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December 18, 2017

Dear MBRF Trustees,

From everyone here at the University of Arizona, we are pleased to provide the 2017 EMBI annual report. This year we’ve made promising discoveries, forged new partnerships, and continued our rich tradition in neuroscience research on the normally aging brain. This year’s report showcases the progress we’ve made toward our shared goal of healthy cognitive aging for everyone in the future. Thank you so much for your continued support. Our work would not be as impactful without your collaboration, and we’re proud to have such an engaged partner in this important and challenging effort.

Sincerely,

Dr. Carol Barnes
Regents’ Professor, Psychology, Neurology and Neuroscience
Evelyn F. McKnight Chair for Learning and Memory in Aging
Director, Evelyn F. McKnight Brain Institute
Director, Division of Neural Systems, Memory and Aging
December 18, 2017

Dear McKnight Brain Research Foundation Trustees,

We are honored to present this year’s annual report on behalf of the University of Arizona’s Evelyn F. McKnight Brain Institute. As you read, I hope you are inspired by the outstanding brain science happening here at the University of Arizona. This annual report is intended to give you a window into the progress we have made, the collaborations we have forged, and our hopes for research and translation in the future.

In the office for Research, Discovery, and Innovation, we are supporting ground-breaking UA researchers who push the boundaries of innovation and generate new knowledge. Our faculty collaborate in novel ways that yield amazing discoveries and breakthroughs both in the University and with peers across the state, nation and world. The Evelyn F. McKnight Institute is a team that embraces the UA’s interdisciplinary spirit. Over the last year, Dr. Carol Barnes and her collaborators have continued their renowned tradition of excellence in neuroscience, memory and aging. This report represents the culmination of all the projects, experiments and collaborations that continue to distinguish our Institute and University.

The Institute also supports the training of the next generation of scholars and innovators. Students play a crucial role in the Institute’s most innovative research and projects, and gain valuable hands-on experience in the faculty’s laboratories. We are proud of the outcomes described in this report, and we are honored to be home to this robust academic center on our campus.

Thank you for your continued support of the University of Arizona Evelyn F. McKnight Institute. No doubt, our progress continues to advance because of your support, and we are grateful for the innovations and scientific insights that you are making possible. Together, we are discovering the mysteries of the brain that advance our understanding of healthy aging in new ways every year to address the ultimate goal for all of us to live their longest and healthiest lives.

Sincerely,

Robert C. Robbins, M.D.  Kimberly Andrews Espy, Ph.D.  Andrew Comrie, Ph.D.
President  Senior Vice President for Research  Senior Vice President for Academic Affairs & Provost

Senior Vice President for
Summary of scientific achievements since last report

The director and other members of the Evelyn F. McKnight Brain Institute at the University of Arizona have had another productive year. The full list of publications can be found on pages 8 through 11. The following outlines some of these accomplishments that directly relate to mechanisms of age-related memory loss, first from the director’s and associate director’s laboratories, and then from other Evelyn F. McKnight Brain Institute (EMBI) affiliate faculty’s laboratories.

**Barnes**

The Barnes laboratory collaborated with Adam Gazzaley (UCSF) and Sara Burke (McKnight, UF) to examine alterations in executive function that occur in normal cognitive aging in rhesus macaques (these data are reported in Gray et al., 2017). The behavioral experiments were designed to assess alterations in executive function in monkeys that Gazzaley has shown to occur in older human participants. The behavioral tests given to the young and old monkeys involved assessments of attentional updating and monitoring processes to determine whether older monkeys also show multi-tasking deficits analogous to older humans. The data obtained from an interference task and a reversal learning task revealed that older animals are impaired on both of these tasks, compared to their young counterparts. Interestingly, however, the levels of performance on the object reversal task were not correlated with levels of performance in the interference task, suggesting differential effects of aging on independent prefrontal cortical circuits.

The Barnes laboratory collaborated with Meredith Hay (EMBI affiliate faculty), John Konhilas (UA), and Todd Vanderah (UA) to examine the effects of modifying inflammatory processes (via the angiotensin system) in a novel preclinical model of congestive heart failure (these data are reported in Hay et al., 2017). The goal of the experiment was to determine if this treatment could prevent heart failure-related cognitive decline that is common after such events in older individuals. We were able to produce myocardial infarction in the mouse, with a 50-70% decline in ejection fraction by endocardiography. The group given the angiotensin 1-7 treatment for four weeks showed significantly less cognitive impairment than did non-treated mice, but the treatment had no effect on cardiac function, suggesting specific neuroprotection of this compound.

The Barnes laboratory collaborated with Scott Moffat (Georgia Institute of Technology), Jan Wiener (Ageing and Dementia Institute, Bournemouth University, Poole, UK), and Thomas Wolbers (Aging and Cognition Research Group, Magdeburg, Germany) to produce a review of the aging navigational system literature across rodent, nonhuman primate, and humans for the prestigious journal Neuron (reported in Lester et al., 2017). The researchers each brought different expertise to the synthesis of this literature and attempted, for the first time, to define and clarify terms used to describe types of navigation used in both the human and nonhuman literature. This allowed the researchers to integrate findings more accurately across species, discuss how cognitive aging affects the brain’s navigation circuits, and describe the behavioral and neural underpinnings of the deficits observed in navigational computations in old age.

The Barnes laboratory collaborated with Tom Beach (Banner Sun Health Research Institute, AZ) and Jiong Shi (Barrow Neurological Institute, AZ) to determine whether levels of pituitary adenylate cyclase activating polypeptide (PACAP) and amyloid plaque density might covary in the aging nonhuman primate brain (these data are reported in Han et al., 2017). The researchers hypothesized that, because PACAP has been shown to play a positive role in mitochondrial function, it may be a ‘protective factor’ in the presence of beta amyloid toxicity. Consistent with their hypothesis, the researchers found that plaques increased in a region-specific manner across age in these monkeys, PACAP levels decreased at older ages, and both were correlated with a decline in memory in the older monkeys.

The Barnes laboratory collaborated with Andrew Maurer (McKnight, UF) and Sara Burke (McKnight, UF) to assess the integrity of interneuron function in the perirhinal cortex of aged, cognitively characterized rats (these data are reported in Maurer et al., 2017). The researchers report that the lower firing rates previously observed in aged rat...
perirhinal cortical principal cells are associated with weaker interneuron activity and reduced excitatory input onto inhibitory cells in this structure. We predict that therapeutics targeting this synaptic connection may be beneficial for some of the declines in cognition observed in normal aging.

The Barnes laboratory collaborated with David Sweatt (McKnight, UAB), Matt Huentelman (EMBI affiliate faculty), and Tom Foster (McKnight, UF) on an experiment that employed next-generation RNA sequencing to examine gene expression differences related to aging-related changes in hippocampal subfields and selective cognitive declines (these data are reported in Lanov et al., 2017). The researchers report significant differences among hippocampus regions CA1, CA3, and dentate gyrus in the expression of specific genes and in the relationship of specific genes to cognitive decline. Importantly, the researchers used two sequencing platforms and were able to demonstrate good cross-platform concordance in the gene counts and in detecting differences in expression.

The Barnes laboratory examined amygdala cell and local field potential correlates of decision-making behaviors in young and older rats (these data are reported in Samson et al., 2017). Older adults tend to use strategies that differ from those used by young adults to solve decision-making tasks, and the researchers found that older rats also appear to use different strategies than their younger counterparts. Along with behavioral differences, the researchers observed age- and task-specific increases in the power of beta oscillations in the amygdala when older rats learned or decided between rewards of different size. It is thought that beta oscillations can engage a broad network across many regions of the brain. The increase in beta power in old rats (not in young) may reflect differences in strategies used by older animals in decision-making tasks and suggest a mechanism through which reward networks may be expanded during aging.
Summary of scientific achievements since last report

Continued

Ryan
The Ryan laboratory conducted a study to evaluate the effect of visual integration on memory in young and aged adults (these data are reported in Memel and Ryan, 2017). They report that visual integration methods benefit associative memory performance in both young and older adults similarly. Interestingly, while both younger and older adults showed increased activation of hippocampus in MRI scans during these tasks, the memory performance of older adults was most strongly predicted by prefrontal rather than temporal lobe activation, and the younger adults showed stronger temporal lobe activation than did the older participants. These data suggest a mechanism for improving associative memory in older adults.

Alexander
The Alexander (EMBI affiliate faculty) laboratory along with Wright (McKnight, U Miami), Moeller (Columbia), Sacco (McKnight, U Miami), Stern (Columbia), and DeCarli (UC Davis) examined groups of individuals that received brain scans and cognitive testing (these data are reported in Kern et al., 2017). The participants (60 to 86 years) were split into those who had normal blood pressure, those with pharmacologically controlled hypertension, or those with uncontrolled hypertension. The uncontrolled hypertension group showed the most gray matter volume decline and white matter lesion load, and the normotensive individuals showed the least. The researchers conclude that white matter lesions from small-vessel disease are associated with reduced gray matter volume and are dependent on blood pressure management. These data provide neural documentation of the importance of maintaining a normotensive profile for promoting good executive function and memory.

The Alexander laboratory collaborated with Raichlen (UA) to propose a model of adaptive capacity of the body and brain to help explain the mechanisms underlying the exercise and brain health, which was published in the prestigious journal TINS (reported in Alexander and Raichlen, 2017). The two main questions addressed in this article are what mechanisms underlie age-related brain atrophy and how lifestyle changes influence the trajectory of healthy and pathological aging.

Brinton
The Brinton (EMBI affiliate faculty) laboratory tested the safety profile of an estrogen formulation in perimenopausal and postmenopausal women (these data are reported in Hernandez et al., 2017). The particular phytoestrogen chosen for this trial (an estrogen receptor beta-selective phytoestrogen) is thought to promote neuronal survival without exerting feminizing activity in the periphery. The 12-week clinical trial evaluated cognitive performance and vasomotor symptoms, but it was designed to demonstrate safety and was not powered to assess cognition. No adverse effects were noted; therefore, the researchers conclude that this formulation is well tolerated. Thus, the data support the conduct of further trials to expand the duration and number of participants tested.

The Brinton laboratory, along with a number of her collaborators at USC, edited a series of papers on the metabolic-inflammatory axis in brain aging and neurodegeneration, which included an overview of the role of changes in energy metabolism and inflammation in aging (the introduction is Yin et al., 2017). This series of papers explores ideas of the pivotal role that mitochondrial health and function plays in brain aging, along with inflammatory processes and microglia senescence. The goal of this series of papers is to focus efforts on effective ways to positively impact brain health.
**Chou**
The Chou (EMBI affiliate faculty) laboratory, along with collaborators from Duke University, examined the hypothesis that aging is associated with increased fronto-parietal involvement in attentional guidance (these data are reported in Madden et al., 2017a). Participants ranged from 19 to 78 years of age. Search reaction time measures indicated that bottom-up attentional guidance was relatively constant as a function of age, and fronto-parietal fMRI activation related to target detection was also constant as a function of age. The main difference noted in these visual search tests appeared in individuals beginning at about 35 years of age, where there was a decrease in resting state functional connectivity in visual sensory regions. These findings suggest that search reaction time changes occur relatively early in adulthood, and are maintained throughout normative aging into the eighth decade.

The Chou laboratory, along with collaborators from Duke University, examined the resting state functional connectivity and white-matter hyperintensity volumes as mediators of age-related changes in fluid cognitive processes (these data are reported in Madden et al., 2017b). In adults ranging in age from 19 to 79 years, the researchers found that general levels of analysis involving composite measures of fluid cognition and imaging modalities did not result in the detection of changes or significant relationships with age. The specific measure of resting-state functional connectivity of sensorimotor networks, however, was found to be a significant mediator of age-related decline in executive function. The researchers suggest that specific models of neurocognitive disconnection are needed for sensitive analyses of cognitive decline in aging.

**Glisky**
The Glisky and Mehl (EMBI affiliate faculty) laboratories examined the efficacy of learning and using an online social networking website as an intervention to maintain or enhance cognitive function in older adults (these data are reported in Myhre et al., 2017). The online Facebook group showed a significant increase in an executive function associated with complex working memory tasks. No significant change in the daily diary or waitlist control groups was observed. No other measures of cognitive function or social interactions showed differential improvement as a result of this online treatment. The researchers conclude that learning and using an online social networking site can provide specific benefits for complex working memory problems in this group of healthy older adults.

**Grilli**
The Grilli (EMBI affiliate faculty) laboratory, in collaboration with Glisky (EMBI affiliate faculty), examined whether cognitively healthy older adults who carry the APOE4 allele of the apolipoprotein E gene (a risk factor for late-onset Alzheimer’s disease) benefit from semantic elaboration or imagination-generated self-reference based processing in memory for emotional and nonemotional narratives (these data are reported in Grilli et al., 2017). Both carriers and noncarriers of the E4 allele benefited from self-referencing methods compared to semantic elaboration methods. The older non-E4 carriers showed the expected emotional enhancement of memory effect; however, the E4 carriers did not. This suggests that deficits in emotional memory may be an early cognitive marker of abnormal decline in aging adults.
Publications in peer-reviewed journals

Dopaminergic cell in the lateral ventral tegmental area of an old, memory-impaired monkey.


Chawla, M.K., Sutherland, V.L., Olson K., McNaughton, B.L., and Barnes, C.A. (2017) Behavior-driven Arc expression is reduced in all ventral hippocampal subfields compared to CA1, CA3 and dentate gyrus in rat dorsal hippocampus. Hippocampus, in press.


Publications in peer-reviewed journals


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<thead>
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<th>Author(s)</th>
<th>Title</th>
<th>Journal</th>
<th>Volume, Issue, Pages (Year)</th>
</tr>
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<tbody>
<tr>
<td>Zajkowski, W., Kossut, M., and Wilson, R.C.</td>
<td>A causal role for right frontopolar cortex in directed, but not random, exploration.</td>
<td>eLife</td>
<td>6, e27430 (2017)</td>
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</table>
Rats are prepared for studies to examine the role of brain oscillations in hippocampal function and brain aging.
Presentations at scientific meetings


Barnes, C.A. Aging is not a disease: Normal lifespan changes in brain circuits critical for memory. Distinguished Sackler Visiting Lecture, Collaborative Program in Neuroscience, University of Toronto, February 2017.


Barnes, C.A. Brain circuit changes that contribute to age-related declines in cognition. Hagey Lecture, University of Waterloo, Waterloo, Canada, March 2017.

Barnes, C.A. The ‘youngfield’ of neuroscience: One senior scientists’ retrospective. Student Colloquium, University of Waterloo, Waterloo, Canada, March 2017.


Barnes, C.A. Session Chair: Fixing memory: Interventions that target the hippocampus. Spring Hippocampal Research Conference, Taormina, Italy, June 2017.
Presentations at scientific meetings
Continued

Brinton, R.D. Sex Steroids and the Brain. What the Brain Has Taught Us About Sex Steroids. University of California at Santa Barbara Seminar, Santa Barbara, CA, June 2017.


Cowen, S. Neuro-electro-chemical transmitter analytics research. IBM Cloud University Conference, Berlin, Germany, October 2017.

Presentations at scientific meetings

Continued


Presentations at scientific meetings

Continued


Presentations at public (non-scientific) meetings or events


**Brinton, R.D.** Architects of Change Luncheon Speaker, Mount St. Mary’s University, Los Angeles, CA, March 2017.


**Alexander, G.E.** The Brain-Exercise Connection. Tucson Medical Center Brain Week, Tucson, AZ, April 2017.

**Cowen, S.L.** Tucson Festival of Books Presenter. Dr. Cowen’s lab developed an electronic-brain demonstration system called “Brian the Brain” for teaching K-12 students about neurophysiology (NSF funded). Dr. Cowen and his students demonstrated the device at the Festival of Books and at a local high school. Tucson, AZ, Spring 2017.

**Ryan, L.** Good for the heart, Good for the brain. La Posada Continuing Care Retirement Community, Green Valley, AZ, August 2017.


Awards


Jessica Andrews-Hanna, Ph.D., Kavli Foundation/National Academy of Science Frontiers of Science Fellow (2017)

Carol Barnes, Ph.D., University of New Mexico Department of Psychology Quad-L Award in recognition of significant scientific contributions in the areas of learning, memory, and cognition (2017)

Roberta Brinton-Diaz, M.D., Ph.D., Alzheimer’s Drug Discovery Foundation Melvin R. Goodes Prize for Excellence in Alzheimer’s Drug Discovery (2017)

Roberta Brinton-Diaz, M.D., Ph.D., NIA MERIT (Method to Extend Research in Time) Award, R37AG053589, Aging and Estrogenic Control of the Bioenergetic System in Brain (2017-2022)

Lalitha Madhavan, M.D., Ph.D. University’s Visionary Leadership Maria Teresa L’Velez Outstanding Faculty Mentor Award (2017)

Lynn Nadel, Ph.D., American Psychological Foundation Gold Medal for Life Achievement in the Science of Psychology (2017)

Mary-Francis O’Conner, Ph.D., American Psychosomatic Society 75th Anniversary Award for recognition of contributions to our understanding of the integration of emotion, social relationships, and health (2017)
Complete Faculty List

Director

• Carol A. Barnes, Ph.D., Regents’ Professor, Psychology, Neurology and Neuroscience; Director, Evelyn F. McKnight Brain Institute; Evelyn F. McKnight Chair for Learning and Memory in Aging; Director, Division of Neural Systems, Memory and Aging

Associate Director

• Lee Ryan, Ph.D., Professor and Head, Psychology; Director, Cognition and Neuroimaging Labs, University of Arizona

Strategic Advisory Committee

• Martha A. Brumfield, Ph.D., President and Chief Executive Officer, Critical Path Institute; Research Professor, Pharmacology and Toxicology, University of Arizona
• Eric M. Reiman, M.D., Ph.D., Professor, Psychiatry; Associate Head for Research and Development (Phoenix Campus), University of Arizona; Director, Arizona Alzheimer’s Disease Consortium; Executive Director, Banner Alzheimer’s Institute; Clinical Director, Neurogenomics Program, Translational Genomics Research Institute (TGen)
• Leslie P. Tolbert, Ph.D., Regents’ Professor, Neuroscience and Cellular and Molecular Medicine, University of Arizona

Scientific Advisory Committee

(Biographical sketches included in following pages; all scientific advisors are also affiliate faculty)

• Geoffrey L. Ahern, M.D., Ph.D., Professor, Neurology, Psychology and Psychiatry; Medical Director, Behavioral Neuroscience and Alzheimer’s Clinic; Bruce and Lorraine Cumming Endowed Chair in Alzheimer’s Research, University of Arizona
• Gene E. Alexander, Ph.D., Professor, Psychology, Psychiatry and Neuroscience; Director, Brain Imaging, Behavior and Aging Lab, University of Arizona
• Carol A. Barnes, Ph.D., Regents’ Professor, Psychology, Neurology and Neuroscience; Director, Evelyn F. McKnight Brain Institute; Evelyn F. McKnight Chair for Learning and Memory in Aging; Director, Division of Neural Systems, Memory and Aging, University of Arizona
• Roberta Diaz Brinton, Ph.D., Professor, Pharmacology, Neurology and Psychology; Director, Center for Innovation in Brain Science
• Stephen L. Cowen, Ph.D. Assistant Professor, Psychology, Division of Neural Systems, Memory and Aging, Evelyn F. McKnight Brain Institute, University of Arizona
• Elizabeth Glisky, Ph.D., Professor, Psychology, University of Arizona
• Naomi E. Rance, M.D., Ph.D., Professor, Neurology, Cell Biology and Anatomy, and Pathology; Associate Head, Pathology, University of Arizona
• Lee Ryan, Ph.D., Professor, Psychology; Director, Cognition and Neuroimaging Labs, University of Arizona
Additional Affiliate Faculty

