). That said, the majority of human administration and genetic studies have focused on oxytocin rather than arginine vasopressin.

There is some evidence that administration of oxytocin improves social memory in animals and humans (Striepens et al., 2011). For example, in humans, it enhances face recognition (Savaskan et al., 2008; Rimmele et al., 2009). As a recent meta-analysis suggested, there are specific improvements found in the recognition of happy and fearful faces, and, under certain conditions, angry faces (Shahrestani et al., 2013). In addition, intranasal oxytocin increases facial trustworthiness and attractiveness ratings (Theodoridou et al., 2009), interpersonal trust, and the willingness to take social risks (Kosfeld et al., 2005; Baumgartner et al., 2008). It also has been shown to influence social approach, attachment, and bonding processes (Scheele et al., 2013). In a reciprocal manner, social bonding can affect plasma oxytocin levels in humans (Schneiderman et al., 2012). Additionally, intranasal oxytocin increased positive relative to negative behaviors during a laboratory couple conflict and reduced post-conflict and stress-elicited cortisol levels (Ditzen et al., 2009; Quirin et al., 2011; Cardoso et al.,

2013). The latter finding supports interaction effects between oxytocin and cortisol. This potential stress reducing-effect of oxytocin is further informed by evidence that individuals with increased plasma oxytocin healed faster and had a greater number of positive interactions with partners during a 24-h hospital stay (Gouin et al., 2010; see Taylor et al., 2006 for a discussion of oxytocin's role during relaxation vs. stress; see also Feldman et al., 2011). Differing theories about the role of oxytocin in socioemotional processes include oxytocin's role in augmenting the activation of social reward neural circuits, in increasing the salience of social stimuli, in reducing social anxiety, and in promoting social approach in both humans and animals (Yoshida et al., 2009; Zink and Meyer-Lindenberg, 2012; De Dreu, 2014; MacDonald and Feifel, 2014).

Of note, however, there have been inconsistencies across studies reported in the literature. In particular, there is evidence that the response to oxytocin administration varies as a result of personal, contextual, and methodological factors such as sex, genes, distribution and density of oxytocin receptors, and dispositional variables such as trait anxiety, social setting, and specific task instructions and measures (see Bartz et al., 2011; Guastella and MacLeod, 2012, for a balanced discussion).

Though it has been conceptualized as a uniquely "social neuropeptide," a recent theory suggests that oxytocin's well-documented social effects are part of its larger, more general function, namely the biasing of approach-avoidance motivational processes (of which social motivations are exemplars; Harari-Dahan and Bernstein, 2014). This more general function frames our current understanding of the effects of oxytocin on non-social cognition. On one hand, several studies suggest a potential amnesic effect of oxytocin administration for non-social information (Ferguson et al., 2000; Rimmele et al., 2009; Herzmann et al., 2012). For example, there is evidence of worsened verbal memory performance after single-dose oxytocin administration (Ferrier et al., 1980; Fehm-Wolfsdorf et al., 1984; Bruins et al., 1992; Heinrichs et al., 2004). Moreover, Ansseau et al. (1987) documented significant amnesia in a patient with obsessive compulsive disorder after use of intransasal oxytocin over 4 weeks. However, this latter result needs to be interpreted with caution given the single-case nature of this study. On the other hand, these previous findings contrast recent work in a sample of schizophrenic patients that showed improved performance following intranasal oxytocin administration over a period of 3 weeks on several measures of non-social verbal memory, with effects particularly pronounced for short-term recall (Feifel et al., 2012).

Critical also in the present context—and different from the work on cortisol or estrogen and testosterone—is that current studies on oxytocin's role in cognitive and socioemotional functioning in humans have almost exclusively been conducted with young adults (but see Barraza et al., 2013; Campbell et al., 2014). As recently summarized (Ebner et al., 2013; Huffmeijer et al., 2013), the existing evidence on oxytocin and aging in animal research is mixed. Some studies find no noticeable effects of aging on the oxytocin system (Wierda et al., 1991; Arletti et al., 1995), while other studies report age-related change (Fliers and Swaab, 1983; Arsenijevic et al., 1995; Melis et al., 1995). Notably, some of the studies reporting comparability of the oxytocin system across older and young subjects refer to peripheral oxytocin levels (Fliers and Swaab, 1983; Zbuzek et al., 1988; Melis et al., 1992) whereas several of the studies documenting age-related change examine central oxytocin levels (Fliers and Swaab, 1983; Melis et al., 1992; Arsenijevic et al., 1995; Parker et al., 2010). Thus, given that oxytocin has two modes of action, locally, as neurotransmitter, and, peripherally, as a hormone (MacDonald and MacDonald, 2010), it is possible that aging may change oxytocin transmission in the central nervous system but not in the neurohypophyseal-pituitary (i.e., peripheral) system (Melis et al., 1999). The relationship between oxytocin levels in these two "spaces" (brain/cerebrospinal fluid vs. peripheral) and their relationship to brain activity is an active area of exploration (Kagerbauer et al., 2013; Striepens et al., 2013; Crockford et al., 2014). Also, the often profound interpersonal and relational changes associated with advanced age (i.e., loss of partner, reduction of social networks) and evidence of the protective effect of social relationships on age-related cognitive outcomes (Ellwardt et al., 2013) suggest a key role of this profoundly social hormone in the aging process (Feldman, 2012).

MODULATORY ROLE OF SEX ON THE RELATIONSHIP BETWEEN HORMONES AND FUNCTIONAL LEVELS IN AGING

It is already known that sexual dimorphism marks many aspects of the aging process (e.g., differential disease rates in men vs. women). In this review we consider sex as a contributor to individual differences in the relationship between hormones and functional ability in aging. In particular, there is evidence that cortisol, estrogen, testosterone, and oxytocin show different profiles in men and women, especially as they age. Therefore, interactions between these hormones in young adults may differ from the interplay of these hormones in older adults. These sex-specific effects of hormones on cognitive and socioemotional function in aging have not been sufficiently addressed in the current literature.

Sex differences have been an integral part of our discussion of the effects of the sex hormones estrogen and testosterone among older adults. Similarly, there is evidence for sex-specific effects of cortisol. For example, research in humans suggest that older women (Seeman et al., 1997; Comijs et al., 2010) and young men (Wolf et al., 2001; Schoofs et al., 2013) may be most susceptible to cortisol's effects in cognitive and socioemotional domains. Also, there is evidence that cortisol is associated with declines in hippocampal volume for older men but not older women (Pruessner et al., 2001; Bouix et al., 2005). Kudielka et al. (2004) highlight the complexity of evaluating age by sex effects in their examination of responses to psychosocial stress. In their study, older women showed the highest plasma cortisol stress response compared to all other groups. In contrast, for salivary cortisol, older men showed a higher response compared to older women. Similarly, young men compared to young women showed a greater salivary cortisol response to a battery of cognitive tests, while older men compared to older women showed lesser salivary cortisol in response to those tasks (Seeman et al., 2001).

Higher stress responses in older women than older men may be related to estrogen changes in post-menopausal women. This is supported by evidence of increased HPA axis responses to psychosocial stress after as compared to before menopause (Lindheim et al., 1992; Kudielka et al., 1999). Animal work also suggests an

impact of estrogen on HPA axis regulation in the form of a potentiating effect of estrogen treatment on corticosterone levels (Burgess and Handa, 1992; Carey et al., 1995; Weiser and Handa, 2009). However, few experimental studies have been conducted on this topic in humans and with contradictory results. For example, in young men, a 48-h estradiol application resulted in elevated cortisol responsivity (Kirschbaum et al., 1996). In contrast, longer term estradiol treatment in post-menopausal women did not alter psychosocial stress-induced HPA axis responses (Lindheim et al., 1992; Kudielka et al., 1999; but see Del Rio et al., 1998). Work by Sharma et al. (2014) showed an inhibitory effect of estrogen administration in older women compared to a stimulatory effect of testosterone administration in older men on HPA axis activity. In particular, estrogen heightened cortisol negative feedback of the HPA system, thereby providing a signal to suppress further hormone release. These findings are in line with research that estrogen may act directly on the adrenal gland and central HPA targets to alter HPA axis feedback (Figueiredo et al., 2007). They also suggest a possible beneficial role for estrogen treatment in reducing cortisol hyper-responsiveness in post-menopausal women (Veldhuis et al., 2013). However, among post-menopausal women, estradiol treatment predicted increased negative mood and impaired cognition after a psychosocial stressor (Newhouse et al., 2008, 2010; Dumas et al., 2013). Different findings in animals vs. humans, young vs. older adults, and in response physiological vs. psychological indices of stress highlight the need for more research to elucidate the nature of the estrogen–cortisol relationship. Identification of the modulatory dynamics between estrogen and cortisol are likely to inform understanding of the effects of hormones on cognitive and socioemotional aging, especially for older women who experience declining levels of estrogen after menopause.

Regarding sex-specific effects of oxytocin, there is a broad animal literature documenting distinct roles of oxytocin in males and females (see MacDonald, 2012, for references). In contrast, human research examining the role of oxytocin in the context of cognitive and socioemotional functioning particularly via administration studies has been largely conducted in men. This bias is rapidly changing, with recent studies sending a strong signal of sex differences in the dynamics and actions of the human oxytocin system (MacDonald, 2012). In oxytocin administration studies, sex effects have been demonstrated for oxytocin's impact on emotional empathy responses (Hurlemann et al., 2010), amygdala response to emotional images and faces (Guastella et al., 2009; Domes et al., 2010; Marsh et al., 2010; Rupp et al., 2014), conversational intimacy and eye contact (Liu et al., 2012), risk taking (Patel et al., 2014), emotional and cardiovascular responses to a social stressor (Kubzansky et al., 2012), and kinship and competition recognition (Fischer-Shofty et al., 2013).

These sex-specific differences can be framed in the context of the long evolutionary history of oxytocin, and its role in sexually dimorphic reproductive imperatives and survival strategies (Carter, 2014). Among the sex differences which influence our understanding of oxytocin's function is the dominant female role in infant nurturance in most mammalian species. In addition, there are sex differences in relational and stress-regulatory strategies. These suggest that females are more prone to "tend and befriend" (Taylor et al., 2000) while males are biased to "compete and defeat" (David and Lyons-Ruth, 2005; Smeets et al., 2009; Van Vugt, 2009; Gabor et al., 2012). Recent reviews and theoretical proposals address the interactions between the steroid sex hormones estrogen and testosterone and the neuropeptide oxytocin with respect to their differential actions in neural networks activity (van Anders et al., 2011; Bos et al., 2012; McCall and Singer, 2012). They offer a more detailed exploration of the more proximal, neurobiological aspects of distal, phenotypic effects.

One such example is the Steroid/Peptide Theory of Social Bonds (S/P Theory) by van Anders et al. (2011). This theory offers an integration of diverse literatures on different hormones into a single heuristic. In particular, it addresses some of the paradoxes that arise when applying the testosterone "challenge hypothesis" to different types of social bonds. According to the S/P Theory, testosterone moderates the social effects of oxytocin (and also arginine vasopressin), thereby facilitating a distinction between sexual intimacy (associated with high oxytocin and high testosterone) and nurturant intimacy (associated with high oxytocin and low testosterone). The S/P theory—and others like it (see Bos et al., 2012, for a similar construal)—offer a useful perspective to the dynamic, social context- and sex-specific role of neuropeptides (e.g., oxytocin) and steroid hormones (testosterone, and by extension estrogen) over the lifespan. For example, the association of high oxytocin and low testosterone with nurturant intimacy (i.e., loving, warm contact with others) has implications for our understanding of hormonal contributions to changes in partnered sexuality across the lifespan and also for the different social bonds unique to the aging process (i.e., grand-parenting).

Taken together, our understanding of the complex interrelationship between sex hormones, cortisol, oxytocin, and cognitive and socioemotional functioning has grown. However, the modulatory role of sex on the relationship between these different hormones and functional domains, particularly as it pertains to the aging process, is still limited and future research is warranted.

INTEGRATIVE APPROACH ON THE ROLE OF HORMONES IN COGNITIVE AND SOCIOEMOTIONAL AGING: HORMONES AS "DIFFERENCE MAKERS"

As reviewed above, currently known is that chronically high levels of the stress hormone cortisol exert neurotoxic effects on the aging brain with primarily negative impacts on cognition and socioemotional functioning. In contrast, the sex hormones estrogen and testosterone appear to have neuroprotective effects in cognitive aging, but may decrease prosociality under certain conditions and in interaction with other hormones. A relative newcomer in this arena is the neuropeptide oxytocin, which seems to largely benefit socioemotional functioning but has some mixed effects in this domain and has not yet been studied in the contexts of aging and effects on cognition. Importantly, in addition to singular effects, research relating hormones to cognitive and socioemotional functioning in aging reveals complex, interdependent effects across hormones. Several of these interdependent effects have been discussed throughout the paper and, specifically, in the context of the modulatory role of sex

on the relationship between hormones and functional levels in aging.

Despite various publications on these diverse topics, we are still at the beginning of understanding both the specific effects and the interactive relationships of hormones in their role in aging. In this review we have taken an integrative perspective. In particular, we have discussed the wide-ranging effects of cortisol, estrogen, testosterone, and oxytocin, as well as their complex interactions. Thus, we have reached beyond the traditional approach of describing specific functions of individual hormones (e.g., primary behavioral responses such as stress response for cortisol, reproduction or aggression for sex hormones, and mother–infant bonding for oxytocin), and toward a more multidimensional, systemic, complexity-embracing approach.

In line with this approach—and with an eye toward future studies—we propose applying Kendler's (2012) model of empirical pluralism to the study of hormonal influences in aging. Within this approach, we believe that the hormones reviewed above constitute "difference makers," which are amenable to both correlative study (i.e., studying correlations between hormone function, brain, and behavior) and mechanistic study (i.e., following an interventionalist model of causality; Kendler and Campbell, 2009). When applied to the investigation of the neurobiology of aging, this approach notes that important difference-making factors are distributed across multiple biological levels of analysis (i.e., genetics, molecular and systems neuroscience, neuropsychology), as well as situated within different social, political and cultural contexts (Kendler, 2012). This perspective allows for an adequate representation of the complex recursive interactions and patchy causality of hormonal effects on the two interrelated but separate domains of cognition and socioemotional functioning. In particular, we propose that future study of hormones and aging will benefit from examination of complex individual-environment interactions and consideration of biological (e.g., sex, genetic, neurochemical, neurostructural, functional), psychological (e.g., personality, experience, coping), and higher-order contextual (e.g., relational events, social milieu) factors (Kendler, 2012). Within this model, so-called difference makers are measurable factors which can be experimentally examined and viewed as risk factors on or across each of these domains. Examples of such factors are parenting styles, stressful life events, or societal support. In particular, hormonal effects are known to vary as a function of inherent biological characteristics related to an individual's sex as well as genetic makeup and are likely modulated by temporal, relational, and social processes associated with aging. These factors interact with psychological processes and higher-order social-contextual

BOX 1 | Suggested avenues for future research.

Description of a comprehensive pattern of hormonal change in aging

What are the age differences in adulthood in central and peripheral levels and actions of cortisol, estrogen, testosterone, and oxytocin? Do these differences follow a general, hormone-specific model, or is there a global pattern of change associated with aging? To what extent do salivary and blood-based hormone levels tap into central vs. peripheral hormone functions in aging? What are the age-related changes associated with type, density, and specific location of hormonal receptors, in addition to levels of the hormone itself, and to what extent do those changes affect functional levels?

Systematic investigation of functional specificity of effects

How does the impact of cortisol, estrogen, testosterone, and oxytocin vary across functional domains? Which cognitive and socioemotional functions benefit – and which suffer – from age-related change in different hormonal levels?

Consideration of interactive effects among hormones

How do levels of cortisol, estrogen, testosterone, and oxytocin interact to influence age-related changes in cognitive and socioemotional functioning? What are unique and what are joint functions of central and peripheral hormones in aging? Are levels of one hormone contingent on levels of other hormones? Are particular ratios of hormone production in aging associated with certain patterns of function?

Examination of modulating role of sex

To what extent are the effects of cortisol, estrogen, testosterone, and oxytocin in aging modulated by sex? For example, are cortisol's actions in predicting a worse aging trajectory affected by the effects of sex hormones? How might individual differences in the oxytocin system – known to have sex-dependent effects – interact with other hormonal systems?

Emphasis on individual genetic and epigenetic variation in the endocrine system

What genetic polymorphisms are involved in regulation of specific hormones (e.g., *NR3C1* and *FKBP5* for cortisol; *ESR1* and *ESR2* for estrogen; *NR3C4* for testosterone; *OXTR* and *CD38* for oxytocin) and how are those genetic variations associated with functional age-related change? What are epigenetic processes (i.e., methylation, acetylation) that mediate the relationship between hormones and behavior? How does aging influence these epigenetic processes?

Identification of historical, relational, and environmental influences on hormones

How do historical parameters (e.g., childhood trauma) influence hormonal factors and outcomes in aging? To what extent do age-related changes in relational influences like quality and quantity of relationships (e.g., loss of partner, reduced social networks, increased loneliness) and environmental factors (e.g., home-dwelling vs. institution) affect the endocrine system? Do hormones serve as mediators of some of the known causal effects of these "external" factors on functional levels in aging?

Identification of hormonal associations in healthy vs. pathological aging

How do associations between hormones and functional levels vary across healthy vs. pathological aging trajectories? For example, how does the relation between cortisol activity and depression affect cognition in aging?

factors, including personality traits, previous experiences, coping styles, and cultural settings. And together they modulate physiological responses, epigenetic modifications, and subsequent hormonal and brain changes across the lifespan.

PROMISING FUTURE DIRECTIONS

We have identified selected topics (summarized in **Box 1**) which we believe have great potential to advance understanding of the effects of hormonal systems on cognitive and socioemotional aging. We propose a research focus toward description of a comprehensive pattern of hormonal dynamics in aging. Such a program would integrate central and peripheral hormone function and strive to enhance knowledge of hormone-specific as well as global age-related change. Moving forward, a thorough description of other hormones, such as progesterone and vasopressin that appear to act in concert with estrogen and oxytocin, in their role on cognition and socioemotional functioning is warranted. This will further clarify the complex relationship between biological, psychological, and social factors that contribute to individual differences in aging trajectories.

Our review and reflections, for the most part, focused on central hormone levels, which we acknowledge may not be equivalent to peripheral levels. For cortisol, high correlations are observed between blood and saliva (Gozansky et al., 2005; Restituto et al., 2008; VanBruggen et al., 2011), allowing researchers to assess salivary cortisol as a proxy for both central and peripheral functions (Hellhammer et al., 2009). However, for oxytocin, the correlations between blood and saliva are less well-understood (Feldman et al., 2011). Of note, there is exciting emerging research in humans of a positive correlation between cerebrospinal fluid and plasma oxytocin concentrations. This evidence validates central and peripheral markers of oxytocin and suggests that measurements of peripheral levels of some hormones may well-reflect central levels (Carson et al., 2014). Therefore, moving forward, it will be crucial to thoroughly examine both salivary and blood-based hormone levels in the attempt to determine overlap and dissociation of central and peripheral hormone functions.

Given the multidirectionality of aging across functional domains, a systematic investigation of functional specificity of endocrine effects will be particularly informative. It will be crucial to consider modulatory effects among various hormones as well as biological factors (including sex), to draw a comprehensive picture of the effects of hormones in cognitive and socioemotional aging. In line with a recently proposed model of the effects of oxytocin in aging (AGeNeS-OT model; Ebner et al., 2013), individual genetic (i.e., neuropeptidergic individuality; MacDonald, 2012) and epigenetic variation in endocrine systems (often as the result of early experience; McGowan, 2012; Bohacek et al., 2013) constitute important factors that need increased attention in future research (Di Napoli et al., 2014). Identification of genetic polymorphisms involved in hormone regulation as well as epigenetic modulations active in the aging process and their associations with functional levels will be particularly crucial in this context. Said differently, within this multi-level explanatory framework, systematic examination of historical, relational, and environmental influences on hormones and on functional levels in aging is needed. Also, examination of the dissociation between hormone-brain-behavior relationships in normal vs. pathological aging has the potential to further inform clinical interventions.

