THE UNIVERSITY OF ARIZONA

Evelyn F. McKnight Brain Institute

Full Lives Through Healthy Minds

Annual Report 2020

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Summary of scientific achievements since last report

The Director, co-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 affiliate faculty publications can be found on pages 4 through 14. The following highlights some of the accomplishments made in 2020 by EMBI faculty in Tucson. For brevity I have chosen examples that fall into three primary categories: peer-reviewed nonhuman animal experiments and human experiments that **directly relate to mechanisms of age-related memory loss**, and publications relevant to aging and to age-associated diseases. EMBI faculty participating in the work mentioned are listed in bold, the full citations can be found in the publication section.

Nonhuman animal aging experiments

While we have previously applied magnetic resonance imaging (MRI) to examine brain changes in normative aging in humans and nonhuman primates, these methods have not been used in rodent models of aging. We used a 7T MRI method in young and old, memory-impaired rats and applied multivariate network scaled subprofile model analysis and voxel-based morphometry to these data. We identified a regional network covariance pattern that distinguished young brains from aged brains in rats, involving reductions in volume in frontal and temporal lobe association areas. Greater expression of the age-related network pattern was associated with poorer spatial learning. These data from rats suggest remarkable parallel changes to those observed in primates and support the potential of using these methods in translational intervention studies (**Alexander, Barnes, Trouard**).

In another study we used MRI methods as well as electrophysiological assessments of auditory and visual system function in adult and aged macaques to better understand the changes that commonly occur in these sensory systems in older individuals. This study applied diffusion MRI and probabilistic tractography analyses to investigate the integrity of the major corticocortical and ascending auditory and visual white matter pathways in the brain. While we did find age-related changes in white matter connectivity that correlated with sensory function within each domain, the pattern of change was different between sensory systems. That is, the white matter changes in the auditory system were in corticocortical connections, while the changes observed in the visual system were in the thalamocortical white matter tracts. These observations argue against a generalized white matter tract deterioration in aging (**Trouard, Barnes, Burke**).

We have examined hippocampal sharpwave ripples during waking states in young and aged rats, as this waking ripple phenomenon is hypothesized to reflect planning and memory retrieval. Several novel observations emerged from these studies, including the fact that aged rats express more ripples, but that young rats express higher ripple rates. While during periods of rest ripple frequencies were lower in old rats, the aged rats showed the ability to increase ripple rates during behavior to levels equivalent to young rats. Given the involvement of waking ripples in memory retrieval, a possible consequence of slower movement speeds in older animals is to provide more opportunity to replay task-relevant information. This may act to compensate for age-related declines in ripple rate during task performance and thus may result in some reduction of age-related declines in memory. (**Cowen, Barnes**)

Human aging experiments

Two different experiments examined the impact of normative aging on executive functions. The first was designed to examine the degree to which the language that people use in their natural daily interactions, carries information about key cognitive functions associated with age-related cognitive

decline. In an observational study in which individuals wore the 'electronically activated recorder' (the EAR), a log of daily conversations as they unfolded were recorded. Higher overall executive function (particularly working memory) was correlated with more analytic, complex and specific language markers. This suggests that patterns of daily word use can be predictive of executive of older individuals (**Grilli, Glisky, Mehl**). Another study examined three independent but correlated components of executive function in young and older adults – set shifting, inhibition, and updating. When they compared the factor structure amongst these components, shifting, updating and inhibition in young adults seemed to operate relatively independently, whereas in older adults these components were more correlated. They suggest that, as people age and processing becomes less efficient, older individuals may rely increasingly on general executive control processes, reallocating their limited resources to optimize performance (**Glisky, Alexander, Ryan**).

Another study examined the differences between younger and older individual's ability to construct scenarios about future events – or episodic future thinking. They found that older adults had more difficulty imagining future events that are rich in episodic detail compared to young. When they examined whether there was a difference between imagining positive or negative episodic events, both younger and older individuals showed reduced episodic specificity for imagining negative compared to positive or neutral events (**Andrews-Hanna, Grilli**). These investigators also examined the possible differences between young and old adults in the way in which episodic autobiographical memories are retrieved. There are two retrieval routes typically used to recall these autobiographical memories, a 'direct one' in which the memory is almost instantaneously retrieved, and a 'generative one' in which general knowledge is used to cue retrieval of the memory. They found that older adults engage in direct retrieval less than do younger individuals, and suggest that this may contribute to an age-related shift away from detail-specific memories towards more general memories (**Grilli, Andrews-Hanna**)

Another group of investigators examined whether physical sports activity may play a role in maintaining a healthy brain. They examined cerebral white matter hyperintensities using MRI, which is thought to be a proxy for brain white matter health. They found that those older adults with low levels of sports activity showed greater white matter hyperintensity volumes than those older adults who had high physical activity. These results may suggest that engaging in high levels of activity may be an important lifestyle factor that can help to diminish white matter lesion load in old age, potentially reducing the impact of brain aging (**Alexander, Trouard**). In another study, these investigators used brain MRIs to determine whether there was a neural signature of subjective memory complaints in older individuals. They found a relationship between age, subjective memory complaints, and a reduced volume of the right hippocampus. The relationship between memory complaints, right hippocampal volume and objective memory scores, however, was only significant in individuals with hypertension and not in non-hypertense individuals. This suggests a key role that vascular risk plays in brain and cognitive health (**Trouard, Alexander**). In another study, two measures of exercise – time spent in moderate to vigorous physical activity and cardiorespiratory fitness - were examined in middle-aged to older adults. When brain volume was examined in relation to these two variables in over 7,000 people from the UK Biobank study (ages 45-80), the effects on brain volume of physical exercise were not identical to those of cardiovascular fitness. They suggest that there may be beneficial effects of exercise on the brain above and beyond the effects related to cardiovascular fitness (**Alexander**).

One other study examined the effects of combining cognitive training with exercise on performance in older adults. There were four groups in this intervention pilot: 1) cognitive training alone, 2) aerobic exercise alone, 3) combined aerobic exercise and cognitive training, and a video-watching control. The effects of these treatments on a dual-task walking test and a serial subtraction test

during a two-minute walk was assessed after 6 and 12 weeks of treatment. The combined exercise and cognitive training group showed improvements of the dual task tests after only 6 weeks of treatment, while the exercise and cognitive treatments did not show improvement until the 12-week test. Although larger studies need to be conducted, they conclude that these data suggest that there are benefits for simultaneous aerobic and cognitive training over and above each modality alone (**Alexander**).

Barnes was invited to contribute an opinion piece for Trends in Neurosciences, which she prepared along with EMBI Affiliate Faculty Matt Huentelman, and U19 Precision Aging Network grant participant Zhao Chen. In this piece we proposed a reinvention of experimental approaches taken to study the brain and aging, with the aim of better matching cognitive healthspan with human lifespan. Past studies of cognitive aging in humans have included sample sizes that tended to be underpowered, were not sufficiently representative of national population characteristics, and often lacked longitudinal assessments. As a step to address these shortcomings, we propose a framework that encourages interaction between electronic-based and face-to-face study designs. We argue that this will achieve the necessary synergy to accelerate progress in the discovery and application of personalized interventions to optimize brain and cognitive health (**Huentelman, Barnes**).

Human aging and disease experiments

Two studies examined the effects of repetitive transcranial magnetic stimulation (rTMS), a noninvasive brain stimulation technique, on cognitive outcomes in older individuals with mild cognitive impairment or Alzheimer's disease. In the first study, a meta analysis was performed on 13 published datasets, and revealed an overall medium to large effect size favoring active rTMS over sham rTMS in the improvement of cognitive functions. It also identified brain regions that were particularly responsive to this stimulation (**Chou**). The other study examined motor evoked potentials after rTMS that was paired with either voluntary muscle contraction, or not paired, in groups of older individuals grouped by cognitive status (from normal to AD). While modified plastic responses were robust in the normative aging group in the voluntary contraction condition, it was diminished in the cohorts of cognitively impaired individuals. The authors suggest that noninvasive brain stimulation might be effectively used in normative aging studies, and could be a biomarker of cognitive decline (**Chou, Fuglevand, Wilson, Rapcsak**).

Another approach has focused on risk factors for cognitive health. In one study, neuroinflammation that emerges during mid-life aging was studied in both a rodent model of endocrine aging and in human aging. Both the translational model and human microarray analyses indicated a sex difference in neuroinflammatory profile with females showing elevated neuroimmune activation, while males showed a profile consistent with lower neuroimmune activation. These data have implications for the therapeutic interventions that should be examined during mid-life that may differ depending on the sex of the individual (**Brinton**). We also reviewed the literature on how hypertension and cardiovascular disease are key risk factors for both brain function and cognitive aging. We contend that we must first understand the mechanisms common to the converging risk factors in hypertension and age-related cognitive impairment – which includes brain inflammation. Once the risk factors for a given individual are identified and understood, then the design of person-specific therapies to optimize brain health can be implemented (**Hay, Barnes, Huentelman, Brinton, Ryan**).

Finding genetic factors that are protective against the risk for Alzheimer's disease may be an important clue to understanding brain and cognitive aging. It is known that each additional copy of the apolipoprotein E4 (APOE4) allele is associated with a higher risk of Alzheimer's dementia, but it

was not known whether APOE2 homozygotes have a particularly low risk. They found that APOE2 was associated with a low Alzheimer's dementia odds ratio compared to APOE2/3, 3/3 and exceptionally low compared to APOE4/4. Understanding how the APOE 2 allele is protective, may provide important clues to disease prevention and cognitive health (**Reiman, Huentelman**).

Most important scientific achievement this year

This is a particularly difficult question to answer, considering all the high quality work on memory and aging that was published in 2020 from faculty in the Arizona EMBI. Furthermore, the Director may have a 'different favorite' finding than would be chosen by her Associate Director – and other Affiliate Faculty may each have their own opinion on which discovery was 'the most important' in their mind during the year 2020. Therefore, I will reframe this question to the following and will answer it: *What were the important achievements made this year with respect to facilitating high levels of productivity and discovery in the future*?

I have two examples from this year: The first is that I am the PI on a submission of a new RO1 that aims to understand the basis of brain and cognitive resilience that received an extremely good priority score in 2020, and will likely be approved by NIA Council February 2021. I am very excited about the potential findings that will arise from the experiments proposed in this 5 year grant that range from examining brains from human cohorts with exceptional and normative cognitive aging as well as individuals with Alzheimer's disease, tissue culture approaches, and rodent models. A second significant achievement was to have resubmitted for the September 25, 2020 deadline the U19 grant to NIA entitled Precision Aging Network: Closing the Gap between Cognitive Healthspan and Human Lifespan – a 1282 page document. I am excited that many faculty in the Miami EMBI are participating in this effort with EMBI faculty in Arizona, and am grateful that the MBRF gave additional support to Miami for collection of pilot data that definitely strengthened our resubmission. This grant will be reviewed at the end of February 2021. As PI, I can say that it is a beautiful document (but of course I may be biased) – we will know soon whether our reviewers agree.

Publications in peer-reviewed journals

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Publications (other)

Andrews-Hanna J, Christoff K, and **O'Connor** MF. (in press) Dynamic regulation of internal experience. In: R Lane, L Ryan, and L Nadel (Eds.). The Neuroscience of Enduring Change: The Neural Basis of Talk Therapies. New York, NY: Oxford University Press U.S.A, pp 89-191.

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Maresh, E.L. and **Andrews-Hanna, J.R.** (in press) Putting the "me" in "mentalizing": Constructs describing the interplay between self and other with implications for social anxiety disorder. In M. Gilead & K. Ochsner (Eds)., The Neural Basis of Mentalizing. New York, NY: Springer Press.

Raffaelli, Q., Wilcox, R. and **Andrews-Hanna, J.R.** (2020) The Neuroscience of Imaginative Thought: An Integrative Framework. In A. Abraham (Ed.), The Cambridge Handbook of Imagination. Cambridge, U.K.: Cambridge University Press.

Presentations at scientific meetings and public events

Alexander, GE. Exercise, cognition, and brain health in aging and Alzheimer's Risk. Arizona Alzheimer's Consortium Retreat, Lake Havasu, AZ. January 2020.

Andrews-Hanna, J. The Changing Landscape of Everyday Autobiographical Thought: Relevance to Aging and Alzheimer's Risk. Arizona Alzheimer's Consortium Retreat, Lake Havasu, AZ. January 2020.

Barnes, C.A. Aging, Memory, and the Brain. Tulane Brain Institute Distinguished Lecture, Tulane University, New Orleans, LA, January 2020. (Invited)

Grilli, M.D. (January 2020). The relationship between memory and photography. LIGHT event at the Center for Creative Photography, University of Arizona, Tucson, AZ, January 2020.

Barnes, C.A. Memory and the Aging Brain, 11th Annual Emerging Scientist Symposium, University of California, Irvine, CA, February 2020 (Invited Keynote Address)

Mehl, M. R., Danvers, A., Reyes, R., Towards automatic assessment of daily social context: Our journey trying to automate conversation detection in naturalistic ambient audio. New Media and Technology Pre-Conference of the Annual Conference of the Society for Personality and Social Psychology, New Orleans, LA, February 2020 (Invited).

Wank, A.A., Robertson, A., **Rapcsak**, S.Z. and **Grilli**, M.D. Impaired personal trait knowledge in a case of medial temporal lobe amnesia. International Neuropsychological Society Conference, Denver, CO, February 2020. (Poster)

Chou, Y.-H., TMS to Enhance Cognitive Function in Cancer Patients. Cancer Imaging Program Meeting, University of Arizona, Tucson, AZ. May 2020.

Ekstrom, A.D. How do we represent space, Memory Group, Univ. California @ Davis, May 2020 (invited speaker, zoom)

Ekstrom, A.D. Human spatial navigation and episodic memory: Inspiration and divergence from rodent models, University of Magdeburg, June 2020 (invited speaker, zoom)

Alexander, GE. Taking a look at the aging brain: Effects of lifestyle and health risk factors. Invited virtual talk for APA election to Fellow, Div. 20, Adult Development and Aging. Washington, DC. August 2020.

Andrews-Hanna, J. The Imaginative Brain: A Glimpse into the Neuroscience of Imagination and Creativity, Tucson Hard-Science Science Fiction Group, Tucson, AZ, August 2020 (Invited Speaker, Zoom)

Cowen, S.A. The Plastic Hippocampus: Shifting Place Fields, Memory Consolidation, and Aging, University of Nevada, Las Vegas, NV, September 2020. (Invited Speaker, zoom)

Grilli, M.D., Conceptual and contextual remembering: Insights from neuropsychological studies. Context and Episodic Memory Symposium, University of Pennsylvania (Invited discussant, virtual meeting)

Ekstrom, A.D. Immersive virtual reality and its potential applications in clinical science, University of Arizona College of Medicine, Phoenix, October 2020 (invited speaker, zoom)

Grilli, M.D., Autobiographical memory, aging, and Alzheimer's disease risk, Neuropsychology and Neuroimaging Lecture Series. VA Boston Healthcare System, Boston, MA. October 2020 (Invited, virtual meeting)

Andrews-Hanna, J. The Universe Within: A Window into Wandering and Sticky Minds University of Colorado Boulder Cognitive Seminar Series, Boulder, CO. November 2020 (Invited Speaker, Zoom)

Grilli, M.D., The sounds of healthy aging. Gerontological Society of America Annual Meeting, November 2020 (discussant, virtual meeting)

Awards

Gene Alexander, Ph.D., Elected Fellow, American Psychological Association Division 20, Adult Development and Aging .