- Jessica Andrews-Hanna, Ph.D., Assistant Professor, Psychology, University of Arizona
- E. Fiona Bailey, Ph.D., Associate Professor, Physiology, University of Arizona
- Heather Bimonte-Nelson, Ph.D., Associate Professor, Honors Disciplinary Faculty; Behavioral Neuroscience Program Director, Arizona State University
- Ying-hui Chou, Ph.D., Assistant Professor, Psychology, University of Arizona
- Paul Coleman, Ph.D., UA Associate, Evelyn F. McKnight Brain Institute, University of Arizona; Research Professor, The Biodesign Institute, Neurodegenerative Disease Research Center, Arizona State University
- Fabian Fernandez, Ph.D., Assistant Professor, Psychology, University of Arizona
- Ralph F. Fregosi, Ph.D., Professor, Physiology, University of Arizona
- Andrew J. Fuglevand, Ph.D., Associate Professor, Physiology, University of Arizona
- Katalin M. Gothard, M.D., Ph.D., Professor, Physiology, University of Arizona
- Matt Grilli, Ph.D., Assistant Professor, Psychology, University of Arizona
- Meredith Hay, Ph.D., Professor, Physiology, University of Arizona
- Matthew J. Huettel, Ph.D., UA Associate, Evelyn F. McKnight Brain Institute, University of Arizona; Associate Professor, Neurogenomics Division, Translational Genomics Research Institute
- Anita Koshy, M.D., Assistant Professor, Neurology, University of Arizona
- Lalitha Madhavan, MBBS, Ph.D., Assistant Professor, Neurology, University of Arizona
- Diano Marrone, Ph.D., UA Associate, Evelyn F. McKnight Brain Institute; Assistant Professor, Psychology, Wilfrid Laurier University
- Matthias R. Mehl, Ph.D., Professor, Psychology, University of Arizona
- Lynn Nadel, Ph.D., Regents’ Professor, Psychology, University of Arizona
- Janko Nikolich-Zugich, M.D., Ph.D., Professor and Chairman, Immunobiology; Co-Director, Arizona Center on Aging, University of Arizona
- Mary-Frances O’Conner, Ph.D., Assistant Professor, Psychology, University of Arizona
- Mary Peterson, Ph.D., Professor, Psychology, University of Arizona
- Steve Rapcsak, M.D., Professor, Neurology, Psychology and Speech, Hearing and Language Pathology, University of Arizona; Chief, Neurology Section, VA Medical Center
- Linda L. Restifo, M.D., Ph.D., Professor, Neurology, Neuroscience, Cell Biology and Anatomy, and BIO5 Institute, University of Arizona
- David A. Sbarra, Ph.D., Professor and Director of Clinical Training, Psychology, University of Arizona
- Anne C. Smith, Ph.D., Associate Research Scientist, Evelyn F. McKnight Brain Institute, University of Arizona
- Ted P. Trouard, Ph.D., Professor, Biomedical Engineering, University of Arizona
- Robert C. Wilson, Ph.D., Assistant Professor, Psychology, University of Arizona
- Pixuan ‘Joe’ Zhou, Ph.D., Adjunct Research Professor, Optical Sciences, University of Arizona
**Biographical Sketch**

Geoffrey Lawrence Ahern, M.D., Ph.D.
Professor

### Education/Training

<table>
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<th>Degree</th>
<th>Year(S)</th>
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<tbody>
<tr>
<td>SUNY, Purchase College</td>
<td>B.A.</td>
<td>1976</td>
<td>Psychology</td>
</tr>
<tr>
<td>Yale University, New Haven</td>
<td>M.S.</td>
<td>1978</td>
<td>Psychology</td>
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<tr>
<td>Yale University, New Haven</td>
<td>Ph.D.</td>
<td>1981</td>
<td>Psychology</td>
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<tr>
<td>Yale University, New Haven</td>
<td>M.D.</td>
<td>1984</td>
<td>Medicine</td>
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<tr>
<td>Waterbury Hospital, Waterbury</td>
<td>Intern</td>
<td>1984 – 1985</td>
<td>Medicine</td>
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<tr>
<td>Boston University, Boston</td>
<td>Resident</td>
<td>1985 – 1988</td>
<td>Neurology</td>
</tr>
<tr>
<td>Beth Israel Hospital, Boston</td>
<td>Fellow</td>
<td>1988 – 1990</td>
<td>Behavioral Neurology</td>
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### Positions

- **1977 – 1980** Lab Director, Human Psychophysiology Laboratory, Yale University, New Haven
- **1985 – 1988** Teaching Fellow, Department of Neurology, Boston University School of Medicine, Boston
- **1988 – 1990** Instructor, Department of Neurology, Harvard Medical School, Boston
- **1988 – 1990** Attending Neurologist, Beth Israel Hospital, Boston
- **1990 – 1996** Assistant Professor, Neurology and Psychology, University of Arizona, Tucson
- **1990** Attending Neurologist, University Medical Center, Tucson, Arizona
- **1990 – 1996** Medical Director, Behavioral Neurology Unit, University of Arizona, Tucson
- **1990** Director, Neurobehavioral Laboratory, University of Arizona, Tucson
- **1990** Member, Committee on Neuroscience, University of Arizona, Tucson, Arizona
- **1996 – 1999** Associate Professor, Neurology and Psychology, University of Arizona, Tucson
- **1996** Director, Behavioral Neuroscience & Alzheimer’s Clinic, University of Arizona, Tucson
- **1999 – 2002** Associate Professor, Neurology, Psychology, Psychiatry, University of Arizona, Tucson
- **2002** Professor, Neurology, Psychology, and Psychiatry, University of Arizona, Tucson
- **2007** Professor, Evelyn F. McKnight Brain Institute, University of Arizona, Tucson
- **2007** Bruce and Lorraine Cumming Endowed Chair in Alzheimer’s Research
Biographical Sketch
Geoffrey Lawrence Ahern, M.D., Ph.D.

Honors and Awards

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Publications


Biographical Sketch
Gene E. Alexander, Ph.D.

Education/Training

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<tr>
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<th>Degree</th>
<th>Year(S)</th>
<th>Field Of Study</th>
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<tr>
<td>Pomona College, Claremont, CA</td>
<td>B.A.</td>
<td>5/1983</td>
<td>Psychology</td>
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<tr>
<td>Loyola University of Chicago, Chicago, IL</td>
<td>M.A.</td>
<td>5/1987</td>
<td>Clinical Psychology</td>
</tr>
<tr>
<td>Loyola University of Chicago, Chicago, IL</td>
<td>Ph.D.</td>
<td>1/1992</td>
<td>Clinical Psychology</td>
</tr>
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Personal Statement

Gene E. Alexander, Ph.D., is professor in the Departments of Psychology and Psychiatry, in the Evelyn F. McKnight Brain Institute, and in the Neuroscience and Physiological Sciences Graduate Programs of the University of Arizona. He is director of the Brain Imaging, Behavior and Aging Lab; a member of the Scientific Advisory Committee for the Arizona Evelyn F. McKnight Brain Institute; chair of the Research Committee in the Department of Psychology; and a member of the BIOS Institute and the MRI Operations Committee at the University of Arizona. Prior to coming to Arizona, Dr. Alexander was chief of the Neuropsychology Unit in the Laboratory of Neurosciences in the Intramural Research Program at the NIA. Dr. Alexander is a fellow of the American Psychological Association (Division 40) Society for Clinical Neuropsychology and the Association for Psychological Science. His research has been supported by grants from the National Institutes of Health, McKnight Brain Research Foundation, and the state of Arizona. Dr. Alexander has more than 20 years of experience as a neuropsychology and neuroimaging researcher on the effects of aging and risk factors for age-related neurodegenerative disease. He uses structural and functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) with novel network analyses to investigate the effects of multiple health and lifestyle factors on the cognitive and brain changes associated with healthy and pathological aging, with the goal of developing new interventions for the effects of cognitive aging.


Research and Professional Experience

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<td>1988 - 1989</td>
<td>Clinical Psychology Intern</td>
<td>Dept. of Psychiatry &amp; Behav Sci, Univ of Washington, Seattle, WA</td>
</tr>
<tr>
<td>1989 - 1992</td>
<td>Research Fellow</td>
<td>Dept. of Brain Imaging, NYSPI and Columbia University, NY, NY</td>
</tr>
<tr>
<td>1991 - 1993</td>
<td>Research Scientist I</td>
<td>Dept. of Brain Imaging, NYSPI and Columbia University, NY, NY</td>
</tr>
<tr>
<td>1993 - 1999</td>
<td>Staff Fellow to Sr. Staff Fellow</td>
<td>Laboratory of Neurosciences, NIA, NIH, Bethesda, MD</td>
</tr>
<tr>
<td>1993 - 1999</td>
<td>Chief</td>
<td>Neuropsychology Unit, Laboratory of Neurosciences, NIA, NIH, Bethesda, MD</td>
</tr>
<tr>
<td>1999 - 2003</td>
<td>Research Associate Professor</td>
<td>Dept. of Psychology, Arizona State University, Tempe, AZ</td>
</tr>
<tr>
<td>2001 - 2009</td>
<td>Director</td>
<td>Data Management and Statistics Program/Core, Arizona ADC, AZ</td>
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Biographical Sketch
Gene E. Alexander, Ph.D.

Honors and Awards

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<tr>
<th>Year</th>
<th>Role</th>
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<td>1996–1999</td>
<td>Staff Recognition Awards (annual), Laboratory of Neurosciences, IRP, NIA, NIH</td>
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<td>2000–Present</td>
<td>Reviewer, Alzheimer’s Association Research Grant Program</td>
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<td>2003–2007</td>
<td>Member, Study Section, Clinical Neuroscience and Disease, IRG, CSR, NIH</td>
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<td>2003</td>
<td>Member, SEP, Women’s Health Initiative Memory Study, Review Branch, NHLBI, NIH</td>
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<td>2004</td>
<td>Member, Special Emphasis Panel, Alzheimer’s Disease Center Grant Review, NIA, NIH</td>
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<td>2005–2007</td>
<td>Member, Specialist Review Cmte, Psychology: Exp/Clinical, Fulbright Scholar Program</td>
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<td>2006</td>
<td>Chair, SEP, Clinical Neuroscience &amp; Disease, ZRG1 BDCN-E, IRG, CSR, NIH</td>
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<td>2008</td>
<td>Member, SEP, Prog Proj Review Group, Recovery from Illness, ZAG1 ZIJ-8 O1, NIA, NIH</td>
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<td>2008</td>
<td>Member, Study Section, Brain Injury &amp; Neurovasc. Path., ZRB 1 BDCN-L (07), CSR, NIH</td>
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<td>2008</td>
<td>Member, SEP, SPRINT Center Review, ZHL1 CCT-B C2 1, NHLBI, NIH</td>
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<td>2008–Present</td>
<td>Member, Neuroimaging Workgroup, International Conf. on Alzheimer’s Disease/STAART</td>
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<td>2009</td>
<td>Reviewer, SEP, Challenge Grant Panel #10, ZRG1 BDA-A 58 R, CSR, NIH</td>
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<td>2009</td>
<td>Member, SEP, P30 Faculty Recruitment in Biomedical Research Core Centers, NIA, NIH</td>
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<td>2009</td>
<td>Member, SEP, RC2 Grand Oppt. Grants in Genetics, Epigenetics &amp; Genomics, NIA, NIH</td>
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<td>2009</td>
<td>Member, SEP, Program Project Review Group, Brain Dopamine, ZAG1 ZIJ-8 J3, NIA, NIH</td>
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<td>Member, SEP, Prog. Proj. Rev. Group, Neuroimaging and Aging, ZAG1 ZIJ-5 JF, NIA, NIH</td>
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<td>2010</td>
<td>Member, Neurological Sciences &amp; Disorders K Review Committee, NSD-K, NINDS, NIH</td>
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<td>Member, Neurosciences of Aging Review Committee, NIA-N, NIA, NIH</td>
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<td>Member, SEP, Prog. Proj. Rev., Exercise, Motor Deficits, &amp; Aging, ZAG1-ZIJ-9, NIA, NIH</td>
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<td>2010</td>
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<td>2011</td>
<td>Chairperson, Member Special Emphasis Panel, ZAG1 ZIJ-7 (J1), NIA, NIH</td>
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</table>
**Biographical Sketch**

Gene E. Alexander, Ph.D.

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**Contribution to Science**

*Brain Imaging and Cognitive Effects of Age-Related Dementia.* My early research interests focused on understanding brain-behavior relationships in the context of Alzheimer’s dementia with the use of functional and structural neuroimaging methods combined with measures of cognition and demographic characteristics. My initial work in this area, with Dr. Yaakov Stern, led to the first functional neuroimaging findings to suggest the potential for a brain-based, cognitive reserve against the effects of Alzheimer’s disease. My research then expanded to include measures of cerebral metabolism with PET, further supporting the concept of cognitive reserve and the use of PET as a method to evaluate treatments to delay or diminish declines in cerebral metabolism over time in Alzheimer’s dementia.


Brain Imaging and Cognitive Effects of Healthy Aging: In more recent years, my research program has focused on the effort to better understand heterogeneity across the spectrum from successful to pathological aging. This work includes studies of healthy aging across the adult age range using structural and functional brain imaging methods combined with standardized and computerized measures of cognition. Additionally, I have an interest in extending my research in humans to nonhuman animal models of aging and age-related disease. The following publications provide examples of my work using both univariate and novel multivariate network analysis methods to evaluate patterns of brain structure in older adults, as well as functional brain regions and cognitive processes impacted by brain aging.


Method Development, Evaluation, and Implementation for Neuroimage Analysis Approaches: My work also includes the development, evaluation, and implementation of novel analysis methods for neuroimaging data. Early in the course of my research, I recognized the importance of applying analysis methods that have the potential to more fully capture the rich regional information obtained within functional and structural brain images. My work in this area has focused on the application of novel multivariate network analysis methods to characterize regional patterns of covariance in brain scans to better understand the effects of brain aging and age-related disease. I have applied this approach to PET cerebral metabolism, functional MRI, and multimodal approaches that combine across imaging modalities. I have also performed the first application of this approach to structural MRI in both humans and in a nonhuman primate model of aging. The example publications below illustrate my research efforts in this area.

Large Multi-Institutional Collaborative Projects: Additionally, my research has included participation in several large multi-institutional collaborative research projects that have had a significant impact on the field, including supporting efforts to identify imaging methods for the evaluation of treatments, to aid diagnosis, and to enhance prevention research for Alzheimer’s disease and dementia. These projects have included the Alzheimer’s Disease Neuroimaging Initiative (ADNI), for which I served as a member of the MRI and PET Cores, as well as other multi-institutional projects on APOE risk and pathology confirmed dementia. These projects focused on the use of neuroimaging methods using PET and MRI for the evaluation of brain effects in Alzheimer’s disease and in those at increased genetic risk for age-related dementia. Examples of my collaborative publications are illustrated below.


Health, Lifestyle, and Genetic Risk Factors for Pathological Aging. A major focus of my current research interests includes integrating health status, lifestyle characteristics, and genetics with brain imaging and cognitive testing to investigate healthy and pathological brain aging. For example, my work was the first to demonstrate an interaction between age and hypertension on brain volume in aging, and has contributed to our understanding of how the APOE $ɛ4$ allele impacts cognition and brain structure over the adult lifespan. I have also recently proposed a new hypothesis suggesting that demands for exercise may have interacted with APOE status to influence the evolution of the human lifespan, which was recently featured on the cover of Trends in Neurosciences.


Biographical Sketch
Gene E. Alexander, Ph.D.


Publications above selected from more than 143; complete list of published work in MyBibliography: [link]

Research Support
Ongoing

NIA R01 AG049464-01 Alexander, Barnes, Coleman (MPIs) 8/1/14 – 3/31/20
Epigenetic, Neuroimaging and Behavioral Effects of Hypertension in the Aging Brain
The goal is to determine epigenetic changes induced by hypertension in brain regions important for cognition.
Role on Project: Contact PI

McKnight Brain Research Foundation Alexander, Cohen, Levin, Wadley (MPIs) 9/1/15 – 12/31/18
McKnight Inter-Institutional Cognitive Aging Assessment Core
The goal is to provide standardized clinical and cognitive measures for multi-institutional brain aging research.
Role on Project: A PI

McKnight Brain Research Foundation Alexander, Cohen, Rundek, Visscher (MPIs) 1/1/15 – 12/31/18
McKnight Inter-Institutional Neuroimaging Core and Brain Aging Registry
The goal to establish neuroimaging acquisition and a multisite brain aging registry to study brain aging.
Role on Project: A PI

NIA R01 AG054077-01 Cohen, Marsiske, Woods (MPIs) 9/1/16 – 8/31/21
Augmenting Cognitive Training in Older Adults – The ACT Grant
This multisite RCT will evaluate cognitive training and transcranial direct current stimulation for brain aging.
Role on Project: PI of the UA Field Center and UA subcontract

State of Arizona/Banner Health Subcontract Alexander (PI) 7/1/17 – 6/30/18
Influence of Health & Lifestyle Factors on Brain Aging and the Risk for Alzheimer’s Disease
The goal is to study health and lifestyle factors that alter effects of brain aging and cognitive health.
Role on Project: PI

NIA R03 AG055020-01 Su (PI) 7/15/17 – 4/30/19
Ultra-sensitive and Label-free Detection of Alzheimer’s Disease Biomarkers
This goal is to evaluate a highly sensitive method to identify Alzheimer’s biomarkers in fluid samples.
Role on Project: Co-Investigator
Biographical Sketch
Gene E. Alexander, Ph.D.

NIA P30 AG019610-17 Reiman (PI) 7/1/16 – 6/30/21
Arizona Alzheimer’s Disease Core Center
This center provides core resources to support Alzheimer’s Disease research in the Arizona region.
Role on Project: Co-Investigator and member of the Data Management and Statistics Core

NIH 3 R01 AG031581 Reiman, Caselli (MPIs) 4/1/14 – 3/31/19
Brain Imaging, APOE & the Preclinical Course of Alzheimer’s disease
The goal is to characterize the brain changes in those at risk for Alzheimer’s disease with the APOE e4 allele.
Role on Project: Dr. Alexander is Co-Investigator and PI of the UA subcontract.

NIH R01 AG049465-01 Barnes (PI) 8/1/14 – 3/31/19
Neural System Dynamics and Gene Expression Supporting Successful Cognitive Aging
The goal is to use cognitive, neurobiological and molecular methods to test reserve in a rodent model of aging.
Role on Project: Co-Investigator

UA15-011 Alexander, Raichlen (MPIs) 2/5/15 – 12/31/17
Tech Launch Arizona Wheelhouse
Evaluation of the Aerobic Training System for Enhancing Cognitive Performance in Older Adults
The goal of this project is to evaluate the benefits of exercise on cognitive function in healthy aging
Role on Project: A PI

Selected Completed Recent Research Support

NIH 1 R01 AG025526 Alexander (PI) 4/1/07 – 7/31/14
Neuroanatomical Substrates of Aging & Cognitive Decline (w/ NCE)
The goal is to study how health status and genetic risk for AD affect the brain and cognitive changes in aging.
Role on Project: PI

NIMH/NIA 2 R01 MH57899-01A1 Reiman (PI) 7/1/98 – 6/30/13
PET, APOE, & the Preclinical Course of Alzheimer’s Disease
The goal is to characterize the brain changes in individuals at risk for Alzheimer’s disease with APOE e4.
Role on Project: Co-Investigator and PI of the UA subcontract

NIA 1 U01 AG024904-01 Weiner (PI) 10/1/04 – 9/30/10
Alzheimer’s Disease Neuroimaging Initiative (ADNI)
The goals are to test the ability of MRI and PET to track the brain changes in MCI and Alzheimer’s dementia.
Role on Project: Co-Investigator, member of MRI and PET Cores, and PI for UA subcontract
Biographical Sketch

Carol A. Barnes, Ph.D.
Regents’ Professor, Psychology, Neurology and Neuroscience

**Education/Training**

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<tr>
<th>Institution &amp; Location</th>
<th>Degree</th>
<th>Year(S)</th>
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<tr>
<td>University of California, Riverside, CA</td>
<td>B.A. (Honors)</td>
<td>1971</td>
<td>Psychology</td>
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<td>Carleton University, Ottawa, Ontario, Canada</td>
<td>M.A.</td>
<td>1972</td>
<td>Psychology</td>
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<tr>
<td>Carleton University, Ottawa, Ontario, Canada</td>
<td>Ph.D. (Cum laude)</td>
<td>1977</td>
<td>Psychology</td>
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**Personal Statement**

Dr. Barnes has been interested in the brain circuits responsible for memory and how these circuits change during aging for more than four decades. She has applied behavioral and electrophysiological methods to the study of plasticity and circuit properties of the medial temporal lobe over that time, including in vivo evoked field potential recordings in chronically implanted freely behaving rats, and intracellular andextracellular recordings in vitro. She was instrumental (with McNaughton) in the development of ensemble tetrode recording methods for single units in awake young and old rats. More recently she has extended these methods to young and aged nonhuman primates, with chronic implants of hyperdrive recording devices that are capable of individually lowering multiple tetrodes into the hippocampus while monkeys behave. Another approach she uses to understand behavior-driven circuits is the single cell gene expression imaging method “catFISH,” which was developed in her laboratory (Guzowski et al., 1999). The immediate early gene Arc is induced in a cell-specific fashion in the brain by neural activity associated with attentive, active behavior. With this method the activity history of individual cells in a population can be determined for two different time points within the same animal (ex vivo). This method contributed to moving the field closer to the goal of behavior-driven whole brain imaging with single cell resolution. Dr. Barnes directs the Evelyn F. McKnight Brain Institute at the University of Arizona and the Division of Neural Systems, Memory and Aging. She is actively involved in collaborative projects with scientists within the state of Arizona, across the United States and the world. She has a track record of conducting difficult, systematic, and thorough studies with interdisciplinary teams, as well as with her own students and postdoctoral fellows – projects that have been followed through to publication (254 total, H index 94), a number of which are now classic references on brain aging and behavior.