One aim of this paper was to raise consciousness about a "hormonal level of explanation" in brain-based aging processes. We are confident that adoption of a view on hormones as difference markers in cognitive and socioemotional aging in the context of a multidimensional, systemic approach will spur new research and help move forward this exciting domain of inquiry.

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Behavioral/Cognitive

Re-Opening the Critical Window for Estrogen Therapy

Linda A. Bean,[1] Ashok Kumar,[1] Asha Rani,[1] Mike Guidi,[2] Awilda M. Rosario,[3] Pedro E. Cruz,[3] Todd E. Golde,[3] and Thomas C. Foster[1]

[1]Department of Neuroscience, McKnight Brain Institute, University of Florida, Gainesville, Florida 32611, [2]Noldus Information Technology, Leesburg, Virginia 20176, and [3]Department of Neuroscience, Center for Translational Research in Neurodegenerative Disease, University of Florida College of Medicine, Gainesville, Florida 32610

A decline in estradiol (E2)-mediated cognitive benefits denotes a critical window for the therapeutic effects of E2, but the mechanism for closing of the critical window is unknown. We hypothesized that upregulating the expression of estrogen receptor α (ERα) or estrogen receptor β (ERβ) in the hippocampus of aged animals would restore the therapeutic potential of E2 treatments and rejuvenate E2-induced hippocampal plasticity. Female rats (15 months) were ovariectomized, and, 14 weeks later, adeno-associated viral vectors were used to express ERα, ERβ, or green fluorescent protein (GFP) in the CA1 region of the dorsal hippocampus. Animals were subsequently treated for 5 weeks with cyclic injections of 17β-estradiol-3-benzoate (EB, 10 μg) or oil vehicle. Spatial memory was examined 48 h after EB/oil treatment. EB treatment in the GFP (GFP + EB) and ERβ (ERβ + EB) groups failed to improve episodic spatial memory relative to oil-treated animals, indicating closing of the critical window. Expression of ERβ failed to improve cognition and was associated with a modest learning impairment. Cognitive benefits were specific to animals expressing ERα that received EB treatment (ERα + EB), such that memory was improved relative to ERα + oil and GFP + EB. Similarly, ERα + EB animals exhibited enhanced NMDAR-mediated synaptic transmission compared with the ERα + oil and GFP + EB groups. This is the first demonstration that the window for E2-mediated benefits on cognition and hippocampal E2 responsiveness can be reinstated by increased expression of ERα.

Key words: aging; ERα and ERβ; estrogen; hippocampus; learning and memory; NMDA receptor

Significance Statement

Estradiol is neuroprotective, promotes synaptic plasticity in the hippocampus, and protects against cognitive decline associated with aging and neurodegenerative diseases. However, animal models and clinical studies indicate a critical window for the therapeutic treatment such that the beneficial effects are lost with advanced age and/or with extended hormone deprivation. We used gene therapy to upregulate expression of the estrogen receptors ERα and ERβ and demonstrate that the window for estradiol's beneficial effects on memory and hippocampal synaptic function can be reinstated by enhancing the expression of ERα. Our findings suggest that the activity of ERα controls the therapeutic window by regulating synaptic plasticity mechanisms involved in memory.

Introduction

Beneficial effects of estrogen replacement on cognitive function during the perimenopausal period are widely accepted; however, prescribing estrogen therapy to women experiencing cognitive problems remains controversial (Rocca et al., 2011; Maki, 2013). This controversy is based on findings from the Women's Health Initiative Memory Study (WHIMS), which examined estrogen effects on women that were postmenopausal for ~15 years. These results suggest that estrogen therapy did not improve cognitive function (Espeland et al., 2004; Shumaker et al., 2004). Animal and clinical studies have provided evidence for a critical time interval for therapy initiation (i.e., a therapeutic or critical window) such that advanced age and/or extended hormone deprivation result in a loss of the E2-mediated beneficial effects (Gibbs, 2000; Foster et al., 2003; Daniel et al., 2006; Rocca et al., 2011).

E2 induces changes in hippocampal anatomy, physiology, transcription, and Ca^{2+} signaling cascades that are opposite to that observed during aging, suggesting possible mechanisms for hormonal regulation of cognitive function (Foster, 2005; Aenlle and

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Correspondence should be addressed to either Dr. Thomas C. Foster or Dr. Ashok Kumar, Department of Neuroscience, McKnight Brain Institute, University of Florida, P.O. Box 100244, Gainesville, FL 32610-0244, E-mail: foster1@ufl.edu or kash@ufl.edu.

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Foster, 2010). Hippocampal E2 responsiveness declines with advancing age or extended hormone deprivation (Foster, 2005, 2012a; Bean et al., 2014). NMDAR synaptic responses are increased at hippocampal CA1 synapses 48 h after E2 treatment (Woolley et al., 1997; Smith and McMahon, 2006; Snyder et al., 2011) and the ability of E2 to enhance NMDAR responses is reduced by extended hormone deprivation (Smith et al., 2010; Vedder et al., 2014). Episodic spatial memory depends on NMDAR function (Foster, 2012b). Therefore, a decline in NMDAR-mediated synaptic transmission is associated with age-related deficits in episodic memory (Foster, 2012b; Kumar and Foster, 2013; Lee et al., 2014). In female rats, delay-dependent spatial episodic memory is particularly sensitive to the history of E2 treatment (Gibbs, 2000; Markham et al., 2002; Markowska and Savonenko, 2002; Foster et al., 2003; Daniel et al., 2006). Therefore, the loss of NMDAR responsiveness to E2 may contribute to the loss of E2's beneficial effects on spatial episodic memory.

The mechanism for the closing of the therapeutic window is unknown, but may involve a shift in estrogen receptor (ER) expression (Foster, 2005, 2012a; Bean et al., 2014). Estrogen's actions are mediated through two classical nuclear ERs, ERα and ERβ. Expression of both ER subtypes declines in the hippocampus of aged rodent models (Adams et al., 2002; Mehra et al., 2005; Waters et al., 2011; Zhang et al., 2011). Studies using viral-vector-mediated expression of hippocampal ERα and ERβ suggest that ERα is critical in maintaining cognitive function in young and middle-aged animals (Foster et al., 2008; Witty et al., 2012; Han et al., 2013). These results suggest that closing of the therapeutic window may be due to decreased activity of ERα and/or ERβ and that increased receptor expression in the hippocampus could rejuvenate estrogen responsiveness and reopen the therapeutic window.

The current study explores the hypothesis that increased expression of ERα or ERβ will reinstate estrogen's beneficial effects, enhancing NMDAR synaptic responses and cognitive function at a time point when estrogen therapy alone has no effect (i.e., after the closing of the critical window). We used an adeno-associated virus (AAV) to upregulate ERα, ERβ, or green fluorescent protein (GFP) in the hippocampus of female rats (18.5 months) that had been ovariectomized 14 weeks earlier. After viral injections, rats were treated with cyclic injections of 17β-estradiol-3-benzoate (EB) or oil for 5 weeks. Learning and memory on the spatial water maze was assessed 48 h after an EB/oil treatment. After behavioral testing, cyclic injections continued until the hippocampus was collected for histology, Western blot analysis, or examination of NMDAR function in an *in vitro* hippocampal slice preparation. Animals that received both AAV-ERα and EB treatment had enhanced episodic spatial memory. Electrophysiological recordings revealed that the combined expression of ERα with EB treatment enhanced the NMDAR component of synaptic transmission. Together, our results provide strong evidence for the idea that the critical window depends on ERα activity, such that increasing ERα expression reinstates hippocampal responsiveness to E2 treatment.

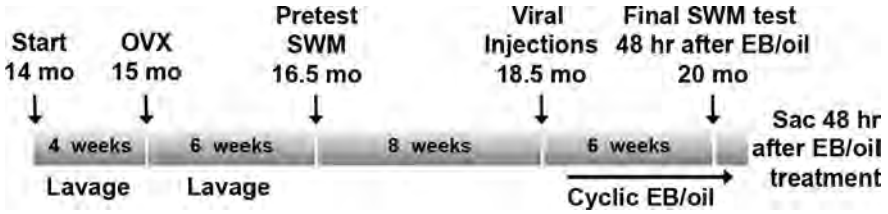

Figure 1. Experimental timeline. Female Fischer 344 rats were received at 14 months of age and lavaged to examine the estrous cycle before removal of the ovaries at 15 months. Five to 6 weeks after OVX, the animals were behaviorally tested in the spatial water maze and assigned to ER or EB/oil treatment groups. Eight weeks later, 14 weeks after OVX, stereotaxic surgery was used to deliver viral vectors encoding ERα, ERβ, or GFP bilaterally into the dorsal hippocampi. The animals were allowed 1 week to recover and were then given cyclic injections of EB or oil for 5 weeks. Final behavioral assessment in the water maze was at 20 months of age and initiated 48 h after the seventh cycle of EB/oil treatment. Cyclic EB/oil treatments continued (1–7 additional cycles) and rats were sacrificed (Sac) 48 h after a final EB/oil treatment for electrophysiology, histology, and Western blot analysis.

Materials and Methods

Subjects

Eighty female Fischer 344 rats (14 months of age) were obtained from National Institute on Aging colony (Taconic) through the University of Florida Animal Care and Service Facility. Animals were housed 2 per cage and maintained on a 12:12 h light/dark cycle (lights on at 6:00 A.M.). All procedures involving animal subjects were reviewed and approved by the Institutional Animal Care and Use Committee at the University of Florida and were performed in accordance with guidelines established by the U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals. Food and water were provided *ad libitum* until surgery, after which animals were switched to a casein-based chow (Cincinnati Lab Supply); this diet has lower levels of phytoestrogens compared with soy-based rat chow. For the experimental timeline, please refer to Figure 1. Eight animals had to be removed from this study due to health concerns. The final six experimental groups included: ERα + EB ($n = 13$), ERβ + EB ($n = 11$), GFP + EB ($n = 13$), ERα + oil ($n = 12$), ERβ + oil ($n = 11$), and GFP + oil ($n = 12$).

Endocrine status and efficacy of EB treatment

Vaginal lavage was performed each day for 2–3 weeks to confirm an estrous cycle before ovariectomy (OVX), after OVX for 1 week to validate removal of the ovaries and during EB/oil treatment to confirm efficacy of treatment. Every morning between 9:00 and 11:00 A.M., vaginal secretions were collected from each animal using a smooth-tipped glass eye dropper and 1 drop (~20–30 μl) of sterile 0.9% saline. Vaginal secretions were placed on glass slides. The phase of the estrous cycle was recorded after viewing the unstained wet slide under low magnification on a light microscope. Determination of the estrous phase (proestrus, estrus, metestrus, and diestrus) was based on the cytology of the collected cells (nucleated epithelial cells, cornified squamous epithelial cells, and leukocytes) (Marcondes et al., 2002).

At the time rats were killed, 48 hours after the final EB treatment, blood was collected and centrifuged at 5000 rpm for 10 min at 4°C. The plasma was stored at −20°C for subsequent analysis. Plasma E2 levels were measured by using a mouse/rat estradiol ELISA kit (Calbiotech). In addition, 2-cm-long sections of the right uterine horn (cut at the base) were removed and weighed to confirm efficacy of EB treatments.

OVX

Female rats received bilateral OVX at 15 months of age using aseptic procedures as described previously (Kumar and Foster, 2002; Sharrow et al., 2002; Foster et al., 2003; Kumar and Foster, 2004). Briefly, isoflurane (Piramal Healthcare) was administered in O_2 using an isoflurane anesthesia system (VetEquip). Induction of anesthesia was initiated within an induction chamber using a 4% concentration of isoflurane. After transfer to a nose cone, a 1.5–2% concentration was used for maintenance of the surgical plane of anesthesia. O_2 was delivered at 1 L/min. The ovaries were removed and the overlying muscle was sutured and the skin stapled to close the incisions. Subcutaneous injections of buprenorphine 0.03 mg/kg and 5–10 ml of saline were given for pain and hydration, respectively.

Hippocampal AAV injections

Fourteen weeks after OVX and 8–9 weeks after pretest behavioral characterization (Fig. 1), AAV1 (2 μl; ~3.0×10^{13} transducing units) encoding ERα, ERβ, or GFP was bilaterally injected into the CA1 region of the dorsal hippocampus (anterior/posterior −3.3 mm and medial/lateral ±

2 mm of bregma, dorsal/ventral −2.6 to −2.8 mm) using a Kopf stereotaxic frame. Techniques for hippocampal injection of virus have been described previously (Foster et al., 2008; Lee et al., 2012; Lee et al., 2014).

Spatial water maze

Five to 6 weeks after OVX, animals were pseudorandomly assigned to virus (i.e., ER expression) and treatment groups and characterized for visual and spatial discrimination on the spatial water maze (Pretest). A second series of spatial and cue discrimination testing occurred 5–6 weeks after the intrahippocampal injections of viral vectors and the initiation of EB or oil treatment (Final test). For Pretest characterization, rats were first trained on a cue version of the spatial water maze. Three days later, rats were trained in a 1 d spatial discrimination version using previously described methods (Foster et al., 2003; Foster and Kumar, 2007; Guidi and Foster, 2012; Kumar et al., 2012; Lee et al., 2012; Kumar and Foster, 2013; Guidi et al., 2014). Briefly, animals were first habituated to the pool by 3 30 s free swims with gentle guidance to a platform that extended 1 cm above the water line and supported a visible white flag. Cue training consisted of 5 blocks of 3 trials with all training occurring in 1 d. Release points and platform locations were randomized across trials. At the beginning of each trial, rats were placed into the water and given 60 s to find the escape platform. If the animal did not escape within the allotted time, it was gently guided to the platform. For spatial discrimination, the escape platform was hidden 1.5 cm beneath the water level and remained in the same location throughout the training. Large extramaze cues were placed on black curtains that surrounded the pool. Training consisted of five blocks of three trials, followed by a 60 s free swim probe trial to test acquisition of a spatial search strategy. For probe trials, the platform was removed and the animal was released from the quadrant opposite the goal quadrant (Guidi and Foster, 2012). A refresher-training block followed the probe trial to reinforce the location of the submerged platform (Guidi and Foster, 2012). A final Pretest retention probe was administered 24 h after spatial training. For both cue and spatial training, the intertrial intervals were 20 s and interblock intervals were ~15 min.

Due to poor 24 h retention observed during the Pretest retention probe trial (see Fig. 4*D*), the spatial training task was modified for the Final test under the experimental conditions. The acquisition probe was conducted immediately after the end of Block 4 and followed by a refresher block (Block 5). After the completion of Block 5, there was a 1 h delay before the retention probe, which was followed by a second refresher block (Block 6). Twenty-four hours later, the animals were subjected to a single training block (Block 7) before a final probe trial. After the final probe trial, the cue discrimination task was again administered to insure that virus or injection treatments did not result in visuomotor impairments. EthoVision video tracking software (Noldus) was used to record the distances traveled, the time spent in each quadrant, and the total time in the arena. For each probe trial, quadrant search time was used to calculate a discrimination index (DI) score using the formula $(G - O)/(G + O)$, where G and O represent the percentage of time spent in the goal quadrant and quadrant opposite the goal, respectively.

Estradiol treatments

Subcutaneous injection of EB elevates blood E2 levels shortly after injection and E2 levels stabilize into the physiological range over the next 24–48 h (Woolley and McEwen, 1993). In addition, cyclic injections of EB given 48 h before behavioral testing improve memory retention in the water maze task for young and middle-aged OVX female rats (Sandstrom and Williams, 2001) and middle-aged mice (Aenlle et al., 2009). Therefore, aged female rats (~300 g) received either EB (10 μg in 100 μl of oil vehicle, ~33 μg/kg) or oil (100 μl) injected subcutaneously at the nape of the neck on 2 contiguous days of a 5 d cycle. The injections were initiated 1 week after viral injection and continued for 7 cycles before behavior testing (Final test). After behavioral testing, cyclic EB/oil treatments continued (1–7 more cycles) and rats were pseudorandomly killed for electrophysiology, histology, and Western blot analysis 48 h after the final EB/oil treatment (Fig. 1).

Hippocampal slice preparation and electrophysiological recordings

Methods for hippocampal slice preparation and electrophysiological recordings have been published previously (Bodhinathan et al., 2010; Kumar et al., 2012; Kumar and Foster, 2013, 2014; Lee et al., 2014). Briefly, 48 h after the final EB/oil treatment, the rats were deeply anesthetized using isoflurane and decapitated with a guillotine (MyNeuroLab). The brains were quickly removed, the hippocampi dissected, and slices (~400 μm) were cut parallel to the alvear fiber using a tissue chopper (Mickle Laboratory Engineering). The slices were placed in a recording chamber (Warner Instruments) and continuously bathed with oxygenated artificial CSF (aCSF) containing the following (in mM): 124 NaCl, 2 KCl, 1.25 KH_2PO_4, 2 $MgSO_4$, 2 $CaCl_2$, 26 $NaHCO_3$, and 10 D-glucose at the rate of 2 ml/min and 30 ± 0.5°C. The aCSF had been previously bubbled with 95% O_2 and 5% CO_2 for 20 min and the pH was adjusted to 7.4.

Field EPSPs (fEPSPs) were recorded from the stratum radiatum of the CA1 region of the hippocampus using glass micropipettes (4–6 MΩ) filled with aCSF and placed 1 mm away from the stimulating electrode as described previously (Bodhinathan et al., 2010; Kumar and Foster, 2013; Lee et al., 2014). A concentric bipolar stimulating electrode (outer pole: stainless steel, 200 μm diameter; inner pole: platinum/iridium, 25 μm diameter) was localized to the middle of the stratum radiatum to stimulate CA3 inputs onto CA1. Using a SD9 stimulator (Grass Instruments), field potentials (0.033 Hz) were induced by diphasic stimulus pulses (100 μs). Signals were then amplified, filtered (1 Hz and 1 kHz) and saved on a computer for later offline analysis.

Methods to isolate the NMDAR-mediated component of the fEPSP (NMDAR-fEPSP) have been described previously (Bodhinathan et al., 2010; Kumar and Foster, 2013; Lee et al., 2014; Guidi et al., 2015). After recording of the total-fEPSP, slices were subsequently bathed in aCSF containing low extracellular Mg^{2+} (0.5 mM), 6,7-dinitroquinoxaline-2,3-dione (DNQX, 30 μM, Sigma-Aldrich), and picrotoxin (PTX, 10 μM; Tocris Bioscience). The DNQX was initially dissolved in dimethylsulfoxide (Sigma-Aldrich) before dilution in aCSF and PTX was initially dissolved in ethanol before dilution in aCSF. Input–output curves for the total-fEPSP and NMDAR-fEPSP slope were constructed for increasing stimulation strength. EPSP slope (mV/msec) was calculated as the difference between two cursors, separated by 1 ms, and placed on the middle portion of the descending phase of the EPSP.

Immunohistochemistry

Forty-eight hours after the last cycle of EB/oil treatment, 3 animals from each group were perfused using 4% paraformaldehyde (PFA) in 1× PBS. Brains were harvested, postfixed in 4% PFA for 2 h, and placed into 30% sucrose in PBS at 4°C until fully infiltrated. The brains were then embedded in Tissue-Tek O.C.T. Compound (Ted Pella) before sectioning. To determine viral vector expression specificity, sections (16 μm) were incubated with primary antibodies against the cmyc-tag (A21281, 1:2000 dilution; Invitrogen), NeuN (MABN140, 1:500 dilution; Millipore), glial fibrillary acidic protein (GFAP, Z0334, 1:500; Dako), or ERα (MC20, 1:200 dilution; Santa Cruz Biotechnology) overnight at 4°C, washed 3 × 15 min in PBS, and then incubated in Alexa Fluor 594 or Alexa Fluor 488 secondary antibody (1:500 dilution; Invitrogen) for 1 h at room temperature. Sections were washed and counterstained with DAPI (0.1 μg/ml in PBS). Stained slides were viewed on a Leica DM2500 upright fluorescent microscope equipped with an Optronics camera and images were captured using MagnaFire software.