Robert Brinton-Diaz, Ph.D., Appointed Regents Professor, University of Arizona, Tucson, AZ.

Lynn Nadel, Ph.D., Distinguished Scientific Contribution Award, American Psychological Association (APA), 2020.

Faculty

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 Emerita, 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 Emeritus, Psychology, University of Arizona (Emeritus)
- 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

(Select biographical sketches included in following pages)

- 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. Huentelman, 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, andBIO5 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. 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

Biographical Sketch

Geoffrey Lawrence Ahern, M.D., Ph.D.
Professor, Neurology, Psychology, and Psychiatry

Education/Training

Institution & Location	Degree	Year(S)	Field of Study
SUNY, Purchase College	B.A.	1976	Psychology
Yale University, New Haven	M.S.	1978	Psychology
Yale University, New Haven	Ph.D.	1981	Psychology
Yale University, New Haven	M.D.	1984	Medicine
Waterbury Hospital, Waterbury	Intern	1984 – 1985	Medicine
Boston University, Boston	Resident	1985 – 1988	Neurology
Beth Israel Hospital, Boston	Fellow	1988 – 1990	Behavioral Neurology

Personal Statement

I am a professor of neurology, psychology, and psychiatry at the University of Arizona College of Medicine. I also have an appointment as professor in the Evelyn F. McKnight Brain Institute at the University of Arizona and hold the Bruce and Lorraine Cumming Endowed Chair in Alzheimer's Research. I am a board-certified neurologist with subspecialty board certification in behavioral neurology and neuropsychiatry. Over the past 25 years, I have served as principal investigator or sub-investigator in more than 45 clinical trials in Alzheimer's disease, including those from the pharmaceutical industry as well as the Alzheimer's Disease Cooperative Study (ADCS). I am the director of the University of Arizona clinical arm of the Arizona Alzheimer's Disease Core Center. For the Brain Imaging and Fluid Biomarkers Core, I provide oversight in the acquisition of CSF and blood samples at the University of Arizona.

1. Beach TG, Adler CH, Sue SI, Serrano G, Shill HA, Walker DG, Lue LF, Roher AE, Dugger BN, Maarouf C, Birdsill AC, Intorcia A, Saxon-Labelle M, Pullen J, Scroggins A, Filon J, Scott S, Hoffman B, Garcia A, Caviness JN, Hentz JG, Driver-Dunckley E, Jacobson SA, Davis KJ, Belden CM, Long KE, Malek-Ahmadi M, Powell JJ, Gale LD, Nicholson LR, Caselli RJ, Woodruff BK, Rapcsak SZ, Ahern GL, ShiJ, Burke AD, Reiman EM, and Sabbagh MN. (2015) Arizona study of aging and neurodegenerative disorders and brain and body donation program. Neuropathology, 35:354-389.
2. Filon J, Intorcia A, Sue LI, Vazquez Arreola E, Wilson J, Davis KJ, Sabbagh MN, Belden CM, Caselli RJ, Adler CH, Woodruff BK, Rapcsak SZ, Ahern GL, Burke AD, Jacobson SA, Shill HA, Driver-Dunckley E, Chen K, Reiman EM, Beach TG, and Serrano G. (2016) Gender differences in Alzheimer's disease: Brain atrophy, histopathology burden, and cognition. Journal of Neuropathology and Experimental Neurology, 75:748-754.

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

Honors and Awards

1994	Cited in S Naifeh and GW Smith (eds.) The Best Doctors in America	1994 – 1995
1996	Cited in S Naifeh and GW Smith (eds.) The Best Doctors in America, Pacific Region	1996 – 1997
1998	Cited in S Naifeh and GW Smith (eds.) The Best Doctors in America	1998 – 1999
2003	Cited in S Naifeh and GW Smith (eds.) The Best Doctors in America	2003 – 2004
2005	Cited in S Naifeh and GW Smith (eds.) The Best Doctors in America	2005 – 2006
2007	Cited in S Naifeh and GW Smith (eds.) The Best Doctors in America	2007 – 2008
2009	Cited in S Naifeh and GW Smith (eds.) The Best Doctors in America	2009 – 2010
2010	Cited in S Naifeh and GW Smith (eds.) The Best Doctors in America	2011 – 2012
2013	Cited in S Naifeh and GW Smith (eds.) The Best Doctors in America	2013
2014	Cited in S Naifeh and GW Smith (eds.) The Best Doctors in America	2014
2015	Cited in S Naifeh and GW Smith (eds.) The Best Doctors in America	2015 – 2016

Contribution to Science

Paraneoplastic syndromes are entities in which the body produces an antibody against a malignancy, which occasionally reacts against tissues and the brain, leading to a number of characteristic syndromes. During my fellowship, I came upon a patient with intractable epilepsy and severe memory difficulties. Ultimately, he was found to have testicular cancer. In collaboration with the group at Memorial Sloan-Kettering in New York, we were able to identify and characterize a new paraneoplastic antibody, anti-Ta (named after the first two initials of the patient). This antibody was ultimately found to be one of the causes of limbic encephalitis. The field has clearly grown over the past 25 years, and now the anti-Ta antibody has been characterized as coming from the family of the anti-Ma1/ Ma2 paraneoplastic antibody class.

1. Ahern GL, O'Connor M, Dalmau J, Coleman A, Posner JB, Schomer DL, Herzog AG, Kolb DA, Mesulam MM. (1994) Paraneoplastic temporal lobe epilepsy with testicular neoplasm and atypical amnesia. Neurology, 44:1270-1274.
2. O'Connor M, Sieggreen MA, Ahern GL, Schomer D, Mesulam MM. (1997) Accelerated forgetting in association with temporal lobe epilepsy and paraneoplastic encephalitis. Brain and Cognition,35:71-84.

In graduate school, I developed an interest in cerebral lateralization, particularly for emotional processes. Without going into a great deal of detail about the evidence for same, the general principal that appears to have emerged over the past three decades is that while the right hemisphere seems to be more involved in handling emotional issues in general, the left hemisphere tends to be a bit more 'positive' in terms of the emotional valence it handles and the right hemisphere tends to be more 'negative.' Over the years, I have investigated this phenomenon with such wide-ranging techniques as lateral eye movements, facial EMG, EEG spectral analysis, FDG PET scanning, and unilateral hemispheric inactivation produced in the Wada test (the latter studies are considered below under the Wada test).

1. Ahern GL and Schwartz GE. (1979) Differential lateralization for positive versus negative emotion. Neuropsychologia, 17:693-698.
2. Schwartz GE, Ahern GL, and Brown SL. (1979) Lateralized facial muscle response to positive and negative emotional stimuli. Psychophysiology, 16:561-571.
3. Ahern GL and Schwartz GE. (1985) Differential lateralization for positive versus negative emotion in the human brain: EEG spectral analysis. Neuropsychologia, 23:745-755.
4. Lane RD, Reiman EM, Ahern GL, Schwartz GE, and Davidson RJ. (1997) Neuroanatomical correlates of happiness, sadness, and disgust. American Journal of Psychiatry, 154:926-933.

The intracarotid amobarbital test, otherwise known as the Wada test (after its inventor, Juhn Wada), is a technique in which each cerebral hemisphere is transient and activated via the use of sodium amytal injected into the ipsilateral carotid artery. This test is done to determine language dominance, as well as the potential for memory dysfunction, in patients in whom unilateral temporal lobectomy is being considered for intractable epilepsy. Utilizing this technique, I was able to make a number of observations regarding how each cerebral hemisphere handles positive and negative emotion. This includes not only self-report, but the ability to perceive emotion in the faces of others.

1. Ahern GL, Schomer DL, Kleefield J, Blume H, Cosgrove GR, Weintraub S, and Mesulam MM. (1991)Right hemisphere advantage for evaluating emotional facial expressions. Cortex, 27:193-202.
2. Ahern GL, Herring AM, Tackenberg JN, Schwartz GE, Seeger JF, Labiner DM, Weinand ME, and Oommen KJ. (1994) Affective self-report during the intracarotid sodium amobarbital test. Journal of Clinical and Experimental Neuropsychology, 16:372-376.

I was also able to show that the two hemispheres are different in their ability to control heart rate and heart rate variability.

3. Ahern GL, Sollers J, Lane RD, Labiner DM, Herring AM, Weinand ME, Hutzler R, and Thayer J.(2001) Heart rate and heart rate variability changes in the intracarotid sodium amobarbital (ISA)test. Epilepsia, 42, 912-921.

Finally, using EEG spectral analysis, I was able to quantify the time course and spatial extent of hemispheric inactivation during the Wada test.

4. Ahern GL, Labiner DM, Hutzler R, Osburn C, Talwar D, Herring AM, Tackenberg JN, Weinand ME, and Oommen KJ. (1994) Quantitative analysis of the EEG in the intracarotid amobarbital test: I. Amplitude analysis. EEG & Clinical Neurophysiology, 91:21-32.

Hemispatial neglect is a well-known neurological phenomenon that is usually associated with lesions in the right hemisphere. Having trained under Dr. Marsel Mesulam, I was exposed to this phenomenon early in my career. In association with my colleagues, we published a number of reports that elucidated this phenomenon. For instance, we were able to show (in the same patient) that posterior lesions in the right hemisphere led to a greater involvement of the sensory aspects of

neglect, while anterior lesions in the right hemisphere led to greater involvement in the motoric intentional aspects of neglect.

1. Daffner KR, Ahern GL, Weintraub SW, and Mesulam MM. (1990) Dissociated neglect behavior following sequential strokes in the right hemisphere. Annals of Neurology, 28:97-101.

We were also able to demonstrate that right hemispatial neglect, which is usually a transient phenomenon, might be more long lasting if there were to be bilateral involvement of attentional systems in the brain.

2. Weintraub SW, Daffner, KR, Ahern GL, Price BH, and Mesulam MM. (1996) Right hemispatial neglect and bilateral cerebral lesions. Journal of Neurology, Neurosurgery, and Psychiatry, 60:342-344.

In a later study, I was able to show that neglect was not an all-or-none phenomenon, but that it could vary in severity depending on the degree of hemispheric dysfunction. This study was performed in patients undergoing the Wada test. During maximal inactivation of the right hemisphere, left hemispatial neglect was quite severe. But as the Amytal wore off, the neglect became profound and this phenomenon correlated perfectly with other measures of right hemispheric function, including the degree of EEG slowing.

3. Ahern GL, Herring AM, Labiner DM, and Weinand ME. (1998) Quantification of hemispatial neglect during the intracarotid amytal procedure. Journal of the International Neuropsychological Society,4:1-7.

Complete list of published work in My Bibliography

http://www.ncbi.nlm.nih.gov/sites/myncbi/geoffrey.ahern.1/bibliography/48871570/public/?sort=date&direction=ascending

Research Support

2018-2023 Alzheimer's Disease Core Center – UAHSC Clinical Core. Protocol # P30 AG19610-01, National Institute on Aging. Total grant: $51,686 / year; Ahern - $15,755 / year; 10% salary support, 10% effort. (overall PI: E. Reiman, MD).

2018-2024 A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of CNP520 in Participants at Risk for the Onset of Clinical Symptoms of Alzheimer's Disease. (Generation 2) Protocol # CCNP520A2202J. Novartis. Total grant: $95,456 / patient. 2% salary support, 2% effort.

Biographical Sketch

Gene Alexander, Ph.D.
Professor, Psychology and Psychiatry

Education/Training

Institution & Location	Degree	Year(S)	Field of Study
Pomona College, Claremont, CA	B.A.	1983	Psychology
Loyola University of Chicago, Chicago, IL	M.A.	1987	Clinical Psychology
Loyola University of Chicago, Chicago, IL	Ph.D.	1992	Clinical Psychology

Personal Statement

I am a professor in the Departments of Psychology and Psychiatry, the Evelyn F. McKnight Brain Institute, the BIO5 Institute, and the Neuroscience and Physiological Sciences Graduate Programs at the University of Arizona. I also am director of the Brain Imaging, Behavior and Aging Lab; a member of the Internal Scientific Advisory Committee for the state-supported Arizona Alzheimer's Consortium; a member of the ADCC Executive Committee, and director of the Brain Imaging and Fluid Biomarkers Core for the NIA Arizona Alzheimer's Center. Prior to coming to Arizona, I was chief of the Neuropsychology Unit in the Laboratory of Neurosciences in the Intramural Research Program at the NIA. I served as a member of the NIA Neuroscience of Aging Study Section and am a fellow of the Association for Psychological Sciences and the American Psychological Associations Society for Clinical Neuropsychology. My research is supported by the NIA, the State of Arizona and Arizona Department of Health Services, and the McKnight Brain Research Foundation. I have over 25 years of experience as a neuroimaging researcher on the effects of aging and risk factors for age-related neurodegenerative disease. I use structural and functional magnetic resonance imaging (MRI) and positron emission tomography (PET) 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.

1. Kern KC, Wright CB, Bergfield KL, Fitzhugh M, Chen K, Moeller JR, Nabizadeh N, Elkind MSV, Sacco RL, Stern Y, DeCarli C, and Alexander GE. (2017) Blood pressure control in aging predicts cerebrala trophy related to small-vessel white matter lesions. Frontiers in Aging Neuroscience, 9, 132.
2. Cohen RA and Alexander GE. (in press) Using the Telephone Interview for Cognitive Status and Telephone Montreal Cognitive Assessment for evaluating vascular cognitive impairment: Promising call or put on hold? Stroke. (Invited editorial)
3. Alexander GE. (2017) An emerging role for imaging white matter in the preclinical risk for Alzheimer disease: Linking ß-amyloid to myelin. JAMA Neurology, 74(1), 17-19. (Invited editorial)
4. Raichlen DA and Alexander GE. (2017) Adaptive Capacity: An evolutionary neuroscience model linking exercise, cognition, and brain health. Trends in Neurosciences, 40(7), 408-421.

Research and Professional Experience

1988 – 1989	Clinical Psychology Intern, Department of Psychiatry & Behavioral Science, University of Washington, Seattle
1989 – 1992	Research Fellow, Dept. of Brain Imaging, NYSPI and Columbia University, NY
1991 – 1993	Research Scientist I, Dept. of Brain Imaging, NYSPI and Columbia University, NY
1993 – 1999	Staff Fellow to Sr. Staff Fellow, Laboratory of Neurosciences, NIA, NIH, Bethesda

1993 – 1999	Chief, Neuropsychology Unit, Laboratory of Neurosciences, NIA, NIH, Bethesda
1999 – 2003	Research Assoc Professor, Dept. of Psychology, Arizona State University, Tempe
2001 – 2009	Director, Data Management and Statistics Program/Core, Arizona ADC
2003 – 2007	Professor, Psychology Dept., Arizona State University, Tempe
2007 – Present	Professor, Psychology Dept & Evelyn F McKnight Brain Institute, University of Arizona, Tucson
2007 – Present	Director, Brain Imaging, Behavior & Aging Lab, Psychology Dept., University of Arizona, Tucson
2007 – Present	Professor, Neuroscience Graduate Interdisciplinary Program, University of Arizona, Tucson
2011 – Present	Professor, Physiological Sciences Graduate Interdisciplinary Program, University of Arizona
2017 – Present	Member, BIO5 Institute, University of Arizona, Tucson
2017 – Present	Professor, Department of Psychiatry, College of Medicine Tucson, University of Arizona

Honors and Awards

1996 – 1999	Staff Recognition Awards (annual), Laboratory of Neurosciences, IRP, NIA, NIH
2011 – Present	Fellow, Association for Psychological Science
2012 – Present	Co-Director, Annual Conference on Successful Aging, University of Arizona
2017 – Present	Fellow, American Psychological Association Division 40, Society for Clinical Neuropsychology
2019 – Present	Fellow, American Psychological Association Division 20, Adult Development and Aging

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.