**Positions**

1978 Research Associate, Dalhousie University, Dept. Psychology, Halifax, Canada
1979 – 1980 NRSA Postdoctoral Fellow, Institute of Neurophysiology, Oslo, Norway
1981 NATO Postdoctoral Fellow, Cerebral Functions Group, University College, London, England
1982 – 1985 Assistant Professor, Department of Psychology, University of Colorado, Boulder
1985 – 1989 Associate Professor, Department of Psychology, University of Colorado, Boulder
1989 – 1990 Professor, Department of Psychology, University of Colorado, Boulder
1990 – 2006 Professor, Psychology, Neurology, ARL NSMA, Univ. Arizona, Tucson
2006 Regents’ Professor, Psychology, Neurology, Univ. of Arizona, Tucson
2006 Director, Evelyn F. McKnight Brain Institute, University of Arizona, Tucson, AZ
2006 Evelyn F. McKnight Endowed Chair for Learning and Memory in Aging, Univ. of Arizona
2008 Director, Division of Neural Systems, Memory and Aging, University of Arizona, Tucson
2009 – 2016 Associate Director, BIO5 Institute, University of Arizona, Tucson
2009 Regents’ Professor, Neuroscience, University of Arizona, Tucson
**Biographical Sketch**

Carol A. Barnes, Ph.D.

*continued*

## Honors

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<td>1972 - 1974</td>
<td>Ontario Graduate Fellowship</td>
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<td>1979 - 1981</td>
<td>NRSA Individual Postdoctoral Fellowship, NIH</td>
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<td>1981 - 1982</td>
<td>NATO Fellowship in Science, NSF</td>
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<td>1984 - 1989</td>
<td>Research Career Development Award, NIH</td>
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<td>1987 - 1991</td>
<td>Neuroscience, Behavior and Sociology of Aging Committee A, NIA</td>
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<td>1989 - 1994</td>
<td>Research Scientist Development Award, Level II, NIMH</td>
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<td>1991 - 1997</td>
<td>Medical and Scientific Advisory Board, Alzheimer’s Association</td>
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<td>1994 - 1999</td>
<td>Research Scientist Award, NIMH</td>
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<td>National Science Advisory Council, American Federation for Aging Research</td>
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<td>1996 - 2000</td>
<td>Councilor, Society for Neuroscience</td>
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<td>1997 - 2000</td>
<td>Medical and Scientific Advisory Council, Alzheimer’s Association</td>
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<td>1999 - 2004</td>
<td>Board of Scientific Counselors, NIMH</td>
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<td>2000 - 2002</td>
<td>Secretary, Society for Neuroscience</td>
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<td>2004</td>
<td>MERIT Award, National Institute on Aging, NIH</td>
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<td>2004</td>
<td>Elected Norwegian Royal Society of Sciences and Letters</td>
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<td>2006</td>
<td>Regents’ Professor, University of Arizona</td>
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<td>2006</td>
<td>Evelyn F. McKnight Endowed Chair for Learning and Memory in Aging, University of Arizona</td>
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<td>2007</td>
<td>Fellow, American Association for the Advancement of Science</td>
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<td>2010</td>
<td>Elected: Mika Salpeter Lifetime Achievement Award, Society for Neuroscience</td>
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<td>2011</td>
<td>Elected: Galileo Fellow, College of Science, University of Arizona</td>
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<td>2013</td>
<td>Ralph W. Gerard Prize in Neuroscience, Society for Neuroscience</td>
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<td>2014</td>
<td>American Psychological Association Award for Distinguished Scientific Contributions</td>
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<td>2017</td>
<td>Quad-L Award, University of New Mexico</td>
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## Contribution to Science

Some of my early work was inspired by two fundamental discoveries in the early 1970s. The first was the discovery of the likely biological basis of memory formation in the brain in 1973 by Terje Lomo, Tim Bliss, and Tony Gardner-Medwin. They used patterned electrical stimulation to experimentally induce changes in synaptic strength in the hippocampus, enabling the study of the process the brain may use to lay down memory traces (long-term potentiation, or LTP). In that same time period, O’Keefe and Nadel were circulating a monograph, which eventually turned into a classic and influential book (The Hippocampus as a Cognitive Map, 1978) that suggested that hippocampal function could be evaluated in animals by assessing spatial memory. These ideas made it possible to design experiments to interrogate how the brain acquires, stores, and retrieves information across the lifespan. Using awake, freely behaving rats with chronically implanted electrodes that could monitor the induction and decay of LTP over weeks, we obtained the first concrete evidence that LTP persistence and the durability of memory...
were related, and that a decline in its persistence was associated with poorer spatial memory in old animals. This relationship held in young rats as well – the better the animal’s memory, the more durable was LTP. For these experiments, I developed a novel spatial memory task (“the Barnes maze”), which was conceived of and the methods published long before the more widely used, and conceptually similar, Morris water maze. The 1979 paper referenced below introduced the Barnes maze and provided the first demonstration that LTP and memory are associated – providing the groundwork for an explosion of research on the biophysical and molecular mechanisms of memory across the lifespan.


Other work that is now classic in the field of brain aging is the first detailed analysis of the biophysical characteristics of aging neural tissue in vitro. These studies provided some of the early evidence that the pattern of biophysical change in the hippocampus was not that of general deterioration, but was highly selective, and in some cases suggested adaptation of function in response to perturbation of the neural system. These studies laid the groundwork to support the contention that “aging is not a disease,” but a highly selective biological process, that has a comparatively subtle impact on brain and behavior compared to pathological conditions such as Alzheimer’s disease. In fact, the 1980 study referenced below was the first demonstration of biological compensation at the level of synaptic transmission in aging and suggested that these kinds of adaptive processes may play an important role in the function of the aging nervous system.


Having established that plasticity mechanisms like LTP are altered at older ages, and that, with some important exceptions, most biophysical properties of aged hippocampal neurons are intact, I extended my work from an assessment of the impact of age on the function of artificially activated networks to those activated by behavior. These were the earliest studies to examine behavior-driven single cell firing characteristics in the aged hippocampus. We developed better recording methods over the years (the tetrode, the hyperdrive device) that enabled recording from many hippocampal cells simultaneously. This made it possible to characterize how the hippocampus constructs a “cognitive map” (as proposed by O’Keefe and Nadel in 1978) of the surrounding environment. We showed that there are distinct changes in spatial representations within the hippocampus – with the older animals appearing...
to occasionally retrieve the wrong map (in CA1) upon repeated exposures to an environment. In addition, we have shown plasticity-related defects in the construction of these maps, changes in the replay of these maps during sleep in aged rats, as well as altered network functions of other temporal and frontal lobe structures.


My lab has developed a behavior-driven single cell imaging method that expands on the methods developed for the conduct of high-density electrical recordings from single cells. This method uses the expression of the immediate early gene Arc that can monitor activity over hundreds of thousands of cells across the brain (the catFISH method). With this method, we have been able to identify a number of selective activity changes with age within hippocampal and other temporal lobe circuits and identify transcriptional repression mechanisms that may be responsible for the reduction in behavior-induced Arc expression. This method is now used extensively not only in applications for understanding aging circuits, but in many other areas of systems neuroscience.


A final area in which my work has made a large impact is the examination of cognition and brain function in the aged nonhuman primate. We have developed methods for chronic high-density electrophysiological recording for behaving monkeys, which allows assessment of whether the basic principles of age-related brain changes in rats generalize to the primate brain. This is a critical gap to bridge, as the ultimate goal is to understand the human brain and cognitive aging. Because geriatric macaques are a precious experimental resource, studies generated from these animals will become classic in the field. In addition to the high-density recordings obtained from young and aged monkeys, we have been able to relate MRI imaging variables to cognitive test batteries productively, and more recently we have developed methods for telemetered recordings in nonhuman primates who are completely unrestrained. All of these approaches have contributed to a deeper understanding of the neural basis of behavior and how this changes over the lifespan.

Biographical Sketch

Carol A. Barnes, Ph.D.


Dr. Barnes, full list of publications can be found at:
https://scholar.google.com/citations?hl=en&user=ujQTWgJAAAAJ&view_op=list_works

Research Support

Ongoing

NIA 1 R01 AG003376 Barnes: PI 01/01/16 – 11/30/20 (project period)
Neurobehavioral Relations in Senescent Hippocampus
This research program is directed towards an understanding of the decline in spatial cognition and memory with age. Nonhuman primates are assessed behaviorally and electrophysiologically (hippocampus, perirhinal cortex), and the ensemble activity of the entorhinal and perirhinal cortical units in young and old rats are examined.
Role on Project: PI

NIA 1 RO1 AG05058 Barnes: PI 09/1/15 – 05/31/20 (project period)
NIH/NIA
Cell Assemblies, Brain Adaptation and Cognitive Aging
The aims of this grant are to better understand the underlying causes of two hallmarks of cognitive aging – behavioral slowing and multitasking deficits. We will examine how the aging brain adapts to the changed dynamics intrinsic to both hippocampus and PFC in rats, and how these structures interact or compete during aging, as well as the cellular correlates of multitasking in an aging primate model, to assess how aging weakens the resilience of working memory circuits in the face of interference.
Role: PI

NIA 1 RO1 AG049465 Barnes: PI 08/01/14 – 03/31/19 (project period)
Neural System Dynamics & Gene Expression Supporting Successful Cognitive Aging
The major goal of this project is to understand the basis of differing cognitive trajectories that occur even over the lifespan of inbred rat strains. Methods used include cognitive assessment batteries for frontal and temporal lobe regions, 7T MRI scanning methods, transcriptional evaluation, and circuit activity pattern assessment using the Arc catFISH single cell imaging method devised in Barnes’ laboratory. All methods are applied to animals of different ages and aptitudes so that the underlying basis of differential cognitive functioning across the lifespan may be identified.
Role on Project: PI
Biographical Sketch

Carol A. Barnes, Ph.D.

continued

NIA 1 RO1 AG049464 Coleman/Barnes/Alexander: PI’s 08/01/14 – 03/31/19 (project period)
Epigenetic, Neuroimaging & Behavioral Effects of Hypertension in the Aging Brain
The major goals of this project are to determine what hypertension-induced epigenetic changes occur in a transgenic rat model of hypertension. Blood pressure can be slowly elevated in this rat model from middle to older ages, mimicking the course of hypertension development observed in human aging. Epigenetic changes induced by hypertension that occur in temporal and frontal lobe structures will be measured and related to behavioral assays of these regions as well as with high resolution MRI scans to assess grey and white matter integrity.
Role on Project: PI (Multi-PI)

NIA 1 R01 AG048907 Huentelman/Barnes: PI’s 09/30/14 – 05/31/18 (project period)
CATT: Development and Application of a Neuronal Cell Activity-Tagging Toolbox
Our overall goal of this EUREKA award is to develop methods to label cells that were active during a defined temporal period and utilize a new approach to investigate the impact of aging on the circuit elements engaged by those behaviors as well as the transcriptional function of those behavior-driven labeled cells. The “Cell Activity-Tagging Toolbox” will provide a means to “permanently mark” the specific cells that were engaged in a defined behavioral experience. This is an extension of the catFISH methodology that can only labels cells for minutes to hours after a behavior.
Role: PI (Multi-PI)

NIA 5 P30 AG019610 Reiman: PI 08/15/16 – 06/30/21 (project period)
Arizona Alzheimer’s Disease Core Center
Dr. Barnes serves as director of the Ad Hoc review program for research proposals for the Arizona Alzheimer’s Disease Core Center.
Role on Project: Co-Investigator

NIA 1 T32 AG044402 Barnes: PI 05/01/16 – 04/30/21 (project period)
Postdoctoral Training, Neurobiology of Aging and Alzheimer’s Disease
Dr. Barnes serves as program director, Dr. Paul Coleman and Eric Reiman as co-directors, and Dr. Matthew Huentelman and Health Bimonte-Nelson as associate directors of this statewide postdoctoral training grant focused on training postdoctoral fellows in the Arizona Alzheimer’s Consortium, consisting of six participating institutions statewide.
Role: PI

Completed in last three years

NIA 5 R37 AG012609 Barnes: PI 07/01/09 – 06/30/15 (project period)
Cell Assemblies, Pattern Completion and the Aging Brain
This award was designed to assess whether there are age differences in the network properties of ensembles of cells recorded in hippocampus and prefrontal cortical regions that change computations in these areas to produce cognitive deficits in aged rats in vivo.
Role on Project: PI
Biographical Sketch

Roberta Diaz-Brinton
Director, Center for Innovation in Brain Science, University of Arizona Health Sciences; Professor, Pharmacology and Neurology, College of Medicine

Education/Training

<table>
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<th>Degree</th>
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<th>Field Of Study</th>
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<td>University of Arizona, Tucson, AZ</td>
<td>B.A.</td>
<td>05/1979</td>
<td>Psychobiology</td>
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<td>University of Arizona, Tucson, AZ</td>
<td>M.A.</td>
<td>08/1981</td>
<td>Neuropsychology</td>
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<tr>
<td>University of Arizona, Tucson, AZ</td>
<td>Ph.D.</td>
<td>08/1984</td>
<td>Psychobiology &amp; Neuropharmacology</td>
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<td>Rockefeller University, NY</td>
<td>Postdoc</td>
<td>07/1987</td>
<td>Neuropharmacology &amp; Neuroendocrinology</td>
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Personal Statement

I am the inaugural director of the Center for Innovation in Brain Science at the University of Arizona Health Sciences and professor of Pharmacology and Neurology, College of Medicine, University of Arizona as of May 9, 2016, and, during the transition, remain professor of Pharmacology and Pharmaceutical Sciences, Biomedical Engineering and Neurology, at the University of Southern California. My research has focused broadly on the mechanisms by which the aging brain develops late onset Alzheimer’s disease. I lead two large programs of research that are organized under the following main themes: 1) Female Aging Brain and Sex Differences in Transitions of Aging leading to late-onset AD, and 2) Allopregnanolone regenerative systems neurobiology and regenerative therapeutic for Alzheimer’s disease. These programs of research are supported by the National Institute on Aging (R01, P01, U01, U54) and by philanthropic foundations. Our research spans discovery to IND enabling translation to clinical trials. We have advanced our basic science discoveries into two clinical trials that target different mechanisms of action and steroid systems in the brain. Fundamental insights that have emerged from our research indicate that the aging brain is dynamic and adaptive. The dynamic adaptive nature of the aging brain has led to an increasing focus on transition states of the aging brain and their plasticity and limits. Further, we have developed extensive experience in translational research to enable FDA INDs, regulatory strategy, and therapeutic development. The nature of our research requires effective and collaborative teams that are mission focused. Teams that I lead include basic, translational, and clinical scientists and technology transfer professionals. During the course of my academic career, I have mentored predoctoral and postdoctoral fellows, undergraduates and, through the Science Technology and Research Program inner city Los Angeles, high school students.

Positions and Honors

Positions

2016 – Present  Director, Center for Innovation in Brain Science, Professor of Pharmacology and Neurology, College of Medicine, University of Arizona, Tucson, Arizona
2001 – 2017  Professor, Department of Pharmacology and Pharmaceutical Sciences, School of Pharmacy, Professor, Department of Biomedical Engineering, Viterbi School of Engineering, Professor, Department of Neurology, Keck School of Medicine University of Southern California
2007 – 2014  Director of Preclinical Translation and Regulatory Support, USC Clinical and Translational Science Institute (USC and Children’s Hospital Los Angeles)
2009 – Present  Professor of Neurology, Keck School of Medicine, University of Southern California
2016 – Present  Director of the Center for Innovation in Brain Science, Professor of Pharmacology, College of Medicine, University of Arizona
**Biographical Sketch**

Roberta Diaz-Brinton

*continued*

**Select Professional Service**

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<th>Year</th>
<th>Role</th>
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<tr>
<td>1999 – Present</td>
<td>Member, Scientific Review Board of Alzheimer’s Drug Development Foundation, NY</td>
</tr>
<tr>
<td>2005 – 2009</td>
<td>External Advisory Board NIH/NIA Women’s Health Initiative Memory Study</td>
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<tr>
<td>2007 – 2008</td>
<td>NIH Blue Ribbon Panel on NIMH Intramural Research Programs</td>
</tr>
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<td>2007 – 2013</td>
<td>Member, Alzforum Scientific Advisory Board</td>
</tr>
<tr>
<td>2008</td>
<td>NIH Blueprint Initiative on K-12 Activities</td>
</tr>
<tr>
<td>2009 – 2011</td>
<td>Member, Society for Neuroscience Board of Councilors</td>
</tr>
<tr>
<td>2009 – 2013</td>
<td>Member, NIMH IRP Board of Scientific Councilors, NIH</td>
</tr>
<tr>
<td>2013 – 2016</td>
<td>Member, Society for Neuroscience, Committee on Committees</td>
</tr>
<tr>
<td>2013 – 2017</td>
<td>Member, NIH Center for Scientific Review Advisory Council</td>
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<tr>
<td>2015 – Present</td>
<td>Board of Governors, Alzheimer’s Drug Discovery Foundation, New York, NY</td>
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<tr>
<td>2015 – Present</td>
<td>Chair, Medical &amp; Scientific Advisory Council Alzheimer’s Association, Los Angeles, CA</td>
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**Select Honors**

<table>
<thead>
<tr>
<th>Year</th>
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<tbody>
<tr>
<td>1999</td>
<td>Laboratory Named “The Norris Foundation Laboratory for Neuroscience Research”</td>
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<tr>
<td>2003</td>
<td>University of Southern California Remarkable Woman Award</td>
</tr>
<tr>
<td>2005</td>
<td>Woman of the Year, California State Senate</td>
</tr>
<tr>
<td>2006</td>
<td>Science Educator of the Year, Society for Neuroscience</td>
</tr>
<tr>
<td>2009</td>
<td>North American Menopause Society /Wyeth Pharmaceuticals SERM Research Award</td>
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<tr>
<td>2010</td>
<td>Presidential Citizens Medal, President Barack Obama</td>
</tr>
<tr>
<td>2014</td>
<td>Los Angeles Woman of the Year, LA Magazine</td>
</tr>
<tr>
<td>2015</td>
<td>Scientist of the Year Award, Alzheimer’s Drug Discovery Foundation</td>
</tr>
<tr>
<td>2017</td>
<td>Disruptive Women to Watch in 2017, Disruptive Women in Health Care</td>
</tr>
<tr>
<td>2017</td>
<td>Recipient: NIH MERIT (Method to Extend Research in Time) Award; for outstanding record of scientific achievement as principal investigator on National Institute of Aging (NIA) research projects.</td>
</tr>
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</table>

*Complete list of published work in MyBibliography:*


**Contribution to Science**

The focus of my research has been to discover mechanisms leading to late-onset Alzheimer’s disease and to translate those insights into therapeutics to prevent, delay, and treat the disease. Results of my systems biology research programs have resulted in fundamental discoveries of steroid action in the brain that have been translated into two independent clinical trials targeting different receptor systems and mechanisms of action. Research endeavors in my laboratory are organized under three major themes: 1) Aging Female Brain and endocrine mechanisms of aging that increase risk of late onset Alzheimer’s disease, 2) Sex Differences in mechanisms leading to late onset Alzheimer’s disease, and 3) Allopregnanolone regenerative systems neurobiology and regenerative therapeutic for Alzheimer’s disease.
The Aging Female Brain and endocrine mechanisms of aging that increase risk of late-onset Alzheimer’s disease program of research is devoted to understanding the mechanisms underlying the increased lifetime risk of Alzheimer’s in women. Outcomes of this pioneering research indicate that the female brain is highly dependent upon estrogen, which functions as a master regulator of the bioenergetic system of the brain. The perimenopausal transition, unique to the female, results in a bioenergetic shift in the brain from a glucose-dependent brain to a brain dependent on the alternative fuel ketone bodies. The adaptive bioenergetic shift to utilizing ketone bodies as an auxiliary fuel creates a risk for catabolizing brain lipids, myelin, to generate ketone bodies to fuel a starving brain. Based on our discovery science of estrogen action in brain, we developed a GMP clinical grade estrogen receptor beta selective formulation that progressed into a NIA sponsored Phase 1b/2a clinical trial of Phytoserms for Menopause Symptoms and Age-Associated Memory Decline. Results of the PhytoSERM clinical trial are currently being analyzed.


Sex Differences in mechanisms leading to late onset Alzheimer’s disease program investigates the underlying mechanisms for the difference between female and male risk of developing late-onset Alzheimer’s disease. Outcomes of which research indicate that the female and male brain bioenergetically age quite differently in remarkable and unanticipated ways which may be beneficial to the ApoE4- male but may be deleterious to the ApoE4+male.


The allopregnanolone regenerative systems neurobiology and regenerative therapeutic for Alzheimer’s disease programs of research is devoted to elucidating the regenerative mechanisms of the brain and harnessing those mechanisms to both promote endogenous mechanisms of regeneration while simultaneously targeting mechanisms underlying Alzheimer’s disease. Outcomes of this pioneering research indicate that the neurosteroid allopregnanolone significantly increases endogenous neural stem cell generation which restores learning and memory functions to age-associated normal in both males and females. Further allopregnanolone reduces the burden of disease by promoting mitochondrial function and beta amyloid clearance. Based on our discovery science of allopregnanolone regenerative mechanisms, we advanced allopregnanolone through IND-enabling research (PK,PD and toxicology), acquired an FDA
IND to conduct a NIA sponsored Phase 1b clinical trial of allopregnanolone in persons with mild cognitive impairment or early Alzheimer’s disease. The NIA-sponsored clinical trial Allopregnanolone for Mild Cognitive Impairment Due to Alzheimer’s Disease or Mild AD is currently ongoing.