Western blot analysis

The CA1 regions from dorsal hippocampi were isolated, flash frozen in liquid nitrogen, and stored at −80°C. Tissues were sonicated and lysed in radio-immunoprecipitation assay buffer (Thermo Scientific) supplemented with phosphatase inhibitors, protease inhibitors, and EDTA (Thermo Scientific) and centrifuged at 20,000 × *g* for 10 min at 4°C. Protein concentrations were measured using a Pierce BCA protein assay. Lysates were denatured in Laemmli buffer with 2-mercaptoethanol (Bio-Rad) and boiled at 100°C for 5 min before electrophoresis. Aliquots (15–30 μg) and Kaleidoscope protein standards (Bio-Rad) were separated on 7.5% extracellular signal-regulated kinase (ERK) or 4%–15% Tris-HCl gels (Bio-Rad).

For the initial testing of virus expression in cell cultures (see Fig. 3*B*), Western blot analysis used a film method to image and quantify ERα and ERβ protein levels; all other figures for Western blot analysis used the new Li-Cor Odyssey system for analysis and quantification. For the film method, the gels were transferred to PVDF membranes (GE Healthcare). The immunoblots were blocked in Tris-buffered saline (TBS) with 5% nonfat powdered milk and 0.1% Tween 20 for 1 h at room temperature, followed by overnight incubation at 4°C with diluted primary antibodies for ERα (Ab17, RB-1521, 1:1000 dilution; Thermo Scientific), ERβ (H-150, sc-8974, 1:100; Santa Cruz Biotechnology), or cmyc-tag (A21281, 1:2000 dilution; Invitrogen) diluted in blocking buffer solution. Membranes were subsequently incubated with horseradish peroxidase-conjugated secondary antibody directed against the primary antibody (Cell Signaling Technology). Membranes were reacted with an enhanced chemiluminescent substrate (, catalog #RPN2132; GE Healthcare) for visualization. Blots were exposed to BioMaxMR film (Kodak), developed on a film processor (SRX-101A; Konica Medical), and scanned using a GS-800 Calibrated Densitometer (Bio-Rad). Protein levels were quantified using ImageJ software.

For membranes imaged and quantified with the Odyssey infrared scanner (Li-Cor), proteins were transferred to a supported nitrocellulose membrane (catalog #162-0070; Bio-Rad), blocked with Odyssey blocking buffer (catalog #927-50000; Li-Cor) for 1 h, and probed overnight in 4°C with antibodies for ERα (Ab17, RB-1521, 1:1000, Thermo Scientific or MC20, sc-542, 1:500, Santa Cruz Biotechnology), ERβ (D7N, 51-7700, 1:500; Invitrogen), PSD95 (MAB1598, 1:2000; Millipore), synaptophysin (#4329, 1:1000; Cell Signaling Technology), NR2A (M264, 1:1000; Sigma-Aldrich), NR2B (05-920, 1:1000; Millipore), pNR2B (S1303, GTX62089, 1:1000; GeneTex), GluR1 (sc-13185, 1:1000; Santa Cruz Biotechnology), pGluR1 (S831, P1160-831, 1:1000; Phospho-Solutions), total ERK (1:10,000, catalog #9107; Cell Signaling Technology), phosphorylated ERK (pERK, 1:2000, #9101; Cell Signaling Technology), and glyceraldehyde 3-phosphate dehydrogenase (GAPDH; 1:10,000; EnCor Biotechnology). Membranes were incubated with an IRDye 800CW and 680LT secondary antibodies (1:25,000 and 1:20,000, respectively) for 1 h at room temperature, washed with TBST 3 times for 10 min each, and rinsed 3 times with TBS before imaging. Protein expression was normalized to the expression of GAPDH. For statistical analysis, the GAPDH normalized values were normalized to expression in GFP + oil animals.

Statistical analyses

For behavioral and electrophysiological studies, repeated-measures ANOVA and two-way ANOVA for main effects of ER group and treatment were used to identify significant main effects and interactions; Fisher's PLSD were used for *post hoc* comparisons ($p < 0.05$). For completeness, the *F*-score statistics are provided for ANOVAs in which the *p*-values are <0.2. For main effects or interactions that exhibited a tendency toward significance ($0.1 > p > 0.05$), *post hoc* ANOVAs within each treatment or ER group were used to localize specific differences (Hsu, 1996; Huck, 2009). One-group/one-sample *t* tests ($p < 0.05$; Gehring, 1978) were used to determine whether DI scores, calculated from the quadrant search behavior, were different from what was expected by chance (i.e., a DI score = 0).

Construction of AAV vectors

CTR4-ESR1-cmyc and CTR0-ESR2-cmyc. cDNAs for human ESR1 (ERα) and ESR2 (ERβ) were subcloned into a rAAV expression plasmid under the control of the hybrid promoter, chicken β actin (CBA), with a woodchuck hepatitis virus posttranscriptional-regulatory element and bovine growth hormone polyadenylation signal. In addition, the hybrid CBA promoter contained a cytomegalovirus (CMV) enhancer. The cmyc epitope tag DNA sequence was added to the 3′ end of the ER cDNA by PCR. Figure 2 illustrates the plasmid maps for CTR4-ESR1-cmyc and CTR0-ESR2-cmyc. The integrity of the resulting ESR1 and ESR2 plasmid vectors was confirmed by sequencing. Plasmids were subsequently packaged by cotransfecting with AAV1 helper plasmid (pDP1rs) in HEK293T cells. Seventy-two hours after transfection, cells were harvested and lysed in the presence of 0.5% sodium deoxycholate and 50 U/ml benzonase (Sigma-Aldrich) by freeze-thaw cycles. The virus was isolated using a discontinuous iodixanol gradient and affinity purified with an Amicon Ultra filter device 100,000 MVCO (Millipore). Vectors were titered using qPCR (Bio-Rad CFX384). Genomic titers were $\sim 3 \times 10^{13}$ vectors genome per milliliter for each vector.

pcDNA-ERE-TA-SEAP. Additional plasmids were created to assess the function of the ERα and ERβ vectors. DNA for secreted embryonic alkaline phosphatase (SEAP; gift from Dr. Bradley Fletcher, University of Florida) and pcDNA plasmid vector were cut with restriction enzyme NOT1 and then ligated using a rapid ligation kit. The resulting plasmid was cloned, cut with BglII and EcoRI, and ligated with DNA containing the minimal TA promoter and the estrogen response element (ERE). The final plasmid was cloned, purified, and subsequently verified by sequencing. Additional control plasmids were created by removing the ERE sequence (negative control) and by replacing the TA promoter with a constitutively active CMV promoter (positive control).

Transfections. HEK293T cells were maintained in DMEM containing 10% charcoal-filtered serum (Cocalico Biologicals) and 1% penicillin/streptomycin. The day before transfection, cells were plated onto 24-well plates and grown overnight in DMEM containing 10% charcoal-filtered serum. On the day of transfection, the medium was removed and replaced with 0.4 ml of fresh medium. Transfection mixture for each well was prepared by adding 800 ng of ERE-TA-SEAP vector (or control vector) and 800 ng of either CTR4-ESR1-cmyc (ERα), CTR0-ESR2-cmyc (ERβ), or AAV-GFP plasmids to 50 μl of Opti-MEM 1, mixing, and then adding Lipofectamine 2000 (Life Technologies) according to the manufacturer's protocol. This mixture was incubated at room temperature for 20 min and the mixture was added into each well. After a 5 h incubation at 37°C, the cultures were rinsed and allowed to grow overnight at 37°C in fresh medium containing 10% charcoal-filtered serum. EB (1 or 10 nM) or vehicle was added to the culture medium. After overnight incubation, 50 μl of culture media was collected from each culture well, centrifuged at 12,000 rpm for 10 s, and the cleared supernatant was transferred into a fresh microcentrifuge tube. Levels of SEAP in the medium were measured using a Phospha-Light chemiluminescent assay kit (Applied Biosystems) according to the manufacturer's protocol. Samples were run in triplicate, and light emission from the processed samples and SEAP standards were measured using a Bio Tek luminometer with a delay of 2 s and integration time of 5 s. The amount of SEAP in the culture medium samples was calculated from the standard curve. Western blot analysis was also used to verify increased expression of the cmyc-tagged ERs in cell culture.

Results

Functional characterization of ER-containing plasmids and virus

To test the functionality of the ER expression plasmids, HEK293T cells were cotransfected with the CTR4-ESR1-cmyc (ERα), CTR0-ESR2-cmyc (ERβ), or AAV-GFP plasmids and a vector encoding the SEAP reporter under the control of an ERE and a minimal promoter (reporter construct: ERE-TA-SEAP). The SEAP level was influenced differentially by the receptor subtype and dose of EB (Fig. 3*A*). An ANOVA on the SEAP levels indicated a significant difference across groups ($F_{(8,24)} = 19.98$, $p < 0.001$) and *post hoc* tests confirmed that, relative to the control group, expression of ERα alone could drive transcription (Foster et al., 2008). SEAP levels were further increased to an apparent asymptote by addition of 1 or 10 nm EB. For ERβ-transfected cells, SEAP expression was not altered in the absence of EB treatment and expression increased dose dependently after EB treatment. These results indicate that the receptors are functional and confirm that ERα is more effective than ERβ in inducing transcription (Foster, 2012a; Han et al., 2013).

To verify successful packaging of the plasmids into the AAV capsids, cmyc-tagged ERα or ERβ expression was confirmed in cell lysate by Western analysis (Fig. 3*B*). A band of cmyc-tag was localized at the appropriate atomic mass for ERα (~67 kDa) and

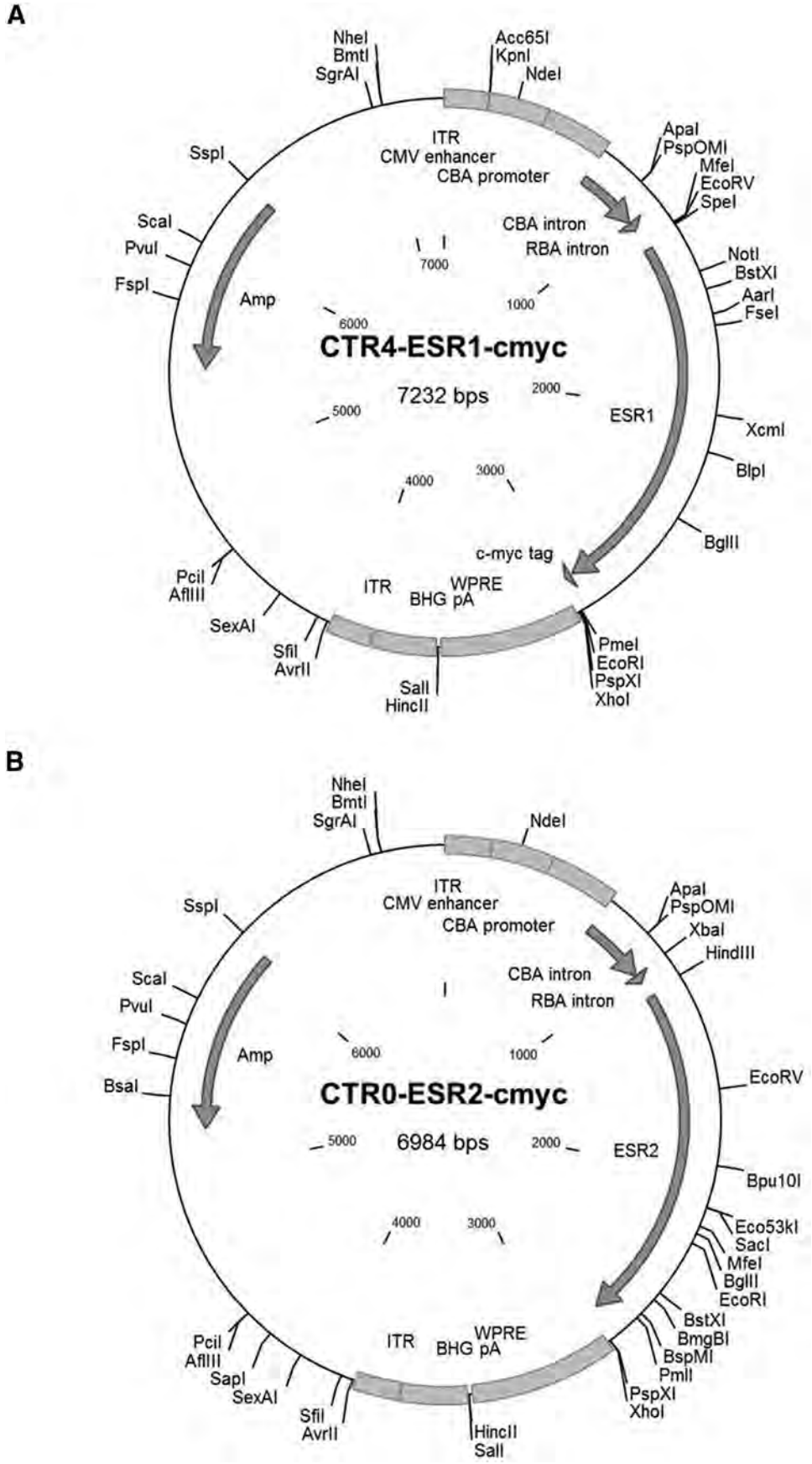

Figure 2. Plasmid maps. ESR1 cDNA for ERα expression (***A***) and ESR2 cDNA for ERβ expression (***B***) were cloned into vectors containing a CBA promoter with a CMV enhancer element. Plasmids were packaged into an AAV1 capsid before stereotaxic injections into the dorsal hippocampus of aged OVX female rats.

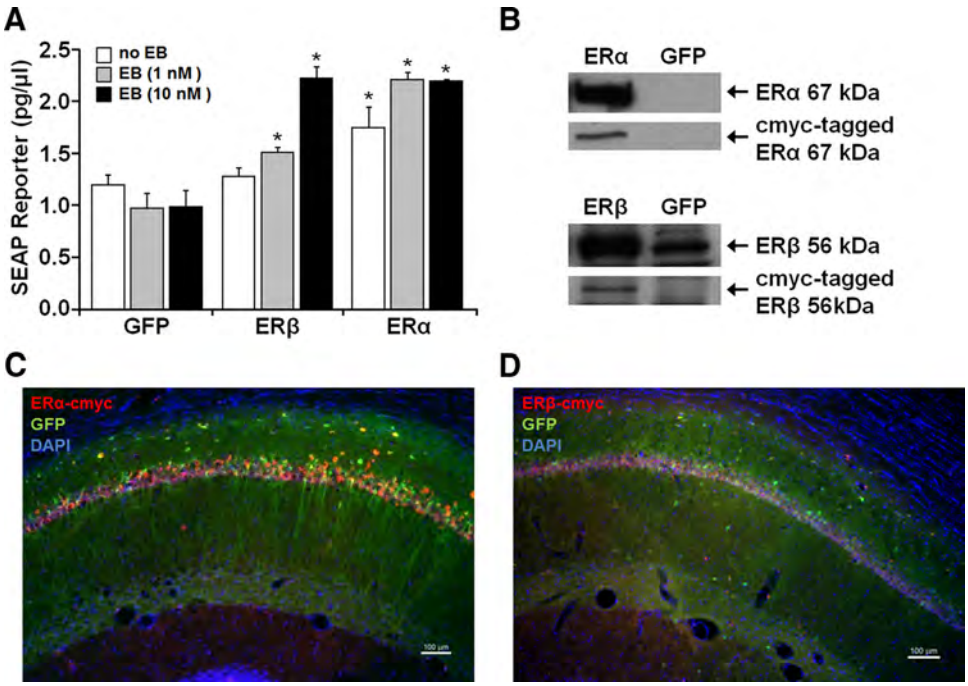

Figure 3. Analysis of functionality and *in vivo* expression of viral vectors. ***A***, Plasmids expressing cmyc-tagged ERα, cmyc-tagged ERβ, or GFP were cotransfected with an ERE-SEAP reporter plasmid in HEK293T cells with the addition of 1 or 10 nM EB treatment or vehicle. SEAP reporter levels were measured 24 h after application of treatments and compared with control groups. These results confirm functionality of the encoded ERs *in vitro*. Asterisks indicate a significant ($p < 0.05$) increase in SEAP expression relative to control. ***B***, Western analysis of HEK293T cells treated with AAV-ERα, AAV-ERβ, or the GFP control virus. Top, For cells treated with AAV-ERα, antibodies for ERα (Ab17) and cmyc-tag (A21281) detected the 67 kDa full-length protein for ERα. Bottom, For cells treated with AAV-ERβ, antibodies for ERβ (H-150) and cmyc-tag (A21281) detected a band at ~56 kDa. Note that HEK293T cells treated with the GFP virus exhibit a band at ~56 kDa, which is increased in cultures treated with AAV-ERβ-cmyc. ***C***, ***D***, Immunofluorescent staining for the cmyc-tag, verified hippocampal expression of ERα and ERβ 4 weeks after injection of ER-encoding vectors. AAV-GFP was mixed with the ER virus in a 1:4 ratio to visualize distribution of expression vectors.

ERβ (~56 kDa). In addition, young female rats were injected with AAV-GFP mixed with the cmyc-tagged ER vector at a 1:4 ratio. Immunofluorescent chemistry for the cmyc tag and visualization of GFP (Fig. 3*C*,*D*) confirmed protein expression in the dorsal hippocampus 4 weeks after injection. Similar to our previous results, expression was largely limited to region CA1 of the hippocampus (Foster et al., 2008; Han et al., 2013). Together, these results established the efficacy of our expression vectors.

Effects of ERα and ERβ expression on spatial learning and memory

After OVX and before virus injections (Fig. 1), cognitive function was assessed on the water maze (Pretest). Repeated-measures ANOVA for the cue task indicated an effect of training on escape path length ($F_{(4,264)} = 19.22$, $p < 0.0001$; Fig. 4*A*) with no effect of ER group or treatment group assignment. For the spatial task, again, there was an effect of training for path length ($F_{(4,264)} = 23.448$, $p < 0.0001$; Fig. 4*B*) in the absence of difference for the preassigned ER and treatment grouping. There was considerable variability in probe trial performance (Fig. 4*C*,*D*); however, ANOVAs indicated no effect of ER or treatment assignment and no interaction on the immediate acquisition (Probe 1). Similarly, no ER, treatment, or ER × treatment interaction differences were observed in the 24 h retention (Probe 2) DI scores for the preassigned groups. The results indicate no group differences before virus injections and EB/oil treatment. A one-group *t* test comparing the DI scores to that expected by chance (i.e., a DI score of 0) indicated that, across all animals, the DI scores were above chance for the acquisition probe trial ($t_{(71)} = 3.93$, $p < 0.0005$), indicating that animals were able to acquire a spatial search strategy. For the 24 h retention probe trial, a one-group *t* test on the DI scores indicated that the animals performed below chance ($t_{(71)} = -5.9$, $p < 0.0001$), indicating that, over the 24 h period, animals abandoned the spatial search strategy focused on the goal quadrant.