1. Stern Y, Alexander GE, Prohovnik I, and Mayeux R. (1992) Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. Ann Neurol, 32, 371-375.
2. Alexander GE, Prohovnik I, Stern Y, and Mayeux R. (1994) WAIS-R subtest profile and cortical perfusion in Alzheimer's disease. Brain and Cognition, 24:24-43.
3. Alexander GE, Furey M, Grady CL, Pietrini P, Brady D, Mentis MJ, and Schapiro MB. (1997)Association of premorbid function with cerebral metabolism in Alzheimer disease: Implications for the cognitive reserve hypothesis. Am J Psychiatry, 154:165-172.
4. Alexander GE, Chen K, Pietrini P, Rapoport SI, and Reiman EM. (2002) Longitudinal PET evaluation of cerebral metabolic decline in dementia: A potential outcome measure in Alzheimer's disease treatment studies. Am J Psychiatry, 159:738-745.

Brain Imaging and Cognitive Effects of Healthy Aging. In more recent years, my research program has sought 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.

1. Alexander GE, Chen K, Merkley TL, Reiman EM, Caselli RJ, Aschenbrenner M, Santerre-Lemmon L, Lewis DJ, Pietrini P, Teipel SJ, Hampel H, Rapoport SI, and Moeller JR. (2006) Regional Network of MRI Gray Matter Volume in Healthy Aging. NeuroReport, 17:951-956.
2. Bergfield KL, Hanson KD, Chen K, Teipel SJ, Hampel H, Rapoport SI; Moeller JR, and Alexander GE.(2010) Age-related networks of regional covariance in MRI gray matter: Reproducible multivariate patterns in healthy aging. NeuroImage, 49:1750-1759.
3. Alexander GE, Ryan L, Bowers D, Foster TC, Bizon JL, Geldmacher DS, and Glisky EL. (2012) Characterizing Cognitive Aging in Humans with Links to Animal Models. Frontiers in Aging Neuroscience, 4:21.
4. Ryan L, Cardoza JA, Barense MD, Kawa KH, Wallentin-Flores J, Arnold WT, and Alexander GE. (2012) Age-related impairment in a complex object discrimination task that engages perirhinal cortex. Hippocampus, 22:1978-1789.

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 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.

1. Alexander GE and Moeller JR. (1994) Application of the Scaled Subprofile Model to functional imaging in neuropsychiatric disorders: A principal component approach to modeling regional patterns of brain function in disease. Human Brain Mapping, 2:79-94.
2. Chen K, Reiman EM, Zhongdan H, Caselli RJ, Bandy D, and Alexander GE. (2009) Linking functional and structural brain images with multivariate network analyses: A novel application of the partial east square method. Neuroimage, 47:602-610.
3. Smith JF, Chen K, Johnson SC, Morrone-Strupinsky J, Reiman EM, Nelson A, Moeller JR, and Alexander GE. (2006) Network analysis of single-subject fMRI during finger opposition task. Neuroimage, 32:325-332.
4. Alexander GE, Chen K, Aschenbrenner M, Merkley TL, Santerre-Lemmon LE, Shamy JL, Skaggs WE, Buonocore MH, Rapp PR, and Barnes CA. (2008) Age-related regional network of magnetic resonance imaging gray matter in the rhesus macaque. Journal of Neuroscience, 28:2710-2718.

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

APOε risk and pathology confirmed dementia. Examples of my collaborative publications are illustrated below.

1. Silverman DHS, Small GW, Chang CY, Lu CS, Kung de Aburto MA, Chen W, Czernin J, Rapoport SI, Pietrini P, Alexander GE, Schapiro MB, Jagust WJ, Hoffman JM, Welsh-Bohmer KA, Alavi A, Clark CM, Salmon E, de Leon MJ, Mielke R, Cummings JL, Kowell AP, Gambhir SS, Hoh CK, and Phelps ME. (2001) Neuroimaging in evaluation of dementia: Regional brain metabolism and long-term outcome. JAMA, 286:2120-2127.
2. Jack CR Jr, Bernstein MA, Fox NC, Thompson P, Alexander G, Harvey D, Borowski B, Britson PJ, Whitwell J, Ward C, Dale AM, Felmlee JP, Gunter JL, Hill DL, Killiany R, Schuff N, Fox-Bosetti S, Lin C, Studholme C, DeCarli CS, Krueger G, Ward HA, Metzger GJ, Scott KT, Mallozzi R, Blezek D, Levy J, Debbins JP, Fleisher AS, Albert M, Green R, Bartzokis G, Glover G, Mugler J, and Weiner MW. (2008)The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. J Magnetic Resonance Imaging, 27:685-91.
3. Reiman EM, Chen K, Liu X, Bandy D, Yu M, Lee W, Ayutyanont N, Keppler J, Reeder SA, Langbaum JB, Alexander GE, Klunk WE, Mathis CA, Price JC, Aizenstein HJ, DeKosky ST, and Caselli RJ.(2009) Fibrillar amyloid-beta burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. Proceedings of the National Academy of Sciences USA, 106:6820-6825.
4. Leow AD, Yanovsky I, Parikshak N, Hua X, Lee S, Toga AW, Jack CR, Bernstein MA, Britson PJ, Gunter JL, Ward CP, Borowski B, Shaw LM, Trojanowski JQ, Fleisher AS, Harvey D, Kornak J, Schuff N, Alexander GE, Weiner MW, Thompson PM; for the ADNI study. (2009) Alzheimer's Disease Neuroimaging Initiative: A one-year follow up study using tensor-based morphometry correlating degenerative rates, biomarkers and cognition. Neuroimage, 45:645-655.

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 and the risk for Alzheimer's disease. 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 APOε ε4 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.

1. Strassburger TL, Lee HC, Daly E, Szczepanik J, Krasuski JS, Mentis MJ, Salerno JA, DeCarli C, Schapiro MB, and Alexander GE. (1997) Interactive effects of age and hypertension on structural brain volumes. Stroke, 28:1410-1417.
2. Alexander GE, Bergfield KL, Chen K, Reiman EM, Hanson KD, Lin L, Bandy D, Caselli RJ, and Moeller JR. (2012) Gray matter network associated with genetic risk for Alzheimer's disease in young to early middle-aged adults. Neurobiology of Aging, 33:2723-2732.
3. Caselli RJ, Reiman EM, Osborne D, Hentz JG, Baxter LC, Hernandez JL, and Alexander GE. (2004)Longitudinal changes in cognition and behavior in asymptomatic carriers of the APOE ε4 allele. Neurology, 62:1990-1995.
4. Raichlen DA and Alexander GE. (2014) Exercise, APOE genotype, and the evolution of the human lifespan. Trends in Neurosciences, 37:247-255.

Complete list of published work in My Bibliography

http://www.ncbi.nlm.nih.gov/sites/myncbi/gene.alexander.1/bibliography/41140485/public/?sort=date&direction=ascending [Google Scholar H-Index = 76]

Research Support

NIA R01 AG064587 Alexander, Bowers, Woods (MPIs) 8/01/19 – 4/30/24
Revitalizing Cognition in Older Adults at Risk for Alzheimer's Disease with Near-Infrared Photobiomodulation
The goal of this project is to determine whether NIR stimulation has potential for enhancing cognition in cognitively normal but "at risk" individuals for Alzheimer's disease.
Role on project: Dr. Alexander is MPI.

NIA RO1 AG049464 Alexander, Barnes, Coleman (MPIs) 8/1/14 – 3/31/21
Epigenetic, Neuroimaging and Behavioral Effects of Hypertension in the Aging Brain
To determine epigenetic changes induced by hypertension in brain regions important for cognition.
Role on Project: Contact PI

NIA 3P30AG019610-19S1 Alexander (Core Leader), Reiman (PI) 9/15/18 – 8/31/21
Brain Imaging and Fluid Biomarkers Core
The goal of this supplement grant is to establish a new core to support brain imaging and biomarker research as part of the Arizona Alzheimer's Disease Center.
Role on Project: Core Leader

NIA R01 AG054077 (PI UA Sub: Alexander; MPIs: Woods, Cohen, Marsiske) 9/1/16 – 4/30/21
Augmenting Cognitive Training in Older Adults
The goals of this study are to learn ways to augment cognitive training outcomes in the elderly and to advance understanding of the underlying mechanisms associated with enhanced cognition during training.
Role on Project: PI of the UA subcontract.

NIA R56 AG067200 Alexander/Raichlen (MPIs) 9/15/20 - 8/31/21
Physical Activity Predictors of Cognitive and Brain Health in the Risk for Alzheimer's Disease
The goal is to investigate how differences in physical activity metrics influence Alzheimer's disease risk.
Role on Project: MPI.

McKnight Brain Research Foundation Bowers, Alexander, Woods (MPIs) 5/1/18 – 4/30/21
A Pilot Intervention with Near Infrared Stimulation: Revitalizing Cognition in Older Adults
To evaluate the potential of near infrared light as an intervention for healthy cognitive aging.
Role on Project: PI

McKnight Brain Research Foundation Alexander, Cohen, Levin, Wadley (MPIs) 9/1/15 – 12/31/22
McKnight Inter-Institutional Cognitive Aging Assessment Core
The goal is to apply clinical and cognitive measures for multi-institutional brain aging research.
Role on Project: PI

McKnight Brain Research Foundation Alexander, Cohen, Visscher, Wright (MPIs) 1/1/15-12/31/22
McKnight Inter-institutional Neuroimaging Core and Brain Aging Registry
The goal to establish neuroimaging acquisition and a multi-site brain aging registry to study brain aging.
Role on Project: MPI

McKnight Brain Research Foundation Williamson (PI) 10/1/19-9/30/21
Transcutaneous Vagal Nerve Stimulation and Cognitive Training to Enhance Cognitive Performance in Healthy Older Adults
The goal of this project is to determine whether tVNS augments cognitive training associated improvements in cognition.
Role on Project: PI of the UA subcontract.

AZ Alzheimer's Consortium (ADHS) Alexander (PI) 7/1/11 – 6/30/21
Modifiable Health & Lifestyle Factors in Brain Aging and Alzheimer's Disease
The goal of this project is to investigate cerebrovascular risk factors for brain aging and cognitive health in humans and animal models.
Role on Project: PI

NIA 3P30 AG019610 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 for the Data Management and Statistics Core.

NIA R03 AG055020 Su (PI) 7/1/17 – 4/30/20
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

NIA R01 AG061888 Wilson (PI) 9/1/19-8/31/24
Evaluating the Neurocomputational Mechanisms of Explore-Exploit Decision Making in Older Adults
The goal of this project is to develop and test a neurocomputational model that describes explore-exploit decision making throughout the lifespan.
Role on Project: Co-Investigator

NIA R01 AG062543 Chou (PI) 5/1/20--04/31/25
Enhancement of Hippocampal Plasticity Using Repetitive Transcranial Magnetic Stimulation
The goal is to develop a hippocampal rTMS protocol and evaluate its effects in older adults at risk for AD.
Role on Project: Co-Investigator.

NIA U19 AG057377-03S1 McLean (sub PI; Promislow (PI)) 7/1/20--6/30/21
Development of Cognitive and Physical Activity Biomarkers for a Companion Dog Model of AD
The goal is to develop cognitive tests and actigraphy for a companion dog model of Alzheimer's disease.
Role on Project: Site Co-Investigator.

NIA R01AG054077-05S2 Woods/Cohen/Marsiske (MPIs) 5/1/20-04/30/21
Augmenting Cognitive Training in Older Adults: the ACT COVID Ancillary Study
The purpose is to investigate the effects of social isolation from the COVID-19 pandemic in older adults.
Role on Project: PI of the UA Subcontract.

Biographical Sketch

Jessica Andrews-Hanna, Ph.D.
Assistant Professor, Psychology

Education/Training

Institution & Location	Degree	Year(S)	Field of Study
Duke University, Durham, NC	B.A.	2003	Biology, Psychology
Washington University, St. Louis, MO	M.A.	2006	Neuroscience
Harvard University, Cambridge, MA	Ph.D.	2009	Psychology
University of Colorado, Boulder, CO	Postdoc	2014	Cognitive Neuroscience

Personal Statement

My research seeks insight into the psychological and neural mechanisms underlying internally-guided thought and its top-down regulation. Related to this central theme, I am passionate about exploring such thoughts across the lifespan, and in a variety of neurodegenerative diseases and mental health conditions, with a goal of developing interventions to help individuals harness the beneficial aspects of internally-guided cognition and live happier, healthier lives. I currently direct the Neuroscience of Emotion & Thought (NET) Laboratory at the University of Arizona, where I am an Assistant Professor in the Department of Psychology and the Cognitive Science Program. My lab employs a multi-method approach, combining methods spanning task-related functional MRI, resting state functional connectivity MRI (RSFC) / graph theory, fMRI meta-analyses, and behavioral assessments in the lab and daily life. For example, to quantify emotion and thought in everyday life, my team recently developed Mind Window, a cross-platform ecological momentary assessment app extending our previous app, Where's My Mind?. My theoretical expertise in cognitive, social neuroscience, and affective neuroscience, combined with my strong methodological background in neuroimaging and ecological momentary assessment make me well positioned to contribute to this project.

1. Andrews-Hanna, J.R., Smallwood, J.S., & Spreng, R.N. (2014). The default network and self-generated thought: Component processes, dynamic control, and clinical relevance. Annals NY Acad Sci (The Year in Cognitive Neuroscience), 1316, 29-52. PMCID: PMC4039623
2. Andrews-Hanna, J.R., Reidler, J., Poulin, R., & Buckner, R.L. (2010). Functional-anatomic fractionation of the default network. Neuron, 65, 550-562. PMCID: PMC2848443
3. Andrews-Hanna, J.R., Snyder A.Z, Vincent J.L., Lustig C., Head D, Fox M.D., Raichlen M.E., & Buckner, R.L. (2007). Evidence for large-scale network disruption in advanced aging. Neuron, 56(5), 924-935. PMCID: PMC2709284
4. Andrews-Hanna, J.R., Grilli, M.D., & Irish, M. (2019, Mar 26). A review and reappraisal of the default network in normal aging and dementia. Oxford Research Encyclopedia of Psychology.