**Research Support**

**Active**

NIH / NIA R37-AG053589* (previously R01-AG053589) 03/15/2017 – 02/28/2022

Aging and Estrogenic Control of The Bioenergetic System In Brain

The proposed program of research is designed to first test estrogenic control of the bioenergetic system in the female brain requires: 1) both nuclear and mitochondrial genomes; 2) integration of gene expression across both genomic compartments, and 3) activation of rapid signaling cascades to provide real-time feedback on bioenergetic performance. Second, that loss of estrogen in the aging female brain leads to a systematic disintegration of estrogenic control of nuclear and mitochondrial genomes followed by decline in bioenergetic sensing mechanisms.

*Recipient NIH MERIT (Method to Extend Research in Time) Award, recognizing outstanding scientific contributions and allowing for up to 5 years noncompetitive extension.

Role: PI

NIH / NIA U01-AG047222 (Brinton) 06/15/2014 – 02/28/2019

Allopregnanolone a Regenerative Therapy for Alzheimer’s: FDA-Required Toxicology

This project addresses the urgent need to develop therapeutics to prevent, delay, and treat Alzheimer’s disease (AD). A promising regenerative medicine, Allo, is being developed. Allo activates the brain’s own regenerative ability while also reducing the pathology of AD. Studies proposed here are required by the FDA to ensure that Allo is safe to use for extended period of time to generate new neurons, restore cognitive function, reduce AD pathology and to regenerate the connective tracts of the brain.

Role: PI

NIH / NIA UF1-AG046148 (Brinton) 09/20/2013 – 08/31/2017

Allopregnanolone Regenerative Therapeutic for MCI/AD: Dose Finding Phase I

This project addresses the urgent need to develop therapeutics to prevent, delay, and treat Alzheimer’s disease (AD) in those at greatest risk, the aged. A promising regenerative medicine approach is to activate the brain’s endogenous regenerative ability while also reducing the pathology of AD. We propose here to conduct a Phase 1 clinical study of the neurosteroid allopregnanolone (Allo), which promotes the generation of new neurons, restores cognitive function, reduces AD pathology and regenerates white matter in brain.

Role: PI
**Biographical Sketch**

Roberta Diaz-Brinton

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**Completed**

NIH / NIA R34 AG049652 (Brinton) 09/30/2014 – 08/31/2016

**Systems Pharmacology for Predictive Alzheimer’s Therapeutics: SysPharmRx-AD**

Our goal is to develop therapeutics to prevent, delay, and cure Alzheimer’s disease. The proposed planning grant to create an Alzheimer’s Disease Translational Center for Predictive Drug Development is a critical step to realizing this goal.

Role: PI

NIH / NIA R01 AG032236 (Brinton) 07/01/2009 – 07/31/2016

**Estrogen-Induced Neuroprotective Mitochondrial Mechanisms**

The overall aim of this project is to determine the mechanisms and long-term consequences of estrogen on mitochondrial function in brain. Our target outcome is sustaining mitochondrial function to sustain neurological health for prevention of neurodegenerative diseases associated with mitochondrial dysfunction.

Role: PI

U01 AG031115 (Brinton) 04/15/2008 – 03/31/2014 NIH/NIA

**Development of Allopregnanolone as a Neurogenic Regenerative Therapeutic Agent**

The goal is to develop allopregnanolone as a safe and efficacious therapeutic to prevent or treat age-associated memory deficit. This a translational therapeutic development project to conduct preclinical analyses required for an Investigational New Drug (IND) application to the FDA to determine the efficacy of allopregnanolone as a neurogenic regenerative and disease modifying agent for Alzheimer’s disease.

Role: PI

NIH / NIA R01 AG033288 (Schneider) 06/01/2010 – 05/31/2015

**Estrogen Receptor-Beta PhytoSERMs for Management of Menopause and Age-Associated Memory Decline: Pilot Development Trials.**

Role: PI

NIH / NIA 2P50 AG005142-26A1 (Chui) 07/01/2012 – 03/31/2015

**Alzheimer Disease Research Center Project 2 – Brinton**

Role: PI Project 2

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**Perimenopause in Brain Aging and Alzheimer’s Disease**

The Perimenopause in Brain Aging and Alzheimer’s Disease Program Project will determine how the brain changes during the perimenopausal transition and how these changes can lead to development of early risk factors for developing Alzheimer’s disease. The goal of these studies is the early identification of those at greatest risk for developing AD and the window of opportunity for interventions to prevent Alzheimer’s disease in those at greatest lifetime risk, postmenopausal women.

Role: Program PI; PL Administrative Core A, Project 1 and Project 4
Biographical Sketch
Ying-hui Chou
Assistant Professor of Psychology

Education/Training

<table>
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<th>Institution &amp; Location</th>
<th>Degree</th>
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<th>Field Of Study</th>
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<tr>
<td>National Taiwan University, Taipei</td>
<td>BS</td>
<td>06/1994</td>
<td>Occupational Therapy</td>
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<tr>
<td>Boston University, Boston, MA</td>
<td>MS</td>
<td>01/2001</td>
<td>Occupational Therapy</td>
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<tr>
<td>Boston University, Boston, MA</td>
<td>ScD</td>
<td>01/2005</td>
<td>Movement and Rehabilitation Sciences</td>
</tr>
<tr>
<td>Brigham and Women’s Hospital/Harvard Medical School, Boston, MA</td>
<td>Postdoctoral</td>
<td>07/2005</td>
<td>Brain Imaging</td>
</tr>
<tr>
<td>Duke University Medical Center, Durham, NC</td>
<td>Postdoctoral</td>
<td>04/2012</td>
<td>Gerontology and Brain Imaging</td>
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<tr>
<td>Duke University Medical Center, Durham, NC</td>
<td>Other training</td>
<td>04/2012</td>
<td>Transcranial Magnetic Stimulation</td>
</tr>
<tr>
<td>Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA</td>
<td>Other training</td>
<td>06/2013</td>
<td>Transcranial Magnetic Stimulation</td>
</tr>
<tr>
<td>Duke University Medical Center, Durham, NC</td>
<td>Postdoctoral Fellow</td>
<td>08/2013</td>
<td>Brain Imaging</td>
</tr>
<tr>
<td>Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA</td>
<td>Other training</td>
<td>03/2015</td>
<td>Transcranial Direct Current Stimulation</td>
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Personal Statement

I received postdoctoral training in brain imaging and cognitive science at Surgical Planning Lab of Brigham and Women’s Hospital/Harvard Medical School, Duke Brain Imaging and Analysis Center, and Duke Aging Center. In addition, I have been trained to operate non-invasive brain stimulation protocols (e.g., TMS and transcranial direct current stimulation) at the Berenson-Allen Center for Noninvasive Brain Stimulation of Harvard Medical School and Duke Psychiatry. I am currently an assistant professor of psychology at the University of Arizona (since August 2016). My laboratory focuses on applications of noninvasive brain stimulation and advanced brain imaging techniques to the development of image-guided noninvasive brain stimulation protocols for clinical populations and studying causal relations among brain networks. Over the years I have developed strong expertise in brain imaging, noninvasive brain stimulation, and cognitive science. I have produced 22 peer-reviewed journal articles and one book chapter.

## Positions and Honors

### Positions and Employment

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<tr>
<th>Year</th>
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<tr>
<td>199 – 1995</td>
<td>Occupational Therapist, Department of Psychiatry</td>
<td>Taipei Veterans General Hospital, Taiwan</td>
</tr>
<tr>
<td>1995 – 1997</td>
<td>Occupational Therapist, Department of Physical Medicine and Rehabilitation</td>
<td>National Taiwan University Hospital, Taiwan</td>
</tr>
<tr>
<td>2001 – 2003</td>
<td>Research Assistant, Center for Neurological Rehabilitation</td>
<td>Boston University, Boston, MA</td>
</tr>
<tr>
<td>2001 – 2003</td>
<td>Teaching Assistant of (1) Neurological Systems and (2) Scientific Inquiry</td>
<td>Department of Physical Therapy, Boston University, Boston, MA</td>
</tr>
<tr>
<td>2004 – 2005</td>
<td>Postdoctoral Fellow of Radiology</td>
<td>Brigham and Women's Hospital/Harvard Medical School, Boston, MA</td>
</tr>
<tr>
<td>2005 – 2008</td>
<td>Chair and Assistant Professor</td>
<td>Department of Occupational Therapy, Fu-Jen Catholic University, Taiwan</td>
</tr>
<tr>
<td>2008 – 2011</td>
<td>Maternity Leave</td>
<td></td>
</tr>
<tr>
<td>2011 – 2013</td>
<td>Postdoctoral Fellow, Center for Aging and Human Development and Brain Imaging and Analysis Center</td>
<td>Duke University Medical Center, Durham, NC</td>
</tr>
<tr>
<td>2013 – 2016</td>
<td>Medical Instructor</td>
<td>Brain Imaging and Analysis Center, Duke University Medical Center, Durham, NC</td>
</tr>
<tr>
<td>2016</td>
<td>Assistant Professor of Psychology</td>
<td>University of Arizona, Tucson, AZ</td>
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### Other Experience and Professional Memberships

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<tr>
<td>1999 – 2001</td>
<td>Member, American Occupational Therapy Association</td>
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<td>2005 – 2006</td>
<td>Member, International Society of Magnetic Resonance in Medicine</td>
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<td>2011 – 2012</td>
<td>Member, Cognitive Neuroscience Society</td>
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### Honors

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<th>Year</th>
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<tr>
<td>1999</td>
<td>The Study Abroad Scholarship, Ministry of Education, Taiwan</td>
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<tr>
<td>2000</td>
<td>The Carolyn Kohn Memorial Scholarship, American Occupational Therapy Foundation, USA</td>
</tr>
<tr>
<td>2005</td>
<td>The Educational Stipend Award, International Society for Magnetic Resonance in Medicine, USA</td>
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<tr>
<td>2006</td>
<td>The E.K. Zavoisky Stipend, International Society for Magnetic Resonance in Medicine, USA</td>
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<tr>
<td>2007</td>
<td>The Fu-Jen University Excellence in Teaching Award, Fu-Jen Catholic University, Taiwan</td>
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Contribution to Science

Resting-state fMRI and its applications to cognitive science and clinical populations. Resting-state functional connectivity measured by fMRI has played an essential role in understanding brain functional networks and their relations to cognitive function and diseases. Measures of resting-state functional connectivity refer to temporal correlations of fMRI signals between spatially distinct brain regions when participants are not performing a perceptual or behavioral task. In a longitudinal study, we acquired resting-state fMRI data of healthy participants nine times during one year. Our findings indicate that the functional connectivity measures exhibit outstanding long-term reproducibility and are potentially suitable as biomarkers for monitoring disease progression and treatment effects in clinical trials and individual patients. In a series of studies, we documented age- and disease-related alterations in resting-state functional connectivity, their correlations with cognitive function and symptom severity, and treatment effects using functional connectivity as an outcome measure. This body of work has demonstrated the usefulness of resting-state functional connectivity for understanding cognitive function and for clinical applications.


Repetitive transcranial magnetic stimulation for neurodegenerative disorders. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that has been closely examined as a possible treatment for Parkinson’s disease (PD). However, results evaluating the effectiveness of rTMS in PD are mixed, mostly due to low statistical power or variety in individual rTMS protocols. Recently, we published a meta-analysis of 20 clinical trials in 470 patients with PDa. Pooled evidence suggests a significant medium effect size favoring active rTMS over sham rTMS for reducing motor symptoms. Findings of our meta-analysis highlight the need for multimodal studies that combine the use of rTMS and different neuroimaging techniques when developing an rTMS treatment protocol. As a first step to combine the rTMS and brain imaging techniques, we measured both motor symptoms and brain functional connectivity before and after a 10-session, 5 Hz, rTMS intervention targeting the primary motor cortex in patients with multiple system atrophyb. Our results showed significant rTMS-related changes in motor symptoms and functional connectivity. Specifically, 1) significant improvement of motor symptoms was observed in the active-rTMS group, but not in the sham-rTMS group; and 2) several functional links involving the default mode, cerebellar and limbic networks exhibited positive changes in functional connectivity in the active-rTMS group. Moreover, the positive changes in functional connectivity were associated with improvement in motor symptoms for the active-rTMS group. The present findings suggest that rTMS may improve motor symptoms by modulating functional links connecting to the default mode, cerebellar and limbic networks, inferring a future therapeutic candidate for patients with multiple system atrophy.


Biographical Sketch

Ying-hui Chou

continued
Virtual reality. When I was a graduate student at Boston University, my projects were to investigate how virtual reality technology could be used to investigate perception and motion interaction. We had successfully combined the virtual reality apparatus and three-dimensional motion analysis system to investigate perceptual-motor interaction. These studies demonstrate the usefulness of virtual reality in modulating locomotion and will facilitate the development of systematic approaches for effective preventive and therapeutic intervention for gait dysfunction in older adults and patients with Parkinson’s disease. Virtual reality is compatible with many brain-imaging techniques and has allowed researchers to evaluate typical and atypical brain function when users are immersed in a virtual reality environment. We published a book chapter in 2012 summarizing research findings that combine both virtual reality and brain imaging technologies. This chapter has been downloaded 2,668 times from the publisher’s website (http://www.intechopen.com/books/statistics/virtual-reality-in-psychological-medical-and-pedagogical-applications/applications-of-virtual-reality-technology-in-brain-imaging-studies).


Complete list of published work In MyBibliography:

RESEARCH SUPPORT

Current

Arizona Alzheimer’s Consortium Pilot Program Chou (PI) 07/01/2017 – 06/30/2018
Use of TMS and fMRI Measures to Assess the Risk of Conversion of MCI to Dementia
In this pilot project, we propose probing cortical excitability and plasticity in individuals with MCI in order to assess the diagnostic potential of TMS-evoked responses.

Arizona Alzheimer’s Consortium Pilot Program Wilson (PI) 07/01/2017 – 06/30/2018
The Neural Substrates of Explore-exploit Decisions in Old Age
The purpose of the study is to understand the neural systems underlying explore-exploit decisions and how these systems change in old age and with cognitive decline.
Role: Co-Investigator
Biographical Sketch

Ying-hui Chou

Completed

R01-AG039684  Madden (PI)  04/22/2012 – 05/31/2016
NIH/NIA
Neuroimaging of Visual Attention in Aging
The major goal of this project is to investigate structural and functional connectivity of the brain in relation to age-related differences in visual attention performance.
Role: Co-Investigator

R01-MH098301  Madden, Wang (PI)  02/01/2013 – 06/30/2016
NIH/NIMH
Dorsal Cingulate Activity and Cognitive Decline in Late-Life Depression
The long-term goals of the proposed project are to better understand the neural mechanisms linking depression and cognitive impairment, establish biomarkers for early identification of depressed individuals at risk for cognitive impairment, and understand the neural plasticity of late-life depression with and without cognitive impairment following prevention programs and clinical interventions.
Role: Co-Investigator

R21-DA033083  McClernon (PI)  10/01/2014 – 12/30/2014
NIH/NIDA
Environments as Smoking Cues: Imaging Brain Substrates, Developing New Treatments
The overarching goal of our collaborative research program is to increase the efficacy of CETs by incorporating contextual cues from the smoker’s real-world smoking environment into treatment, thereby preventing renewal.
Role: Co-Investigator

K23-AG032867  Whitson (PI)  10/01/2012 – 07/13/2013
NIH/NIA
Developing Interventions to Improve Function in Seniors with Comorbid Conditions
The goal of the study is to develop interventions that improve functional outcomes in patients who suffer from particularly disabling combinations of conditions.
Role: Post-doctoral Scholar

T32-AG000029  Cohen (PI)  03/21/2011 – 04/21/2012
NIH/NIA
Behavior and Physiology in Aging
The goal of this Duke Aging Center Postdoctoral Training Program is to continue to train highly skilled research scientists who have strong backgrounds in substantive areas related to aging and who also have the potential for leadership in gerontological research.
Role: Post-doctoral Scholar

Private Foundation  Chen (PI)  2006 – 2007
Changhua Christian Hospital Research Fund, Taiwan
Effect of Repetitive Transcranial Magnetic Stimulation on Cortical Excitability in Patients with Epilepsy
The purpose of the study was to investigate the effect of repetitive transcranial magnetic stimulation on cortical excitability in patients with epilepsy.
Role: Co-Investigator

Private Foundation  Chen (PI)  2006 – 2007
Changhua Christian Hospital Research Fund, Taiwan
Effect of Repetitive Transcranial Magnetic Stimulation on Cortical Excitability in Patients with Epilepsy
The purpose of the study was to investigate the effect of repetitive transcranial magnetic stimulation on cortical excitability in patients with epilepsy.
Role: Co-Investigator
Biographical Sketch

Stephen Cowen
Assistant Professor

Education/Training

<table>
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<th>Institution &amp; Location</th>
<th>Degree</th>
<th>Year(S)</th>
<th>Field Of Study</th>
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<tbody>
<tr>
<td>University of Wisconsin, Madison, Wisconsin</td>
<td>BBA</td>
<td>05/1992</td>
<td>Management and Marketing</td>
</tr>
<tr>
<td>University of Arizona, Tucson, Arizona</td>
<td>PHD</td>
<td>05/2007</td>
<td>Psychology and Neuroscience</td>
</tr>
<tr>
<td>The Neurosciences Institute, San Diego, California</td>
<td>Postdoc</td>
<td>06/2008</td>
<td>Neuroscience</td>
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Personal Statement

A fundamental and unresolved question in neuroscience is how the activities of tens of billions of interconnected neurons become coordinated during learning, decision making, and sleep. Resolving this question is important as dysregulated neural coordination contributes to disorders such as Parkinson’s disease (PD), epilepsy, Down syndrome, and schizophrenia, and may also contribute to cognitive deficits associated with normal aging. My research seeks to understand the mechanisms by which the timing of the activities of ensembles of neurons and dopamine release is coordinated during learning and sleep. Towards this end, my laboratory has developed novel instrumentation that allows, for the first time, the simultaneous measurement of the activities of large groups of neurons and fast changes in dopamine release (Parent et al., 2017). This instrument integrates high-density single-unit/local-field recording technologies to measure neural activity in rodents during decision making, navigation, and sleep with fast-scan cyclic voltammetry for the measurement of dopamine release. My laboratory is using this tool to investigate the role that dopamine plays in regulating neuronal coordination in behaving and resting animals, and we are working towards testing this device in animal models of PD and normal aging. Our ongoing and funded work on PD involves the investigation of sleep-associated oscillatory activity in PD. This work is supported by a grant from the Michael J. Fox Foundation. Specifically, we are exploring how cortico-striatal coordination is altered during sleep in a genetic form of PD (the LRRK2 G2019S mutation). We are testing the hypothesis that sleep spindles, corticothalamic oscillations associated with slow wave sleep and memory consolidation, are enhanced in this particular mutation.

My lab also investigates the roles that high-frequency brain oscillations play in learning, memory, and disease. For example, we have found that normal aging is associated with a significant decrease in the frequency of oscillations in the hippocampus that are associated with memory formation. With regard to disease, my laboratory is investigating how ketamine and ketamine-induced high-frequency activity in the striatum reduces dyskinesias in PD. Data collected in my laboratory now suggest that ketamine simultaneously enhances cortico-striatal coherence at high frequencies (~135 Hz) and reduces coherence at theta and beta frequencies (~8-30 Hz) – frequency ranges associated with Parkinsonian motor symptoms.

To assist other researchers studying these topics, my students and I have designed, built, and freely distributed custom microelectrode microdrives, data acquisition software, data-analysis software, inertial measurement systems, and automated mazes designed for the assessment decision making in rodents.


Biographical Sketch

Stephen Cowen


Positions and Honors

Positions and Employment

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<thead>
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<th>Institution</th>
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<tr>
<td>2007 – 2008</td>
<td>Postdoctoral Fellow</td>
<td>The Neurosciences Institute, San Diego, CA</td>
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<tr>
<td>2008 – 2010</td>
<td>Research Fellow</td>
<td>The Neurosciences Institute, San Diego, CA</td>
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<tr>
<td>2010 – 2012</td>
<td>Associate Fellow</td>
<td>The Neurosciences Institute, San Diego, CA</td>
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<td>2012 – present</td>
<td>Assistant Professor</td>
<td>University of Arizona, Tucson, AZ</td>
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<td>Department of Psychology</td>
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Other Experience and Professional Memberships

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<td>1997 – present</td>
<td>Member, Society</td>
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Honors

Recipient of a 1998-1999 National Science Foundation training grant.
Awarded the 2010 Blasker-Rose-Miah technology development grant from The San Diego Foundation.

Contribution to Science

Aging is associated with altered single-unit coordination and local-field oscillatory activity. The hippocampus is critical for the formation of episodic memories, and this capacity is reduced over the course of normal aging. Sharp-wave ripple events are high-frequency (~150 Hz) oscillations generated in the hippocampus, and these events have been implicated in the stabilization of long-term memories. Our analysis of these oscillations and of correlated single-unit activity in rats identified key changes that occur through the course of aging. Specifically, results from our analysis indicate that aging is accompanied by a decline in the oscillation frequency and rate of occurrence of these oscillations and that individual neurons fire less reliably within each ripple event. Together, these changes may contribute to age-associated memory decline.