Fourteen weeks after OVX, virus encoding ERα, ERβ, or GFP was delivered to the hippocampus by stereotaxic surgery. One week after the viral vector injections, animals were treated with EB or oil delivered by subcutaneous injection on 2 adjoining days in a 5 d cyclic regimen (Fig. 1). Treatments were continued for 5 weeks before behavior testing. Cognitive performance on the spatial version of the water maze was again assessed (Final test). At this time, animals were 20 months of age, 6 weeks after virus injections, and testing began 48 h after the previous EB/oil treatment. Due to poor retention during the pretest (Fig. 4*D*), the protocol was altered such that the retention probe trial was delivered 1 h after training Block 4; this was followed by a refresher training block. An ANOVA on the swim speed, averaged across Blocks 1–5, indicated no effect of ER group and no ER group × treatment interaction (Fig. 5*A*). There was a trend ($F_{(1,66)} = 3.33$, $p = 0.073$) for a treatment effect due to slower swim speed in EB-treated animals, which is consistent with previous work (Foster et al., 2003; Talboom et al., 2008). A repeated-measures ANOVA for escape path length (distance) across training Blocks 1–5 for the spatial task indicated significant main effects of training ($F_{(4,264)} = 24.69$, $p < 0.0001$), a tendency for an effect of ER group ($F_{(2,66)} = 2.81$, $p = 0.068$) in the absence of an effect of treatment ($F_{(1,66)} = 2.08$, $p = 0.15$), and no ER group × treatment interaction (Fig. 5*B*). *Post hoc* tests for ER group effects collapsed across treatments indicated that animals expressing ERβ exhibited increased distance to escape relative to animals expressing ERα ($p < 0.05$; Fig. 5*C*). *Post hoc* tests also indicated a tendency ($p = 0.098$) for poorer performance of ERβ-expressing

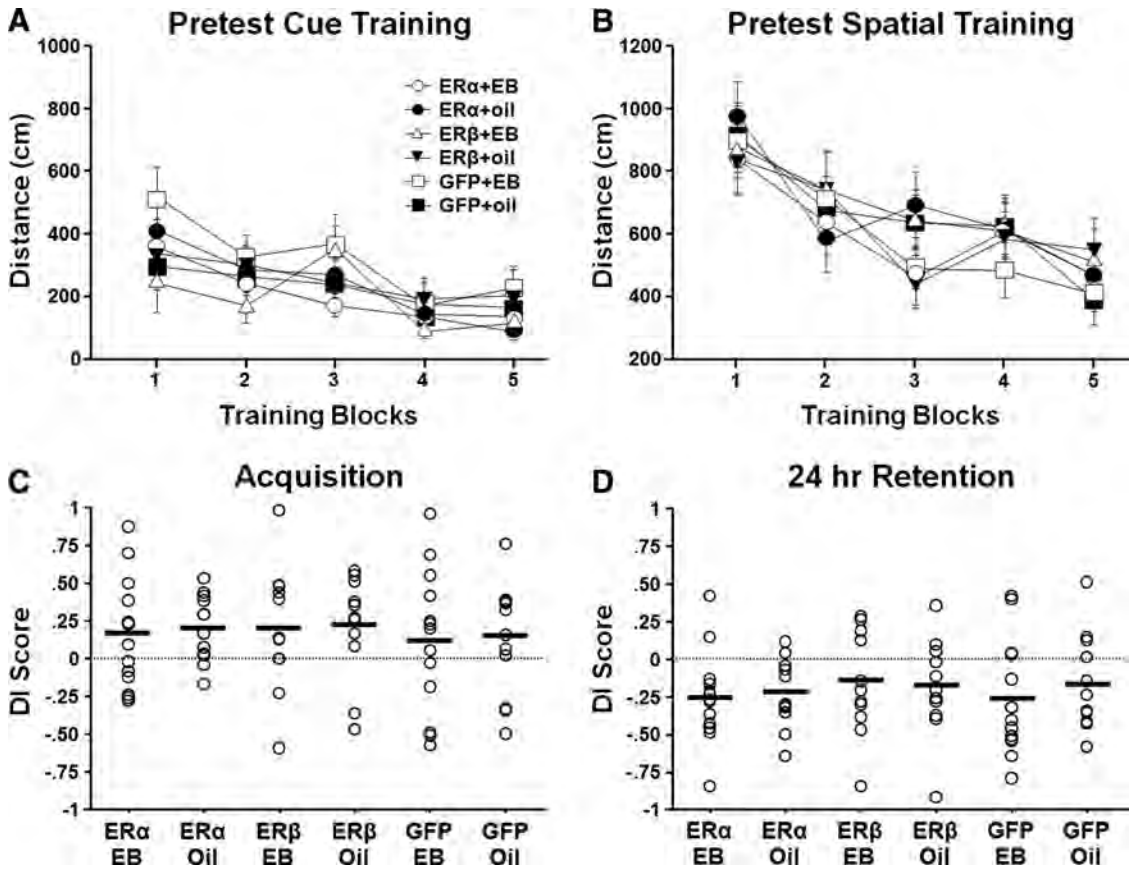

Figure 4. Water maze Pretest indicates no initial difference in performance of the treatment groups. Rats were pseudorandomly assigned to ER and EB/oil treatment groups. For this and all subsequent figures, circle = ERα, triangle = ERβ, square = GFP, open = EB, and filled = oil. Five to 6 weeks after OVX and before virus injections, animals were tested on the cue task (***A***) and spatial discrimination task (***B***). The symbols indicate the mean escape distance (±SEM) for each training block. Individual DI scores and mean (bar) for the acquisition (***C***) and 24 h retention probe (***D***) trials. No group differences were observed. Across all groups, animals exhibited acquisition of a spatial discrimination with impaired retention 24 h later.

animals relative to GFP controls. The difference was mainly due to increased path length for the ERβ-treated animals in Blocks 2 ($F_{(2,66)} = 3.36, p < 0.05$) and 5 ($F_{(2,66)} = 3.09, p = 0.052$). *Post hoc* tests indicated a significant increased escape distance for ERβ relative to ERα on Block 2 and a significant increase in distance for ERβ relative to ERα and GFP on Block 5. Despite the group difference during training, no differences were observed for the initial training block and Block 4 immediately preceding the acquisition probe trial. Therefore, initial performance was the same and all groups appear to learn, although there may have been differences in the rate of learning.

An ANOVA of the DI scores for the acquisition probe trial indicated no effect of ER group or treatment and no ER group × treatment interaction ($F_{(2,66)} = 2.22, p = 0.12$; Fig. 6*A*). In contrast, an ANOVA on the DI scores for the 1 h retention probe trial indicated an effect of treatment ($F_{(1,66)} = 6.74, p < 0.05$) and a tendency for an interaction of ER group and treatment ($F_{(2,66)} = 2.85, p = 0.065$). The treatment effect was due to an increase in the retention DI scores of EB-treated rats (Fig. 6*B*) and subsequent ANOVAs indicated an effect of EB only for the ERα group ($F_{(2,34)} = 4.83, p < 0.05$), such that ERα + EB exhibited increased retention relative to ERα + oil. Importantly, EB treatment had no effect in the GFP or ERβ groups, consistent with the idea that a long duration of estrogen deprivation results in a decrease in E2's ability to improve memory (i.e., closing of the critical window). ANOVAs for ER group effects within each treatment condition indicated that the tendency for the ER group by treatment interaction was due to an ER group effect for EB-treated animals ($F_{(1,23)} = 17.07, p < 0.001$). *Post hoc* comparisons confirmed superior performance by the ERα + EB group such that the DI scores for animals expressing ERα + EB were greater than DI scores for the GFP + EB group ($p < 0.05$), with a tendency ($p = 0.09$) for better performance by the ERα + EB group relative to the ERβ + EB group. No effect of ER group, treatment, or interaction was observed for the escape distance on the refresher block (Block 6) administered after the retention probe trial (Fig. 5*B*).

The next day, animals were given a block of training (Block 7), which was immediately followed by a final probe trial. No effect of ER group, treatment ($F_{(1,66)} = 2.38, p = 0.13$), or interaction was observed for the escape distance during the training block (Fig. 5*B*). An ANOVA on the DI scores for the final probe trial indicated an effect of ER group ($F_{(2,66)} = 3.41, p < 0.05$; Fig. 6*C*) in the absence of a treatment effect or an interaction. *Post hoc* tests indicated better performance for ERα ($p < 0.05$) and a tendency ($p = 0.051$) for better performance by GFP-treated groups relative to the ERβ-treated groups. For the final cue discrimination test, an ANOVA on average swim speed indicated a tendency ($F_{(1,66)} = 2.90, p = 0.09$) for a slower swim speed of EB-treated animals in the absence of an effect of ER group or an interaction. For escape distance, an ANOVA indicated a training effect ($F_{(4,264)} = 14.44, p < 0.0001$) in the absence of a main effect of ER group, treatment, or interactions; though the ER group × training interaction was ($F_{(8,264)} = 1.47, p < 0.17$). Together, these

results suggest that differences in spatial learning/memory were not likely due to differences in sensory-motor function (Fig. 7).

Overall, these results indicate that a long duration of E2 deprivation limits subsequent beneficial effects of E2 treatment on memory. Expression of ERβ was ineffective in improving cognition and associated with impaired learning. Finally, increasing the expression of ERα in hippocampal CA1 neurons restores the cognitive enhancing effects of E2 in aged female rats.

Influence of increased ERα expression and treatment on synaptic transmission

To examine the possibility that modification of NMDAR function underlies the reopening of the critical window, a subset of ERα + EB (n = 5/10 animals/slices), GFP + EB (n = 4/8 animals/slices), ERα + oil (n = 4/8 animals/slices), and GFP + oil (n = 4/8 animals/slices) animals were used for electrophysiological examination. After behavioral characterization, cyclic injections of EB/oil were continued (range 1–7 cycles, mean 4.12 ± 0.44 cycles) and hippocampal slices were prepared 48 h after the final EB treatment. Input–output curves for the total-fEPSP (Fig. 8*A*) and NMDAR–fEPSP (Fig. 8*B*) slope (mV/msec) were constructed from extracellular field recordings from the CA1 region of hippocampal slices. An ANOVA on the total-fEPSP response, repeated across stimulation intensities, indicated a main effect of stimulus intensity ($F_{(7,210)} = 29.73$, $p < 0.0001$), a tendency ($F_{(1,30)} = 4.17$, $p = 0.05$) for a treatment effect due to increased responses for EB-treated animals, and an interaction of stimulus intensity and treatment ($F_{(7,210)} = 3.31$, $p < 0.005$) in the absence of an ER group effect (Fig. 8*A*).

After collection of the total-fEPSP responses, the recording medium was switched to a medium which permitted the isolation of the NMDAR component of synaptic transmission (Bodhinathan et al., 2010; Kumar and Foster, 2013; Lee et al., 2014; Guidi et al., 2015). An ANOVA, repeated across stimulation intensities, indicated a main effect of stimulus intensity ($F_{(7,210)} = 36.20$, $p < 0.0001$), ER group ($F_{(1,30)} = 5.62$, $p < 0.05$), and treatment ($F_{(1,30)} = 7.56$, $p < 0.05$) and an ER group × treatment interaction ($F_{(1,30)} = 5.88$, $p < 0.05$) on the NMDAR response (Fig. 8*B*). The increase in the NMDAR-mediated synaptic response was specific to ERα + EB animals. ANOVAs within each ER group indicated a treatment effect ($F_{(1,16)} = 8.63$, $p < 0.01$) only in the ERα-expressing group with increased NMDAR-fEPSPs in ERα + EB relative to ERα + oil. Similarly, an effect of ER expression was observed for animals treated with EB ($F_{(1,16)} = 7.09$, $p < 0.05$) such that the NMDAR-fEPSP was increased in ERα + EB relative to GFP + EB.

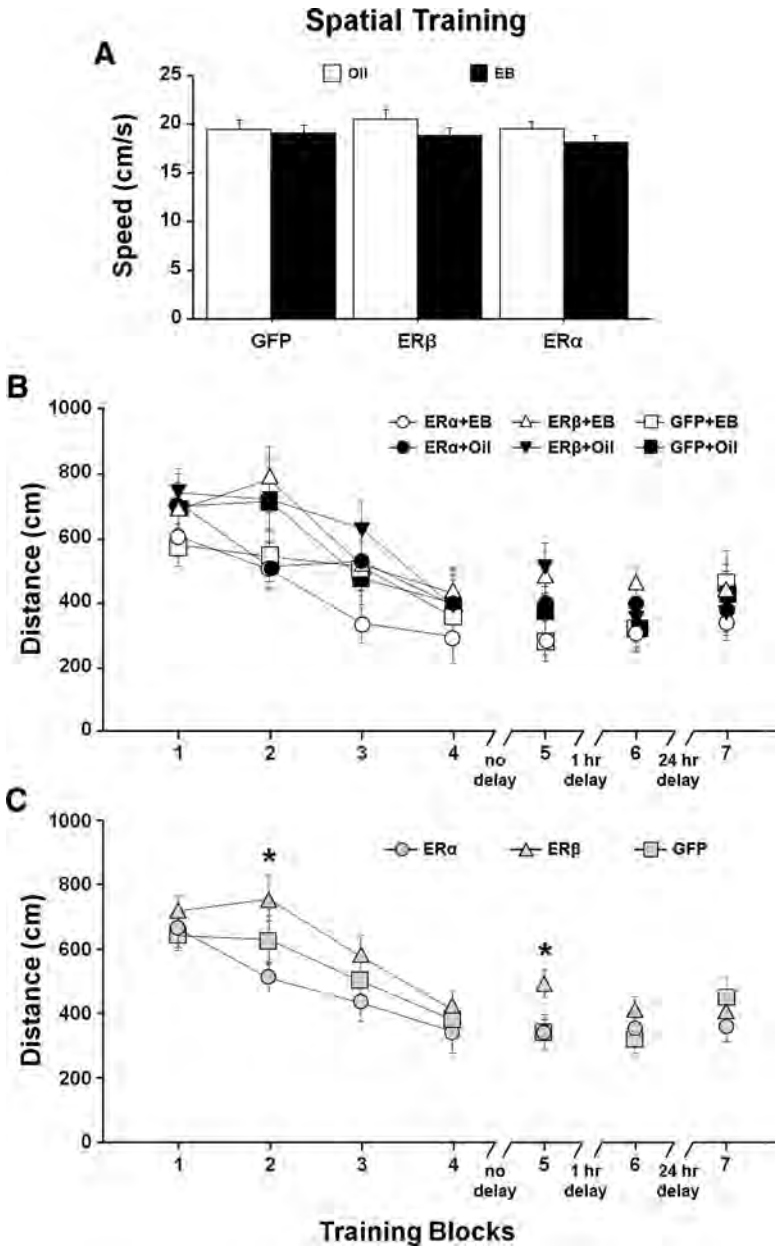

Figure 5. Spatial discrimination performance after differential expression of ER and EB/oil treatment. ***A***, Mean swim speed (+ SEM) across training Blocks 1–5 for EB (filled bars)- and oil (open bars)-treated animals. Symbols indicate the mean (±SEM). ***B***, Escape path length to the submerged platform for the ER and treatment groups. ***C***, Mean (±SEM) escape path length collapsed across EB/oil treatments (gray) for each ER group, illustrating the shortest and longest escape distances in ERα and ERβ groups, respectively. The asterisks indicate trial blocks during acquisition training with significant ($p < 0.05$) differences between ERβ and other groups.

Finally, to determine the relative influence of enhanced expression of ERα and EB treatment, the ratio of NMDAR response/total-fEPSP response was calculated for the highest three stimulation levels (32, 36, and 40 V; Fig. 8*C*). The ratio was increased with increasing stimulation intensity ($F_{(2,60)} = 11.73$, $p < 0.0001$) in the absence of an ER group or treatment effect ($F_{(1,30)} = 1.95$, $p = 0.17$). However, an interaction was observed for the ER group × treatment condition ($F_{(1,30)} = 7.62$, $p < 0.01$). *Post hoc* ANOVA's examining treatment effects in each ER group indicated a treatment effect only for animals expressing ERα such that an increase in the NMDAR response/total response ratio was observed in the ERα + EB group relative to ERα + oil group ($F_{(1,16)} = 8.22$, $p < 0.05$). *Post hoc* ANOVAs examining ER group

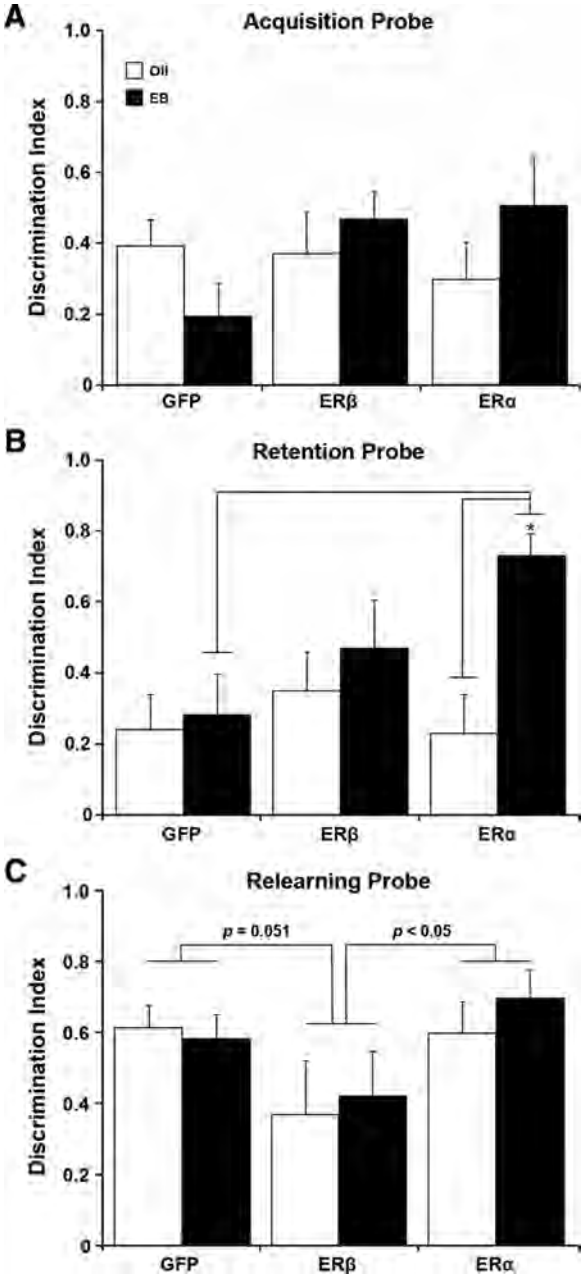

Figure 6. Expression of AAV-ERα in conjunction with EB treatment improved retention of spatial information for platform location. ***A–C***, Bars represent the mean (±SEM) DI score calculated from performance on the probe trials for rats injected with AAV vectors encoding ERα, ERβ, or GFP and subsequently treated with EB (filled bars) or oil (open bars). ***A***, Acquisition probe trial directly followed Block 4 of the spatial discrimination task. ***B***, Retention probe trial followed a 1 h delay between Blocks 5 and 6. Superior performance was seen in EB-treated rats injected with the AAV expressing ERα. Asterisk indicates significant difference ($p < 0.05$). ***C***, The probe trial immediately followed a refresher block the day after spatial training. The *p*-values above the bars indicate for differences between the ERα and GFP groups and animals with viral-mediated expression of ERβ.

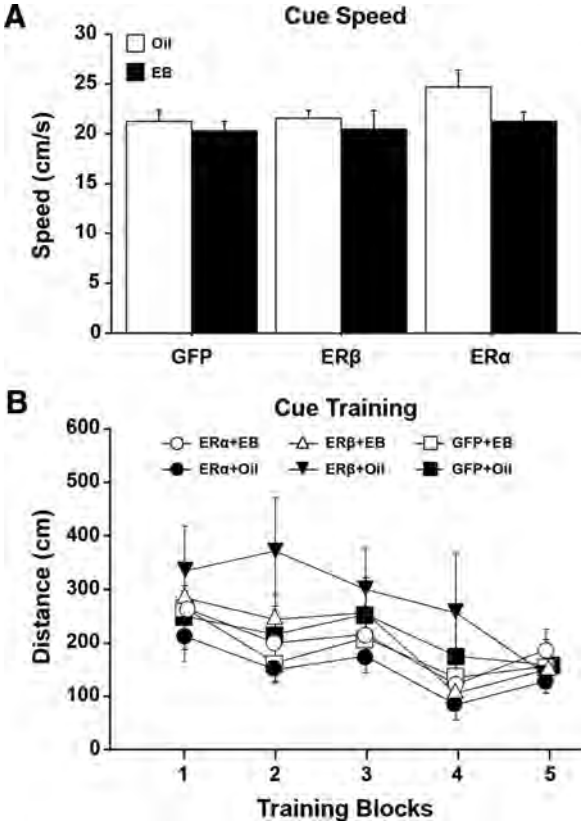

Figure 7. Expression of ERα, ERβ, or GFP and EB/oil treatments did not influence sensorymotor abilities examined as average swim speed (***A***) or distance (***B***) to find the visible platform across the training blocks on a cue discrimination task administered after the completion of the probe trial on day 2.

effects in the separate treatment groups indicated that, for animals treated with EB, the ratio was increased in the ERα + EB relative to GFP + EB ($F_{(1,16)} = 7.01$, $p < 0.05$).