Positions

2017 – Present	Assistant Professor, Department of Psychology; Interdisciplinary Program in Cognitive Science, University of Arizona
2014 – 2016	Research Scientist/Associate, Institute of Cognitive Science, University of Colorado, Boulder
2009 – 2014	Postdoctoral Fellow, Institute of Cognitive Science, University of Colorado, Boulder

Honors

2003	Graduated with Distinction at Duke University
2004 – 2006	Washington U. in St. Louis Cognitive, Computational, and Systems Neuroscience Fellowship
2006	Washington U. in St. Louis Alzheimer's Disease Research Center Travel Fellowship
2007 – 2008	Harvard University Sosland Family Graduate Fellowship Award
2008	Thompson Reuter's Science Watch Award for Fast-Breaking Paper
2009	Harvard Psychology Department Excellence in Teaching Award
2011	NIMH Summer Institute in Cognitive Neuroscience Fellow
2011 – 2014	Ruth L. Kirschstein National Research Service Award (NRSA) Postdoctoral Fellowship
2012	Intermountain Neuroimaging Consortium Pilot Funding Award
2013	Mind & Life Summer Research Institute Fellow
2013	Neuron 25 Year Anniversary: Featured influential paper from 2010
2015	Science of Prospection Award, Templeton Foundation
2016	Neuroimage Editor's Choice Award best paper (2016)
2017	Kavli Foundation / U.S. National Academy of Science Frontiers of Science Fellow
2018	Faculty Appreciation Award, University of Arizona Women's Volleyball Team
2018	Fellow of the Psychonomics Society
2018	Early Investigator Award, Society of Experimental Psychologists
2020	Galileo Circle Curie Award for "Rising Star" in Academic Scholarship, University of Arizona

Contribution to Science

Across a series of studies employing task-related fMRI and fMRI meta-analyses, resting-state functional connectivity, graph theory, and experience sampling methods, my research was the first to demonstrate that the brain's default network is organized into interacting subsystems that support different aspects of internally-guided cognition. These components allow us to retrieve past information and flexibly recombine this information into imagined episodes, reflect upon ours and others' mental states, and guide decision making by computing the affective significance and personal meaning of incoming information. Collectively, this line of work led to a novel neurocognitive model of autobiographical thought as a multi-faceted phenomenon comprising several interacting component processes.

1. Andrews-Hanna JR, Reidler J, Poulin R, and Buckner RL. (2010) Functional-anatomic fractionation of the default network. Neuron, 65:550-562.
2. Andrews-Hanna JR, Smallwood JS, and Spreng RN. (2014) The default network and self-generated thought: Component processes, dynamic control, and clinical relevance. Annals NY Acad Sci – Special Issue: The Year in Cognitive Neuroscience (Invited Review), 1316: 29-52.
3. Andrews-Hanna JR, Smallwood JS, and Spreng RN. (2014) The default network and self-generated thought: Component processes, dynamic control, and clinical relevance. Annals NY Acad Sci – Special Issue: The Year in Cognitive Neuroscience (Invited Review), 1316:29-52.
4. Andrews-Hanna JR, Saxe R, and Yarkoni T. (2014) Contributions of episodic retrieval and mentalizing to autobiographical thought: Evidence from functional neuroimaging, resting-state connectivity, and fMRI meta-analyses. Neuroimage 91:324-335

Since its delineation in the early 2000s, the brain's default network has largely been viewed as a passive, task-negative brain system with minimal contributions to goal-directed cognition. My work is widely recognized for challenging these predominant views, revealing that the default network plays a key role in several active and goal-directed forms of internally-guided cognition spanning autobiographical and imaginative thought, and theory of mind. Some of my more recent work uses dynamic behavioral approaches and dynamic functional connectivity to explore how network interactions between the default network and other large-scale brain networks unfold and change over time.

1. Andrews-Hanna JR. (2012) The brain's default network and its adaptive role in internal mentation. The Neuroscientist, 18:251-70.
2. Andrews-Hanna JR, Saxe R, and Yarkoni T. (2014) Contributions of episodic retrieval and mentalizing to autobiographical thought: Evidence from functional neuroimaging, resting-state connectivity, and fMRI meta-analyses. Neuroimage, 91:324-335.
3. Zabelina DL and Andrews-Hanna JR. (2016) Dynamic network interactions supporting internally-oriented cognition. Current Opinion Neurobiology, 40:86-93.
4. Dixon M, Andrews-Hanna JR, Spreng RN, Irving ZC, Mills C, Girn M, and Christoff K. (2017) Interactions between the default network and dorsal attention network vary across default subsystems, time, and cognitive states. Neuroimage, 147:632-649.

A large portion of my research involves developing new methods to examine autobiographical thought, including its spontaneous emergence. My work in this domain has revealed that spontaneous thought is a frequent, heterogeneous, and often adaptive phenomenon that can be quantified through rigorous, ecologically-valid experimental investigation. My 2010 paper in the Journal of Neurophysiology was the first to link individual differences in resting state connectivity within the default network to spontaneous autobiographical thoughts. In later work, I developed a novel Autobiographical Thought Sampling Task, and used clustering approaches to distill autobiographical thoughts into major content dimensions that explain nearly 50% of the variance in traits relevant to mental health. My team also developed a smartphone application called MindMirror to assess the content, correlates and consequences of spontaneous and deliberate autobiographical thoughts as they emerge in real-world settings.

1. Andrews-Hanna JR, Reidler J, Huan, C, and Buckner RL. (2010) Evidence for the default network's role in spontaneous cognition. Journal of Neurophysiology, 104:322-335.
2. Christoff K, Irving Z, Fox KC, Spreng RN, and Andrews-Hanna JR. (2016) Mind-wandering as spontaneous thought: A dynamic framework. Nature Reviews Neuroscience, 17:718-731.
3. Smallwood J and Andrews-Hanna JR. (2013) Not all minds that wander are lost: The importance of a balanced perspective on the mind-wandering state. Frontiers in Psychology – Special Issue on Mind-Wandering, 4:441.
4. Zabelina D, Friedman NP, and Andrews-Hanna JR (2019) Unity and diversity of executive functions in creativity. Consciousness and Cognition, 68:47-56.

Several of my completed and ongoing research projects characterize the nature of internally-guided cognition, and the brain systems that support it, in aging and neurodegenerative disease. For example, my 2007 Neuron article was the first to reveal that normal aging is associated with functional connectivity alterations in default and external attention systems (even in individuals confirmed by PIB-PET to have no known amyloid deposition), and that these alterations relate to individual differences in white matter integrity and cognition. My more recent work has shown that changes in default network connectivity in older adults are accompanied by alterations in the content and frequency of task-unrelated thought, and also extends these questions to Alzheimer's disease, behavioral variant Frontotemporal dementia, Semantic dementia and Parkinson's disease. In

a theoretical review, MPI Grilli and I integrated research in this field into a neurocognitive theory of normal and pathological aging that we aim to test in the proposed work.

1. Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Fox MD, Raichle ME, and Buckner RL (2007) Evidence for large-scale network disruption in advanced aging. Neuron, 56:924-935.
2. Andrews-Hanna, J.R., Grilli, M.D., and Irish, M. (2019) A review and reappraisal of the default network in normal aging and dementia. Oxford Research Encyclopedia of Psychology. doi: 10.1093/acrefore/9780190236557.013.384.
3. Irish M, Goldberg ZL, Alaeddin S, O'Callaghan C, and Andrews-Hanna JR (2019) Age-related changes in the temporal focus and self-referential content of spontaneous cognition during periods of low cognitive demand. Psychological Research, 83(4), 747-760.
4. O'Callaghan C, Shine M, Andrews-Hanna JR., and Irish M (2019) Hippocampal atrophy and intrinsic brain network dysfunction relate to alterations in mind wandering in neurodegeneration. PNAS, 116:3316-3321.

While much of my research provides support for the adaptive functions of autobiographical thought, the experience can also be associated with significant costs, disrupting task performance and hindering psychological well-being. My work reveals that the ability to regulate the *content* of one's thoughts as well as the *occurrence* of self-generated thought based on contextual demands are two important factors that constrain the costs and benefits of self-generated cognition. Of particular interest are several recent and ongoing projects that examine dysfunctional styles of thinking in depression, anxiety, and maladaptive repetitive thought as a transdiagnostic construct. Integrating neuroimaging with behavioral assessments reveals that dysfunctional self-generated thought in depression and anxiety is accompanied by alterations in the function of - and interaction between - default and executive control networks.

1. Andrews-Hanna JR, Kaiser R, Turner A, Reineberg A, Godinez D, and Banich MT (2013) A penny for your thoughts: dimensions of self-generated thought content and relationships with individual differences in emotional well-being. Frontiers in Psychology – Special Issue on Mind-Wandering, 4, 900.
2. Kaiser RH, Andrews-Hanna JR, Wager TD, and Pizzagalli D (2015) Large-scale network dysfunction in Major Depressive Disorder: Meta-analysis of resting-state functional connectivity. JAMA Psychiatry, 72:603-611.
3. Arch JJ, Wilcox R, Ives L., Sroloff A, and Andrews-Hanna JR (2020) Off-task thinking among adults with and without social anxiety disorder: An ecological momentary assessment study. Cognition & Emotion, 19:1-3.
4. Pelletier-Baldelli A, Andrews-Hanna JR, and Mittal V (2017) Resting state connectivity dynamics in individuals at risk for psychosis. Journal of Abnormal Psychology, 127(3):314-325

Complete list of published work in My Bibliography

https://www.ncbi.nlm.nih.gov/myncbi/jessica.andrews-hanna.1/bibliography/public/

Research Support

NIMH R01 MH125414 Andrews-Hanna & Sbarra (MPIs) final NOA pending
Connected Lives - Overcoming the Self through Empathy (CLOSE): A dyadic, multi-method study
Role on Project: Multiple PI

NIA R56 AG068098 Grilli & Andrews-Hanna (MPIs) 09/15/20-08/31/21
Tracking autobiographical thoughts: a smartphone-based approach to the detection of cognitive and neural markers of Alzheimer's disease risk
Role on Project: Multiple PI

Canadian Institutes of Health Research Christoff (PI) 04/01/20-03/31/25
Investigating the dynamics of thought using brain connectivity and experience sampling.
Role: Co-Applicant

NIA R03 AG060271 Grilli: PI 4/15/19-3/31/21
The episodic autobiographical memory hypothesis of preclinical Alzheimer's disease: Developing a new approach for early cognitive detection and measurement of Alzheimer's disease.
Role on Project: Co-Investigator

NIA R56 AG061888 Wilson: PI 9/30/18 – 8/31/20
Evaluating the Neurocomputational Mechanisms of Explore-Exploit Decision Making in Older Adults
Role on Project: Co-Investigator

Univ of Arizona Psychology Pilot Grant Andrews-Hanna, Sbarra: PI 3/18/19 - 3/17/20
Maladaptive repetitive thought and psychopathology: The mediating role of neural dyadic empathy.
Role on Project: PI

AZ Alzheimer's Consortium (ADHS) Andrews-Hanna: PI 7/01/19 - 6/30/20
Uncovering neurocognitive links between Alzheimer's disease and depression in mid-life to early aging
Role on Project: PI

AZ Alzheimer's Consortium (ADHS) Grilli: PI 7/01/19 - 6/30/20
Improving clinical neuropsychological assessment of subtle cognitive decline and mild cognitive impairment
Role on Project: Co-Investigator

NINDS R01 NS109819 Ekstrom (PI) 7/01/20-6/30/25
Precision and binding as two dimensions of medial temporal lobe amnesia
Role on Project: Co-Investigator

Mind & Life Foundation Varela Grant Maresh (PI) 12/20/19-12/19/21
Overcoming the self: A multi-method investigation of trait mindfulness, self-other overlap, and egocentricity in romantic relationships.
Role on Project: Faculty Mentor

AZ Alzheimer's Consortium (ADHS) Andrews-Hanna (PI) 07/01/20-06/30/21
Why is the glass half-full? Sources of the positivity effect in healthy aging and AD risk.
Role on Project: PI

AZ Alzheimer's Consortium (ADHS) Grilli (PI) 07/01/20-06/30/21
Autobiographical memory, future thinking, and neuropsychology in Hispanics
Role on Project: Co-Investigator

NIA R01 AG061888 Wilson (PI) 01/01/20-12/31/24
Evaluating the neurocomputational mechanisms of explore-exploit decision making in older adults
Role on Project: Co-Investigator

Biographical Sketch

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

Education/Training

Institution & Location	Degree	Year(S)	Field of Study
University of California, Riverside, CA	B.A. (Honors)	1971	Psychology
Carleton University, Ottawa, Ontario, Canada	M.A.	1972	Psychology
Carleton University, Ottawa, Ontario, Canada	Ph.D. (Cum laude)	1977	Psychology

Personal Statement

I have been interested in the brain circuits responsible for memory and how these circuits change during aging for more than four decades. I have 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 and extracellular recordings in vitro. I was instrumental (with McNaughton) in the development of ensemble tetrode recording methods for single units in awake young and old rats. More recently I have 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 use to understand behavior-driven circuits is the single cell gene expression imaging method “catFISH,” which was developed in her laboratory. 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. I direct the Evelyn F. McKnight Brain Institute at the University of Arizona and the Division of Neural Systems, Memory and Aging. I am actively involved in collaborative projects with scientists within the state of Arizona, across the United States and around the world. I have a track record of conducting difficult, systematic, and thorough studies with interdisciplinary teams, as well as with my own students and postdoctoral fellows – projects that have been followed through to publication (281 total, H index 104), 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, University of Arizona, Tucson
2006	Regents Professor, Psychology, Neurology, University of Arizona, Tucson
2006	Director, Evelyn F. McKnight Brain Institute, University of Arizona, Tucson

2006	Evelyn F. McKnight Endowed Chair for Learning and Memory in Aging, University of Arizona, Tucson
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

Honors

1969	NSF Summer Research Fellowship
1971	Phi Beta Kappa
1972 – 1974	Ontario Graduate Fellowship
1979 – 1981	NRSA Individual Postdoctoral Fellowship, NIH
1981 – 1982	NATO Fellowship in Science, NSF
1984 – 1989	Research Career Development Award, NIH
1987 – 1991	Neuroscience, Behavior and Sociology of Aging Committee A, NIA
1989 – 1994	Research Scientist Development Award, Level II, NIMH
1991 – 1997	Medical and Scientific Advisory Board, Alzheimer's Association
1994 – 1999	Research Scientist Award, NIMH
1994 – 1997	National Advisory Council on Aging, NIA
1995 – 1999	National Science Advisory Council, American Federation for Aging Research
1996 – 2000	Councilor, Society for Neuroscience
1997 – 2000	Medical and Scientific Advisory Council, Alzheimer's Association
1999 – 2004	Board of Scientific Counselors, NIMH
2000 – 2002	Secretary, Society for Neuroscience
2003 – 2006	President-Elect (2003-04), President (2004-05), Past-President (2005-06), Soc for Neuroscience
2004	MERIT Award, National Institute on Aging, NIH
2004	Elected Norwegian Royal Society of Sciences and Letters
2006	Regents' Professor, University of Arizona
2006	Evelyn F. McKnight Endowed Chair for Learning and Memory in Aging, University of Arizona
2007	Fellow, American Association for the Advancement of Science
2010	Elected: Mika Salpeter Lifetime Achievement Award, Society for Neuroscience
2011	Elected: Galileo Fellow, College of Science, University of Arizona
2013	Ralph W. Gerard Prize in Neuroscience, Society for Neuroscience
2014	American Psychological Association Award for Distinguished Scientific Contributions
2017	Quad-L Award, University of New Mexico
2018	Elected Member, National Academy of Sciences
2018	Museum of Contemporary Art Local Genius Award

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.