A. Ripple oscillation during slow wave sleep and spiking activity (colored dots) of simultaneously-recorded hippocampal neurons.

B. Ripple frequency is significantly reduced in healthy aged rats.
Neural correlates of working memory can be tightly coupled with body movements. In 1971, three seminal papers were published that provided compelling evidence that the mammalian brain is capable of forming high-level and sensory-independent representations of imagined stimuli and environments. The first of these studies reported the discovery of delay cells in the prefrontal cortex (Fuster and Alexander; Kubota and Niki) and the second reported the first observation of place cells in the hippocampus (O’Keefe and Dostrovsky). A question that guides me throughout my career is how such representations are sustained through time. In one of my first investigations, I measured the activities of ensembles of neurons in the medial prefrontal cortex as rats performed memory-guided behaviors. Analysis confirmed that prefrontal neurons exhibit clear delay activity for expected cues and outcomes; however, detailed analysis of head movements determined that nearly all of these “delay neurons” were exceptionally sensitive to small changes in body posture. Indeed, the movements themselves were highly selective for the stored memories. A parsimonious explanation for this result was that animals adopted embodied solutions for solving the working-memory task where unique movements were used to help animals offload working memory demands to the body. Our results further demonstrated that higher-order regions such as the frontal cortex are exceedingly sensitive to lower-order inputs such as motor efference-copy and somatosensory information.


Anterior-cingulate neurons are involved in post-decision action maintenance and value prediction. The previously-described observation that motor activity plays a role in modulating “delay cell” activity in the prefrontal cortex motivated a search for theories of frontal function that incorporate representations of body movement. One theory proposes that the anterior cingulate cortex, a subregion of the medial prefrontal cortex, plays a critical role in the evaluation of the cost of physical effort. Evidence from rodents and primates suggests that neurons in the anterior cingulate cortex integrate information about expected effort to guide cost-benefit decision making. To identify the physiological correlates of this evaluative process, I used arrays of single-unit electrodes to record ensemble activity in the anterior cingulate cortex as animals made effort- and reward-guided evaluations. Unexpectedly, results indicated that neurons responding to the anticipated effort responded at least 100 milliseconds after animals made their decision, suggesting that these neurons do not contribute to deliberation, but, instead, may be involved in sustaining goal-directed behaviors after decisions are made. Our observations led me to the proposal that the anterior cingulate cortex facilitates “perseverance” by regulating both glutamatergic and dopaminergic transmission in the motor cortex and dorsal striatum.


Expanding the traditional view of the hippocampal representation of space. The discovery of the hippocampal place cell (O’Keefe and Dostrovsky, 1971) provided convincing physiological evidence that the hippocampus creates a cognitive map of the environment. With time, it was found that the response properties of these place cells were more nuanced than expected. For example, “place cells” were found to be sensitive to both location and trajectory and that these neurons coupled their activity to specific phases of the hippocampal theta (7 Hz) oscillation. My research contributed to the expansion of the traditional view of the place cell by challenging the view that spatial coding in the hippocampus is an exclusive property of principal cells. Together with Drew Maurer and Bruce McNaughton, we determined that inhibitory interneurons convey precise information about space, and that this information is only
identifiable if the phase of the theta rhythm at which interneurons fire is accounted for. We used this phase-based definition of the place field to improve upon existing measures of place-field sizes, an approach which became useful in quantifying how the spatial scale of the cognitive map changes in different regions of the hippocampus.

The second way my research extended the understanding of hippocampal function resulted from my collaboration with Dr. Douglas Nitz and our investigation of repeating place fields – a recently discovered phenomenon whereby multiple fields appear when animals visit locations with similar behavioral or visual features (Derdikman et al., 2009). Dr. Nitz and I observed that these repeating fields shift forward in space as animals run on spiral-shaped tracks. Further experiments revealed that this shift was most likely due to a buildup of inertial navigation error, suggesting that animals were actually using an inertial/vestibular strategy as opposed to a visual cue based navigation strategy – even in brightly-lit rooms. This is an interesting contribution, as one assumption in the field is that inertial navigational strategies are only employed when visual cues are unavailable.


**Development of technologies for the neuroscience community.** From the onset of my scientific career, I have worked to develop software and hardware to assist the neuroscience community. Below is a list of some of these contributions and ongoing projects:

- Ultrasound measurement of electrical brain activity. I am a collaborator on Brain Initiative R24 (Lead PI: Russel Witte, UA) to develop a non-invasive ultrasound system for the measurement of electrical activity in the brain. The system capitalizes on the acoustoelectric effect, and my role is to validate the system’s effectiveness by comparing in vivo measurements obtained from the ultrasound system with measurements obtained from traditional electrophysiology.
- Simultaneous dopamine and single-unit/local-field measurement. Awarded a 2014 NSF BRAIN EAGER grant to develop technologies for the simultaneous recording of the activities of ensembles of neurons and real-time measurement of dopamine release. Since receiving support, we have produced working versions of this device and successfully tested the device in anesthetized and awake and behaving rats (methods paper under review). The next stage of development will be to improve the hardware and software to improve robustness and ease of use.
- To better characterize fine body movements in animals as they perform decision-making behaviors, I developed a novel 9-axis head-mounted inertial measurement system. Prototypes of this system are being developed for three laboratories for the investigation of brain-body interactions in the hippocampus, parietal cortex, and prefrontal cortex.
• Designed and built numerous automated maze systems for the training and testing of decision-making and memory-driven behaviors. The design and required software is freely available. I helped set up these systems in the laboratories of three collaborators and they continue to be used.

• Produced an interactive graphical system for real-time and off-line spike sorting (Waveform Cutter, Cowen 2002). This tool became an integral part of MClust (David Redish, U. Michigan), one of the most popular open-source spike-sorting systems.

Complete list of published work on NCBI NIH Bibliography:

Research Support
R44MH114776 R44 NIMH: High Density, Miniaturized, Zero Switching, Stimulation and Recording Headstage for Small Animals (Role: Co-investigator, PI: Daniel S Hedin) 8/01/17 – 1/31/18
Objective: Develop new technologies for simultaneously stimulating and recording the activities of groups of individual neurons in behaving animals.

LuMind Foundation: Brain Development, Sleep and Learning in Down Syndrome (Role: Co-Investigator, PI: Jaime Edgin) 1/01/17 – Present
Objective: Identify neural signatures of sleep dysfunction in Down-syndrome subjects (EEG).

11014.01, Michael J Fox Foundation Cowen, Stephen Cowen (PI) 08/01/17 – 07/31/19
Identification of Network and Oscillatory Signatures Of The LRRK2 Mutation
Objective: Identify neural biomarkers that distinguish the LRRK2 genetic form of Parkinson’s disease from healthy controls and idiopathic Parkinson’s disease.

1R24MH109060-01, NIMH R24 Brain Initiative Grant, Russel Witte (PI) 11/01/15 – 10/31/18
My role: Co-investigator
High Resolution Electrical Brain Mapping by Real-time and Portable 4D Acoustoelectric Imaging
Objective: Develop new technologies for in vivo acoustoelectric imaging of neural activity.

DBI-1450767, NSF Stephen Cowen (PI) 09/01/14 – 08/31/17
NSF BRAIN-EAGER: Integrated Measurement of Dopamine Release and Large-Scale Ensemble Activity in Behaving Animals
Objective: Develop novel technology for the simultaneous recording of the activities of individual neurons and dopamine release in freely behaving animals.

NS084026-01A1, NIH-NINDS R01 Gene Gurkoff (PI). My role: Co-investigator 06/01/14 – 09/01/18
Restoring Functional Connectivity Following TBI
Objective: Assist investigation of functional connectivity changes associative traumatic brain injury and following deep-brain stimulation therapy. Support for travel to assist with inter-region LFP surgical procedures and recording.
Biographical Sketch
Fabian Fernandez, Ph.D.
Assistant Professor of Psychology and Neurology at the University of Arizona

Education/Training

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<td>University of Florida, Gainesville, FL</td>
<td>B.Sc.</td>
<td>2002</td>
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<td>Stanford University, Palo Alto, CA</td>
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<td>2008</td>
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<td>University of Colorado, Denver, CO</td>
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<td>Neuropharmacology</td>
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<td>Johns Hopkins University, Baltimore, MD</td>
<td>Postdoctoral</td>
<td>2015</td>
<td>Translational Neurosci</td>
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Personal Statement
I see many parallels between running a laboratory and operating a technology startup. My vision is to use the lab as a vehicle to identify promising basic research that—if strategically rounded out with a little more investment—could have a disproportionate impact on the way diseases of the nervous system are conceptualized and treated. This perspective informs my current work on circadian rhythms and aging, as well as a previous project I led concerning the design of a treatment for intellectual disability in people with Down syndrome (please see Fernandez et al., Nature Neuroscience, 2007, Jamie Edgin & Fabian Fernandez, New York Times, “The Truth about Down Syndrome,” and item 1 in Publications and Career Contributions).

Based in part on professor Art Winfree’s conjectures on circadian singularity and other research suggesting disrupted rhythms in aging, I have recently used a photic manipulation to take away circadian function and “cognition” from a healthy animal (i.e., the Siberian hamster; Fernandez et al., Science, 2014). The central question that frames my laboratory’s day-to-day activities at the University of Arizona is whether we can design a photic intervention to do the opposite: can we design short-lived light pulses with specific color temperatures, intensities, or frequency schedules that will restore disrupted rhythms and cognition back to normal in older individuals with existing memory/circadian problems? And corollary to this central question: can we do it while the person is sleeping—i.e., at a time when the circadian pacemaker, ironically enough, is most responsive to light stimulation from the retina?

To accomplish this long-term goal, my lab is in the process of developing a technology that emits a precise printed array of LED point lights with predetermined wavelength characteristics and intensity fluctuations that could be optimal for kick-starting rhythms. This device will deliver light from a long-wear contact lens in integrated bursts at times of night when the circadian system is primed to adapt in response to photic input. A natural bedfellow to these efforts is ongoing to: 1) code-break the language by which light can be used as a repetitive stimulus to shift the operation of the brain’s circadian clock and rehabilitate it when it has weakened, and 2) identify individual differences in circadian profile that will increase the risk of memory impairment as a person ages. At the intersection of this data, we hope to uncover important principles for how to use naturally occurring facets of dawn- or dusk-like twilight to strengthen the pacemaker specifically in those forecast to experience circadian-linked memory troubles with normal aging (or those whose troubles might accelerate progression of Alzheimer’s disease).

In my training and previous experimental work, I have demonstrated a resolve to tackle tough problems and to find elegant solutions that might find their way into everyday life. It is this tenacity that I bring to my current and future work in circadian science.

Positions and Honors

Positions and Employment

1999 – 2002 University Scholars undergraduate research fellow with Dr. Darragh P. Devine, University of Florida, Gainesville.
2002 – 2008 PhD research in neuroscience with Dr. Craig C. Garner, Stanford University, Palo Alto, CA.
Biographical Sketch
Fabian Fernandez, Ph.D.

continued

2009 – 2012 Senior Scientist and Consultant, Intellimet LLC.
2012 – 2015 Research Associate with Dr. Roger H. Reeves, Johns Hopkins University, Baltimore, MD.
2015 Assistant Professor, Department of Psychology and Neurology, and BIO5 Fellow, University of Arizona, Tucson, AZ

Other Experience and Professional Memberships

2003 – 2004 Stanford University Neuroscience Program Journal Club Organizer
2003 – 2004 Stanford University Professional Development Organizer
2012 Consulting, GABA mechanisms for pharmaceutical trials of cognitive enhancement, Balance Therapeutics
2014 NIH Summit with NCATS: Next Steps for Down Syndrome Therapeutics
2014 Ad Hoc Reviewer for Proceedings of the National Academy of Sciences USA, Neurobiology of Aging, Neurobiology of Learning & Memory, and Journal of Alzheimer’s Disease, among others
2015 Member, Society for Research on Biological Rhythms
2015 Member, Association for Psychological Science
2016 Elected to the Faculty Executive Advisory Committee (FEAC) of the UA Department of Psychology
2016 Arizona Alzheimer’s Consortium, UA Internal Scientific Advisory Board Member
2016 Reviewer, Flanders Research Foundation (FWO), Belgium
2017 Reviewer, Medical Research Council (MRC), United Kingdom
2017 Reviewer, Velux Stiftung Foundation, Switzerland

Honors

2000 Peter J. Sones Endowed Scholarship, University of Florida, Gainesville
2001 Charles Vincent McLaughlin Endowed Scholarship, University of Florida, Gainesville
2001 Phi Beta Kappa Honor Society
2002 BSc, summa cum laude, self-tailored IDS program
2003 – 2006 NSF Predoctoral Fellowship (GRFP #2003014684)
2007 – 2008 Ruth L. Kirschstein NRSA Research Service Award (NINDS, 1F31NS056571)
2008 – 2009 La Fondation Jérôme-Lejeune Postdoctoral Fellowship
2014 U.S. Patent, 8,729,067, Pharmacological Treatment of Cognitive Impairment
2015 Fellow Award, BIO5 Institute, University of Arizona, Tucson
2016 Bisgrove Scholar Award, Science Foundation Arizona (SFAz)

Publications and Career Contributions

My early publications were concerned with therapeutics research in animal models of intellectual disability. While at Stanford University, I spearheaded efforts to “cure” memory problems in Ts65Dn mice, animals with a genetic background similar to individuals with Down syndrome (DS). For decades, it was assumed that nothing could be done to improve cognitive function in the DS population. The condition results from the over-expression of ~200 categorically-diverse genes that steer development of the brain in a completely different direction from that of the typical one.
By 2004, it became clear, however, that the Ts65Dn DS model showed one central difference in brain signaling that could contribute to the animal’s difficulties with learning and memory: an increase in the signaling of a neurotransmitter called GABA. I established that higher-than-normal GABA was a key therapeutic target—drugs that reduced this transmitter in the brain also restored the ability of these mice to remember novel objects and to navigate mazes.

These findings, published in Nature Neuroscience, were commented on in Lancet and the Journal of the American Medical Association and reported in the international press (UK Telegraph, Reuters, LA Times, Scientific American, Bloomberg, etc). They have been replicated by several laboratories around the world and are currently the basis for clinical trials by Roche and Balance Therapeutics to evaluate the ability of GABA antagonists to raise IQ in children and young adults with DS.

The last decade has seen disruptive innovation in DS research and a rethinking of treatment approaches for intellectual disability. This would not have been possible without a purpose-driven program of study and a naïve willingness to transform a new idea into value for a medically underserved area of society. Having devised a treatment approach that might be relevant for the developmental disabilities experienced by people with DS early on, I turned my attention to the fact that these individuals experience another phase of cognitive decline as they age. This process is an accelerated form of normal aging and, in some with DS, is thought to bear resemblance to Alzheimer’s disease. A consensus in industry and academia suggests the memory problems accompanying normal aging and those typifying progression of dementia are coordinated by multiple factors. Over the past decade, I have explored how one of these factors—circadian arrhythmia—interferes with memory function in older animal models of DS and have focused my lab’s efforts to mapping arrhythmia’s effects with relevance to the older general population.

Since 2005, my colleague, Dr. Norman Ruby, and I have explored how circadian arrhythmia impairs memory function using a novel animal model, the Siberian hamster (Phodopus sungorus) (PNAS 2008; PLoS 2013; Science, 2014). Circadian misalignment due to shift work or jet-lag is well-known to impair memory in humans. However, circadian arrhythmia in rodents induced by clock gene knockouts or surgical lesion of the suprachiasmatic nucleus (SCN), the brain’s clock, is reported to have very little effect on memory. Dr. Ruby and I reasoned that this long-held disconnect occurred because the SCN remains developmentally and structurally intact in humans but not in these rodent models. What if the impairments brought on by circadian dysfunction resulted, not from the loss of a “good-functional” SCN (i.e., degeneration), but from the gain of a “bad-defective” SCN that was now sending error signals to memory systems in the medial temporal lobe? What if the proper phenotypic expression of arrhythmia in the brain – and its effects on behavior – require preservation of circuitry from “malfunctioning” SCN areas to their downstream targets? What if key aspects of this expression are lost upon severing SCN connections? We addressed these issues in the Siberian hamster, a species that can be rendered circadian arrhythmic by a simple, one-time photic treatment that does not interfere with SCN structure or development/genetics. We found that hamsters with persistent light-induced arrhythmia actually have severe deficits in spatial and object recognition memory that can be rescued by subsequent ablation of the SCN. These data suggest that chronic arrhythmia per se does not cause memory impairments in animals – or presumably humans – as has been historically believed. Rather, in line with our hypothesis, an intact, but dysrhythmic SCN is necessary to realize these deficits (Fernandez et al., Science, 2014).

**Education/Training**

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<th>Year(S)</th>
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<td>University of Toronto</td>
<td>Post-Doc</td>
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**Personal Statement**

The goal of my research has been to gain an understanding of the cognitive and neural mechanisms of memory and executive function, how they change with normal aging and brain damage, and how to reduce the impact of memory disorders in everyday life. My early research focused on designing rehabilitation methods for people with severe memory disorders to help them learn new information relevant in their daily lives. For the past 20 years, I have been exploring individual differences in memory and executive function in normal aging, and how they predict performance in a variety of cognitive tasks and in the real world. To this end, we developed and normed composite measures of memory and executive function in normally aging older adults, which we have tracked longitudinally for several years, and which have yielded a rich dataset with the potential to reveal the variables most critical for successful aging. We have shown that these composite neurocognitive measures predict performance in a variety of memory and cognitive tasks, including source memory and prospective memory, in both older adults and patients. During the past 10 years, my students and I have continued to explore ways to improve memory in a variety of special populations and have shown mnemonic benefits of self-referential processing and self-imagination in older people and in young people with memory deficits. Most recently, we have become interested in the potential for social engagement to provide cognitive benefits for older people through the use of internet communication tools such as Facebook and through intergenerational interactions. We observed benefits in some aspects of executive function but not others, and are continuing work focused on the benefits of intergenerational communication for both young and older adults. We have also found a relation between executive function and hearing loss in older adults. To gain a deeper understanding of the specifics of executive function in these studies, we have constructed an executive function battery for older adults to allow us to explore specific sub-components of executive function that may work together or independently in different cognitive tasks.

**Biographical Sketch**

Elizabeth L. Glisky

*continued*

**Positions and Honors**

**Positions**

1987 – 1989 Visiting Assistant Professor, Department of Psychology, University of Arizona

1989 – 1995 Assistant Professor, Department of Psychology, University of Arizona

1995 – 1999 Associate Professor, Department of Psychology, University of Arizona

1999 Professor, Department of Psychology, University of Arizona

2000 – 2002 Head, Interdisciplinary Program in Gerontology, University of Arizona

2004 – 2008 Associate Head and Director of Graduate Studies, Dept. of Psychology, University of Arizona

2006 Professor, Evelyn F. McKnight Brain Institute

2008 – 2009 Acting Head, Department of Psychology, University of Arizona

2010 – 2015 Head, Department of Psychology, University of Arizona

**Honors & Awards**


1981 – 1982 University of Toronto open fellowship

1982 – 1983 Ontario Government scholarship

1983 – 1986 University of Toronto postdoctoral award to research fellow

1989 – 1990 University of Arizona, Provost’s Teaching Award.

2003 Social and Behavioral Sciences Research Professorship

2006 Fellow of the Association for Psychological Science

2011 Elizabeth Hurlock Beckman Award for educational leadership and translational work in cognitive rehabilitation

**Contribution to Science**

In 1986, I published the first of several papers showing that severely amnesic patients could learn considerable amounts of new information. Prior to that time, there were no reports of any significant new learning capabilities in amnesic patients. The method that I developed was called the method of vanishing cues, and it was based on new empirical findings and theories by my colleague Dan Schacter, showing that people with amnesia, although severely impaired in explicit memory, could nevertheless demonstrate preserved implicit memory. My contribution was to take those findings of intact implicit memory and translate them into real world clinical outcomes for memory-impaired individuals. In several publications, we showed that these patients, using the method of vanishing cues, could learn new vocabulary, computer programming, and even a complex set of procedures for a new job. We concluded that the method was successful because it tapped into intact implicit memory allowing people to learn new things even though they had no explicit memory. The method was later explored and extended by many others in the field of neuropsychological rehabilitation and is still used clinically today.


In the early 90s, studies of source memory began to appear in the literature, with findings that source memory deficits were found in memory-impaired patients only if they had damage to frontal brain regions. In addition, some studies noted that older people performed more poorly on source memory tasks, and debate ensued about the relative contributions of frontal (FL) and medial temporal (MTL) brain regions to source memory. I became interested in the possibility that individual differences in older adults, many of whom were experiencing declining memory function, might inform this question. I decided to use neuropsychological tests designed to measure memory function, dependent on the MTLs, and executive function, dependent on the FLs, to look at individual differences in older adults. I normed a battery of tests on 227 older adults yielding two composite measures: one that tapped fundamental memory functions dependent on the MTLs and one that measured executive function, depending on the FLs. These composite measures were then used to predict performance on item and source memory tasks respectively, and later on other kinds of memory tasks, including prospective memory. The idea was picked up by several other researchers to explore brain-behavior relations in older adults, and the use of neuropsychological tests in older adults has now become quite commonplace.