Western analysis and immunohistochemistry

Western blot analysis and immunofluorescent chemistry were used to confirm viral-mediated ER expression for tissue harvested 48 h after the last injection. Immunofluorescent chemistry ($n = 3$ from each group) confirmed enhanced expression of the virally delivered ER throughout the dorsal hippocampus, which was largely localized to the CA1 region of the hippocampus (Fig. 9*A*). The anterior/posterior spread of ER expression was ~2800 μm throughout the dorsal hippocampus, which is consistent with our previous work using AAV (Lee et al., 2012). Using a neuronal marker (NeuN) and an astrocyte marker (GFAP), we confirmed that virally mediated expression of ERα was restricted to neurons in the CA1 region (Fig. 9*B*,*C*). Western blot analysis ($n = 4–8$ per group) of ER expression established ERα immunoreactivity at ~67 kDa (Fig. 9*D*). Quantification of human ERα was accomplished using the Ab17 antibody raised against an N-terminal sequence of human ERα. The results indicated a significant increase in expression of human ERα for animals injected with AAV-ERα relative to AAV-GFP ($F_{(1,14)} = 14.38$, $p < 0.005$) in the absence of a treatment and treatment × ER group interaction. The endogenous rat ERα was examined using the MC-20 antibody raised against the last 20 aa of the mouse ERα; this sequence is identical to the C terminus of the rat ERα, but differs from the C terminus of the human ERα by 6 aa (Bollig-Fischer et al., 2012). Again, a band was observed at ~67 kDa (Fig. 9*E*); however, no difference in endogenous expression was observed as a result of ERα or GFP expression, treatment, or the interaction. Immunoreactivity for the ERβ antibody was observed at ~56 kDa and two other bands were observed at ~63 and ~61 kDa from tissue lysate isolated from the CA1 region of the dorsal hippocampus (Fig. 9*F*). Analysis of the ~56 kDa ERβ band indicated an effect of ERβ or GFP virus injection ($F_{(1,20)} = 24.38$, $p < 0.0001$) in the absence of an effect of treatment or an

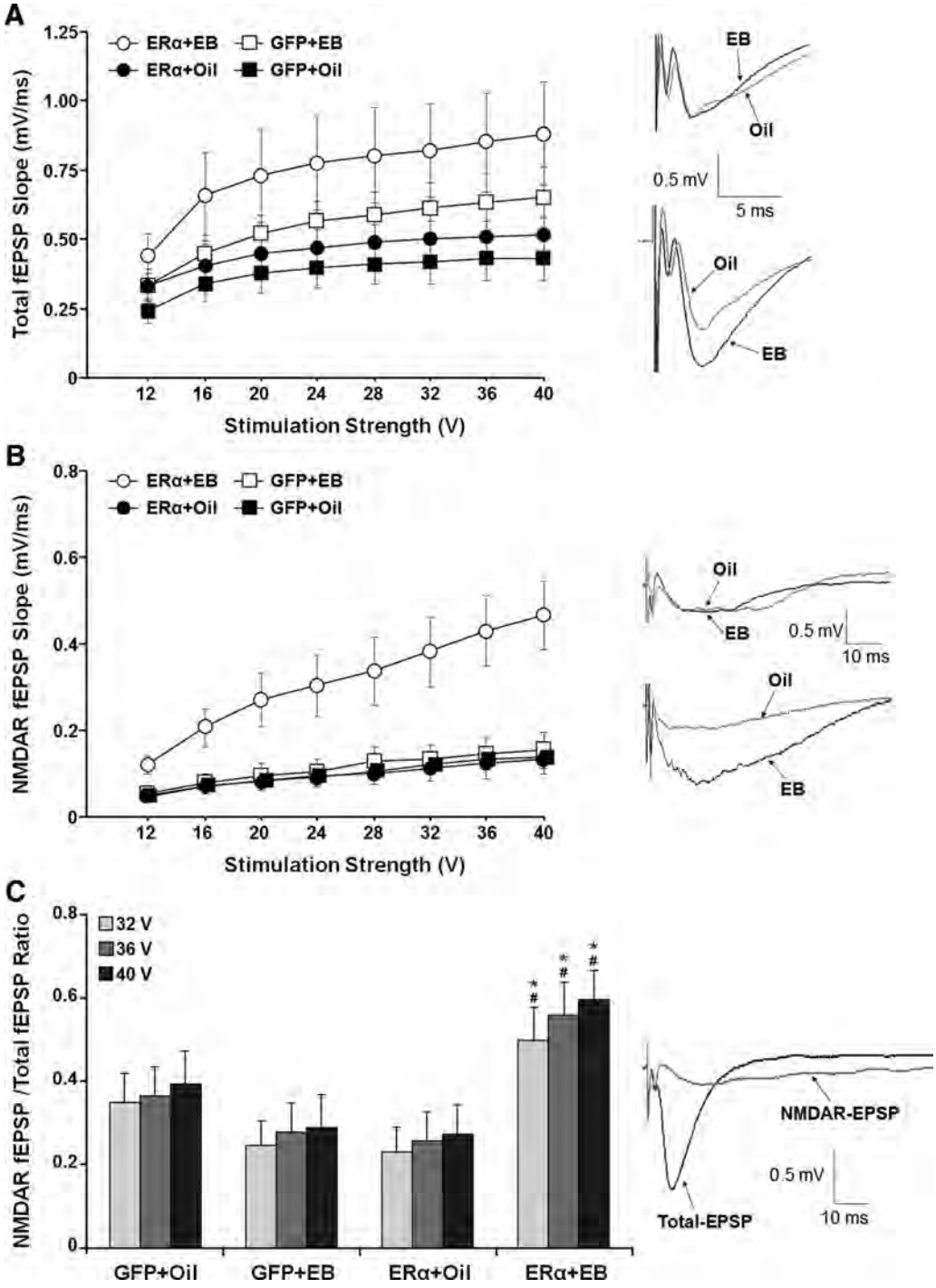

Figure 8. Expression of ERα in conjunction with EB treatment enhanced the NMDAR-synaptic response in the hippocampus of aged female rats. Input–output curves are illustrated for the mean slope of the total-fEPSP (***A***) and NMDAR-fEPSP (***B***). EB treatment was associated with an increase in the total-fEPSP response, which was particularly evident for animals that received AAV-ERα. After collection of the total-fEPSP, the NMDAR component of the synaptic response was isolated. In contrast to the total-fEPSP, the EB-mediated increase in NMDAR-fEPSP was specific to animals that received AAV-ERα. The insets in ***A*** and ***B*** show representative traces of synaptic responses from animals injected with AAV-GFP (top) and AAV-ERα (bottom) and treated with EB (black line) or oil (gray line). ***C***, The ratio of the NMDAR-fEPSP/total-fEPSP for the highest stimulation intensities (32– 40 V) was increased in the ERα + EB group. Asterisks indicate significant ($p > 0.05$) treatment effect, with greater NMDAR-fEPSP/total-fEPSP ratio in the ERα + EB group relative to the ERα + oil group. Pound signs indicate a significant ER group effect with a greater NMDAR-fEPSP/total-fEPSP ratio in ERα + EB group relative to GFP + EB group. The inset shows the total-fEPSP and isolation of NMDAR-fEPSP from the same slice.

interaction. No effect of virus injection, treatment, or the interaction was observed for the 63 and 61 kDa bands, which may represent nonspecific binding, although ERβ variants within this range have been described previously (Solakidi et al., 2005; Alvarez-Delgado et al., 2010).

Western blot analysis ($n = 3$–7 per group) was used to assess possible molecular changes in the CA1 region of the hippocampus for animals expressing ERα or GFP and treated 48 h earlier with EB or oil. We examined the expression of proteins that respond to E2 treatment in young animals and are thought to

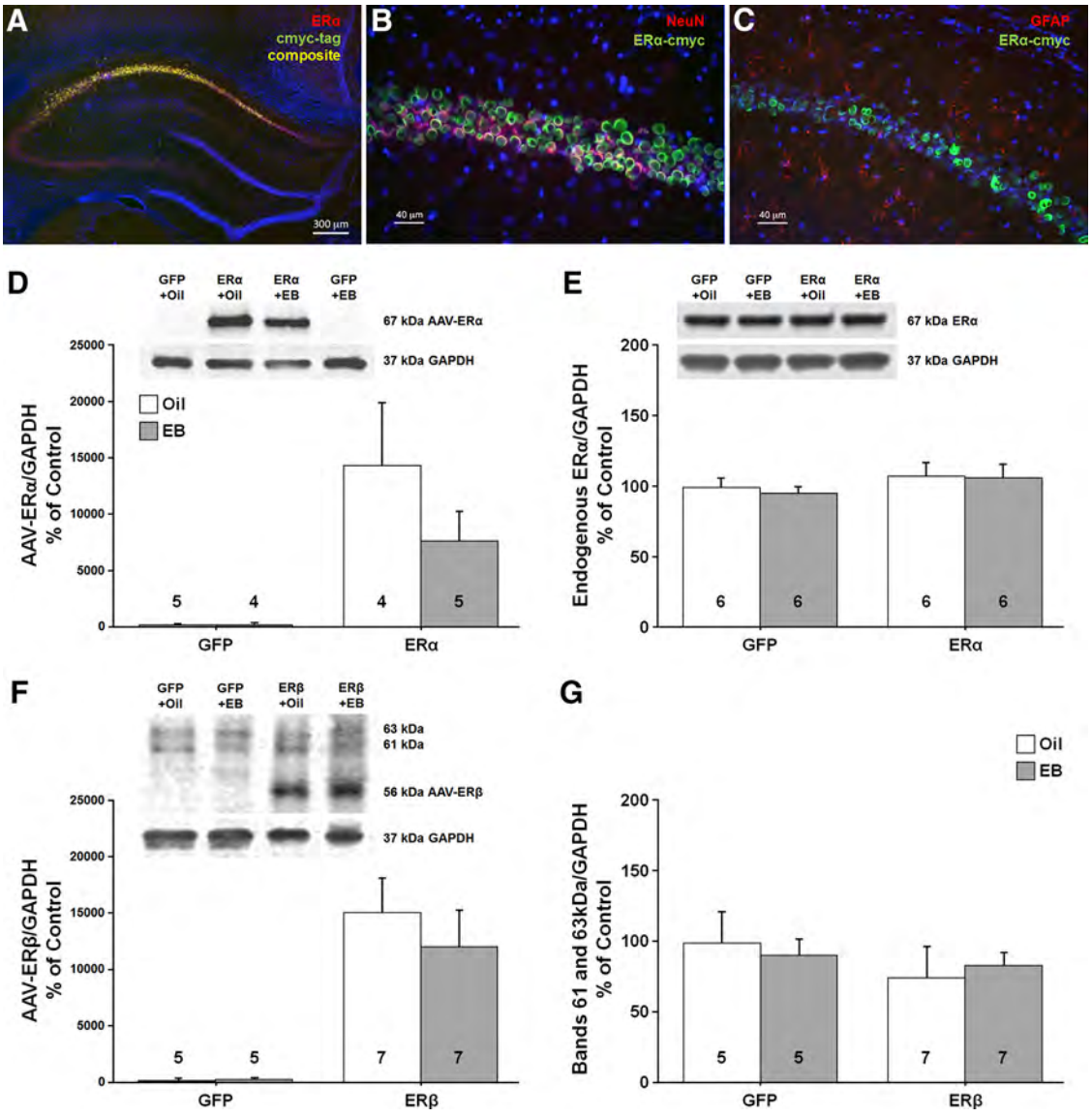

Figure 9. Western blots and histology were used to confirm increased ER expression in neurons of the dorsal hippocampus. Immunofluorescent chemistry (***A***–***C***) showing expression of ERα within the CA1 region of the hippocampus. ***A***, Merged image shows expression of AAV-ERα tagged with cmyc (green), and ERα (red). ***B***, ***C***, Cmyc (green) tagged to ERα was expressed mainly in neurons immunostained with a neural marker (NeuN, red; ***B***), but not in astrocytes immunostained with the glial marker, glial fibrillary acidic protein (GFAP, red; ***C***). Images ***A***–***C*** were counterstained with the nuclear marker DAPI (blue). ***D***, ***E***, Western blots using an antibody selective against the human ERα (***D***) or rat ERα (***E***) confirmed a band at ~67 kDa. Animals injected with virus carrying ERα exhibited increased expression of the human ERα and no difference was observed for endogenous ERα. ***F***, ***G***, An antibody against ERβ confirmed that the ERβ vector increased the expression of human ERβ (~56 kDa; ***F***) in the absence of a change in the 63 and 61 kDa bands (***G***). For these and subsequent Western blots, the numbers in or above the bars indicate the number of samples used in the analysis.

contribute to E2-dependent synaptic plasticity. Previous work suggested a correlation between E2-mediated increased NMDAR synaptic transmission and an increase in dendritic spines (Woolley et al., 1997; Smith and McMahon, 2005). Further, the synaptic proteins postsynaptic density 95 (PSD95) and synaptophysin are increased after E2 treatment in young animals (Brake et al., 2001; Frick et al., 2002; Akama and McEwen, 2003; Spencer et al., 2008a; Waters et al., 2009). However, no effect of ER group, treatment, or interaction was observed for PSD95 and no effect of ER group, treatment, or interaction was observed for synaptophysin (Fig. 10*A*,*B*). E2 treatment in younger animals increases markers of glutamate receptors, GluR1, NR2B, and NR2A (Cyr et al., 2001; Adams et al., 2004; Morissette et al., 2008; Waters et al., 2009; Qu et al., 2013). No effect of ER group, treatment, or interaction was observed for the NR2B and NR2A subunits of NMDARs and the GluR1 glutamate receptor subunit (Fig. 11*A*–*C*).

E2 treatment activates signaling cascades (Foster, 2005; Zadran et al., 2009; Kumar et al., 2015), including ERK, which can increase synaptic transmission, possibly through the phosphorylation of glutamate receptors (Xu et al., 2010; Logan et al., 2011; Raval et al., 2012). No effect of ER group or treatment was observed for the phosphorylation state of NR2B(S1303), GluR1(S831), ERK1, or ERK2 (Fig. 12*A*–*C*).

Hormone treatment efficacy

To determine the efficacy of our EB treatments, blood E2 levels were measured and the right uterine horns were weighed. ANOVAs indicated a main effect of EB treatment on plasma E2 levels ($F_{(1,66)} = 18.011$, $p < 0.0001$; ERα + EB: 65.8 ± 22.9

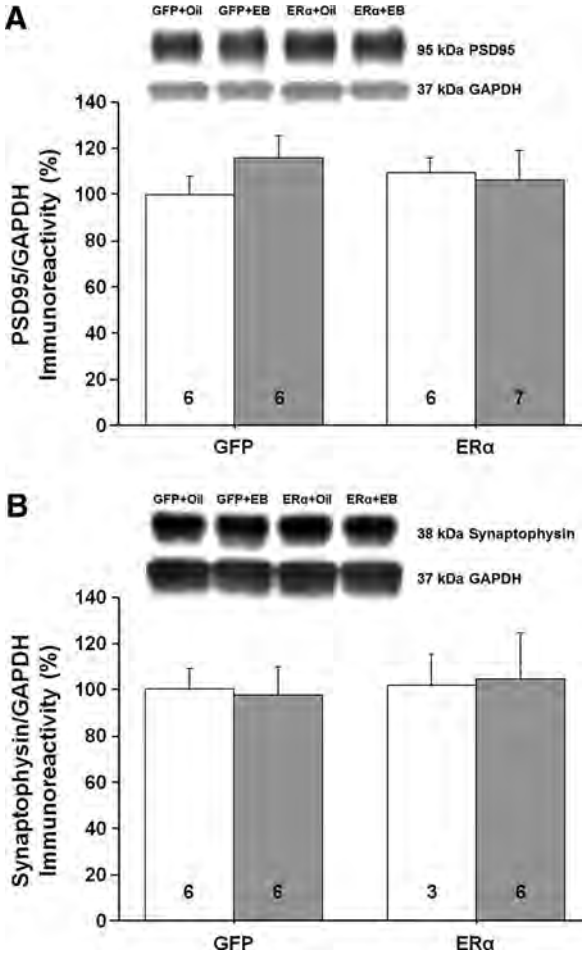

Figure 10. Western blots to assess the possible growth of dendritic spines in the CA1 region of the hippocampus for animals expressing ERα or GFP. The bars represent the means (±SEM) for the expression of the synaptic proteins PSD95 (***A***) and synaptophysin (***B***).

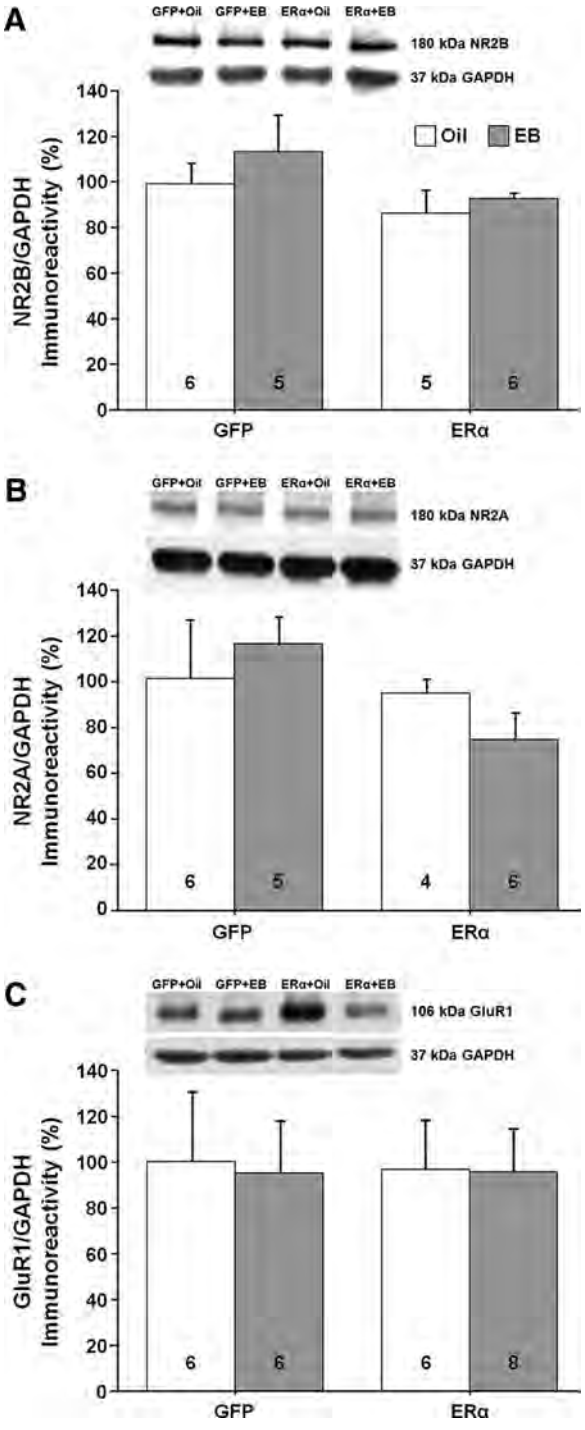

Figure 11. Western blots of glutamate receptor expression in the CA1 region of the hippocampus for animals expressing ERα or GFP. The bars represent the means (±SEM) for the expression of the NR2B subunit (***A***), the NR2A subunit (***B***), and the GluR1 subunit (***C***).

pg/ml mean ± SEM, ERβ + EB: 45.0 ± 20.2, GFP + EB: 53.0 ± 18.3, ERα + oil: 3.0 ± 0.7, ERβ + oil: 1.0 ± 0.3, or GFP + oil: 2.8 ± 0.8) and uterine weight ($F_{(1,66)} = 212.26$, $p < 0.0001$; ERα + EB: 0.33 ± 0.02 g mean ± SEM, ERβ + EB: 0.29 ± 0.01, GFP + EB: 0.33 ± 0.03, ERα + oil: 0.11 ± 0.02, ERβ + oil: 0.09 ± 0.01, or GFP + oil: 0.09 ± 0.01). No effect of ER group or interaction of ER group and treatment was observed for plasma E2 or uterine weight.