1. Barnes CA. (1979) Memory deficits associated with senescence: A neurophysiological and behavioral study in the rat. Journal of Comparative and Physiological Psychology, 93:74-104.
2. Barnes CA, Nadel L, and Honig WK. (1980) Spatial memory deficit in senescent rats. Canadian Journal of Psychology, 34:29-39.
3. Barnes CA and McNaughton BL. (1985) An age-comparison of the rates of acquisition and forgetting of spatial information in relation to long-term enhancement of hippocampal synapses. Behavioral Neuroscience, 99:1040-1048.
4. Barnes CA, Rao G, and Houston FP. (2000) LTP induction threshold change in old rats at the perforant path – granule cell synapse. Neurobiology of Aging, 21:613-620.

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.

1. Barnes CA and McNaughton BL. (1980) Physiological compensation for loss of afferent synapses in rat hippocampal granule cells during senescence. Journal of Physiology (Lond), 309:473-485.
2. Barnes CA, Rao G, and McNaughton BL. (1987) Increased electrotonic coupling in aged rat hippocampus: A possible mechanism for cellular excitability changes. Journal of Comparative Neurology, 259:547-558.
3. Barnes CA, Rao G, Foster TC, and McNaughton BL. (1992) Region-specific age effects on AMPA sensitivity: Electrophysiological evidence for loss of synaptic contacts in hippocampal field CA1.Hippocampus, 2:457-468.
4. Barnes CA, Rao G, and McNaughton BL. (1996) Functional integrity of NMDA-dependent LTP induction mechanisms across the lifespan of F344 rats. Learning and Memory, 3:124-137.

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.

1. Barnes CA, Suster MS, Shen J, and McNaughton BL. (1997) Multistability of cognitive maps in the hippocampus of old rats. Nature, 388:272-275.
2. Shen J, Barnes CA, McNaughton BL, Skaggs WE, and Weaver KL. (1997) The effect of aging on experience-dependent plasticity of hippocampal place cells. Journal of Neuroscience, 17:6769-6782.
3. Gerrard JL, Burke SN, McNaughton BL, and Barnes CA. (2008) Sequence reactivation in the hippocampus during slow wave sleep is impaired in aged rats. Journal of Neuroscience, 28:7883–7890.
4. Schimanski LA, Lipa P, and Barnes CA. (2013) Tracking the course of hippocampal representation during learning: When is the map required? Journal of Neuroscience, 33:3094-3106.

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.

1. Guzowski JF, McNaughton BL, Barnes CA, and Worley PF. (1999) Environment-specific expression of the immediate-early gene Arc in hippocampal neuronal ensembles. Nature Neuroscience,2:1120-1124.
2. Penner MR, Roth TL, Chawla MK, Hoang LT, Roth ED, Lubin FD, Sweatt DJ, Worley PF, and Barnes CA. (2011) Age-related changes in Arc transcription and DNA methylation within the hippocampus. Neurobiology of Aging, 32:2198-2210.
3. Penner MR, Parrish RR, Hoang LT, Roth TL, Lubin FD, and Barnes CA. (2016) Age-related changes inEgr1 transcription and DNA methylation within the hippocampus. Hippocampus, 26:1008-1020.
4. Thome A, Marrone DF, Ellmore TM, Chawla MK, Lipa P, Ramirez-Amaya V, Lisanby SH, McNaughton BL, and Barnes CA. (2017) Evidence for an evolutionarily conserved memory coding scheme in the mammalian hippocampus. Journal of Neuroscience, 37:2795–2801.

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.

1. Skaggs WE, McNaughton BL, Permenter M, Archibeque M, Vogt J, Amaral DG, and Barnes CA.(2007) EEG sharp waves and sparse ensemble unit activity in the macaque hippocampus. Journal of Neurophysiology, 98:898-910.
2. Thome A, Erickson CA, Lipa P, and Barnes CA. (2012) Differential effects of experience on tuning properties of macaque MTL neurons in a passive viewing task. Hippocampus, 22:2000-2011.
3. Engle J, Machado C, Permenter M, Vogt J, Maurer A, Bulleri A, and Barnes CA. (2016) Network patterns associated with navigation behavior are altered in aged nonhuman primates. Journal of Neuroscience, 36:12217-12227.
4. Thome A, Gray DT, Erickson CA, Lipa P, and Barnes CA. (2016) Memory impairment in aged primates is associated with region-specific network dysfunction. Molecular Psychiatry, 21:1257-1262.

Complete list of published work in My Bibliography

https://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/40630328/?reload=publicURL

Research Support

NIA R01 AG003376 Barnes (PI) 1/1/16 - 11/30/21

Neurobehavioral Relations in Senescent Hippocampus

The research 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.

NIA R01 AG05058 Barnes (PI) 9/1/15 - 5/31/21

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 multi-tasking 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 multi-tasking in an aging primate model, to assess how aging weakens the resilience of working memory circuits in the face of interference.

NIA R01 AG049465 Barnes (PI) 8/01/14 3/31/20

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.

NIA R01 AG049464 Coleman, Barnes, Alexander (MPI) 8/1/14 - 3/31/21

Epigenetic, Neuroimaging & Behavioral Effects of Hypertension in the Aging Brain

Major project goals 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: Principal Investigator (Multi-PI)

NIA P30 AG019610 Reiman (PI) 8/15/16 - 6/30/21
Arizona Alzheimer's Disease Core Center
Dr. Barnes serves as Director of the Ad Hoc review program for research proposals for the Center.
Role: Co-Investigator

NIA T32 AG044402 Barnes (PI) 5/1/16 - 4/30/21
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 (six participating institutions).
Role: Principal Investigator

NIA R21 AG061421 Stern (PI) 10/1/18 - 9/30/21
Collaboratory on Research for Cognitive Reserve and Resilience
Dr. Barnes role is to serve with a group of 6 Co-I's to build the infrastructure to organize workshops, databases, and facilitate award of pilot grants that will guide efforts to reach consensus on the most effective operational definitions for brain and cognitive reserve so that experiments can be directed at understanding underlying mechanism of these concepts.
Role: Co-Investigator

Biographical Sketch

Roberta Diaz-Brinton, Ph.D.
Director, Center for Innovation in Brain Science
Regents Professor, Pharmacology, Psychology and Neurology

Education/Training

Institution & Location	Degree	Year(S)	Field of Study
University of Arizona, Tucson, AZ	B.A.	1979	Psychobiology
University of Arizona, Tucson, AZ	M.A.	1981	Neuropsychology
University of Arizona, Tucson, AZ	Ph.D.	1984	Psychobiology & Neuropharmacology
Rockefeller University, NY	Postdoc	1987	Neuropharmacology & Neuroendocrinology

Personal Statement

I am the 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. The Center for Innovation in Brain Science is focused on discovery, translational, and clinical research for mechanistically driven therapeutic development age-associated neurodegenerative diseases including Alzheimer's. My research has focused broadly on the mechanisms through which the aging brain develops late onset Alzheimer's disease (AD). Towards that goal, I lead three programs of discovery research and two programs in translational / clinical research. Our discovery research programs focus on systems biology of: 1) Mechanisms underlying risk of Alzheimer's during female brain aging with particular focus on estrogen regulation of bioenergetic, immune and resilience systems of biology ; 2) Sex differences in mechanisms underlying risk of AD and 3) Regeneration and repair mechanisms and therapeutics for Alzheimer's. Our translational and clinical research programs focus on therapeutic development to prevent, delay and reverse AD with emphasis on hormonal, bioenergetic and regenerative regulators. Our research spans discovery to IND enabling translation to clinical trials and is supported by the National Institute on Aging and philanthropic foundations. 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, their plasticity, limits and vulnerability. In the female brain, dismantling of estrogen signaling is a key regulator of midlife aging transition state in the female brain. Further, we have developed extensive experience in translational research to enable FDA INDs, regulatory strategy and therapeutic development. These efforts have advanced our basic science discoveries into two clinical trials that target different mechanisms of action and steroid systems in the brain. The nature of our research requires effective and collaborative teams that are mission focused. Our NIA Perimenopause in Brain Aging and Alzheimer's Disease Program Project is an exemplar of our approach. Teams that I lead include basic, translational and clinical scientists and technology transfer professionals. During the course of my academic career, I have mentored 26 predoctoral and 23 postdoctoral fellows, 10 undergraduates and, through the USC Science Technology and Research (STAR) Program, inner city Los Angeles, 50 high school students in my laboratory and 600 STAR Program wide. Currently, I am PI on a translationally oriented Alzheimer's disease and related dementias NIA T32 (AZ-TRADD) for Predoctoral Fellows and mPI on the NIDNS URBRAIN R25 training grant for Diné Tribal College students (Tsaile, Arizona), Navajo Nation.

Positions

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 –	Professor of Neurology, Keck School of Medicine, Univ of Southern California
2016 – Present	Director, Center for Innovation in Brain Science, Professor of Pharmacology, College of Medicine, University of Arizona, Tucson, Arizona
2017 – Present	Professor of the Evelyn F. McKnight Brain Institute, Psychology, Neurology, College of Medicine, University of Arizona, Tucson, Arizona

Honors

1996	University of Southern California Associates Award for Teaching Excellence
2003	University of Southern California Remarkable Woman Award
2005	10 Best Minds, US News & World Report
2005	Woman of the Year, California State Senate
2006	Science Educator of the Year, Society for Neuroscience
2009	North American Menopause Society /Wyeth Pharmaceuticals SERM Research Award
2010	Presidential Citizens Medal, President Barack Obama
2014	Los Angeles Woman of the Year, LA Magazine
2015	Scientist of the Year Award, Alzheimer's Drug Discovery Foundation
2017	Disruptive Women to Watch in 2017, Disruptive Women in Health Care
2017	Alzheimer's Drug Discovery Foundation, Melvin Goodes Prize for Excellence in Alzheimer's Drug Discovery
2017	National Academy of Inventors
2020	Elected Regents Professor, University of Arizona

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 mechanisms underlying the increased lifetime risk of Alzheimer's in women. Outcomes of this pioneering research indicate that the estrogen is a master regulator of the bioenergetic and immune systems 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 ClinicalTrials.gov Identifier: NCT01723917

1. Brinton RD, Yao J, Yin F, Mack WJ, and Cadenas E. (2015) Perimenopause as a neurological transition. Nat Rev Endocrinol, 11:393-405.
2. Mishra A, Shang Y, Wang Y, Bacon E, Yin F and Brinton RD (2020) Dynamic Neuroimmune Profile during Mid-life Aging in the Female Brain and Implications for Alzheimer Risk. iScience, 23(12):101829. doi: 10.1016/j.isci.2020.101829.
3. Wang Y, Mishra A and Brinton RD (2020) Transitions in metabolic and immune systems from pre-menopause to post-menopause: implications for age-associated neurodegenerative diseases. F1000 Research, doi: 10.12688/f1000research.21599.1.
4. Schneider LS, Hernandez G, Zhao L, Franke AA, Chen YL, Pawluczyk S, Mack WJ, Brinton RD (2019) Safety and feasibility of estrogen receptor-beta targets phytoSERM formulation for menopausal symptoms: phase 1b/2a randomized clinical trial. Menopause, 26:874-884.

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 that may be beneficial to the Apoε4- male but may be deleterious to the Apoε4+male.

1. Mosconi L, Berti V, Quinn C, McHugh P, Petrongolo G, Varsavsky I, Osorio RS, Pupi A, Vallabhajosula S, Isaacson RS, de Leon MJ, Brinton RD. (2017) Sex differences in Alzheimer risk: Brain imaging of endocrine vs chronologic aging. Neurology, 89:1382-1390.
2. Rahman A, Schelbaum E, Hoffman K, Diaz I, Hristov H, Andrews R, Jett S, Jackson H, Lee A, Sarva H, Pahlajani S, Matthews D, Dyke J, de Leon MJ, Isaacson RS, Brinton RD, Mosconi L. (2020) Sex-driven modifiers of Alzheimer risk: A multimodality brain imaging study. Neurology, 95:e166-e178. doi: 10.1212/WNL.0000000000009781.
3. Riedel BC, Thompson PM, Brinton RD. (2016) Age, APOE and sex: Triad of risk of Alzheimer's disease. J Steroid Biochem Mol Biol, 160:134-147.
4. Arnold M, Nho K, Kueider-Paisley A, Massaro T, Huynh K, Brauner B, MahmoudianDehkordi S, Louie G, Moseley MA, Thompson JW, John-Williams LS, Tenenbaum JD, Blach C, Chang R, Brinton RD, Baillie R, Han X, Trojanowski JQ, Shaw LM, Martins R, Weiner MW, Trushina E, Toledo JB, Meikle PJ, Bennett DA, Krumsiek J, Doraiswamy PM, Saykin AJ, Kaddurah-Daouk R, Kastenmüller G. Sex and APOE ε4 genotype modify the Alzheimer's disease serum metabolome. Nature Communications, ;11:1148.

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 ClinicalTrials.gov Identifier: NCT02221622. The Phase 1 NIA sponsored clinical trial Allopregnanolone for Mild Cognitive Impairment Due to Alzheimer's Disease or Mild AD has been

completed and results are under review. An NIA sponsored Phase 2 clinical trial is scheduled to being recruitment in September 2020.

1. Hernandez G, Solinsky C, Mack W, Kono N, Rodgers K, Yu C, Mollo A, Lopez C, Pawluczyk S, Bauer G, Matthews D, Shi Y, Law M, Rogawski M, Schneider L and Brinton, R.D. (2020) Safety, tolerability, and pharmacokinetics of allopregnanolone as a regenerative therapeutic for Alzheimer's disease: A single and multiple ascending dose phase 1b/2a clinical trial. Alzheimer's & Dementia (NY), 6(1):e12107. doi: 10.1002/trc2.12107.
2. Brinton RD. (2013) Neurosteroids as regenerative agents in brain: Therapeutic implications. Nature Rev. Endocrinol., 9:241-250.
3. Chen S, Wang JM, Irwin RW, Yao J, Liu L, and Brinton RD. (2011) Allopregnanolone promotes regeneration and reduces ß-amyloid burden in a preclinical model of Alzheimer's disease. PLoS, 6(8):e24293. doi: 10.1371/journal.pone.0024293.
4. Wang JM, Singh C, Liu L, Irwin RW, Chen S, Chung EJ, Thompson RF, and Brinton RD. (2010)Allopregnanolone reverses neurogenic and cognitive deficits in mouse model of Alzheimer's disease. Proc Natl Acad Sci U S A., 107:6498-503.