Prospective memory—remembering to do things in the future—came into the mainstream literature in the mid-90s as interest began to shift somewhat to real-world memory problems. Little research or theory existed at that time concerning how memory for future intentions differed from the more classically studied memory for past experiences, or whether it might depend on different brain regions. In 1996, I was asked to write a chapter for a book on Prospective Memory, the first of its kind, on the neuropsychology of prospective memory. The chapter was largely speculative, since little laboratory research had been done on prospective memory at all. In that chapter, I proposed that executive functions associated with frontal regions of the brain were probably implicated because of the self-initiation that was required to remember a future intention and the potential need for planning, functions that are associated with executive control. This was the beginning of a series of experiments both in my lab and in others.
looking at the differential contributions of memory and executive function to prospective memory and retrospective memory. Although prospective memory is still an area that attracts only a small number of researchers, the added insights from neuropsychology have made a significant contribution to theory development and to understanding the underlying mechanisms of prospective memory.


In 1977, Rogers, Kuiper, and Kirker published a paper showing that processing information in relation to the self, enhanced memory more than semantic processing – what has been called the “self-reference effect.” Rogers et al. interpreted this finding as evidence of special mnemonic properties of the self, while others suggested it just involved deeper processing. This debate continues. What has added to the evidence concerning the potential benefits of self-reference is more recent research in aging. Although there was one study in the 1980s, it was not until the mid-2000s where research in self-referential processing in aging again surfaced, and we were at the forefront of this renewed interest. We completed our first study in 2005 and published our first paper on aging and self-reference in 2009.

One other paper preceded us in 2007. What we showed was that older adults (over the age of 75) showed a decreased benefit of semantic processing on memory, but showed the same added benefit for self-referential processing as did younger adults, suggesting again that the self had special mnemonic properties. Since then several other studies have appeared in the literature looking at the self-reference effect in older adults. In our lab, we decided to try to enhance the effect even further, combining self-referential processing with imagery – what we have called self-imagination. In a series of experiments, we have demonstrated even greater benefits in memory for self-imagination in both patient and aging populations.


Research Support

Ongoing

Advanced Bionics Corporation 2015 – 18
Cochlear implants and cognitive impairment
Goals are to look at effects of cochlear implants on cognitive function & social engagement in adults over the age of 72.
Role: Co-PI (PI: Jacob); PI (7/17 – 7/18)

Arizona Alzheimer’s Consortium 7/1/17 – 6/30/18
Memory and executive function in normally-aging older adults
The goals are to document changes over time in episodic memory and executive function in normally-aging older adults aged 65+, and to validate an executive function battery for older adults.
Role: PI

Evelyn F. McKnight Brain Research Foundation 7/1/15 – 6/30/18
Inter-Institutional cognitive aging assessment core
My responsibilities are to work with a team at the University of Arizona to develop a core assessment battery for older adults over the age of 85 to be shared across 4 sites.
Role: Co-Investigator (PI: Alexander)

Completed

2011 Cognitive Science Summer RA Award, “Social Networking for Older Adults,” PI.
2012 Western Alliance to Expand Student Opportunities, “Self-imagination in normal aging and mild cognitive impairment,” $2500 to support undergraduate Melisa Crawford.
2012 Evelyn F. McKnight Brain Institute, Pilot project on “Effects of Social Networking on Cognition in Socially-Isolated Older Adults,” PI.
Biographical Sketch
Naomi E. Rance
Professor of Pathology

Education/Training

<table>
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<th>Year(S)</th>
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<td>B.S.</td>
<td>1973</td>
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<td>The Johns Hopkins Hospital</td>
<td>Fellowship</td>
<td>1989</td>
<td>Neuropathology</td>
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Personal Statement

For more than 25 years, our overall goal has been to characterize and understand the physiological significance of the changes that occur in the hypothalamus secondary to menopause. We observed hypertrophy and increased gene expression in a subpopulation of estrogen receptor expressing neurons in the hypothalamic infundibular nucleus of postmenopausal women. These neurons are called KNDy neurons, based on the co-expression of kisspeptin, neurokinin B (NKB), and dynorphin. For many years, our goal was to understand the role of NKB in reproductive regulation. The significance of these studies became widely recognized with the observation that mutations in either the gene encoding NKB or its receptor (NK3R) result in hypogonadotrophic hypogonadism. In the last 10 years, we have focused on studying the role of KNDy neurons in the estrogen modulation of body temperature. The results of these studies allowed us to propose that KNDy neurons play a role in the generation of hot flushes via NK3R signaling in the hypothalamic median preoptic nucleus. Recent clinical trials in have shown that NK3R antagonists effectively reduce the number and severity of hot flushes, thus providing strong support for our hypothesis.

Biographical Sketch
Naomi E. Rance

Positions and Honors
Positions and Employment

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<td>Predoctoral Fellow, Department of Physiology, University of Maryland</td>
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<tr>
<td>1983 – 1986</td>
<td>Resident, Anatomic Pathology, The Johns Hopkins Hospital</td>
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<td>1986 – 1987</td>
<td>Chief Resident, Anatomic Pathology, The Johns Hopkins Hospital</td>
</tr>
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<td>1987 – 1989</td>
<td>Clinical and Research Fellow, Neuropathology Laboratory, The Johns Hopkins Hospital</td>
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<td>1989 – 1995</td>
<td>Assistant Professor, Department of Pathology, University of Arizona College of Medicine</td>
</tr>
<tr>
<td>1989</td>
<td>Chief, Division of Neuropathology, University Medical Center, Tucson, Arizona</td>
</tr>
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<td>1989</td>
<td>Neuropathology Consultant, Forensic Science Center, Pima County, Arizona</td>
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<tr>
<td>1995 – 2000</td>
<td>Associate Professor, Department of Pathology, University of Arizona College of Medicine</td>
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<td>Associate Head, Department of Pathology, University of Arizona College of Medicine</td>
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<tr>
<td>2000</td>
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</table>

Other Experience and Advisory Committees

<table>
<thead>
<tr>
<th>Year</th>
<th>Committee</th>
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<tbody>
<tr>
<td>1993</td>
<td>Advisory Group, Workshop on Menopause, NIH, Bethesda</td>
</tr>
<tr>
<td>1994</td>
<td>Ad Hoc member, Biochemical Endocrinology Study Section, NIH, Bethesda</td>
</tr>
<tr>
<td>1995, 1997</td>
<td>Ad Hoc Reviewer, National Science Foundation</td>
</tr>
<tr>
<td>1997</td>
<td>Ad Hoc member, Biochemical Endocrinology Study Section, NIH, Bethesda</td>
</tr>
<tr>
<td>1998 – 2004</td>
<td>Multiple Site Visit Review Committees, NIH, NIA Program Project Grants</td>
</tr>
<tr>
<td>2001</td>
<td>Advisory Group, NIA Workshop on Primate Models of Menopause, NIH, Bethesda</td>
</tr>
<tr>
<td>2007 – 2012</td>
<td>Scientific Advisory Board, Evelyn McNight Brain Institute, University of Arizona</td>
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<td>2009</td>
<td>Ad Hoc Member, ICER Study Section, NIH Bethesda</td>
</tr>
<tr>
<td>2009, 2010</td>
<td>Ad Hoc Reviewer, Burroughs Welcome Trust</td>
</tr>
<tr>
<td>2011</td>
<td>Ad Hoc Member, ICER Study Section, NIH, Chicago</td>
</tr>
<tr>
<td>2014</td>
<td>Ad Hoc Reviewer, Burroughs Welcome Trust</td>
</tr>
<tr>
<td>2015, 2017</td>
<td>Ad Hoc Member, Neuroendocrinology, Neuroimmunology, Rhythms and Sleep Study Section, NIH, New Orleans, Louisiana (2015) and San Antonio, Texas (2017)</td>
</tr>
</tbody>
</table>
Biographical Sketch
Naomi E. Rance

Invited Speaker (selected)

2004 Symposium Speaker, Annual Meeting of the Endocrine Society of Australia, Sidney, Australia
2004 Reproductive Endocrine Unit, Massachusetts General Hospital, Boston
Annual Meeting of the Endocrine Society, Toronto
2008 First World Conference on Kisspeptin Signaling in the Brain, Cordoba Spain
2009 Magee-Women’s Research Institute and University of Pittsburgh
2010 Physiology Department, University of West Virginia
2011 Netherlands Institute of Neuroscience, Amsterdam
2011 Integrative Physiology Department, University of Colorado, Boulder
2011 Physiology Department, University of Wyoming, Laramie
2012 Symposium Speaker, Annual Meeting of the Endocrine Society, Houston Texas
2012 Barrow Neurologic Institute, Phoenix, Arizona
2012 Second World Conference on Kisspeptin Signaling in the Brain, Tokyo, Japan
2013 Endocrine Grand Rounds, Reproductive Neuroendocrine Unit, Massachusetts General Hospital, Boston
2014 Plenary Speaker, 5th International Symposium on the Physiology and Pharmacology of Temperature Regulation, South Africa
2017 Symposium Speaker, Plenary Symposium on Hot Flashes- 15th World Congress on Menopause, Prague, Czech Republic, September 2016

Honors

1973 Phi Beta Kappa
1983 Rudolph Virchow Prize for Research in Pathology, University of Maryland
1995 John Davis Outstanding Residency Teaching Award, Dept. of Pathology, University of Arizona
1997 Vernon and Virginia Furrow Award for Excellence in Graduate Medical Education, University of Arizona College of Medicine
1999 Basic Science Educator of the Year, University of Arizona College of Medicine
2000 Basic Science Educator of the Year, University of Arizona College of Medicine
2001 Basic Science Educator of the Year, University of Arizona College of Medicine
2002 Basic Science Educator of the Year Lifetime Award, University of Arizona College of Medicine
2007 Vernon and Virginia Furrow Award for Excellence in Innovation in Teaching, University of Arizona College of Medicine
2015 Founder’s Day Speaker, University of Arizona College of Medicine
Contribution to Science

We have characterized changes in the morphology and neuropeptide gene expression that occur in the human hypothalamus secondary to the ovarian failure of menopause. Studies in animal models showed that the changes in neurokinin B and kisspeptin gene expression in postmenopausal women are secondary to withdrawal of ovarian estrogen and not due to age per se.


Based on the dramatic changes in NKB gene expression in postmenopausal women, we hypothesized that NKB neurons participate in the estrogen modulation of LH secretion. This hypothesis is supported by pharmacological and anatomic studies. Using an NK3R agonist conjugated to saporin to ablate KNDy neurons, we show that KNDy neurons are essential for the functioning of the reproductive axis.


Neuroanatomic studies were conducted using dual labeled immunohistochemistry, anatomic tract-tracing and biocytin injections in tissue slices of EGFP-labeled transgenic mice. We described a bilateral network of KNDy neurons within the arcuate nucleus in which these neurons communicate with each other via NK3R and project to GnRH terminals in the median eminence. Connections between arcuate KNDy neurons provides an anatomic framework to explain how KNDy neurons could be coordinated to provide sex-steroid modulation of pulsatile GnRH secretion. Projections to other brain regions suggest that KNDy neurons influence a wide variety of physiologic functions including thermoregulation.


To determine if KNDy neurons could play a role in thermoregulation, a series of studies was performed using a rat model. Anatomical studies showed projections of KNDy neurons to the median preoptic nucleus (MnPO), an important component of the CNS pathway that regulates heat dissipation effectors. Moreover, MnPO neurons express the neurokinin 3 receptor (NK3R), the primary receptor for NKB. Further studies using a rat model strongly supported the hypothesis that KNDy neurons could influence cutaneous vasodilation (flushing) via projections to NK3R-expressing neurons in the MnPO.


**Research Support**

**Ongoing**

Role of Preoptic NK3R Neurons in the Estrogen Modulation of Body Temperature  8/15/2014 – 4/30/2019

Agency/number NIH NIA 1R01AG047887  $1.5 million total award

Principle Investigator: Naomi Rance

This grant explores how preoptic neurons that express the neurokinin 3 receptor participate in the neural circuits regulating body temperature. Our goal is to provide information related to mechanism of menopausal flushes.
Biographical Sketch

Lee Ryan, Ph.D.
Professor, Psychology, Neurology, Neurosciences Program, University of Arizona

Education/Training

<table>
<thead>
<tr>
<th>Institution &amp; Location</th>
<th>Degree</th>
<th>Year(S)</th>
<th>Field Of Study</th>
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<td>University of Toronto, Toronto, Canada</td>
<td>BMus</td>
<td>1979</td>
<td>Music</td>
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<tr>
<td>University of Toronto, Toronto, Canada</td>
<td>MA</td>
<td>1981</td>
<td>Music</td>
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<tr>
<td>University of Toronto, Toronto, Canada</td>
<td>BS</td>
<td>1988</td>
<td>Psychology/Neuroscience</td>
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<tr>
<td>University of British Colombia, Vancouver, Canada</td>
<td>PhD</td>
<td>1992</td>
<td>Clinical/Cognitive Psych</td>
</tr>
<tr>
<td>University of California, San Diego, San Diego, CA</td>
<td>Post-doctoral Fellow</td>
<td>1993 – 1995</td>
<td>Neuropsychology</td>
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Personal Statement

I am a professor and the head of the Department of Psychology in the School of Mind, Brain, and Behavior at the University of Arizona, and the associate director of the Evelyn F. McKnight Brain Institute. Since 1998, I have directed the Cognition and Neuroimaging Laboratory, which provides technical and analysis support for cognitive neuroscience researchers from across the campus utilizing MRI methods. My research focuses on memory, age-related memory decline, and the neural basis of memory. I have published more than 60 scholarly articles utilizing various MRI methods, including functional MRI, ASL perfusion, voxel-based morphometry, and high-resolution diffusion tensor imaging. My research on the neural basis of memory has focused on understanding the hippocampal processes mediating autobiographical and semantic memory, how memory changes across the adult lifespan, how those changes relate to brain structure and function, and the early prediction of Alzheimer's disease. Recent studies using morphometric analyses and diffusion imaging have investigated factors that influence individual differences in age-related cognitive function, including genetic markers, obesity, hypertension, and anti-inflammatory drug use. As a clinical neuropsychologist, I work with individuals and families who are coping with chronic and progressive diseases that effect cognitive functioning, including multiple sclerosis, Parkinson's disease, and Alzheimer's disease. I teach undergraduate and graduate level courses in memory, neuropsychology, neuroanatomy, cognitive neuroscience, and MRI methods and have been very active in mentoring programs at the University of Arizona.

Biographical Sketch

Lee Ryan, Ph.D.

continued

Positions and Honors

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<tr>
<td>1992 – 1993</td>
<td>Clinical internship in Neuropsychology, VAMC, La Jolla, and UCSD, San Diego, CA</td>
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<tr>
<td>1993 – 1996</td>
<td>Research Scientist, Department of Psychiatry, University of California, San Diego</td>
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<tr>
<td>1996 – 2003</td>
<td>Assistant Professor, Department of Psychology, University of Arizona</td>
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<tr>
<td>1998</td>
<td>Participant in Summer Institute on Aging Research, National Institute on Aging</td>
</tr>
<tr>
<td>1998 – Present</td>
<td>Director, Cognition &amp; Neuroimaging Laboratories, University of Arizona</td>
</tr>
<tr>
<td>2000 – Present</td>
<td>Member, Memory Disorders Research Society</td>
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<tr>
<td>2003 – 2014</td>
<td>Associate Professor and Associate Head, Department of Psychology, University of Arizona</td>
</tr>
<tr>
<td>2013 – Present</td>
<td>Associate Director, Evelyn F. McKnight Brain Institute</td>
</tr>
<tr>
<td>2014 – Present</td>
<td>Professor, Department of Psychology, University of Arizona</td>
</tr>
<tr>
<td>2015 – Present</td>
<td>Head, Department of Psychology, University of Arizona</td>
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Contribution to Science

Using fMRI, I demonstrated that the hippocampus remains active during autobiographical memory retrieval, even when the memories are more than 20 years old. This finding, consistent with Multiple Trace Theory, has had a significant impact on the field’s understanding of the role of medial temporal lobe structures in consolidation, storage, and retrieval of old memories. The finding helps to clarify the types of memory impairment associated with medial temporal lobe damage in patients with stroke or other pathology.


Using fMRI, I demonstrated that the hippocampus is important for the retrieval of both episodic and semantic memory, contrary to previous views of the hippocampus as a structure that is primarily or even solely involved in episodic retrieval. These studies have highlighted the interactive nature of these two systems.

Biographical Sketch

Lee Ryan, Ph.D.


My laboratory has shown that cardiovascular health risk factors, including obesity, hypertension, and inflammation, have a negative impact on both the structure and function of the aging brain. These brain changes are associated with increased age-related memory and executive function impairments. These studies are important because they suggest that healthy lifestyles that prevent the occurrence of cardiovascular disease may maintain brain health as well.


Recently, I published a theoretical article that uses neuroscientific evidence to build an integrative memory model to explain the common process of change in psychotherapy. This is the first comprehensive model of its kind, based largely on the concept of memory reconsolidation, that provides an explanatory framework for change across all modalities of psychotherapy. The model also makes predictions regarding ways to increase the efficacy of psychotherapies, as well as predictions regarding the connection between episodic memory and the “self.”


Complete list of published work in MyBibliography:

Research Support

Ongoing

U01 HL131014  Sweitzer, Hay, Ryan, Arai (MPI)  3/01/2017 - 2/28/2021
NHLBI
Evaluation of the Safety and Efficacy of Angiotensin 1-7 to Enhance Cognitive Function in Participants Undergoing Coronary Artery Bypass Graft (CABG) Surgery

This project is designed to evaluate the safety and efficacy of Ang-(1-7) to enhance cognitive function in participants undergoing CABG surgery. Further, by teaming with the unique capabilities of the NIH Clinical Center, these studies will measure, for the first time, post-CABG surgery brain inflammation and microglia activation as measured by PET.
imaging of [11C]PBR28 and test the hypothesis that Ang-(1-7) will result in a decrease in brain inflammation and microglia activation in CABG patients. When completed, this clinical study will have advanced development of a new therapy with potential to treat cognitive impairment in CABG patients.

Role: MPI

AAC Ryan (PI) 7/1/2017 – 6/30/2018
Department of Health Services, State of Arizona

Perirhinal Cortical Structure and Function in Older Adults and Its Role in Memory
This grant studies hippocampal and perirhinal function and how it relates to genetic risk for Alzheimer’s disease in a group of older adults using functional MRI.

Role: PI

Completed

AAC Ryan (PI) 7/1/2016 – 6/30/2017
Department of Health Services, State of Arizona

Memory Functioning in Heart Failure Patients with Risk for Alzheimer’s Disease
This grant studied the hippocampal and perirhinal function in a group of heart failure patients compared to age-matched controls using functional MRI.

Role: PI

AAC Ryan (PI) 7/1/2015 – 6/30/2016
Department of Health Services, State of Arizona

Angiotensin (1-7) Treatment to Improve Cognitive Functioning in Heart Failure Patients
This grant studied the safety and efficacy of Ang-(1-7) to enhance cognitive function in as well as the impact of Ang-(1-7) on inflammatory markers and neuroimaging measures in participants with heart failure.

Role: PI

AAC Ryan (PI) 7/1/2014 – 6/30/2015
Department of Health Services, State of Arizona

The Impact of Family History For Alzheimer’s Disease on Cognition and Brain Function
This grant studied the neural and genetic correlates of family history for Alzheimer’s while controlling for APOE e4 status, using volumetric, diffusion, and ASL perfusion MRI.

Role: PI

HB2354 Ryan (PI) 7/1/1998 – 6/30/2014
Department of Health Services, State of Arizona
Cognition & Neuroimaging Laboratories

This grant provided support for functional neuroimaging research at the University of Arizona focusing on topics relevant to aging, memory, and Alzheimer’s disease, including a pilot grant program for developing new fMRI research projects.