Discussion

Critical window for cognitive function

Consistent with other studies using water escape tasks (O'Neal et al., 1996; Bimonte and Denenberg, 1999; Markham et al., 2002; Foster et al., 2003; Daniel et al., 2005), EB's beneficial effect on cognitive function is specific to delay-dependent retention of novel spatial information (i.e., spatial episodic or working memory). However, E2 effects on episodic memory weaken with advanced age or with extended hormone deprivation, denoting closing of the therapeutic window (Gibbs, 2000; Markowska and Savonenko, 2002; Foster et al., 2003; Daniel et al., 2006). In the current study, EB failed to improve memory in aged OVX animals expressing GFP or ERβ, indicating that these animals were beyond the critical window. In contrast, upregulation of ERα combined with EB treatment improved memory. Therefore, this is the first demonstration that E2-mediated beneficial effects can be reinstated by upregulation of ERα, but not ERβ, in the hippocampus.

Interestingly, hippocampal expression of ERβ resulted in a learning impairment, observed for escape path length during the initial training and the DI score of the final probe trial. These results provide support for a differential role of ERα and ERβ in hippocampal function (Foster, 2012a; Han et al., 2013; Bean et al., 2014). Studies using ERα knock-out (ERαKO) mice demonstrate that ERα is important for maintaining memory in adults

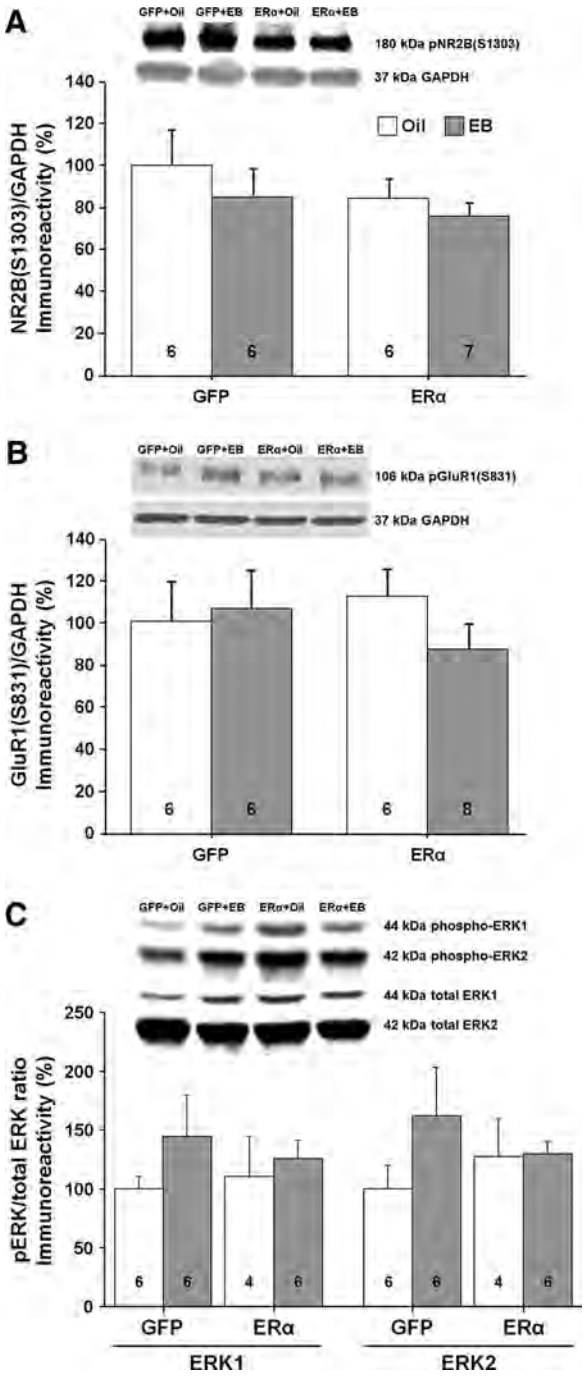

Figure 12. Western blots to assess possible changes in phosphorylation and kinase activity in the CA1 region of the hippocampus for animals expressing ERα or GFP. The bars represent the means (±SEM) for the phosphorylation of NR2B at S1303 (***A***), GluR1 at S831 (***B***), and ERK1/2 (***C***).

(Fugger et al., 2000; Han et al., 2013). Similar to the current study, viral expression of hippocampal ERβ in ERβKO mice impairs spatial learning (Han et al., 2013). The impairment may result from ERβ inhibition of ERα-mediated transcription rendering the hippocampus more vulnerable to the stressors of aging (Foster, 2005, 2012a; Bean et al., 2014).

The required combination of ERα + EB for cognitive benefits is in contrast to our previous work showing that increased ERα expression alone can improve cognition in young ERαKO mice and middle-aged female rats (Foster et al., 2008; Witty et al., 2012). The difference may be due to a decrease in local E2 availability or reduced ligand-independent ERα-mediated transcription in older animals. Synthesis of E2 in the hippocampus declines after OVX (Barker and Galea, 2009). Indeed, a decline in local E2 synthesis may explain why higher levels of plasma E2 are required to improve cognition with advancing age (Foster et al., 2003; Talboom et al., 2008). In addition, during aging, there is a shift in kinase/phosphatase activity, favoring phosphatases (Norris et al., 1998; Sharrow et al., 2002; Jackson et al., 2009). This shift is thought to reduce ERα phosphorylation, diminishing ligand-independent ERα-mediated transcription in older animals (Foster, 2005). In this case, transcription may be enhanced by the combination of ERα upregulation and EB treatment. Regardless of the exact mechanism, the current study supports the idea that ERα activity is an essential component for regulating the critical window.

Mechanisms for rejuvenating the hippocampus

E2 treatment induces plasticity in the hippocampus and E2 responsiveness declines with age. In older animals, E2 fails to induce the growth of spines (Adams et al., 2001b; Akama and McEwen, 2003; Williams et al., 2011) and the transcription of genes related to synaptic function and maintenance of cell health (Aenlle and Foster, 2010). Importantly, the current study supports the idea that the closing of the critical window is associated with an inability of E2 to enhance NMDAR-mediated synaptic transmission (Smith et al., 2010; Vedder et al., 2014). EB induced a robust increase in NMDAR synaptic transmission in animals expressing ERα, but not in GFP controls, again suggesting that GFP animals are beyond the critical window.

It is possible that memory formation during training acted to increase NMDAR responses. In several neural systems, learning induces an increase in the fast component of synaptic transmission, which can be recorded *in vitro* 1–7 d after training (Foster et al., 1996; McKernan and Shinnick-Gallagher, 1997; Power et al., 1997; Barkai and Saar, 2001; Foster and Dumas, 2001; Sacchetti et al., 2001; Schroeder and Shinnick-Gallagher, 2005; Mitsushima et al., 2011). In contrast, NMDAR-mediated synaptic transmission is decreased or unchanged after learning (Zinebi et al., 2003; Quinlan et al., 2004; Mitsushima et al., 2011). It has been suggested that the decline in NMDAR function may preserve changes in the fast synaptic transmission by shifting the threshold for synaptic plasticity (Quinlan et al., 2004). Importantly, previous research indicates that the E2-mediated increase in NMDAR synaptic responses are observed in the absence of behavioral training (Woolley et al., 1997; Smith and McMahon, 2006; Snyder et al., 2011).

Alternatively, it is possible that the combination of ERα + EB increased NMDAR function and it is this increase that mediated improvements in learning and memory. Work with mutant mice and pharmacological studies in rats demonstrate that spatial episodic memory, but not spatial reference memory, depends on hippocampal NMDAR function (Foster, 2012b) and a decline in NMDAR function during aging is associated with impaired episodic, but not impaired reference memory (Foster, 2012b; Kumar and Foster, 2013; Lee et al., 2014; Guidi et al., 2015). Overexpression of the NR2B subunit in the hippocampus enhances learning and memory (Tang et al., 1999; White and Youngentob, 2004; Brim et al., 2013). Moreover, viral-mediated upregulation of antioxidant genes in the hippocampus enhances NMDAR function by altering an age-related shift in redox state (Lee et al., 2012; Lee et al., 2014). In this case, virus expression of antioxidant enzymes rejuvenates the hippocampus, increasing hippocampal NMDAR

function in older animals, and it is an increase in NMDAR function that underlies enhanced episodic memory.

The mechanism for the increase in NMDAR function is an important question that remains to be elucidated. A shift in NR2 subunit composition, favoring NR2B would be expected to increase NMDAR responses and could influence the threshold for synaptic modifiability during learning (Zinebi et al., 2003; Skibinska et al., 2005; Sun et al., 2005; Lebel et al., 2006; Baez et al., 2013; Laeremans et al., 2015). Aging and E2 deprivation are associated with a decline in NR2B mRNA, decreased NR2B ligand-specific binding in the hippocampus, and loss in dendritic spines containing NR2B subunits (Adams et al., 2001a; Cyr et al., 2001; Morissette et al., 2008; Guidi et al., 2015); however, we did not observe a shift in the expression of the different NMDA subunits, consistent with previous work in young animals (Snyder et al., 2011).

Before closing of the critical window, E2 can increase the number of dendritic spines and expression of a number of synaptic molecular markers, including glutamate receptor subunits, suggesting new functional synapses (Frick et al., 2002; Jelks et al., 2007; Spencer et al., 2008b; Waters et al., 2009; Smith et al., 2010; Qu et al., 2013). Therefore, one possibility is that the increase in NMDAR response was due to E2-induced synaptogenesis. However, we did not observe an increase in the expression of glutamate receptor subunits (GluR1, NR2A, or NR2B) or the synaptic markers PSD95 and synaptophysin in the ERα + EB condition.

It is possible that the increase in the NMDAR response was due to a shift in NMDAR trafficking. Glutamate receptor location and function is regulated by kinase/phosphatase activity. E2 alters kinase/phosphatase activity to increase synaptic transmission (Sawai et al., 2002; Sharrow et al., 2002; Foster, 2005; Zadran et al., 2009; Kumar et al., 2015). Therefore, the increase in synaptic responses may have resulted from enzyme activity, including phosphorylation of glutamate receptors (Xu et al., 2010; Logan et al., 2011; Raval et al., 2012). However, the well characterized NR2B S1303 (Chen and Roche, 2007) and GluR1 S831 (Lee et al., 2010) phosphorylation sites were not altered in the ERα + EB group, indicating that receptor phosphorylation does not mediate increased synaptic transmission observed 48 h after E2 treatment (Snyder et al., 2011). Furthermore, pERK, which provides an indication of E2-induced kinase activity, was not altered. Although it is possible that other phosphorylation sites may have influenced glutamate receptors, the idea that the increase in synaptic transmission is due to maintenance of elevated kinase activity and phosphorylation of glutamate receptors seems doubtful.

Genomic actions of ERs, including ligand-independent ERα-mediated transcription, can influence transcription to regulate synaptic function (Murphy and Segal, 1997; Lee et al., 2004; Aenlle et al., 2009; Aenlle and Foster, 2010; Han et al., 2013; Bean et al., 2014). The fact that ERα + EB effects were observed 48 h after treatment suggests a possible transcriptional mechanism. E2 influences transcription of hippocampal genes for growth, inflammation, oxidative stress, mitochondrial function, and synaptic plasticity. In aging male rats, impaired cognition and decreased NMDAR synaptic function is related to oxidative stress and intracellular redox state (Bodhinathan et al., 2010; Foster, 2012b; Kumar and Foster, 2013; Lee et al., 2014). E2 regulates oxidative stress though multiple mechanisms, including transcription (Behl et al., 1995; Kiray et al., 2004; Zhang et al., 2009; Aenlle and Foster, 2010; Irwin et al., 2012; López-Grueso et al., 2014). However, it remains for future studies to determine whether the increase in NMDAR function was related to E2-induced transcription and modulation of the redox state.

In conclusion, our current findings demonstrate that increasing the expression of functional ERα in aged rats after an extended period of ovarian hormone depletion can restore the critical window for estrogen's positive effects on hippocampal synaptic transmission and spatial memory. These results establish ERα activity as an integral part of the mechanism regulating the critical window. The molecular studies indicate that the beneficial effects were not associated with an increased expression of synaptic marker proteins, NMDAR subunits, or the continuous activation of kinase signaling cascades. These results leave open the question of whether the beneficial effects are due to altered transcription or redox state. Future studies should explore interventions or methodologies that facilitate ERα activation specifically in the brain or augment NMDAR synaptic responses as a strategy to detour cognitive decline in aging women.

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CellPress

Molecular aspects of age-related cognitive decline: the role of GABA signaling

Joseph A. McQuail[1,2], Charles J. Frazier[1,2,3], and Jennifer L. Bizon[1,2]

[1] Department of Neuroscience, University of Florida, Gainesville, FL 32610, USA
[2] McKnight Brain Institute, University of Florida, Gainesville, FL 32610, USA
[3] Department of Pharmacodynamics, University of Florida, Gainesville, FL 32610, USA

Alterations in inhibitory interneurons contribute to cognitive deficits associated with several psychiatric and neurological diseases. Phasic and tonic inhibition imparted by γ-aminobutyric acid (GABA) receptors regulates neural activity and helps to establish the appropriate network dynamics in cortical circuits that support normal cognition. This review highlights basic science demonstrating that inhibitory signaling is altered in aging, and discusses the impact of age-related shifts in inhibition on different forms of memory function, including hippocampus-dependent spatial reference memory and prefrontal cortex (PFC)-dependent working memory. The clinical appropriateness and tractability of select therapeutic candidates for cognitive aging that target receptors mediating inhibition are also discussed.

Memory decline in normal aging

Successes in modern medicine have resulted in marked improvements in somatic and peripheral health, and an unprecedented extension of the human lifespan. Such advances, however, are currently outpacing our ability to maintain optimal brain function and cognition later in life. This problem is accentuated by the striking rise in incidence of the age-associated neurological disorder, Alzheimer's disease (AD), characterized by a precipitous decline in cognitive functioning (e.g., loss of memory). It is important to recognize, however, that aging is accompanied by several non-pathological brain changes that, even in the absence of AD, can significantly and deleteriously influence cognitive capacities. Although the contemporaneous decline of cognition in normal aging is less severe than in AD, this type of cognitive decline will affect the vast majority of seniors and can be sufficiently severe as to negatively impact quality of life and endanger personal independence and well-being [1]. With the current emphasis on developing disease-modifying strategies for treatment of AD, other therapeutic approaches that may broadly improve cognitive function across aged populations are often neglected in research and drug-discovery efforts. Such interventions could provide significant individual, medical, and economic benefits, both by treating non-AD-related cognitive dysfunction and by potentially extending the window of good cognitive functioning in individuals with prodromal AD.

While aging is clearly a brain-wide process, changes within the hippocampus and PFC are at the forefront of cognitive aging research because these regions are vital for dissociable forms of memory that are vulnerable to decline at advanced ages. The hippocampus is a region in the medial temporal lobe that is crucial for long-term memory formation and maintenance. Hippocampal memory can be characterized as 'declarative', referring to the ability to remember factual information that can literally be declared (e.g., 'Who is the president of the United States?'), 'episodic' (e.g., remembering the details of a past birthday), or 'spatial' (e.g., remembering the location of one's house or workplace). In contrast to hippocampus-dependent memory, neuronal networks in PFC subserve a form of short-term memory known as 'working memory' which involves maintaining information in mind for a relatively brief duration. This temporary representational knowledge is essential for our ability to seamlessly plan and execute behavior. Notably, given its importance in guiding our current actions, a foundational characteristic of PFC function is the ability to readily and rapidly update information being held in working memory stores in response to environmental demands. This balance between information maintenance and updating has led to the conceptualization of the PFC as a 'mental sketchpad'.

Laboratory rodents are experimentally tractable and translationally appropriate as animal models to investigate the neurobiology underlying age-related memory decline. Aged rats exhibit many of the characteristic cognitive deficits prominent in human aging, including impaired memory functions that are supported by the hippocampus and PFC [2–6]. Behavioral analyses that provide an index of memory function can be paired with anatomical, molecular, electrophysiological, and pharmacological endpoints, allowing mechanisms of brain aging to be directly evaluated against cognitive abilities [7–14]. The Morris water maze is the 'gold standard' assessment for evaluating

Corresponding author: Bizon, J.L. (bizonj@ufl.edu).
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hippocampal memory in rodents. In this spatial navigation task (Figure 1A), rats are placed in a pool of water and must rely on visual cues situated around the maze to learn and remember the location of an escape platform hidden beneath the surface of the water [15]. Damage to the hippocampal formation severely impairs performance on this task, as is evidenced by longer and less-direct swim paths to reach the escape platform [16–18]. Aged rats also are reliably impaired on the water maze task (Figure 1B), with performance mimicking that of rats with hippocampal damage [19–21]. More recently, humans have been tested on virtual navigation assessments that have been reverse-engineered from rodent water maze task designs. Older individuals reliably perform worse than younger adults on these virtual spatial reference memory tasks, underscoring the translational potential of molecular mechanisms identified with the aid of rodent water maze performance [22–24]. It is notable that, despite the fact that many aged rats show pronounced impairment in spatial reference memory as assessed by the water maze, the numbers of principal