Complete list of published work in My Bibliography

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

Research Support

R37 AG053589 MERIT* Brinton 03/15/2017-02/28/2022
Aging and Estrogenic Control of the Bioenergetic System in Brain (previously R01-AG053589)
Role: Principal Investigator

P01 AG026572 Brinton 08/15/2006-05/31/2021
Perimenopause in Brain Aging and Alzheimer's Disease
Role: Principal Investigator; PL Administrative Core A, Project 1 and Project 4

R01 AG063826 Brinton 08/15/2019-04/30/2024
Allopregnanolone as Regenerative Therapeutic for Alzheimer's: Phase 2 Clinical Trial

Role: Principal Investigator

U01 AG047222 Brinton 06/15/2014-06/30/2020
Allopregnanolone a Regenerative Therapy for Alzheimer's: FDA-Required Toxicology
Role: Principal Investigator

Alzheimer's Drug Discovery Foundation 20170902 Brinton 11/01/2017-12/31/2020
Allopregnanolone Novel Patentable Formulations to Advance Commercialization
Role: Principal Investigator

T32 AG061897 Brinton 09/01/2018 – 08/31/2023
Translational Research in Alzheimer's Disease and related Dementias (TRADD)
Role: Principal Investigator

R25 NS107185 Rodgers/Brinton/Boyd 07/01/2019-06/30/2024
Undergraduate Readying for Burgeoning Research for American Indian Neuroscientists
Role: Multiple Principal Investigator

U01 AG063768 Rodgers 09/01/2018 – 08/31/2023
IND Enabling Studies for RASRx 1902, a novel Mas receptor agonist, for treatment of cognitive impairment in patients at risk for Alzheimer's disease.
Role: Co-Investigator

Duke University (sub-R01AG059093) Kaddurah-Daouk 08/01/2018-06/30/2023
Metabolic Networks and Pathways Predictive of Sex Differences in AD Risk and Responsiveness to Treatment
Role: Co-Investigator, Subaward PI

R01 AG057931 Brinton 09/01/2018-05/31/2023
Sex Differences in the Molecular Determinants of Alzheimer's Disease Risk: Prodromal Endophenotype
Role: Principal Investigator

Biographical Sketch

Ying-hui Chou, Ph.D.
Assistant Professor, Psychology

Education/Training

Institution & Location	Degree	Year(S)	Field of Study
National Taiwan University, Taipei	B.S.	1994	Occupational Therapy
Boston University, Boston, MA	M.S.	2001	Occupational Therapy
Boston University, Boston, MA	Sc.D.	2005	Movement & Rehab Sci
Brigham and Women's Hospital Boston, MA	Postdoc	2005	Brain Imaging
Duke University Medical Center, Durham, NC	Postdoc	2012	Gerontology and Brain Imaging
Duke University Medical Center, Durham, NC	Other training	2012	Transcranial Magnetic Stimulation
Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA	Other training	2013	Transcranial Magnetic Stimulation
Duke University Medical Center, Durham, NC	Postdoc	2013	Brain Imaging
Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA	Other training	2015	Transcranial Direct Current Stimulation

Personal Statement

My research has focused primarily on the cognitive and clinical neuroscience of aging and neurodegenerative disorders. Within this framework, my laboratory is particularly interested in integrating magnetic resonance imaging (MRI) and transcranial magnetic stimulation (TMS) techniques to 1) develop MRI-guided therapeutic TMS protocols and 2) explore TMS-derived and image-based biomarkers for early diagnosis and prediction of therapeutic outcomes for individuals with neurodegenerative disorders. I am the Director of Brain Imaging and TMS Laboratory and leading an NIH-funded R01 clinical trial to test MRI-guided hippocampal TMS on memory function in patients with mild cognitive impairment. I teach undergraduate and graduate courses such as cognitive neuroscience, brain rehabilitation, and brain connectivity in the Department of Psychology.

1. Chou YH, Ton That, V., Sundman, M. (2020) A systematic review and meta-analysis of rTMS effects on cognitive enhancement in mild cognitive impairment and Alzheimer's disease. Neurobiology of Aging, 86:1-10.
2. Chou YH., That V T, Chen AY, Sundman M, Huang, H. (2020) Reported TMS-induced seizure cases by population, stimulation protocol, and stimulation site. Clinical Neurophysiology, 131:1019-1020.
3. Chou YH, Hickey PT, Sundman M, Song AW, Chen NK. Effects of repetitive transcranial magnetic stimulation on motor symptoms in Parkinson Disease: A systematic review and meta-analysis. JAMA Neurol., 72: 432-40.
4. Chou YH, You H, Wang H, Zhao YP, Hou B, Chen NK, Feng F. Effect of repetitive transcranial magnetic stimulation on fMRI resting-state connectivity in Multiple System Atrophy. *Brain Connect*. 2015 Apr 22; 5(7): 451-459.

Positions

1994 – 1995 Occupational Therapist, Department of Psychiatry, Taipei Veterans General Hospital, Taiwan

1995 – 1997	Occupational Therapist, Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital, Taiwan
2001 – 2003	Research Assistant, Center for Neurological Rehabilitation, Boston University, Boston, MA
2001 – 2003	Teaching Assistant of (1) Neurological Systems and (2) Scientific Inquiry, Department of Physical Therapy, Boston University, Boston, MA
2004 – 2005	Postdoctoral Fellow of Radiology, Brigham and Women's Hospital/Harvard Medical School, Boston, MA
2005 – 2008	Chair and Assistant Professor, Department of Occupational Therapy, Fu-Jen Catholic University, Taiwan
2008 – 2011	Maternity Leave
2011 – 2013	Postdoctoral Fellow, Center for Aging and Human Development and Brain Imaging and Analysis Center, Duke University Medical Center, Durham, NC
2013 – 2016	Medical Instructor, Brain Imaging and Analysis Center, Duke University Medical Center, Durham, NC
2016	Assistant Professor of Psychology, University of Arizona, Tucson, AZ
2016	Director, Brain Imaging and TMS Laboratory, University of Arizona
2017	Research Associate, Arizona Center on Aging

Honors

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

Contribution to Science

Transcranial magnetic stimulation as treatment and evaluation tools 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 neurodegenerative disorders. We published two meta-analyses examining the effects of rTMS on motor function in Parkinson's disease (PD)a and on cognitive function in Alzheimer's disease (AD) and mild cognitive impairment (MCI)b. Findings of our meta-analyses suggest that 1) rTMS reduces motor symptoms in PD (effect size = 0.46) when high frequency rTMS is applied to the primary motor cortex and when low frequency rTMS is applied at other prefrontal regions; and 2) rTMS improves memory function in AD and MCI (effect size = 0.77) when high frequency rTMS is applied to the left dorsolateral prefrontal cortex and when low-frequency rTMS is applied to the right dorsolateral prefrontal cortex. We extended the findings from the PD meta-analysis to patients with multiple system atrophy. Results of this clinical trial support the therapeutic effect of high frequency rTMS in improving motor symptoms and increasing brain functional connectivity (involving the default mode, cerebellar and limbic networks) in multiple system atrophy. In addition to treatment, TMS can also be used to probe homeostatic metaplasticity. In our recent study assessing neural plasticity with TMSd, we found that homeostatic metaplasticity is diminished in cognitively impaired older adults and this neuroprotective feature remains intact in cognitively normal participants.

1. Chou YH, Hickey PT, Sundman M, Song AW, Chen NK. (2015)Effects of Repetitive Transcranial Magnetic Stimulation on Motor Symptoms in Parkinson Disease: A Systematic Review and Meta-analysis. JAMA Neurol., 72: 432-440.
2. Chou YH, Ton That V, Chen AY, Sundman M. and Huang H. (2020) Reported TMS-induced seizure cases by population, stimulation protocol, and stimulation site. Clinical Neurophysiology, 131(5):1019-1020
3. Chou YH, You H, Wang H, Zhao YP, Hou B, Chen NK, Feng F. (2015) Effect of repetitive transcranial magnetic stimulation on fMRI resting-state connectivity in Multiple System Atrophy. Brain Connect., 5:451-459.
4. Sundman M, Lim K, Ton That V., Mizell JM, Ugonna C, Rodriguez R, Chen NK, Fuglevand AJ, Liu Y, Wilson RC, Fellous JM, Rapcsak S and Chou YH (2020) Transcranial magnetic stimulation reveals diminished homeostatic metaplasticity in cognitively impaired adults. Brain Communications, 2: fcaa203. doi: 10.1093/braincomms/fcaa203

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.

1. Chou YH, Panych LP, Dickey CC, Petrella JR, and Chen NK. (2012) Investigation of long-term reproducibility of intrinsic connectivity network mapping: A resting-state fMRI study. Am J Neuroradiol. May;33(5): 833-8. PMCID: PMC3584561.
2. Chou YH, Chen NK, and Madden DJ. (2013) Functional brain connectivity and cognition: Effects of adult age and task demands. Neurobiol Aging. Aug;34(8): 1925-34 PMCID: PMC3674832.
3. Seeley SH, Chou YH, O'Connor M.F. (2018) Intranasal oxytocin and OXTR genotype effects on resting state functional connectivity: A systematic review. Neurosci Biobehav Rev., 95:17-32.
4. Wang L, Chou YH, Potter GG, and Steffens DC. (2015) Altered synchronization among neural networks in geriatric depression. BioMed Research International, January 11. NIHMSID:NIHMS690881.

Virtual reality and rehabilitation. I was trained as a movement and rehabilitation scientist during my graduate studies investigating gait patterns and how a virtual reality environment would modulate locomotion in healthy older adults and patients with Parkinson's disease. We have 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 more than 2,700 times from the publisher's website.

1. Chou YH, Wagenaar RC, Saltzman E, Giphart JE, Young D, et al. (2009) Effects of optic flow speed and lateral flow asymmetry on locomotion in younger and older adults: a virtual reality study. J Gerontol B Psychol Sci Soc Sci. Mar;64(2):222-31. PMCID: PMC2655160.
2. Giphart JE, Chou YH, Kim DH, Bortnyk CT, Wagenaar RC. (2007) Effects of virtual reality immersion and walking speed on coordination of arm and leg movements. Presence: Teleoperators and Virtual Environments. 16(4): 399-413.
3. Young DE, Wagenaar RC, Lin CC, Chou YH, Davidsdottir S, et al. (2010) Visuospatial perception and navigation in Parkinson's disease. Vision Res. Nov 23;50(23):2495-504. PMCID: PMC3008343.
4. Chou YH, Weingarten C, Madden DJ, Song AW, Chen N. Virtual Reality. Eichenberg C, editor. Rijeka ,Croatia: Intech – Open Access Publisher; 2012. Applications of virtual reality technology in brain imaging studies; p.203-228.

Complete list of published work in My Bibliography

http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40106197/?sort=date&direction=descending

Research Support

NIA RO1 AG062543 Chou (PI) 05/20 – 01/25
Enhancement of hippocampal plasticity using repetitive transcranial magnetic stimulation
Role on Project: PI

NIA U01 EB029834 Witte (PI) 09/20 – 06/25
4D Transcranial Acoustoelectric Imaging for High Resolution Functional Mapping of Neuronal Currents
Role on Project: Co-Investigator

DOD Medical Research Program Discovery Award Killgore (PI) 10/20 – 09/22
Transcranial magnetic stimulation of the default mode network to improve sleep
Role on Project: Co-Investigator

NIA R56 AG061888 Wilson (PI) 9/30/18 - 8/31/23
Evaluating the Neurocomputational Mechanisms of Explore Exploit Decision Making in Older Adults
Role on Project: Co-Investigator

Arizona Alzheimer's Consortium, DHS Chen (PI) 7/1/19 – 6/30/21
Transcranial Magnetic Stimulation for Mild Cognitive Impairment
Role on Project: Project PI

Cancer Center, University of Arizona Kou (PI) 7/1/18 - 6/30/21
Feasibility Study for the Treatment of Post-Chemotherapy Cognitive Impairment with Transcranial Magnetic Stimulation
Role on Project: Co-Investigator

RO1 HD977498 Edgin(PI) 7/20 -6/21
Memory Measures for Clinical Trials in Down Syndrome and Fragile X Syndrome
Role on Project: Co-Investigator

Univ Arizona Faculty Seed Grant Chen (PI) 11/20 – 5/21
Using TMS to Detect Deficits of Cholinergic System in the Aging-MCI-AD Continuum
Role on Project: PI

Biographical Sketch

Stephen Cowen, Ph.D.
Associate Professor, Psychology

Education/Training

Institution & Location	Degree	Year(S)	Field of Study
University of Wisconsin, Madison, Wisconsin	B.B.A	1992	Management and Marketing
University of Arizona, Tucson, Arizona	Ph.D.	2007	Psychology and Neuroscience
The Neurosciences Institute, San Diego, CA	Postdoc	2008	Neuroscience

Personal Statement

A fundamental and unresolved question in neuroscience is how the billions of interconnected neurons in the brain coordinate their activity to support learning, memory, and decision making. Neuromodulators such as dopamine and neural oscillatory activity likely play key roles in both organizing the activities of neurons and in supporting neuroplasticity. Disrupted oscillatory activity and dopamine release are also key contributors to disease states such as substance abuse, depression, age-associated cognitive decline, Parkinson's disease, and schizophrenia. My research seeks to understand now neural ensemble activity and dopamine release are coordinated during behavior and sleep to support learning and memory. Towards this end, my laboratory and the laboratory of Dr. Heien have developed novel instrumentation that allows, for the first time, the simultaneous measurement of the activities of large groups of neurons and fast, "phasic", changes in dopamine release (Parent et al., 2017). We are currently using this tool to determine how electrical brain stimulation of various brain structures can be used to modulate dopamine release (Hill et al. 2017), and how such release impacts neural coordination, plasticity, and learning.

Our laboratory also investigates how synchrony between neurons changes during learning and how synchrony is affected by aging and Parkinson's disease. We have found, for example, that normal aging is associated with a significant decrease in the frequency of fast "ripple" oscillations in the hippocampus that are associated with memory formation (Wiegand et al., 2016; Cowen et al., 2018). My laboratory is exploring whether neural oscillations produced by sub-anesthetic ketamine (Ye et al., 2018) disrupt pathological oscillatory activity associated with Parkinson's disease and dyskinesia. We have also investigated how a genetic form of Parkinson's disease leads to fragmented sleep and disrupted sleep-spindle oscillations associated with memory consolidation (Crown et al., 2020).

1. Crown LM, Bartlett MJ, Wiegand J-PL, Eby AJ, Monroe EJ, Gies K, Wohlford L, Fell MJ, Falk T C, Cowen SL. (2020) Sleep Spindles and Fragmented Sleep as Prodromal Markers in a Preclinical Model of LRRK2-G2019S Parkinson's Disease. Front Neurol 11:324.
2. Hill DF, Parent KL, Atcherley CW, Cowen SL and Heien ML. (2018) Differential release of dopamine in the nucleus accumbens evoked by low-versus high-frequency medial prefrontal cortex stimulation. Brain Stimulation, 11:426-434.
3. Parent KL, Hill DF, Crown LM, Wiegand J-P, Gies KF, Miller MA, Atcherley CW, Heien ML, and Cowen SL. (2017) Platform to enable combined measurement of dopamine and neural activity. AnalChem:acs.analchem.6b03642.
4. Cowen SL, Gray DT, Wiegand J-PL, Schimanski, L.A and Barnes CA (2020) Age-associated changes in waking hippocampal sharp-wave ripples. Hippocampus 30, 28–38.