Role: PI

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Biographical Sketch
Lee Ryan, Ph.D.

continued
Biographical Sketch
Robert C. Wilson
Assistant Professor of Psychology and Cognitive Science

Education/Training

<table>
<thead>
<tr>
<th>Institution &amp; Location</th>
<th>Degree</th>
<th>Year(S)</th>
<th>Field Of Study</th>
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<tr>
<td>University of Cambridge</td>
<td>B.A.</td>
<td>06/2002</td>
<td>Natural Sciences</td>
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<tr>
<td>University of Cambridge</td>
<td>M.Sci.</td>
<td>06/2002</td>
<td>Chemistry</td>
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<tr>
<td>University of Pennsylvania</td>
<td>M.S.E.</td>
<td>05/2003</td>
<td>Bioengineering</td>
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<tr>
<td>University of Pennsylvania</td>
<td>Ph.D.</td>
<td>05/2009</td>
<td>Bioengineering</td>
</tr>
<tr>
<td>Princeton University</td>
<td>Postdoc</td>
<td>12/2014</td>
<td>Psychology and Neuroscience</td>
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Personal Statement

I am an expert in computational neuroscience and mathematical psychology. I have modeled learning and decision making at a variety of levels – from low level neural networks to high level Bayesian inference – and have extensive experience linking theoretical models to experimental data. I have expertise in developing explore-exploit experiments (Wilson et al, JEP:General 2014), building cognitive models of complex tasks (Wilson, R. C., & Niv, Y., 2012), and linking models to behavioral and neural data (Wilson et al. Neuron 2014), and my work on the effects of TMS on explore-exploit behavior (Zajkowski, W., Kossut, M., and Wilson, R. C, in revision).


Positions and Honors

2003 – 2009  Graduate Student, Department of Bioengineering, University of Pennsylvania
2009 – 2014  Postdoctoral Research Associate, Princeton Neuroscience Institute
2015 – Present  Assistant Professor of Psychology and Cognitive Science, University of Arizona
**Biographical Sketch**

Robert C. Wilson

*continued*

**Contribution to Science**

*How humans and animals solve the explore-exploit dilemma. Many decisions in life involve a tradeoff between exploring new options for information and exploiting known options for reliable reward. For example, when dining at a favorite restaurant, do you explore the new ravioli that is sure to be informative, or exploit the known pizza that is sure to be good? Beyond eating out, the explore-exploit dilemma occurs at all levels of decision making, from picking a TV show to watch or a person to marry, and there are real advantages to solving it well. Yet despite its importance, solving the dilemma optimally is intractable in all but the simplest settings and so the question arises as to how we balance exploration and exploitation in practice. In recent work I have shown that humans use two distinct strategies for solving the explore-exploit dilemma: a directed strategy in which information seeking drives exploration by choice, and a random strategy in which behavioral variability drives exploration by chance. In addition, initial studies from my lab and my collaborators suggest that these two strategies rely on dissociable neural networks, with directed exploration dependent of frontal pole, correlating with blink rate and developing over the course of adolescence, while random exploration appears to be tied to norepinephrine. The identification of the two strategies, in addition to experiments with which to quantify them, is already having a significant impact on the field. Versions of my task are currently being run in at least nine different labs around the world to study exploration in mental illness, across development, in animals and in response to drugs.*


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

The role of orbitofrontal cortex in learning and decision making. Orbitofrontal cortex (OFC) has long been known to play an important role in learning and decision making. However, the exact nature of that role has remained elusive. I have recently proposed a new unifying theory of OFC function in which the OFC provides an abstraction of currently available information in the form of a labeling of the current task state. This “cognitive map” of “task space” in OFC is then used as a scaffold for learning and decision making throughout the brain. The theory accounts for many of the puzzling findings related to OFC such as its role in a number of behavioral tasks, as well as more recent findings showing the effect of OFC lesions on the firing of dopaminergic neurons in ventral tegmental area (VTA). This work has been well received by the field and has been cited more than 100 times in just over two years.


Complete list of published work in MyBibliography:
- Lab website (also includes in press articles and conference papers)
  - http://www.u.arizona.edu/~bob/publications.html
- NCBI My Bibliography (published journal papers only)

Research Support
Completed
5T32 MH 65214 Cohen (PI) 04/1/12 – 9/30/13
Postdoctoral training grant

Pending
Sloan Research Fellowship
Dean’s Innovation Fund
Upper left: Recordings from the hippocampus to student brain oscillations in aging. Lower left: Tissue section from an old monkey showing the medial ventral tegmental area (VTA). Green label is for cells containing dopamine; red label is for cells containing the calcium binding protein calbindin; yellow indicates that the cell contains both. Right: Tissue section from an old monkey, showing the lateral VTA (colors are same as from lower left example).
Trainees

**Postdoctoral**

Monica Chawla, Ph.D. (Barnes)
Area of Interest: Immediate early gene expression in aging in the rat

Sevag Kaladchibachi, Ph.D. (Fernandez)
Area of Interest: Age-related changes in circadian responses to light and their effort on memory

Koeun Lim, Ph.D. (Chou)
Area of Interest: Development of image-guided rTMS protocols

Rachel Samson, Ph.D. (Barnes)
Area of Interest: Age-related changes in the amygdala and emotional perception in the rat

Waitsang Keung, Ph.D. (Wilson)
Area of Interest: Age-related changes in exploration and exploitation

Darya Zabelina, Ph.D. (Andrews-Hanna)
Area of Interest: Cognitive neuroscience of attention and creativity

**Predoctoral**

Elize Bason (Brinton)
Area of Interest: Epigenetic regulation of endocrine aging: Transitions of the perimenopausal and menopausal brain

Pradyumna Bharadwaj (Alexander)
Area of Interest: Applications of multimodal brain imaging in the study of cognitive aging

Sarah Cook (Wilson)
Area of Interest: The effect of top-down processing on perceptual decision making

Lindsey Crown (Cowen)
Area of Interest: Investigating how ketamine alters dopamine levels in the brain

Hannah Doolish (Fernandez)
Area of Interest: Effects of frequent long-haul travel on circadian system aging and health

Maunil (Neal) Desai (Brinton)
Area of Interest: Cognitive benefits of allopregnanolone in ApoE 4 to limit progression of Alzheimer’s disease

Daniel Gray (Barnes)
Area of Interest: Circuits involved in working memory and their decline with age in a nonhuman primate model of aging

Mary Katherine Franchetti (Alexander)
Area of Interest: Effects of physical activity and sleep on cognitive and brain aging

Dan Hill (Cowen)
Area of Interest: How the frontal cortex alters dopamine release in aging
Mingzhu Hou (Glisky)
Area of Interest: Source memory and aging

Kous Kondapalli (Barnes)
Area of Interest: Age-related changes and cognitive performance levels in working memory across the entire life span of rats (Master’s degree received 2017)

Bryan Kromenacker (Wilson)
Area of Interest: The interaction between mental effort and mental representations

Colin Kyle (Barnes)
Area of Interest: Brain aging and hippocampal ensembles recorded in the unrestrained young and old nonhuman primate (Master’s received degree 2017)

Ashley Lawrence (Ryan)
Area of Interest: Cardiovascular risk factors and glucose metabolism and the impact on aging

Adam Lester (Barnes)
Area of Interest: Spatial computations made by the entorhinal cortex and how this changes in aging rats

Stephanie Matijevic (Ryan)
Area of Interest: Brain imaging and cognitive changes in normal older adults

Andrew McKinnon (Ryan)
Area of Interest: Brain imaging, cognitive aging, and lifestyle factors

Molly Memel (Ryan)
Area of Interest: The underlying mechanisms of memory impairment in older adults

Aarti Mishra (Brinton)
Area of Interest: Mechanistic role of ApoE4 and inflammation in the development of at-risk aging phenotype in females and its implication on Alzheimer’s disease

Jack-Morgan Mizell (Wilson)
Area of Interest: Age-related changes in exploration and exploitation

Suzanne Moseley (Glisky)
Area of Interest: Hearing loss, cognition, and aging (Doctoral degree 2017)

Laura Nguyen (Alexander)
Area of Interest: Relation of vascular factors to cognition and brain white matter in healthy aging

Minhhkhoi Nguyen (Barnes)
Area of Interest: Whole brain clearing and using branched DNA labelling technique to map IEG expression in the cleared rat brain (Master’s degree 2017)

Stacey Pest (Nadel/Glisky)
Area of Interest: Reconsolidation in normal aging (Doctoral degree 2017)

Angelina Polsinelli (Glisky)
Area of Interest: Meditation, cognition, and emotion in normal aging (Doctoral degree 2017)
Trainees

continued

Quentin Raffaelli (Andrews-Hanna)
Area of Interest: Cognitive neuroscience of spontaneous cognition

Ruth Robbins (Glisky)
Area of Interest: Social networking and cognition in socially isolated older adults

Hashem Sadegiyeh (Wilson)
Area of Interest: Cognitive correlates of exploration and exploitation

Christine Solinsky (Brinton)
Area of Interest: Development of iPSC-based biomarker strategy to identify neuroregenerative responders to allopregnanolone

Ariana Stickel (Ryan)
Area of Interest: Brain imaging, genetics, and cognitive changes in normal older adults

Mark Sundman (Chou)
Area of Interest: Cortical excitability and plasticity of individuals with MCI

Emily Van Etten (Alexander)
Area of Interest: Effects of healthy aging on memory and brain structure

Siyu Wang (Wilson)
Area of Interest: The neural correlates of exploration and exploitation

Yvette (Yiwei) Wang (Brinton)
Area of Interest: Estrogen regulation of mitochondrial genome and implication of mitochondrial genetic variances in therapeutics for Alzheimer’s disease

Jean Paul Wiegand(Cowen)
Area of Interest: Oscillatory activity related to memory formation in aging

Cindy Woolverton (Glisky)
Area of Interest: Effects of intergenerational interactions in young and older adults

Tony Ye (Cowen)
Area of Interest: Effect of Parkinson’s disease and ketamine on oscillatory activity in the aging brain
Drs. Meredith Hay and Lee Ryan (both EMBI affiliate faculty) are conducting a study to evaluate the safety and efficacy of angiotensin 1-7 to enhance cognitive function in participants undergoing coronary artery bypass graft surgery. Many older individuals undergo this surgical procedure and report negative effects on their cognition as a result. The hypothesis is that this drug will result in a decrease in brain inflammation and microglia activation in these individuals, which was predicted on the basis of preclinical animal experiments conducted at the UA. If the hypothesis is supported in this trial, the researchers will apply to conduct further tests.

Dr. Roberta Brinton (EMBI affiliate faculty) is conducting a study to evaluate allopregnanolone as a therapeutic agent to treat age-associated memory deficits. She is conducting a translational therapeutic development project, required for an Investigational New Drug application to the FDA, to determine the efficacy of allopregnanolone as a neurogenic regenerative and disease modifying agent, first for Alzheimer’s disease, and then potentially for normal aging brain health.

Dr. Gene Alexander (EMBI affiliate faculty), together with Cohen (McKnight, UF), Marsiske (McKnight, UF), and Woods (McKnight, UF), are participating in a multi-site evaluation of cognitive training along with transcranial direct current stimulation for its impact on cognitive aging. Dr. Alexander also is engaged in a project, along with Raichlen (UA), on the effects of an aerobic training system for enhancing cognitive performance in healthy older adults.

Dr. Geoff Ahern (EMBI affiliate faculty) is engaged in the following clinical trials:

2015 – 2019 Randomized, Double-Blind, Placebo Controlled, Multi-Center Registration Trial To Evaluate The Efficacy And Safety Of Ttp488 In Patients With Mild Alzheimer's Disease Receiving Acetylcholinesterase Inh. Sponsored by V5V Therapeutics, LLC.


2017 – 2021 Open Label Extension Study for Continued Safety and Efficacy Evaluation of Azeliragon in Patients With Mild Alzheimer’s Disease. Sponsored by V5V Therapeutics, LLC.
Extramural Funding
July 1, 2016 to June 30, 2017

Subcontract PI's: Ahern, Geoffrey L.; Rapcsak, Steven Z. (PI: Reiman)
Project: Arizona Alzheimer’s Disease Core Center Clinical Core (P30 AG019610)
Sponsor: National Institute on Aging
Project Dates: July 2016 – June 2021
Subaward Amount: $132,268 (current year)

Subcontact PI: Alexander, Gene E. (PI’s: Reiman, Caselli)
Project: Brain Imaging, APOE & the Preclinical Course of Alzheimer’s Disease (RO1 AG031581)
Sponsor: National Institute on Aging
Project Dates: May 2014 – March 2019
Subaward Amount: $14,761 (current year)

Project: Augmenting Cognitive Training in Older Adults – The ACT Grant (RO1 AG054077)
Sponsor: National Institute on Aging
Project Dates: July 2016 – June 2021
Subaward Amount: $292,517 (current year)

Subcontract PI: Alexander, Gene E. (PI: Reiman)
Project: Arizona Alzheimer’s Disease Core Center Educational Core (P30 AG019610)
Sponsor: National Institute on Aging
Project Dates: July 2017 – June 2021
Subaward Amount: $18,950 (current year)
Extramural Funding
July 1, 2016 to June 30, 2017
Continued

Co-Investigator: **Alexander, Gene E.** (PI: Su)
Project: Ultra-sensitive and Label-free Detection of Alzheimer’s Disease Biomarkers (R03 AG055020)
Sponsor: National Institute on Aging
Project Dates: August 2017 – July 2019
Award Amount: $85,553 (current year)

Univ Arizona PI: **Alexander, Gene E.** (Multi-PI: Cohen, Rundek, Visscher)
Project: Neuroimaging Core and Brain Imaging Registry
Sponsor: McKnight Brain Research Foundation
Project Dates: January 2015 – December 2018
Subaward Amount: $228,730 (project period)

Co-Investigator: **Andrews-Hanna, Jessica** (PI: Edgin)
Project: Brain Development, Sleep, and Learning in Down Syndrome
Sponsor: LuMind Foundation
Project Dates: July 2017 – June 2018
Award Amount: $193,500 (current year)

Univ. Arizona PI: **Andrews-Hanna, Jessica**
Project: Enhancing Function in Later Life: Exercise and Function Network Connectivity
Sponsor: National Institutes of Health
Project Dates: July 2017 – February 2019
Subaward Amount: $12,533 (current year)

PI: **Barnes, Carol A.**
Project: Neurobehavioral Relations in Senescent Hippocampus (R01 AG003376)
Sponsor: National Institute on Aging
Project Dates: January 2016 – November 2020
Award Amount: $661,687 (current year)

PI: **Barnes, Carol A.**
Project: Cell Assemblies, Brain Adaptation and Cognitive Aging (R01 AG050548)
Sponsor: National Institute on Aging
Project Dates: September 2015 – May 2020
Award Amount: $492,593 (current year)
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<tr>
<th>PI:</th>
<th>Barnes, Carol A. (co-I's: Alexander, Billheimer, Huentelman, Trouard)</th>
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<tr>
<td>Project:</td>
<td>Neural System Dynamics &amp; Gene Expression Supporting Successful Cognitive Aging (RO1 AG049465)</td>
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<tr>
<td>Sponsor:</td>
<td>National Institute on Aging</td>
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<tr>
<td>Project Dates:</td>
<td>August 2014 – March 2019</td>
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<td>Award Amount:</td>
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<th>PI's:</th>
<th>Barnes, Carol A., and Huentelman, Matt J. (co-I: Okuno)</th>
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<tbody>
<tr>
<td>Project:</td>
<td>CATT: Development and Application of a Neuronal Cell Activity-Tagging Toolbox (RO1 AG049464)</td>
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<tr>
<td>Sponsor:</td>
<td>National Institute on Aging</td>
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<tr>
<td>Project Dates:</td>
<td>September 2014 – May 2018</td>
</tr>
<tr>
<td>Award Amount:</td>
<td>$300,969 (current year)</td>
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<tr>
<th>Subcontract PI:</th>
<th>Barnes, Carol A. (PI: Reiman)</th>
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<tr>
<td>Project:</td>
<td>Arizona Alzheimer’s Disease Core Center Ad Hoc Review (P30 AG019610)</td>
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<tr>
<td>Sponsor:</td>
<td>National Institute on Aging</td>
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<tr>
<td>Project Dates:</td>
<td>July 2016 – June 2021</td>
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<tr>
<td>Subaward Amount:</td>
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<tr>
<th>PI:</th>
<th>Barnes, Carol A. (co-I's: Bimonte-Nelson, Coleman, Huentelman, Reiman)</th>
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<tbody>
<tr>
<td>Project:</td>
<td>Postdoctoral Training, Neurobiology of Aging and Alzheimer’s Disease (T32 AG044402)</td>
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<td>Sponsor:</td>
<td>National Institute on Aging</td>
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<td>Project Dates:</td>
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<td>Award Amount:</td>
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<tr>
<th>PI:</th>
<th>Barnes, Carol A. (Mentor on Pre-Doctoral Training Grant for Daniel Gray)</th>
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<tr>
<td>Project:</td>
<td>Neurobiological Basis of Age-related Deficits in Attentional Shifting and Monitoring (F31 AG055263)</td>
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<tr>
<td>Sponsor:</td>
<td>National Institute on Aging</td>
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<tr>
<td>Project Dates:</td>
<td>January 2017 – December 2019</td>
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<td>Award Amount:</td>
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<tr>
<th>PI:</th>
<th>Brinton, Roberta</th>
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<tbody>
<tr>
<td>Project:</td>
<td>Aging and Estrogenic Control of the Bioenergetic System in Brain (R01 AG053589)</td>
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<td>Sponsor:</td>
<td>National Institute on Aging</td>
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<td>Project Dates:</td>
<td>March 2017 – February 2022</td>
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<td>Award Amount:</td>
<td>$309,686 (current year)</td>
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Extramural Funding
July 1, 2016 to June 30, 2017

PI: Brinton, Roberta
Project: Perimenopause in Brain Aging and Alzheimer’s Disease (R01 AG026572)
Sponsor: National Institute on Aging
Project Dates: September 2016 – May 2021
Award Amount: $2,403,900 (current year)

PI: Brinton, Roberta
Project: Manufacturing of Allopregnanolone for Phase 2 Clinical Trial
Sponsor: Alzheimer’s Drug Discovery Foundation
Project Dates: June 2017 – May 2020
Award Amount: $450,000 (project period)

PI: Brinton, Roberta
Project: Perimenopause in APoE4 Brain: Accelerated Myelin Catabolism for Fuel
Sponsor: Alzheimer’s Association
Project Dates: May 2017 – April 2020
Award Amount: $249,280 (current year)

PI: Brinton, Roberta
Project: Bioinformctic Analyses to Find Current Drug Therapies that Can Prevent or Delay Alzheimer’s Disease
Sponsor: The Women’s Alzheimer’s Movement
Project Dates: November 2016 – November 2017
Award Amount: $60,000 (project period)

PI’s: Coleman, Paul D., Barnes, Carol A., and Alexander G.E.
(co-i’s: Billheimer, Huentelman, Trouard)
Project: Epigenetic, Neuroimaging & Behavioral Effects of Hypertension in the Aging Brain (RO1 AG049464)
Sponsor: National Institute on Aging
Project Dates: August 2014 – March 2019
Award Amount: $458,236 (current year)

Subcontract PI: Cowen, Stephen, L.
Project: Restoring Functional Connectivity Following TBI
Sponsor: National Institute of Neurological Disorders and Stroke
Project Dates: February 2014 – January 2019
Award Amount: $20,413 (current year)
Co-I: Cowen, Stephen, L. (Pl: Witte)
Project: High Resolution Electrical Brain Mapping by Real-Time and Portable 4D Acoustoelectric Imaging
Sponsor: National Institute of Mental Health
Project Dates: September 2015 – June 2018
Award Amount: $31,175 (current year)

PI: Cowen, Stephen, L.
Project: Identification of Network, Oscillatory and Behavioral Signatures of LRRK2 Expression
Sponsor: Michael J. Fox Foundation for Parkinson’s Research
Project Dates: May 2017 – May 2019
Award Amount: $199,386 (project period)

Co-I: Cowen, Stephen, L. (Pl: Edgin)
Project: Brain Development, Sleep and Learning in Down Syndrome
Sponsor: LuMind Foundation
Project Dates: July 2017 – June 2018
Award Amount: $10,750 (project period)

PI: Cowen, Stephen, L.
Project: High Density, Miniaturized, Zero Switching, Stimulation and Recording Headstage for Small Animals
Sponsor: Advanced Medical Electronics Corp.
Project Dates: August 2017 – January 2019
Award Amount: $28,750 (project period)

PI: Fernandez, Fabian
Project: 2016 Bisgove Scholar Program
Sponsor: Science Foundation Arizona
Project Dates: August 2016 – July 2018
Award Amount: $200,000 (project period)

PI: Rance, Naomi E.
Project: Role of Preoptic NK3R Neurons in the Estrogen Modulation of Body Temperature
Sponsor: National Institute on Aging
Project Dates: August 2014 – April 2019
Award Amount: $302,094 (current year)
Extramural Funding

July 1, 2016 to June 30, 2017

Continued

Co-I: Rance, Naomi E. (PI: Teske)
Project: Pre-Clinical Model for Sleep Deprivation-Induced Obesity and Hedonic Intake Due to Noise Exposure
Sponsor: National Institute of Neurological Disorders and Stroke
Project Dates: July 2017 – June 2019
Award Amount: $227,208 (current year)

Project: Arizona Alzheimer’s Consortium State-Funded Projects
Sponsor: State of Arizona, DHS
Date: July 2017 – June 2018
Amount: $439,868 (current year)

Co-I: Ryan, Lee (PI: Sweitzer)
Project: Evaluation of the Safety and Efficacy of Angiotensin 1-7 to Enhance Cognitive Function in Participants Undergoing Coronary Artery Bypass Graft (CABG) Surgery
Sponsor: National Heart, Lung, and Blood Institute
Project Dates: March 2017 – February 2021
Award Amount: $745,065 (current year)
**Educational programs focusing on age-related memory loss**

**Event:** The Joan Kaye Cauthorn Annual Conference on Successful Aging: Decisions, Decisions, Decisions: Making Positive Choices As We Age  
**Date:** February, 2017  
**Organizers:** Lee Ryan, Ph.D., and Gene Alexander, Ph.D. (both EMBI affiliate faculty)  
**Venue:** University of Arizona North Ballroom, Tucson, AZ  
**Summary:** This one-day conference was attended by 250 members of the Tucson community and health care workers.