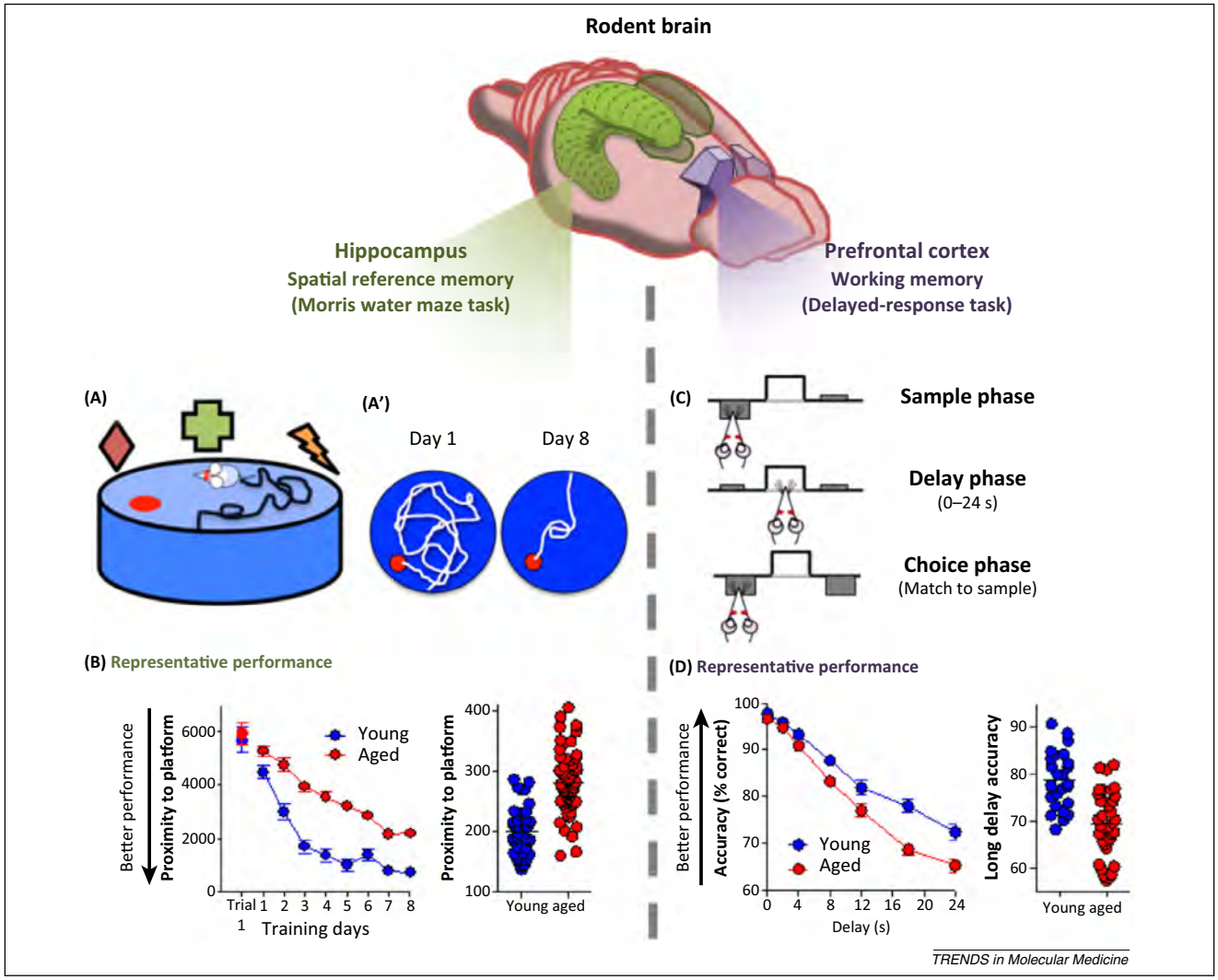

Figure 1. Using rodents to assess age-related decline of hippocampus- and prefrontal cortex (PFC)-dependent memory. (Above) The schematic shows the hippocampus (green) and prefrontal cortex (purple) in rodent brain, which serve spatial reference memory and working memory, respectively. (Below) **(A)** The functionality of the rat hippocampus can be evaluated in spatial learning tasks such as the Morris water maze. The schematic shows the water maze task apparatus in which rats use spatial cues (represented by colored shapes) to learn and remember the location of a stationary escape platform (red circle) hidden beneath the surface in a large tank of water. A' shows representative swim paths from the first (Day 1) and last (Day 8) training days. After training, rats with intact hippocampal function take a more direct path to the platform. **(B)** Representative performance of young adult and aged rats across 8 days of training (three trials per day). While both young and aged rats find the platform more efficiently over time, aged rats are less accurate in their search, indicating attenuated hippocampus-dependent learning and memory function. Notably, deficits are not uniform among the aged rodent population (represented on vertical scatterplot). A subset of aged rats perform on par with young rats, demonstrating a relative preservation of memory function. **(C)** The functionality of the rat prefrontal cortex can be evaluated using delayed response tasks. Such tasks assess working memory, a flexible form of memory that maintains information for a brief duration (seconds) to help guide current and future action. The schematic shows a food-motivated, delayed response task that contains three phases per trial. In the sample phase, rats are presented with one of two sample levers (left or right). Once the rat chooses the sample lever, a delay phase is initiated which ranges from 0 to 24 s. Following the delay interval, both levers are extended and the rat must remember and choose the lever presented in the sample phase to receive a food reward. The lever position in the sample phase is varied randomly across trials such that the rat must rely on trial-unique information to make the correct choice. Rats can perform many such trials in a single session (>100), and the mean accuracy of performance at different delay intervals provides an index of working memory function. **(D)** Both young and aged rats perform comparably, and with a high degree of accuracy, when the delay between the sample and choice phases is brief. At longer delay intervals, aged rats are disproportionately and significantly impaired. There are individual differences in performance among aged rats, with some aged rats maintaining working memory function on par with young rats and some demonstrating marked impairment. Data reproduced from [14,20,35].

cells of the hippocampus are remarkably preserved with age [25–27]. This observation has directed mechanistic investigation of age-related memory decline away from neurodegenerative processes and toward molecular and structural factors that can influence neuronal communication and plasticity.

Although less widely used, similar approaches can be employed to gain insight into the molecular underpinnings of PFC-dependent memory [3]. The rodent PFC is less anatomically elaborate than in primates; however, rats are capable of many complex behaviors and there is evidence for anatomical and functional homology between rodent and primate PFC (reviewed in [28–31]). Such findings provide a strong rationale for using aged rodents to investigate the neural mechanisms of working memory decline. Importantly, under normal circumstances the PFC and hippocampus work together to broadly support memory function spanning across both short and long durations. Support for regional investigation of molecular mechanisms that contribute to age-related memory decline is derived from substantial empirical data across species which highlight that the roles of hippocampus and PFC in memory can be behaviorally dissociated, as can memory impairments that emerge in aged populations. In particular, delayed response tasks are often used to assess PFC-dependent working memory abilities in humans, nonhuman primates, and rodents (recently reviewed in [3,32,33]). These tasks evaluate memory for a position or object over a short duration, with the accuracy of the memory typically being tested in a choice setting. In contrast to spatial reference memory (which involves retaining information about a single location across days), the to-be-remembered information in a delayed response task varies from trial to trial, requiring the subject to continually update the representation being held in mind or remembered. Figure 1C shows a delayed response task in which rats are required to remember the position of a response lever over delay intervals that range from 0 to 24 s. Damage to the medial PFC (mPFC), the rodent homolog of primate dorsolateral PFC, significantly impairs performance on this task in a delay-dependent manner [34]. By contrast, lesions of the hippocampus do not disrupt performance and, if anything, facilitate working memory using the task shown in Figure 1C [34]. These data strongly suggest that any decline in delayed response performance detected in aged rats is likely to be mediated by the PFC and not by the hippocampus. Indeed, while young and aged rats show comparable performance on the delayed response task at short delays, aged rats are disproportionately impaired as the delays over which the subject must remember the lever location become longer [35] (Figure 1D). These data are highly consistent with findings from aged nonhuman primates and humans, which denote both robust age-related behavioral deficits using delayed response tasks [36–39], and a decline in the electrophysiological signatures of working memory maintenance in the aged prefrontal cortex [40].

In agreement with the unique contributions of PFC and hippocampus to memory functions highlighted above, the neural substrates that are believed to enable long-term memory in hippocampus (Box 1) and working memory in PFC (Box 2) are also somewhat distinct. Notably, however, both require sustained excitation of pyramidal neurons as well as coordinated signaling from inhibitory interneurons that synthesize γ-aminobutyric acid (GABA). Under normal circumstances, interneurons regulate the excitation of individual pyramidal cells, and synchrony in neural networks, to establish the complex network dynamics that enable cognition [41,42]. Altered inhibitory signaling within cortical circuits is a central feature of cognitive disabilities across several psychiatric and neurodegenerative diseases [43,44]. Moreover, such cognitive deficits can be reproduced in experimental animal models in which normal GABAergic signaling has been disrupted [45,46]. This

Box 1. The role of interneurons in hippocampal circuits that support spatial reference memory

The hippocampus is anatomically subdivided into discrete subregions based on cellular and synaptic composition. Information flow is unidirectional: the dentate gyrus (DG) is the major input region of the hippocampus, and its constituent granule cells synapse upon CA3 pyramidal neurons that in turn project to CA1 pyramidal neurons (Figure I). Thus, DG–CA3–CA1 constitutes the classic trisynaptic pathway within which durable modifications to synaptic connections enable learning and memory. Importantly, the mechanisms of long-term synaptic modifications that support memory require highly-precise temporal and spatial dynamics that are established in part via GABAergic interneurons distributed throughout hippocampal subfields. Notably, the hilus contains interneurons that modulate both recurrent excitation between dentate granule cells, and glutamatergic mossy fiber projections from the DG to CA3 pyramidal cells. Recent work using optogenetic approaches demonstrates that reducing activity of hilar interneurons impairs spatial reference memory in rodents [122]. These data directly support a role for interneurons in memory and further indicate that alterations in interneuron function in the hippocampus of aged rodents could contribute to memory decline [71,123–125]. Future work using similar approaches to regulate other distinct subclasses of interneurons will be important for elucidating their role in different aspects of memory. With respect to this issue, it is notable that interneurons may not follow the unidirectional pathways described above and, instead, may help to integrate the hippocampus by making connections among all three subdivisions [126].

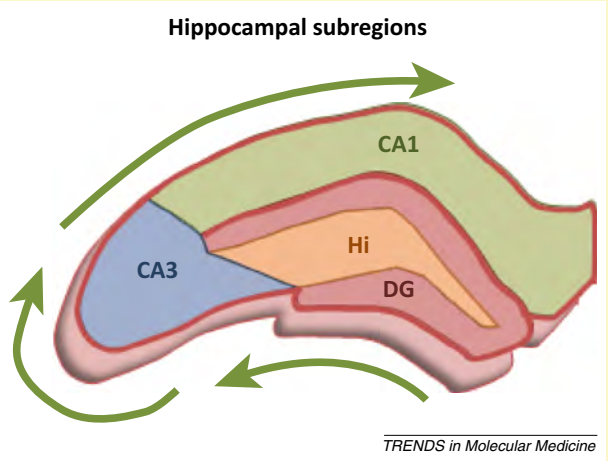

Figure I. Schematic depicts the unidirectional flow of information (green arrows) among synaptic connections between the dentate gyrus (DG; red), CA3 (blue), and CA1 (green). The hilus (Hi; orange) contains interneurons that innervate not only granule cells in the DG but also pyramidal neurons in the CA3.

Box 2. The role of interneurons in PFC circuits that support working memory

Unlike long-term memory, which requires persistent synaptic modification over days, weeks, and years, working memory requires neural activity that is only transiently stable (on the order of seconds), and that enables the information being held to be readily updated or modified. The cellular organization of the PFC is not unidirectional; instead, it is theorized to contain many interconnected microcircuits that respond to specific, preferred stimuli (Figure I). Within this recurrent network, transient activation by a preferred stimulus will excite all other interconnected neurons and sustain activity that persists in the absence of continued sensory stimulation. This persistent firing is presumed to form the basis of mental representation that is working memory [127,128]. Lateral inhibition provided by interneurons (IN) enhances the relative strength of microcircuits that encode salient information by inhibiting neighboring microcircuits encoding irrelevant, competing representations [129]. Indeed, alterations to PFC interneurons that confer lateral inhibition are widely believed to cause disordered working memory in schizophrenic patients [44]. Prefrontal interneurons comprise diverse subtypes that differ based on spiking frequency, synaptic interactions, and molecular markers [129–131]. It will be important in the future to only to clearly delineate which subtypes of interneurons are most affected by age or disease but also to determine the specific contributions of these unique interneuron subclasses to microcircuit function and, ultimately, to memory.

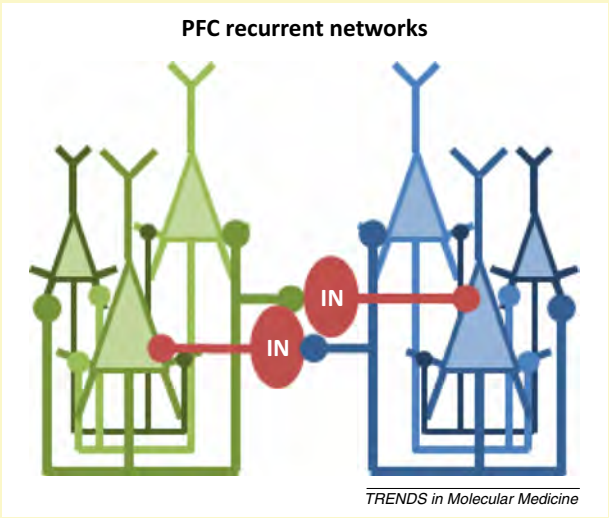

Figure I. Schematic depiction of two theoretical PFC microcircuits (denoted in green or blue), each of which is composed of reciprocally interconnected pyramidal neurons (triangles) that respond to a common stimulus. The sustained activity of these individual networks is presumed to enable the maintenance of a stable mental representation. Collaterals from each microcircuit also innervate an interneuron (IN, red circle) that laterally inhibits adjacent networks encoding competing representations.

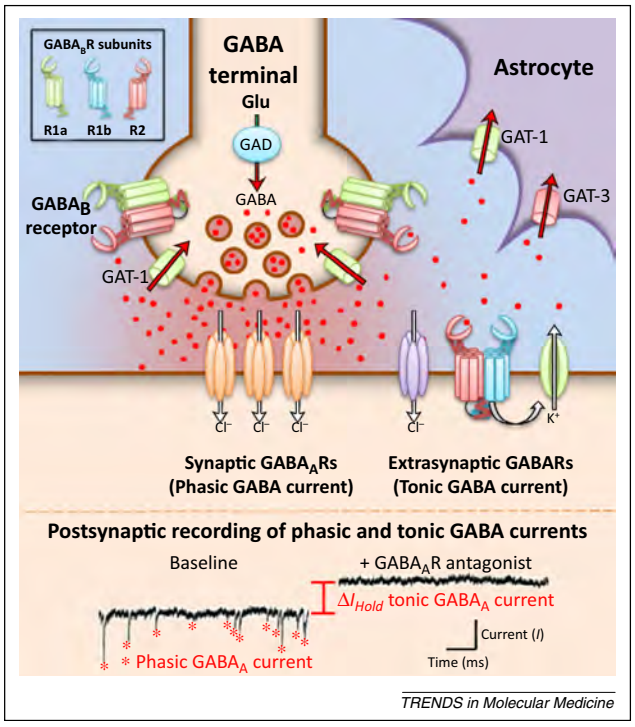

Figure 2. Extrasynaptic GABA$_A$Rs and GABA$_B$Rs mediate tonic inhibition. The schematic shows a GABAergic synapse and diagrams key aspects of GABAergic signaling. GABA is synthesized from glutamate (Glu) in the presynaptic terminal by the enzyme glutamic acid decarboxylase (GAD), and is removed from the extracellular space following synaptic release via membrane-bound transporters. These include the GABA transporter GAT-1, that is localized to neurons and astrocytes, and GAT-3, that is primarily localized to astrocytes. During activity-dependent release, GABA acts at chloride-permeant synaptic receptors (ionotropic GABA$_A$Rs, shown in orange) positioned at postsynaptic sites that closely appose GABA terminals. In addition, GABA can spill over from the synaptic zone to activate high-affinity extrasynaptic GABAergic receptors, including some subtypes of GABA$_A$Rs (purple receptors) as well as metabotropic GABA$_B$Rs (green/blue/red receptors). Notably, GABA$_B$Rs are heterodimers, containing an obligate R2 subunit and a variable R1a or R1b subunit (see inset at top left). GABA$_B$Rs that contain R1a are preferentially targeted to presynaptic terminals where they serve as autoreceptors and regulate GABA release by blocking action potential-dependent exocytosis of GABA-containing vesicles. GABA$_B$Rs that contain R1b are preferentially targeted to dendrites where they contribute to tonic inhibition through opening of potassium channels. The bottom panel shows representative traces from whole cell patch-clamp recordings from a cortical neuron. The trace under baseline conditions shows phasic inhibitory postsynaptic currents (red stars) produced by spontaneous vesicular release of GABA and subsequent activation of synaptic GABA$_A$Rs. Application of a GABA$_A$R antagonist eliminates these phasic currents and also produces a change in the holding current (ΔI_{Hold}) of the postsynaptic cell. The change in holding current is produced by the blockade of extrasynaptic GABA$_A$Rs tonically activated by low levels of ambient GABA.

review will focus on age-related changes in inhibitory signaling that accompany aging, with an emphasis on changes that are likely to affect function through extrasynaptic or presynaptic high-affinity GABAergic receptors. These data will be reviewed in the context of both hippocampus- and PFC-dependent memory, and as the potential basis for therapeutic interventions for optimizing cognitive functioning at advanced ages.

Overview of inhibitory signaling systems

GABA is the primary inhibitory neurotransmitter in the mammalian central nervous system. It is synthesized in presynaptic terminals from L-glutamic acid via a reaction that depends on glutamic acid decarboxylase (GAD; Figure 2). It is loaded into synaptic vesicles by the vesicular GABA transporter (VGAT), and released in an activity-dependent manner when action potentials depolarize the terminal, causing calcium influx and subsequent exocytosis. High concentrations of GABA are transiently produced in the synaptic cleft following action potential-mediated exocytosis, and some synaptically released GABA is believed to escape (or 'spillover') from the synaptic cleft into the extracellular space [47,48]. The exact concentration of this extrasynaptic or ambient GABA depends on a complex interrelationship between this process of spillover and uptake,

the latter of which is mediated by both neuronal and non-neuronal active transport mechanisms. Of these, GAT-1 is a primary neuronal GABA transporter, while GAT-3 is commonly associated with non-neuronal cells [49,50].

Receptors for GABA (GABARs) are broadly divided based on whether they are ionotropic ($GABA_ARs$) or metabotropic ($GABA_BRs$), but activation of either subtype is predominantly inhibitory in mature neurons of the adult nervous system. Ionotropic $GABA_ARs$ are permeant to chloride ions, and thus activation of $GABA_ARs$ typically produces inhibition either by producing a hyperpolarizing current or through a process known as shunting inhibition. Hyperpolarization predominates in cells that have active transport mechanisms to expel chloride, while shunting inhibition plays a more prominent role in cells in which chloride is passively distributed. By contrast, inhibition through metabotropic $GABA_BRs$ is produced through several possible $G_{i/o}$-dependent signaling cascades, typically leading to either opening of potassium-selective ion channels (Figure 2) or inhibition of calcium-selective channels.

The broad inhibitory actions of both $GABA_ARs$ and $GABA_BRs$ can further be divided into several more specific categories typically referred to as phasic inhibition, tonic inhibition, and presynaptic inhibition. Phasic inhibition refers to inhibition produced by transient activation of GABARs in the synaptic cleft after activity-dependent exocytosis of GABA. This type of inhibition is mediated primarily by ionotropic $GABA_ARs$ that contain the γ2 subunit [51,52], although $GABA_BRs$ can also carry a somewhat slower component of the fast synaptic response. Tonic inhibition refers to inhibition mediated by activation of extrasynaptic GABARs that are expressed outside of the synaptic cleft. Across brain regions, this type of inhibition is often mediated by ionotropic $GABA_ARs$ that contain the δ subunit [53,54]. In addition, the α5 subunit is robustly expressed in hippocampus [55–57], and extrasynaptic $GABA_ARs$ containing the α5 subunit have been shown to mediate tonic inhibition in both hippocampus proper and the dentate gyrus [58,59]. Beyond $GABA_ARs$, extrasynaptic $GABA_BRs$ also support tonic inhibitory currents in some brain regions, including PFC [48]. Finally, presynaptic inhibition refers to inhibition of activity-dependent exocytosis of neurotransmitters following activation of GABARs expressed on the presynaptic terminal. GABAergic autoreceptors are expressed on axon terminals that release GABA, while GABAergic heteroreceptors are expressed on other types of axon terminals [60,61].

Accumulating data highlight tonic inhibition as a particularly important regulator of neuronal activity and network dynamics in cortical circuits. Indeed, extrasynaptic GABARs are already attractive therapeutic targets for treatment of a broad range of neurological disorders including depression, schizophrenia, and Parkinson's disease [62–66]. Recent evidence further indicates that GABARs that mediate tonic inhibition are altered in aged hippocampus and PFC, suggesting that normalizing inhibitory signaling at these extrasynaptic receptors may also be of utility in cognitive dysfunction that accompanies the normal aging process.