Positions

2007 – 2008	Postdoctoral Fellow	The Neurosciences Institute, San Diego, CA
2008 – 2010	Research Fellow	The Neurosciences Institute, San Diego, CA
2010 – 2012	Associate Fellow	The Neurosciences Institute, San Diego, CA
2012 – 2019	Assistant Professor	University of Arizona, Tucson, AZ
2019 – present	Associate Professor	University of Arizona, Tucson, AZ Department of Psychology, University of Arizona Graduate Interdisciplinary Program in Neuroscience Graduate Interdisciplinary Program in Cognitive Science Graduate Interdisciplinary Program in Phys. Sciences Graduate Interdisciplinary Program in Applied Biosciences

Honors

1998-1999	Recipient of National Science Foundation training grant
2010	Blasker-Rose-Miah Technology Development grant, 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.

1. Wiegand J-PL, Gray DT, Schimanski LA, Lipa P, Barnes CA, and Cowen SL. (2016) Age is associated with reduced sharp-wave ripple frequency and altered patterns of neuronal variability. J Neurosci.,36:5650–5660.
1. Cowen SL, Gray DT, Wiegand J-PL, Schimanski, LA, and Barnes CA. (2018) Age-associated changes in waking hippocampal sharp-wave ripples. Hippocampus, https://doi.org/10.1002/hipo.23005. [Epub ahead of print]

Ketamine induces brain-region specific patterns of synchrony and desynchrony. Ketamine has been used as a safe and effective anesthetic for over 50 years, and, in the last decade, the potential therapeutic applications of ketamine have expanded considerably. For example, hour to days-long exposure to sub-anesthetic ketamine can provide weeks-long management of depression, post-traumatic stress disorder (PTSD), chronic pain, and L-DOPA-induced dyskinesias (LID). The neural mechanisms by which the therapeutic effects of ketamine are achieved are unknown. Furthermore, little is known about how ketamine alters neural coordination throughout the brain. Understanding the impact of ketamine on neural coordination is important and neural plasticity and communication between brain regions depends on the precise timing of action potentials within and between brain structures. Consequently, we hypothesized that hours-long exposure to ketamine entrains synchronized activity within corticostriatal and hippocampal circuits. To investigate this question, we measure oscillatory activity in behaving rats following administration of low-dose ketamine. We recorded from motor cortex, ventral striatum, dorsal striatum, and hippocampus and found that ketamine induces unique patterns of neural coordination in each brain region studied. Critically, we found that extended exposure to ketamine hyper-synchronizes corticostriatal circuits at delta (~4 Hz), gamma (~50 Hz), and high-frequency (~140 Hz) bands. In stark contrast, activity in the

hippocampus became desynchronized or “noisy”. These data suggest that ketamine facilitates communication and plasticity in corticostriatal circuits and disrupts these processes in the hippocampus. Indeed, desynchronous activity in the hippocampus could reduce the strength of associative networks encoding memories for negative events. Disrupting such networks could have positive therapeutic effects in depression and PTSD. An important next step is to determine if ketamine alters coordination in these brain regions though single-unit ensemble recordings.

1. Ye T, Bartlett MJ, Schmit MB, Sherman SJ, Falk T C, Cowen SL (2018) Ten-Hour Exposure to Low-Dose Ketamine Enhances Corticostriatal Cross-Frequency Coupling and Hippocampal Broad-Band Gamma Oscillations. Front. Neural Circuits 12, 61. doi: 10.3389/fncir.2018.00061

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 glutamatergic and dopaminergic transmission in the motor cortex and dorsal striatum. This proposal may have significant implications for the study of chronic pain, a condition associated with reduced frontal function. Consequently, my laboratory is now investigating the connection between chronic pain and effort-guided decision making through our collaboration with Dr. Frank Porreca.

1. Cowen SL, Davis GA, and Nitz DA. (2012) Anterior cingulate neurons in the rat map anticipated effort and reward to their associated action sequences. J Neurophysiol., 107:2393–2407.
2. Miller MA, Thomé A, and Cowen SL. (2013) Intersection of effort and risk: ethological and neurobiological perspectives. Front Neurosci., 7:208.
3. Cowen SL, Phelps, CE, Navratilova E, McKinzie DL, Okun A, Husain, BS, Gleason SD, Witkin JM, and Porreca FC. (2018) Chronic pain impairs cognitive flexibility and engages novel learning strategies in rats. Pain, 157:1403-1412.

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.

1. Cowen SL and Nitz DA. (2014) Repeating Firing Fields of CA1 Neurons Shift Forward in Response to Increasing Angular Velocity. J Neurosci., 34:232–241.
2. Maurer AP, Cowen SL, Burke SN, Barnes CA and McNaughton BL. (2006a) Organization of hippocampal cell assemblies based on theta phase precession. Hippocampus, 16:785–794.
3. Maurer AP, Cowen SL, Burke SN, Barnes CA and McNaughton BL. (2006b) Phase precession in hippocampal interneurons showing strong functional coupling to individual pyramidal cells. J Neurosci., 26:13485–13492.

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

- 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 (Parent et al., 2017). The next stage of development will be to improve the hardware and software to improve robustness and ease of use.
- Improving voltammetric measurement of dopamine concentration by reducing the effects of biofouling (Seaton et al., 2020) and improving safety and FDA compliance (Siegenthaler et al., 2020).

  1. Seaton BT, Hill DF, Cowen SL, Heien ML C. 2020. Mitigating the Effects of Electrode Biofouling-Induced Impedance for Improved Long-Term Electrochemical Measurements In Vivo. Anal Chem 92:6334–6340.
  2. Siegenthaler JR, Gushiken BC, Hill DF, Cowen SL, Heien ML C. 2020. Moving Fast-Scan Cyclic Voltammetry toward FDA Compliance with Capacitive Decoupling Patient Protection. ACS sensors 5:1890–1899.

- Ultrasound measurement of electrical brain activity. I am a collaborator on Brain Initiative R24 (Lead PI: Russel Witte, U of A) 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.
- 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 brain-body interactions in the hippocampus, parietal cortex, and prefrontal cortex.

Complete list of published work in My Bibliography

https://www.ncbi.nlm.nih.gov/sites/myncbi/1Lk1z2JuTON/bibliography/46504043/public/?sort=date&direction=ascending.

Research Support

R44 MH114776 PI: Hedlin 8/1/19 – 1/1/21
High density, miniaturized, zero switching, stimulation and recording headstage for small animals
Objective: Develop new technologies for simultaneously stimulating and recording brain activity
Role on Project: Co-Investigator

R56 NS109608 PI: Falk 8/1/19 – 8/1/21
Mechanisms of low-dose ketamine treatment for Parkinson's disease
Objective: Identify the circuit and single-neuron properties that drive Parkinson's disease associated oscillations and determine how ketamine works to reduce pathology associated oscillatory activity
Role on Project: Co-Investigator

U01 EM29834 Witte (PI) 9/1/20 – 1/1/24
4D Transcranial Acoustoelectric Imaging for High Resolution Functional Mapping of Neuronal Currents
Role on Project: Co-Investigator

Biographical Sketch

Arne Ekstrom., Ph.D.
Professor, Psychology

Education/Training

Institution & Location	Degree	Year(S)	Field of Study
Brandeis University, Waltham, MA	B.A.	1996	Psychology, Biology
University of Arizona, Tucson, AZ	M.S.	2001	Neuroscience
Brandeis University, Waltham, MA	Ph.D.	2004	Neuroscience

Personal Statement

The primary focus of my research is to better understand the neural basis of human memory, with a particular focus on spatial navigation. I employ several different methodologies to better understand spatial memory, including immersive virtual reality, intracranial EEG, fMRI, and scalp EEG. Studies in my lab focus on how neural signals code space vs. time, how we represent different scales of space, how navigation and episodic memory are represented differently in the brain, and how the different recording modalities used tie together or provide complementary information about underlying brain processes.

Positions

1996 – 1997	Research Assistant	Department of Psychology, Harvard University, Cambridge
2004 – 2009	Postdoctoral Fellow	Division of Neurosurgery and Center for Cognitive Neuroscience, Semel Institute of Neuroscience and Human Behavior, University of California, Los Angeles
2009 – 2014	Assistant Professor	Department of Psychology and Center for Neuroscience, University of California, Davis
2014 – 2018	Associate Professor	Department of Psychology and Center for Neuroscience, University of California, Davis
2018 – 2020	Associate Professor	Department of Psychology and Evelyn F. McKnight Brain Institute, University of Arizona, Tucson
2020 – Present	Professor	Department of Psychology and Evelyn F. McKnight Brain Institute, University of Arizona, Tucson

Honors

1996	B.A., Brandeis University, magna cum laude, High Honors in Neuroscience
1998 – 2000	Flinn Biomathematics Fellow, University of Arizona
2006 – 2009	NIH/NINDS Postdoctoral NRSA fellowship
2008	The Brain Research Institute Distinguished Postdoctoral Fellow in Neuroscience
2011	Hellman Young Investigator Award
2011 – 2012	Alfred P. Sloan Fellow
2012	Kavli Fellow – National Academy of Sciences Kavli Frontiers of Science
2015	Chancellor's Fellow

Contribution to Science

High-resolution hippocampal imaging of human episodic memory. In the work cited below, in addition that cited in the "Publications Relevant to This Proposal" section, we demonstrate mechanisms by which hippocampal subfields store and retrieve spatiotemporal memories, helping to resolve how the human hippocampal subfields contribute to episodic memory. Using high-resolution imaging of the hippocampus along with multivariate pattern analysis, we demonstrate how patterns of activations within hippocampal subfields might be important to memory for details of events. Together, this work has advanced our understanding of how the human hippocampal subfields code spatial and temporal context as part of a more general role in episodic memory.

1. Stokes JD, Kyle C, and Ekstrom AD. (2015) Complementary roles of human hippocampal subfields in differentiation and integration of spatial context. Journal of Cognitive Neuroscience, 27:546-559.
2. Kyle CT, Stokes JD, Lieberman J, Hassan AS, and Ekstrom AD. (2016) Successful retrieval of competing spatial environments in humans involves hippocampal pattern separation mechanisms. ELife, 27, e10499.
3. Copara MS, Hassan A, Kyle C, Libby L, Ranganath C, and Ekstrom AD. (2014) Complementary roles of human hippocampal subregions during retrieval of spatiotemporal context. Journal of Neuroscience, 34:6834-6842.

Immersive virtual reality, behavioral, and neural correlates of human spatial navigation
One of the novel devices we have successfully employed to better model navigation involves an omnidirectional treadmill coupled to a head-mounted display, which provides a means of modeling body-based ambulatory movements otherwise difficult to study in the lab. Our work below also involves testing of patients with focal hippocampal lesions in virtual reality, which has provided novel evidence for precision deficits in navigation. Specifically, such patients search in the correct general vicinity of the target for both same location (egocentric) and different location (allocentric) start points but show deficits in the precision of their searches.

1. Huffman D.J. & Ekstrom A.D. (2019). A modality-independent network underlies the retrieval of large-scale spatial environments in the human brain. Neuron. 104(3): 611-622.
2. Hejtmanek L., Starrett M.J., Ferrer E. & Ekstrom A.D. (2020). How much of what we learn in virtual reality transfers to real-world navigation? Multisensory Research. doi: 10.1163/22134808-20201445.
3. Starrett M.J., Stokes J.D., Huffman D.J., Ferrer E., Ekstrom A.D. (2019). Learning-Dependent Evolution of Spatial Representations in Large-Scale Virtual Environments. Journal of Experimental Psychology: Learning, Memory, and Cognition. 45(3). 497-514.
4. Kolarik B.S., Baer T., Shahlaie K., Yonelinas A.P., and Ekstrom A.D. (2017). Close but no cigar: Spatial precision deficits following medial temporal lobe lesions provide novel insight into theoretical models of navigation and memory. Hippocampus. 28: 31-41.

High-resolution imaging of the human hippocampus and the neural basis of the human hippocampal BOLD signal. Another focus of the lab has been developing ways to better image the human hippocampus using fMRI and to relate these hippocampal BOLD-specific changes to underlying neural activity. Our work has developed novel BOLD sequences for imaging the human hippocampus in-plane with 1.5 mm x 1.5 voxels, which provides functional resolution sufficient to image changes in the neural activity at specific subfields (Ekstrom et al. 2009 Neuroimage). Together, these findings advance current methods in the field for imaging and recording from the human hippocampus.

1. Ekstrom A.D. (2010). How and when the fMRI BOLD signal relates to underlying neural activity: The danger in dissociation. Brain Research Reviews, 62(2):233-44.
2. Ekstrom A.D., Suthana N.A., Millet D., Fried I., & Bookheimer S.Y. (2009). Correlation Between BOLD fMRI and Theta-band Local Field Potentials in the Human Hippocampal Area. Journal of

Neurophysiology, 101, 2668-2678.
3. Ekstrom A.D., Suthana N.A., Behnke E., Salamon N., Bookheimer S.Y., & Fried I. (2008). High-resolution depth electrode localization and imaging in patients with pharmacologically intractable epilepsy. Technical Note. Journal of Neurosurgery, 108, 812-5.

The brain as a network: Graph theory reveals medial temporal lobe and neocortical interactions during successful memory retrieval Multiple brain regions are important to spatiotemporal memory yet how these interact at a "systems" level in the brain is not clear. In Watrous et al. 2013 Nature Neuroscience, using multi-lobular recordings from patients undergoing clinical monitoring, we reported that the medial temporal lobe showed elevated levels of low-frequency coherence with neocortical nodes during correct retrieval of recently encoded events. In Schedlbauer et al. 2013 Scientific Reports, we demonstrated a similar finding using fMRI in healthy human participants (specifically, that connectivity was higher across multiple nodes, specifically to the hippocampus, during correct memory retrieval). In two additional papers (Ekstrom et al.), we outline and test models in which neural specific interactions at specific hubs are critical to both encoding and retrieval of navigation and episodic memories. These findings advance our understanding of how networks of brain areas contribute to human navigation and episodic memory both empirically and theoretically.

1. Watrous A.J., Tandon N., Connor C., Pieters T., & Ekstrom A.D. (2013). Frequency-specific increases in network connectivity underlie successful spatiotemporal memory retrieval. Nature Neuroscience, 16, 349-56.
2. Schedlbauer A., Copara M.S., Watrous A.J. and Ekstrom A.D. (2014). Multiple interacting brain areas underlie successful spatiotemporal memory retrieval in humans. Scientific Reports, 4, 6431.
3. Schedlbauer A.M. and Ekstrom A.D. (2019). Flexible network community organization during the encoding and retrieval of spatiotemporal episodic memories. Network Neuroscience. 3: 1070-1093.
4. Ekstrom A.D., Huffman D., and Starrett M.J. (2019). Interacting networks of brain regions underlie human spatial navigation: A review and novel synthesis of the literature. Journal of Neurophysiology. 118: 3328-3344.