**Other educational programs for scientists on normative aging**

**Event:** U13 Bedside-to-Bench Conference Series on Sensory Impairment and Cognitive Decline  
**Date:** October 2-3, 2017  
**Organizers:** Drs. Heather Whitson and Frank Lin  
**Venue:** Bethesda North Marriott Hotel and Conference Center, Baltimore, MD  
**Summary:** This was supported by NIA and by the American Geriatrics Society to heighten research attention on emerging geriatric clinical issues that have the potential to greatly improve clinical care or prevention for older adults. This workshop brought together scientist experts on auditory sensory loss in aging with those with expertise in cognition. Dr. Barnes was asked to speak on “Animal models of cognition and cognitive assessment.” A white paper summarizing the talks and identifying knowledge gaps and potential research priorities in this area is being drafted.

**Event:** Cognitive Aging Summit III. Cognitive Aging: Resilience and Reserve  
**Date:** April 6-7, 2017  
**Venue:** Bethesda North Marriott Hotel and Conference Center, Baltimore, MD  
**Summary:** This event was sponsored by the Foundation for the National Institutes of Health, the McKnight Brain Research Foundation, and the National Institute on Aging. The goal of this summit was to gather expertise on topics relevant to cognitive aging so that a white paper could be drafted with recommendations on knowledge gaps and research efforts that might be supported to fill those gaps. Dr. Barnes was asked to speak on “Animal models of brain adaptation and compensation in aging” in the session on “How Do We Operationalize Brain Reserve, Cognitive Reserve, Cognitive Resilience and Compensation?”
Collaborative programs

with McKnight institutions and research programs and non-McKnight institutions and research programs

The director, associate director, and affiliate faculty of the Evelyn F. McKnight Brain Institute at the University of Arizona have many collaborative interactions among themselves and other Institute faculty in Tucson and with other McKnight Brain Institutes. In addition, we have extensive collaborations with faculty inside the University of Arizona, across the state, across the country, and around the world. Discussion of publications this year that have relevance to the aging brain and memory and document these interactions include the following, which have already been highlighted on page 8:


The director of the Evelyn F. McKnight Brain Institute at the University of Arizona is in a strong position in the coming year to conduct significant research on memory in the aging brain. In addition to support from the McKnight Brain Research Foundation, her work is supported through five RO1 grants and one postdoctoral training grant. And while we were not chosen to be one of the four finalists for the $100 million MacArthur 100 & Change grant (the final winner is not yet known, but the MacArthur Foundation has supported each of these to develop their plans for the final competition, which took place at the end of 2017), we have made progress on our ideas for a “Precision Aging” approach to the problem of cognitive decline during aging.

Dr. Barnes initially met with Dr. Masliah, the head of the Neuroscience of Aging Program at the National Institute on Aging, in a visit set up in August by Dr. Kimberly Andrews Espy, senior vice president for research at the UA. In this meeting, Drs. Barnes and Espy indicated that EMBI affiliate faculty were working on creating a white paper that would more fully outline our ideas for the creation of a National Precision Aging® Center at the UA. Dr. Masliah was definitely interested and indicated that we should also contact Molly Wagster to get her input on this project. During a retreat in October, Drs. Barnes, Ryan, Hay, and Brinton completed the white paper and sent it to Drs. Masliah and Wagster.

We then met with Drs. Masliah and Wagster at the Society for Neuroscience meeting in Washington, DC, in November. The white paper outlines our vision for the development of a U19 grant, and they gave us advice on the kind of preliminary data that would be required to make the proposal strongest. Dr. Wagster suggested that we contact leaders of several longitudinal cognitive aging studies to determine whether these individuals were interested in data sharing and collaboration with our group. Subsequently, Dr. Barnes contacted Drs. Marilyn Albert and Sue Resnick, both of whom have longitudinal study cohorts (BIOCARD and the Baltimore Longitudinal Study of Aging, respectively) that would be extremely useful for the development of our algorithms to customize therapeutic interventions. We have identified February 18 as a date when we can meet with Albert, Resnick, and Wagster in Baltimore, MD, to explore ideas for data sharing.

This coming year, 2018, promises to be very busy, as our target for submitting this $25 million grant to create a National Precision Aging® Center is mid-September. Drs. Barnes and Brinton trademarked the name “Precision Aging®” this year. The white paper follows on pages 88–90.
I. Requested Action:
Given the national crisis of older individuals living with significant cognitive impairment, The University of Arizona requests support to establish the National Precision Aging® Center. The Center will create a Precision Aging® Cognitive Enhancement (PACE) system tailored to the individual to improve the cognitive health of older Americans.

II. Identified Need:
Cognitive health does not currently match lifespan. Sixteen million people in the USA are living with cognitive impairment (Hurd et al., 2013). Age-related cognitive impairment results in:

- three times more hospitalizations: a $110 billion economic burden to the healthcare system
- loss of independent living: costing $160 billion in informal care yearly
- loss of productivity: worldwide costs in 2018 are expected to exceed 1 trillion US dollars (Wimo et al., 2017)
- increased risk for Alzheimer’s disease: more than1.6 million develop AD annually (Ward et al., 2013).

The current one-size-fits-all approach to our cognitive aging population is not adequate to close the gap between cognitive healthspan and lifespan.

III. Specific Requested Action:
Because of the national crisis of older individuals living with significant cognitive impairment, we request $25M to establish the National Precision Aging® Center at the University of Arizona.

The National Precision Aging® Center will leverage expertise and create novel advances in cognitive aging, big data and machine learning, and meta-omics to achieve the Center’s goal: to develop and commercialize a novel diagnostic tool that will match an individual’s risk profile with a customized therapeutic plan.

The Precision Aging® Cognitive Enhancement System will enable primary health care providers to identify and implement precision solutions for sustaining cognitive health.

We envision five phases of this project:

Phase I: Interrogate large scale longitudinal datasets from across the country to create profiles of risk. Factors considered will include:

- demographic factors: sex, age, race, geographic context, education
- cognition: memory, executive function, processing speed
- vascular factors: blood pressure, lipid profiles, glucose metabolism, obesity
- medical disorders: hypertension, cardiac disease, diabetes, stroke, hypercholesterolemia, metabolic syndrome
- social support: social engagement/isolation, married/cohabiting status, family support, financial health, mental health
- lifestyle factors: physical exercise, smoking, alcohol, diet
- genetic profile: known risk factors for each of the above categories
Phase II: Undertake a gap analysis to establish the mismatch between identified risk profiles in Phase I and current interventions for cognitive impairment. We will:

- identify the missing information in intervention studies that may be important for understanding non-responder outcomes, based on our risk profile analysis
- match these profiles to our identified risk profiles
- examine existing cognitive intervention studies to evaluate characteristics of responders and non-responders

Phase III: Develop and test customized therapeutic interventions that integrate pharmacological and nonpharmacological approaches for specific risk profiles. We will:

- develop and test customized therapeutic interventions in three pilot geographical test regions of the United states – including the southwest, the deep south, and the southeast
- augment the Phase I risk profile with in depth measurements of:
  - meta-omics: transcriptomics, proteomics, metabolomics, epigenomics, microbiomics
  - inflammatory profiles: cytokines, chemokines, T-cell and oxidative markers
  - neuroimaging: structure, function and potential biomarkers
  - cognitive assessment: validated neuropsychological instruments plus novel tests informed by human and animal research

Phase IV: Refine the match between therapeutic interventions tested in Phase III with individual cognitive outcomes. To do this we will:

- evaluate the more detailed information on responders and non-responders collected in Phase III
- adjust the treatments to improve the probability of a positive therapeutic outcome for the non-responders
- evaluate the refined interventions

Phase V: We will work with the private sector to commercialize the Precision Aging® Cognitive Enhancement (PACE) system to optimize cognitive aging for use by healthcare providers. We will:

- develop mobile software to be used in the clinic for customized diagnostics and treatment
- educate health care providers on use of the software
- create cloud-based therapy management and iterative treatment adjustment tools
- establish cloud based therapy management and treatment adjustment tools
- continue to generate and refine outcome-specific therapies through cloud-based data collection
- work towards Medicaid and Medicare reimbursement for the PACE system
IV. Institutional Uniqueness

The University of Arizona: The University of Arizona is ranked as one of the top 20 public research universities nationwide. The university encourages multidisciplinary research through its extensive system of shared research resources, many of which will be utilized for this project.

The University of Arizona was one of the founding members of the National Institutes of Health Precision Medicine Initiative (PMI) cohort program. The NIH PMI cohort will enroll 1 million or more U.S. participants to improve preventions and treatment of disease, based on individual differences in lifestyle, environment and genetics. The National Precision Aging® Center will leverage this cohort to deploy novel technologies to improve cognitive health in aging. Because of our geographic location, we are ideally situated to address cognitive health in people who are medically underserved and historically underrepresented in cognitive aging research.

University Partners: The University of Arizona is internationally known as a leader in the cognitive neuroscience of aging and the basic neural mechanisms of the aging brain. Within the university we have built several strong Institutes and Centers of Excellence that contribute to the cognitive aging research enterprise. These include:

- The University of Arizona Health Sciences and Banner Health
- The Precision Medicine Initiative Center
- The Center for Biomedical Informatics and Biostatistics
- The Center for Innovation in Brain Science
- The Center for Applied Genetics and Genomic Medicine
- The Evelyn F. McKnight Brain Institute
- The BIO5 Institute

Beyond the University of Arizona: We have a wealth of resources across the State of Arizona including:

- The Arizona Alzheimer’s Consortium
  - Banner Sun Health Research Institute
  - The Mayo Clinic Scottsdale
  - Barrow Neurological Institute
  - Arizona State University
  - Banner Alzheimer’s Institute
- The Translational Genomics Institute

V. Summary

The establishment of the National Precision Aging® Center at the University of Arizona will create a novel system tailored to the individual to improve the cognitive health of older Americans. By working to match cognitive health with lifespan, we will decrease hospitalization time, extend independent living, improve productivity and decrease the risk for Alzheimer’s disease.

The University of Arizona is uniquely positioned to lead this national effort and leverage ongoing investments in precision medicine because of our international leadership in cognitive aging and brain health.
Tissue section showing cells in the brain of an old nonhuman primate
Investment report
July 1, 2016 – June 30, 2017

Endowed Chair
Summary for 12 months ending June 30, 2017
Account Name: Evelyn F. McKnight Chair for Learning and Memory in Aging
A. Beginning Balance on July 1, 2016 $ 844,111
B. Investment Growth $ 70,891
C. Distributions (to Endowed Chair Expendible) $ (35,563)
D. Additional Contributions $ –
E. Ending Balance on June 30, 2017 $ 879,439

Institute - Quasi Endowment
Summary for 12 months ending June 30, 2017
Account Name: Evelyn F. McKnight Brain Institute
A. Beginning Balance on July 1, 2016 $ 1,765,466
B. Investment Growth $ 73,639
C. Distributions (to Institute expendable account) $ –
D. Additional Contributions $ –
E. Ending Balance on June 30, 2017 $ 1,839,105

Institute - Permanent Endowment
Summary for 12 months ending June 30, 2017
Account Name: Evelyn F. McKnight Brain Institute
A. Beginning Balance on July 1, 2016 $ 1,017,662
B. Investment Growth $ 142,343
C. Distributions - UAF Development Fee $ (60,000)
Distributions - To Expendable Account $ (67,911)
D. Additional Contributions $ 1,002,500
E. Ending Balance on June 30, 2017 $ 2,034,594
**Additional notes**

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**

N/A

**Technology transfer**

Nothing to report.
The fundraising efforts continue for the Evelyn F. McKnight Brain Institute at the University of Arizona to meet the challenge of raising private philanthropic funds to match the gift from the McKnight Brain Research Foundation to establish a permanent endowment.

Elaine Cunningham, BSN, RN, MBA, began her tenure as director of development with Research, Discovery & Innovation for Life Sciences in February 2017. Her specific focus is centered on basic science research, incorporating interdisciplinary, collaborative efforts to support the philanthropic goals of the Evelyn F. McKnight Brain Institute and the BIO5 Institute. As an accomplished fundraising professional with 20 years of experience, her successful tenures have included development positions at the University of Florida Foundation and the University of Connecticut Foundation. At both universities, her charge was to establish philanthropic programs where none had existed before – one for cancer research within the UF College of Medicine and the other within the UConn School of Nursing. Both incorporated her skill set in cultivating and soliciting major and principal gifts and developing a donor continuum focused around donor-centric interests, as well as expertise in corporate and foundation relations, project management, and operational excellence. Elaine’s reputation of guiding a prospect through the donor continuum has resulted in six- and seven-figure gifts as well as other significant philanthropic commitments.

She also had a successful nursing career with areas of specialty including critical care, cardiology, bone marrow transplant, and home health care and hospice administration. Her expertise extends to marketing for high-end CCRCs and other health care organizations. Throughout her career, she has worked effectively and in partnership with physicians, faculty researchers, administration, central development, boards, colleagues, and volunteers to strategically further institutional objectives and goals.

Since arriving at UA Foundation, Elaine has accomplished the following:

- Collaborated with UAF Prospect Development team to create a viable portfolio of major and principle gift prospects. This is a work in progress, but so far we have defined 50 strong prospects. BWF RDI data analytics* were used to locate constituents with a demonstrated interest in brain topics.
- Worked with UA development colleagues, marketing and communications, RDI, and BIO5 to update the EMBI case statement and begin a website revision to be completed in the first quarter of 2018.
- Collaborated with UAF Annual Giving, which is currently creating collateral pieces for our first direct mail outreach effort, to be sent in the first quarter of 2018.
- In December 2017, solicited donors for $600K on behalf of EMBI Endowment. We expect to know results from these solicitations in the first quarter 2018.
- Traveled to eight states to meet (qualify and cultivate) with 100 prospects and donors.

*The Office of Research, Discovery & Innovation hired Bentz Whaley Flessner (BWF) to conduct a predictive modeling project of the nearly one million households in our donor database. The initial results were delivered in early summer 2017. BWF’s goal is to work collaboratively with us to identify and develop prospect pools for interdisciplinary fundraising initiatives for the Office of Research, Discovery & Innovation. In doing so, they will also identify ways to grow the effectiveness and scope of prospect research services using increasingly powerful analytics tools. Their first project was to develop a prospect pool for the Evelyn F. McKnight Brain Institute.
In addition to the support provided through the Office of Research, Discovery & Innovation to assist with fundraising for the EMBI, Dr. Espy has been extremely proactive in approving recruitments across the University for faculty who have a focus on aging as one dimension of their research. For example, just in the Department of Psychology, we have recruited several assistant professors whose research domain involves cognitive and brain aging, including Drs. Matthew Grilli, Ying-hui Chou, and Jessica Andrews-Hanna. All of these new faculty have become affiliate faculty of the EMBI. Dr. Grilli’s interest is in the clinical and cognitive neuroscience of memory and how memory changes with age. He also heads our neuropsychology efforts at the Watermark Communities facility, “Hacienda at the River” Evelyn F. McKnight Brain Institute Satellite Clinic. Dr. Chou is interested in human brain connectivity and its relation to behavior. She is conducting experiments using MRI image-guided transcranial magnetic stimulation protocols to individually optimize protocols to improve daily function in aging and in clinical populations (i.e., Parkinson’s disease). Dr. Andrews-Hanna is interested in understanding internally guided cognition, with the goal of helping people live happier, healthier lives. She is currently studying how internally guided processes develop across the lifespan and change in old age.

Additionally, the Department of Psychology has successfully recruited Dr. Arne Ekstrom from the Center for Neuroscience at the University of California Davis, and he will be joining the Psychology Department next summer. His research interests are in the neurophysiological basis of human memory, and he uses intracranial EEG, fMRI, and scalp EEG methods to examine this question. He also is interested in collaborating with Dr. Barnes to develop tasks for humans and nonhuman primates with the goal of better understanding the neural basis of age-related memory changes.

Dr. Lee Ryan, head of psychology, has also just been given permission to hire, at a senior level, a faculty member whose field of study is neuroimaging and neuropsychology of aging and dementias. Because of space constraints in the Psychology Building, this person will be given space in a building very close to Life Sciences North that houses the Evelyn F. McKnight Brain Institute (in the BIOS building or the new building next to it, which will be completed next spring). Dr. Barnes is chair of this committee, and the job and advertisement have now been posted.

Another significant example of the University being committed to “building expertise in aging, neuroscience, and clinical trial conduct” is the establishment of the Center for Innovation in Brain Science in the College of Medicine. Dr. Roberta Brinton was recruited from USC to direct and build this center, and she is hiring people now to build basic, clinical, and translational programs in aging and neurodegenerative disease.

Finally, the Department of Molecular and Cellular Biology was given the opportunity to recruit a faculty member whose research included some aspect of understanding the aging process. Dr. Barnes was on the search committee, and the department successfully recruited Dr. George Sutphin, whose research focuses on defining the molecular pathways of aging so that therapeutic targets for clinical interventions can be developed to mitigate the deleterious effects of age. His research utilizes worms, mice, and humans, and he is likely to provide a key bridge across campus in multiple domains of aging work.

In conclusion, the University of Arizona has expended significant resources to grow the already strong community of scientists here whose research is directed at understanding the aging process at many different levels, and to mount a significant fundraising campaign for the McKnight Brain Research Foundation gift to the EMBI.
There were many significant findings published this year, each of which contributes to our understanding of the aging brain and memory loss that occurs during the aging process. I will summarize some of these from the Barnes laboratory.

- Consistent with data from older humans, older monkeys also show deficits in multi-tasking that implicate dysfunction of prefrontal cortical circuits. This is an important observation, as one limitation of a previous human study was that older adults are never matched to younger participants in computer use, and all tests have been conducted on computers. The observations in the aging animal model suggests that the age differences in behavior are due to neural changes in prefrontal cortex and not an artifact of differential computer experience in older individuals. [Gray et al., 2017]

- We showed that one month treatment with angiotensin 1-7 (a powerful anti-inflammatory agent) prevented cognitive decline in a mouse model of congestive heart failure. These preclinical data formed the basis for a successful grant for a clinical trial in bypass patients, using this drug, submitted by EMBI affiliate faculty Meredith Hay and Lee Ryan. [Hay et al., 2017]

- We were given the opportunity by a high-impact journal to synthesize the human, nonhuman primate, and rodent literature on cognitive aging of navigational systems. We discuss the current evidence on how aging affects the brain’s navigational circuits and suggest promising behavioral and neural biomarkers of spatial navigation as potential therapeutic targets aimed at optimizing cognition. [Lester et al., 2017]

- We obtained data that suggest an association between levels of the mitochondrial enzyme PACAP, aging, cognitive function, and amyloid load in nonhuman primates. We noted both similarities, but also important differences, in normal aging monkeys compared to human brains with AD, which show dramatic increases in amyloid load accompanied by striking reductions in PACAP levels. [Han et al., 2017]
Most important scientific achievements this year

- We report on a prototype of a novel high-resolution, high-speed, long working distance, and large field of view confocal fluorescence microscope that may revolutionize our ability to image wide regions of whole brains that have been rendered optically transparent and macro-molecule permeable (this development is reported in Pacheco et al., 2017). We hope to use this new microscope to examine changes in circuit connectivity in normal aging brains.

- We have found one mechanism that may contribute to the hyperexcitability that we have reported in hippocampal cells in monkeys and others have reported in the hippocampus of rats and humans. Namely, we discovered reduced inhibition in the perirhinal cortex of old rats that could contribute to the circuit imbalance in aging and may be an effective therapeutic target for restoring network function. [Maurer et al., 2017]

- We were able to show that two next-generation sequencing platforms were able to validate variability in gene expression associated with hippocampal subfields, age, and cognitive status. In particular, our results confirm that cognitive decline in aging is associated with differential expression in hippocampal region CA1, particularly with respect to genes linked to calcium homeostasis and synaptic plasticity. [Ianov et al., 2017]

- We were able to show that aging impacts network synchrony and activity of neurons in the basal lateral nucleus of the amygdala during discrimination learning and decision making. Specifically, older rats show increased power of beta frequency oscillations in the amygdala during behavior, which younger animals do not show. It is possible that these oscillations engage a network of structures that reflect a restructuring of reward circuits during aging. [Samson et al., 2017]

Respectfully submitted December 18, 2017,

C.A. Barnes, Ph.D.
Regents’ Professor, Psychology, Neurology and Neuroscience
Evelyn F. McKnight Chair for Learning and Memory in Aging
Director, Evelyn F. McKnight Brain Institute
Director, Division of Neural Systems, Memory and Aging