GABAergic signaling alterations in aged hippocampus: impact on spatial memory

Molecular and cellular alterations in hippocampal GABA signaling

Inhibitory interneurons of the hippocampus undergo marked molecular and phenotypic alterations across the lifespan. In particular, beginning in middle-age, many interneurons cease to express GAD [67]. This reduction would be expected to confer less GABA synthesis and a consequent increase in hippocampal excitability. Consistent with this interpretation, and with data from neuropsychiatric conditions in which aberrant excitation is believed to contribute to memory impairment [68–70], the magnitude of decline in GAD-expressing neurons in the hilar region of dentate gyrus strongly predicts the severity of spatial memory deficits among aged rats [71]. Electrophysiological studies provide further evidence for anomalous GABAergic signaling in the aged hippocampus. Specifically, whole cell patch-clamp electrophysiology has been used to isolate and evaluate GABA-mediated currents in individual cells in young and aged hippocampal slices. Studies employing such methods demonstrate a reduced frequency of spontaneous inhibitory postsynaptic potentials (IPSPs) in granule cells of the aged dentate gyrus [72]. Moreover, both the amplitude and frequency of $GABA_AR$-mediated currents, as well as the amplitude and duration of the slow $GABA_BR$-mediated IPSP, are attenuated in aged CA1 pyramidal neurons [73,74].

Although parallel *in vitro* electrophysiological studies have not been conducted in CA3 pyramidal neurons, substantial evidence suggests that aging is accompanied by attenuated GABAergic signaling and aberrant excitability in this hippocampal subregion. Specifically, expression of *gabra5*, that encodes the α5 $GABA_AR$ subunit [75], is reduced in CA3 of aged rats in comparison to young adults. As described above, $GABA_ARs$ containing the α5 subunit are localized extrasynaptically, and these receptors can contribute to tonic inhibition in the hippocampus. In addition to $GABA_ARs$, expression of the $GABA_BR1$ subunit is also reduced throughout the hippocampus of memory-impaired aged rats. Notably, however, lower expression of $GABA_BR1$ is only accompanied by a reduction in $GABA_BR$ coupling to its effector G protein in CA3, suggesting that age-related $GABA_BR$ signaling dysfunction may be particularly pronounced in this hippocampal subregion [11,13]. Functional consequences for these age-related alterations in GABARs findings are illustrated by *in vivo* electrophysiological studies in which CA3 pyramidal neuron activity was monitored in behaving young and aged rats. Specifically, these studies revealed an age-related increase in the average and maximal firing rates of CA3 pyramidal neurons which was coupled to reduced specificity and plasticity associated with the encoding of spatial information [76,77].

GABAergic neuropharmacology and memory function

The findings described above indicate that GABA signaling is attenuated in the aged hippocampus, and provide a compelling rationale for targeting aberrant excitation as a treatment to improve memory function. Building on this rationale, the commonly prescribed anti-epileptic

levetiracetam has been recently shown to enhance the retention of newly learned information over a 24 h time-period in aged rats [78]. While levetiracetam is known to reduce hippocampal excitation, it should be noted that the specific mechanism of action for such effects remains unclear and may not involve direct actions at GABARs. Indeed, it has been suggested that this drug may regulate cellular excitation by inhibition of neurotransmitter release via modulation of calcium channels [79,80]. Notably, however, other pharmacological approaches that more specifically target extrasynaptic GABARs also benefit memory function in rodent models of age-related memory decline. In particular, administration of positive allosteric modulators of α5-containing $GABA_A$Rs improves performance of aged rats in several tests of hippocampus-dependent memory [81]. As the expression of α5-containing $GABA_A$Rs is largely restricted to the hippocampal formation, these findings provide initial evidence that normalizing hippocampal hyper-excitability via enhancement of tonic inhibition may be beneficial for memory function in aging.

GABAergic signaling alterations in aged prefrontal cortex: impact on working memory

Molecular and cellular alterations in PFC GABA signaling

In agreement with findings from hippocampus, there is a reduction in the number of GAD-expressing cells in aged PFC. Notably, however, such reductions are not unique to interneurons in PFC because a subtle reduction in the number of excitatory pyramidal neurons has also been reported in this brain region [82–84]. Moreover, the density of both symmetric (i.e., inhibitory) and asymmetric (i.e., excitatory) synapses decreases with age in the primate PFC [85]. Consistent with the structural data, magnetic resonance spectroscopy of the human brain reveals that both PFC GABA and glutamate concentrations decline in an age-dependent manner, beginning in middle-age [86]. While this body of work strongly supports an age-related reduction in overall PFC neurotransmission, these data do not in and of themselves indicate whether aging shifts PFC neural circuits towards greater or less excitability.

More recent findings, however, are beginning to reveal age-related cellular and molecular changes in PFC, that, unlike in hippocampus, support increased inhibition with advancing age. For example, one study evaluating GABA-signaling protein expression in microdissected rat mPFC showed an increase in expression of GAD, the enzyme important for GABA synthesis, and a decrease in expression of the GABA transporter, GAT-1 [14], in aged relative to young adult (Figure 3). These biochemical data suggest that there is increased production but decreased clearance of extracellular GABA in the aged PFC, findings which together suggest that aged pyramidal neurons in this brain region may be subject to increased inhibition.

Support for this interpretation comes from whole cell patch-clamp electrophysiology studies that have directly assessed GABA activity at PFC synapses. Using this approach, one study found an age-related increase in miniature, but not spontaneous, inhibitory postsynaptic currents (IPSCs) in pyramidal neurons from aged rats that exhibited behavioral impairments [87]. Moreover, in primates, the frequency of spontaneous, but not miniature, ISPCs reportedly increases with age [88]. While both studies provide support for an age-related increase in inhibitory transmission within the PFC, the mechanism for this enhancement is less clear. Recent work has begun to address this issue, building on data from young animals showing that $GABA_B$Rs can mediate tonic inhibition of PFC pyramidal neurons [48]. Specifically, studies compared tonic activation of presynaptic $GABA_B$ autoreceptors expressed on inhibitory inputs to pyramidal cells in young and aged rats [89]. The $GABA_B$R agonist baclofen significantly reduced evoked IPSC amplitude in both young and aged PFC neurons, but the magnitude of this baclofen-mediated inhibition was attenuated in aged neurons. These findings suggest that there is an age-related reduction in functional $GABA_B$ autoreceptors localized to inhibitory inputs onto pyramidal neurons, possibly contributing to dysregulated autoregulation of GABA release (Figure 3). Subsequent experiments revealed further age-related differences in $GABA_B$ autoreceptors. Specifically, in young neurons, application of a $GABA_B$R antagonist shifted evoked IPSC amplitudes above baseline levels, indicating the presence of tonic $GABA_B$ autoreceptor activity. This $GABA_B$R antagonist-mediated shift was significantly attenuated in aged neurons, indicating that there is an age-related loss of tonic inhibition at these $GABA_B$ autoreceptors. Broadly, this body of work shows that aging is associated with a reduction in $GABA_B$R autoregulation of GABA release, which would be expected to increase basal inhibition of pyramidal neurons. This conclusion has been directly supported by findings from other experiments in which selective antagonists of $GABA_A$ and $GABA_B$ receptors reveal an increase in tonic activation of these extrasynaptic receptors on PFC pyramidal neurons [89] (Figure 3).

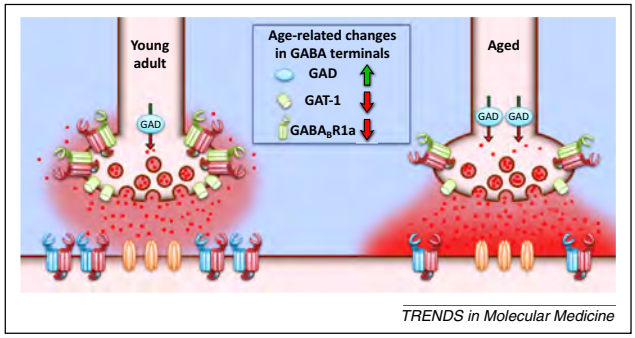

Figure 3. Age-related dysregulation of tonic GABA signaling at prefrontal cortex (PFC) synapses. The schematic shows representative presynaptic terminals from young adult and aged rat PFC that illustrate age-related changes in GABAergic signaling protein expression. Presynaptically, expression of glutamic acid decarboxylase (GAD) is upregulated in the aged PFC, and there is a concurrent reduction in expression of GABA transporter GAT-1 and $GABA_B$R1a [11,14]. These changes suggest an imbalance in the capacity to produce GABA relative to the ability to clear synaptic GABA or inhibit its further release. This biochemical evidence is corroborated by electrophysiological findings that suggest that the loss of autoreceptors manifests as a reduction in presynaptic GABA tone that normally limits further GABA release [89]. Consequently, there is an increase in extracellular GABA that increases the tonic activation of postsynaptic GABA receptors [89]. Together, these alterations would be expected to confer an age-related increase in basal inhibition of PFC pyramidal neurons.

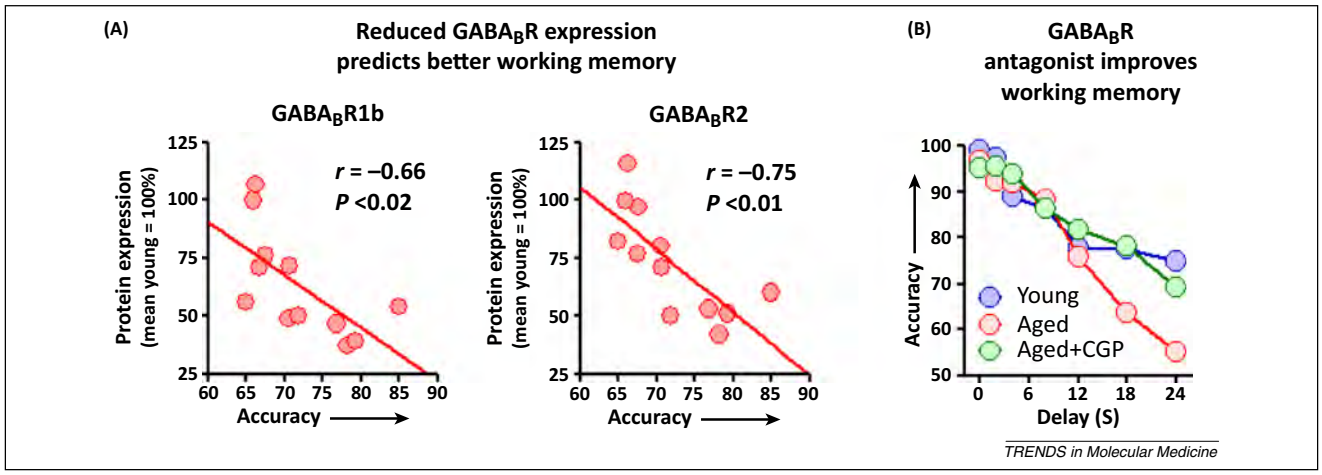

Figure 4. Targeting GABA$_B$R signaling to improve working memory. **(A)** Likely in response to excess GABA$_B$R-mediated inhibition, expression of the subunits that together form postsynaptic GABA$_B$Rs (GABA$_B$R1b and GABA$_B$R2) is reduced in the aged medial prefrontal cortex (mPFC) [11,14]. The downregulation of postsynaptic GABA$_B$Rs might serve to compensate for the excess inhibition described above as well as help to preserve the persistent activity of pyramidal neurons that is required for working memory maintenance. In support of this hypothesis, the bottom-right panel shows that, among aged rats, lower GABA$_B$R1b and GABA$_B$R2 expression strongly predicts better working memory. **(B)** If the downregulation of GABA$_B$Rs is a crucial mechanism for preserved working memory in aging, then blockade of GABA$_B$R signaling should restore working memory in impaired aged subjects. The line graph shows performance of a cohort of aged rats (red circles) that are impaired relative to young adult rats (blue circles) on the delayed response task. Using a within-subjects design, in which the same aged subjects shown in red were administered a GABA$_B$R antagonist CGP55845 (CGP) directly into the PFC (green circles), aged rat performance is restored to that of young adults. Data reproduced from [14].

Overall, the convergent findings from the biochemical and electrophysiological experiments support an increase in tonic inhibition of aged PFC pyramidal neurons. Potentially in response to increased GABA availability, both the GABA$_B$R1 and GABA$_B$R2 subunits, which together form the functional GABA$_B$R complex [90,91], are significantly reduced in the aged PFC, as is maximal baclofen-stimulated GTP exchange, a measure of GABA$_B$R:G protein coupling [11,14]. Notably, downregulation of GABA$_B$Rs in aging might be expected to compensate for age-related elevations in extracellular GABA, thereby preserving an optimal level of excitation required for working memory (Box 2) [92]. Consistent with this interpretation, the expression of both subunits constituting postsynaptic GABA$_B$Rs (R1b and R2) strongly predicts working memory abilities, such that lower GABA$_B$R expression is associated with greater accuracy on a delayed response task (Figure 4A) [14].

GABAergic neuropharmacology and memory function

The molecular and electrophysiological analyses described above demonstrate that tonic inhibition is increased in the aged PFC, and that lower expression of the subunits that comprise postsynaptic GABA$_B$Rs is strongly associated with better working memory abilities among aged rats. Together these findings provide a solid rationale for blocking excess GABA signaling at extrasynaptic GABA$_B$Rs to improve working memory function in aging. As an initial validation of this approach, direct administration of a GABA$_B$R antagonist into the mPFC of aged rats significantly improves working memory function on a delayed response task, such that aged rats reach a level of performance on par with young controls [14] (Figure 4B). These findings were replicated in aged rats using a systemic route of administration, extending the preclinical validation of GABA$_B$Rs as a target for age-related decline in working memory. It is notable that, unlike many pharmacotherapies that can improve cognition, the benefit of GABA$_B$R antagonists was restricted to aged rats. Indeed, systemic administration of a GABA$_B$R antagonist in this study impaired working memory abilities in young rats [14]. These data, considered together with the electrophysiological studies described above, suggest that the differential behavioral effects of GABA$_B$R antagonists in young and aged rats may be mediated by the relative actions of the antagonist in blocking tonic GABA at presynaptic versus postsynaptic sites. Because antagonists exert no direct biological actions, any behavioral output conferred by a GABA$_B$R antagonist will result from displacement of endogenous GABA at these receptors. Specifically, experiments described above suggest that the primary GABAergic tone in young rats is present on presynaptic GABA$_B$Rs. The antagonist acting at these receptors would be expected to block the autoregulation of GABA release, and result in increased extracellular GABA and increased pyramidal neuron inhibition. By contrast, this presynaptic GABAergic tone is lost in aging, suggesting that a GABA$_B$R antagonist administered in the aged PFC preferentially blocks activation of postsynaptic GABA$_B$Rs and thus reduces pyramidal neuron inhibition (Figure 3).

Targeting inhibitory signaling in humans as a treatment for age-related cognitive decline

Given its history as a treatment for epilepsy, and the preclinical data demonstrating spatial memory improvement in aged rodents, levetiracetam represents a tractable clinical candidate for treating age-related decline of hippocampus-dependent memory. Human neuroimaging studies support a relationship between increased hippocampal excitability and memory dysfunction in aging [93,94]. In particular, patients diagnosed with mild cognitive impairment (MCI), who have clinically detectable memory

loss and an increased propensity to develop AD, show significantly increased hippocampal activity compared to normal controls [95–98]. A recent study investigating the effects of levetiracetam in MCI patients reported normalization of DG/CA3 activity and improved recall in a memory task [99]. These data provide an initial proof-of-concept that reducing hippocampal activity may be useful in treating some forms of age-related memory decline.

There have also been initial studies investigating $GABA_BRs$ as a target for alleviating memory decline, with a focus on MCI and AD [100]. One $GABA_BR$ antagonist reached clinical trials for cognition, and this compound was initially tested in MCI patients [101,102]. Patients were treated for 2 months and efficacy was evaluated periodically over the course of the study. Individuals given the $GABA_BR$ antagonist showed significant improvement in working memory, psychomotor speed, and attention compared to placebo controls. An expanded Phase II trial was then conducted in patients meeting the diagnostic criteria for AD, but failed to meet its clinical endpoint. Importantly, the AD patient population may not be the most appropriate for $GABA_BR$ antagonists because these drugs are likely to have their greatest effects in individuals lacking pronounced neurodegeneration [103,104]. Nevertheless, the data from MCI patients are consistent with recent observations in aged rats, and further underscore the potential efficacy of $GABA_BR$ antagonists as a treatment for PFC-mediated cognitive decline in normal aging.

Concluding remarks and future perspectives

The divergent changes in GABAergic signaling that occur in aged hippocampus and PFC offer unique challenges from the perspective of treating memory decline. Based on the mechanistic data described above, therapeutics that target inhibitory changes in one brain region might be expected to exacerbate age-related dysregulation of GABAergic signaling in another. Indeed, these findings align with other work focused on cAMP/protein kinase A signaling, which suggests the need for unique therapeutic approaches for treating hippocampus- and PFC-mediated memory decline. Whereas cAMP activators hold promise for the alleviation of hippocampus-dependent memory impairment [105,106], overactivation of cAMP/PKA signaling in the PFC likely contributes to the manifestation of age-related working memory decline [107–109]. As such, guanfacine, a negative regulator of cAMP/PKA signaling via α2-adrenergic receptors, has emerged as a promising clinical candidate for the improvement of PFC-dependent working memory in older individuals [40,110,111]. Notably, however, the cognitive benefit of guanfacine does not extend to hippocampus-dependent memory [112]. With respect to the region-specific shifts in tonic inhibition described herein, there are some clear directions for future investigation that could clarify strategies for normalizing inhibitory signaling and improving memory function in aging. First, GABA receptor subtypes that are differentially expressed in hippocampus and PFC could be targeted to specifically correct inhibitory signaling disruptions in one brain region while minimizing the influence on the other. For example, given the selective expression of the α5 $GABA_AR$ subunit in hippocampus, systemic administration of positive α5 allosteric modulators is likely to specifically influence GABAergic signaling within this brain region. Additional information regarding concurrent changes to excitatory signaling might reveal other receptor candidates to target for normalizing age-related signaling dysfunction. Indeed, while this review has focused on inhibitory signaling alterations, such changes are tightly linked to excitatory neurotransmission, and it is essential to determine whether there are endogenous, adaptive changes to excitatory signaling pathways in aging that attempt to counteract or rebalance the normal excitatory–inhibitory dynamic. Such compensatory mechanisms may represent important therapeutic targets for treating memory dysfunction.

It should be noted that, although $GABA_BRs$ are widely distributed in brain, a body of work in rodent models indicates that $GABA_BR$ antagonists do not impair performance on hippocampus-dependent memory assessments and that these drugs can actually enhance performance under some conditions [113,114]. The mechanisms for such enhancement are not well understood, but it is plausible that these compounds attenuate aberrant excitation via modulation of $GABA_BR$-mediated autoregulation of GABA release. Notably, the hippocampus and PFC are interconnected, and neurobiological alterations in one region are likely to impact upon the other. For example, working memory aids in the initial encoding of episodic or reference memory. At the same time, retrieval of information from long-term memory into working memory stores is important for appropriate guidance of ongoing behavior. An important topic for future investigation concerns better understanding how modulation of inhibition in hippocampus or PFC impacts the functional connectivity between these regions and within the larger brain circuits that support cognition. Such data may provide insights regarding the clinical approaches that are likely to have the greatest impact in treating cognitive impairment in aging [115,116].

Beyond strategies that uniquely regulate inhibitory/excitatory dynamics in either the PFC or hippocampus, additional investigation directed toward uncovering the causative mechanisms responsible for age-related inhibitory signaling dysfunction may reveal new targets for treating age-related memory decline. For example, emerging evidence suggests that GABAergic interneurons may be particularly vulnerable to the effects of psychogenic stress [117,118]. Because dysregulation of the hypothalamus–pituitary–adrenal (HPA) axis and protracted exposure to glucocorticoids is a well-documented feature of normal aging [8,119–121], normalization of glucocorticoid signaling represents one avenue to explore for the prevention of inhibitory signaling dysfunction across both PFC and hippocampus.

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UNIVERSITY *of* FLORIDA

Evelyn F. and William L. McKnight Brain Institute of the University of Florida
P.O. Box 100015 • Gainesville, FL 32610-0015
352.273.8500

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