Direct recordings from epilepsy patients undergoing seizure monitoring reveal the cellular and oscillatory basis of human spatial navigation. The work summarized below addresses the critical issue of how and in what manner cellular and oscillatory coding mechanisms in the rodent are conserved in humans. In Ekstrom et al. 2003, we establish the presence of both place and view responsive neurons in the hippocampus and parahippocampal cortex, respectively, using direct recordings in patients undergoing surgical monitoring. By demonstrating both place and view coding in the human medial temporal lobe, we helped resolve decades of debate on whether place coding or view coding mechanisms were present in the primate temporal lobes. This paper has been cited more than 1,000 times and forms the foundation of other studies that investigated cellular responses in humans during navigation. Watrous et al. (2011, 2013) establish the presence of low-frequency oscillations during movement and spatial navigation in the human hippocampus. Vass et al. (2016) establish that low frequency oscillations in the human hippocampus code spatial distance by removing sensory and vestibular cues during virtual teleportation. Together, these findings advance our understanding of the extent to which rodent cellular coding mechanisms are both similar and different in the human hippocampus.

1. Ekstrom AD, Kahana MJ, Caplan JB, Fields TA, Isham EA, Newman E, and Fried I. (2003) Cellular networks underlying human spatial navigation. Nature, 425(6954): 184-188. PMID: 12968182.
2. Vass LK, Copara MS, Seyal M. Shahlaie, K, Tomaszewski-Farias S, Shen P, and Ekstrom AD. (2016)Oscillations go the distance: Low frequency human hippocampal oscillations code spatial distance in the absence of sensory cues during teleportation. Neuron, 89:1-7.

3. Bohbot VD, Copara MS, Gotman J, and Ekstrom AD. (2017). Low-frequency oscillations in the human hippocampus during real-world and virtual navigation. Nature Communications, 8:14415.

Research Support

NINDS R01 NS076856 PI: Ekstrom 7/1/12 – 6/30/23

Representation of Spatiotemporal Information in Human Episodic Memory and Navigation

The human hippocampus is critical for both episodic memory and navigation, as indicated by the devastating consequences of neural diseases such as stroke and ischemia. This proposal seeks to leverage functional magnetic resonance imaging and intracranial electrode recordings in patients to address these gaps in knowledge, with potential outcomes providing a more complete framework for understanding how the hippocampal circuitry underlies memory and navigation and how cortical circuits might partially compensate for lost function following hippocampal damage.

NSF BCS-1630296 PI: Ekstrom 9/1/16 – 8/31/21

The Neural Basis of Human Spatial Navigation in Large-scale Virtual Spaces with Vestibular Input

A major gap in our knowledge about human spatial navigation regards the importance of vestibular and other proprioceptive cues (termed "body-based" cues). We propose to cross this barrier in our knowledge by developing a novel set-up in which participants freely ambulate on a 2-D treadmill with a head-mounted display, allowing for full range of motion during navigation. The expected outcomes from this project are a better understanding of how we represent large-scale spaces during free ambulation and the neural basis of direction and distance codes during enriched vs. impoverished body-based cues.

R21 NS120237-01 PI: Ekstrom 09/1/20-08/31/22
NIH/NINDS

Volumetric and connectivity measures of navigation and memory skill acquisition

An important and unresolved question regards the neural basis of acquiring novel cognitive skills, such as improving one's memory by learning to employ a mnemonic strategy or navigating more efficiently through orientation training. Past work has focused primarily on changes in focal brain volume, particularly in the hippocampus, although our preliminary findings suggest that network-wide changes may instead be relevant to such novel skill acquisition. Here, we will directly assess brain volume vs. network-based explanations of cognitive skill acquisition, which could have important ramifications for how we approach rehabilitation after stroke and other forms of neural injury.

NIA R01 AG003376 PI: Barnes 10/1/15 – 9/30/21

Neurobehavioral Relations in Senescent Hippocampus

The objective of this research program is to understand the basis of memory impairments that result from normal aging in rhesus macaques.
Role on Project: Co-investigator

NIA R01 AG061888 PI: Wilson 1/15/20-12/31/24
Evaluating the Neurocomputational Mechanisms of Explore-Exploit Decision Making in Older Adults
Role on Project: Co-investigator

NIMH R01 MH113855 PI: Geng 6/1/18 – 5/31/23

Quantifying the Attentional Template

Problems of attentional control are a core deficit in many mental health disorders, most notably the attention deficit disorders. The proposed work investigates why the quality of attentional control varies between people and situations.
Role on Project: Consultant

Biographical Sketch

Fabian Fernandez, Ph.D.
Assistant Professor, Psychology and Neurology

Education/Training

Institution & Location	Degree	Year(S)	Field of Study
University of Florida, Gainesville, FL	B.Sc.	2002	IDS, Neurobiology
Stanford University, Palo Alto, CA	Ph.D.	2008	Neuroscience
University of Colorado, Denver, CO	Postdoctoral	2009	Neuropharmacology
Johns Hopkins University, Baltimore, MD	Postdoctoral	2015	Translational Neurosci

Personal Statement

Circadian timekeeping is fundamental to human health. Unfortunately, under many clinical circumstances, the temporal organization of our minds and bodies can stray slowly from the Universal Time (UT) that is set with the Earth's rotation. This disorganization has been linked to progression of several age-related and psychiatric diseases. Non-invasive phototherapy has the potential to improve disease outcomes, but the information that the brain's clock tracks in twilight (or any electric light signal) to assure that a person entrains their sleep-wake cycles to the outside world is not understood.

The central theme of my research program is to fill in this blank and to usher in an era where therapeutically relevant "high-precision" light administration protocols are institutionalized at the level of the American Medical and Psychiatric Associations to change the standard of care for a wide variety of conditions that impair quality of life in civilians and Service Members. My model system experience to date includes Drosophila, mice, hamsters, rats, and humans (adults as well as children). Though I have made scientific contributions to other areas of study, namely in Down syndrome research (item 1 in Publications and Career Contributions), the last 7 years of my work have been focused exclusively on the circadian-sleep effects of light where it will stay for the remainder of my career (Contributions, items 2-4). This emphasis has been recognized with a young investigator award from Science Foundation Arizona as well as significant funding from the Velux Stiftung, an international science foundation based in Switzerland seeking to understand and promote the health effects of daylight and artificial light-emission technology. Of the conditions my lab is currently studying, we are particularly interested in how chronic and intermittent light exposure can be designed to: 1. promote healthy aging and recovery from neurological/psychiatric disease, and 2. strengthen adaptive cognitive/emotional responses to being awake in the middle of the night (12-6AM), a key interval of the 24-h cycle that our lab has associated with increased suicide mortality. Our circadian work on mental health is done in very close partnership with the Grandner lab at the University of Arizona (Contributions, item 4).

1. Kaladchibachi S. and Fernandez F. Precision light for the treatment of psychiatric disorders. Neural Plasticity, 5868570, 1-16,2018. PMCID: PMC5821959
2. Fernandez F. Circadian responses to fragmented light: Research synopsis in humans. Yale Journal of Biology & Medicine, 92, 337-348, 2019. PMCID: PMC6585514
3. Killgore W.D., Cloonen S.A., Taylor E.C., Fernandez F., Grandner M.A., and Dailey N.S. Suicidal ideation during the COVID-19 pandemic: The role of insomnia. Psychiatry Research, 290, 113134, 2020. PMCID: PMC7255187

Positions

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
2008 – 2009	Fondation Jérôme-Lejeune fellow with Dr. Alberto C.S. Costa, University of Colorado, Denver
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, Bio5 Fellow, University of Arizona, Tucson

Honors

2000	Peter J. Sones Endowed Scholarship, University of Florida, Gainesville
2001	Charles Vincent McLaughlin Endowed Scholarship, Univ 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)

Contribution to Science

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 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.

1. Fernandez F, Morishita W, Zuniga E, Nguyen J, Blank M, Malenka RC, and Garner CC. (2007)Pharmacotherapy for cognitive impairment in a mouse model of Down syndrome. Nature Neuroscience, 10: 411-413.]
2. Fernandez F and Edgin JO. (2016) Pharmacotherapy in Down syndrome: Which way forward? Lancet Neurology, 15: 776-777.
3. Ruby NF*, Fernandez F, Zhang P, Klima J, Heller HC, and Garner CC. (2010) Circadian locomotor rhythms are normal in Ts65Dn "Down Syndrome" mice and unaffected by Pentylenetetrazole. Journal of Biological Rhythms, 25: 63-66.
4. Fernandez F, Nyhuis CC, Anand P, et al. (2017) Young children with Down syndrome show normal circadian development, but poor sleep efficiency: A cross-sectional study across the first 60months of life. Sleep Medicine, 33: 134-144.

Since 2005, my colleague, Craig Heller and I have explored how circadian dysrhythmia impairs memory function using a novel animal model, the Siberian hamster (Phodopus sungorus). Circadian misalignment due to shift work or jet-lag is well-known to impair memory in humans. However, circadian arrhythmia in rodents resulting from surgical lesion of the suprachiasmatic nucleus (SCN), the brain's clock, has very little effect on memory. Dr. Heller and I reasoned that this long-held disconnect occurred because the SCN remains structurally intact (albeit dysfunctional) in humans, but not in these rodent models. As such, we wondered if the proper phenotypic expression of arrhythmia in the brain–and its effects on memory–might require preservation of circuitry from "malfunctioning" SCN areas to their downstream targets.

We evaluated this possibility in the Siberian hamster, a species that can be rendered circadian arrhythmic by a one-time, external 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 cognitive 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.

1. Ruby NF, Hwang CE, Wessells C, Fernandez F, Zhang P, Sapolsky R, and Heller HC. (2008) Hippocampal-dependent learning requires a functional circadian system. Proceedings of the National Academy of Sciences, 105: 15593-15598.
2. Fernandez F, Lu D, Ha P, Costacurta P, Chavez R, Heller HC, and Ruby NF. (2014) Dysrhythmia in the suprachiasmatic nucleus inhibits memory processing. Science, 346: 854-857.
3. Ruby NF, Fisher N, Patton DF, Paul MJ, Fernandez *, and Heller HC.* (2017) Scheduled feeding restores memory and modulates c-Fos expression in the suprachiasmatic nucleus and septohippocampal complex. Scientific Reports, 7: 6755.

As a model system, the Siberian hamster allowed me and my collaborators to isolate the importance of circadian timekeeping to declarative memory without the confounds of genetic engineering, brain lesioning, or sleep disruption. However, lost on many individuals was the very fact that a benign light stimulus could completely abolish circadian rhythms of physiology and behavior in a wildtype animal—and do so for life. This startling finding has set the backdrop for my current research

program at the UA, where my lab has set out to determine whether the opposite can be achieved: Can we design some logic by which light delivery along the right conditions restores rhythms and mental/physical health back to normal in individuals with existing sleep/circadian problems or those recovering from complex diseases?

Developing patterns of precision light delivery that will strengthen or maintain circadian rhythmicity is not a monolithic endeavor and requires the ability to evaluate many characteristics of light in a rapid, systematic way. To expedite the steps in this process, we have turned to Drosophila as a model organism. Many facets of the circadian system now known to operate in humans were first demonstrated in flies. Like humans, these animals are tasked with entraining to the solar light-dark cycle and evince the same photosensitivity and action spectra to do so. We have used a particular diurnal strain of Drosophila, ananassae, to show that light's effects on the circadian pacemaker are dependent first and foremost on the tempo with which light is administered—not the total photic exposure—as has been historically assumed (e.g., the more light, the better). Given the importance of stimulation patterning in the clock's responses to light, we are now systematically characterizing timekeeping responses to different LED flash protocols tuned for flash intensity, duration, spectrum, and interstimulus interval (among other parameters). We are actively working with collaborators such as Drs. Jamie Zeitzer and Scott Killgore to generalize observations from flies to humans.

1. Negelspach D.C., Kaladchibachi S., and Fernandez F. (2018) The circadian activity rhythm is reset by nanowatt pulses of ultraviolet light. Proceedings of the Royal Society of London B: Biological Sciences, 285, 1884.
2. Kaladchibachi S., Negelspach D.C., and Fernandez F. (2018) Circadian phase-shifting by light: Beyond photons. Neurobiology of Sleep and Circadian Rhythms, 5: 8-14, 2018.
3. Kaladchibachi S., Secor M.A., Negelspach D.C., and Fernandez F. (2019) Longitudinal study of sleep and diurnal rhythms in Drosophila ananassae. Experimental Gerontology, 116, 74-79.
4. Kaladchibachi S., Negelspach D.C., Zeitzer J.M., and Fernandez F. (2019) Optimization of circadian responses with shorter and shorter millisecond flashes. Biology Letters (Royal Society Publishing), 15, 20190371, 2019.

Of the many conditions that could benefit from a greater understanding of nighttime phototherapy, perhaps none stands out more than suicidality. The suicide rate in the US has risen 33% since 1999, emerging as a national public health crisis. The effects of this epidemic have been especially acute for young adults, where suicides are at their highest levels since the government began collecting statistics in 1960. These sobering data create an urgency to understand why young adults commit suicide (the majority do not have a diagnosed mental health condition at time of death). Our previous analyses of CDC data suggest that simply being awake during the middle of the night might confer risk. In collaboration with the Grandner/Killgore labs, we have established that the timing of fatal suicidal injury is 3.6 times more likely to occur at night (12-6am) than during the day when controlling for the number in the population awake, with the highest incidence centered around 3am. This robust temporal pattern of suicide at the population level remains significant when adjusting for demographic variables, symptoms of depression, and does not vary across the month or method of suicide, indicating that seasonal changes in night-length do not affect this risk. Given this particularly strong association, we are actively exploring neuropsychological and neurobiological mechanisms that may explain why nocturnal wakefulness can act as a proximal facilitator of suicidal ideation and ways that these dynamics can be modulated by manipulation of light exposure.

1. Tubbs A.S., Khader W., Fernandez F., and Grandner M.A. (2020) The common denominators of sleep, obesity, and psychopathology. Current Opinion in Psychology, 34, 84-88.
2. Tubbs A.S., Perlis M.L., Basner M., Chakravorty S., Khader W., Fernandez F., and Grandner M.A. (2020) Relationship of nocturnal wakefulness to suicide risk across months and methods of suicide. Journal of Clinical Psychiatry, 81, 19m12964

3. Khader S., Tubbs A.S., Haghighi A., Athey A., Killgore W.D., Hale L., Branas C., Gehrels J.-A., Alfonso-Miller P., Fernandez F-X., and Grandner M.A. (2020) Onset insomnia and insufficient sleep duration are associated with suicide ideation in university students and athletes. Journal of Affective Disorders, 274, 1161-1164.
4. Tubbs A.S., Fernandez F-X., Perlis M.L., Hale L., Branas C., Barrett M., Chakravorty S., Khader W., and Grandner M.A. (2020) Suicidal ideation is associated with morning and nighttime wakefulness in a community sample. Sleep, zsaa128

The Complete List of my Published Work is Available on Google Scholar:

https://scholar.google.com/citations?user=VirL3hwAAAAJ&hl=en&oi=ao

Research Support

Project #1360 Velux Stiftung PI: Fernandez 1/1/20 – 12/31/22

Programming the Circadian Clock with Precision Flashes of LED Light

The basic research conducted in this project will reconceptualize how phototherapy is practiced in the home and clinic. Based on findings that the brain's internal clock is reset by light flashes far shorter than those previously assumed to be functionally relevant, we will develop a dynamic "Morse code" for how such flashes can be strung together to improve circadian health during old age.

Role: Principal Investigator

Biographical Sketch

Elizabeth L. Glisky., Ph.D.
Professor, Psychology (Emerita)

Education/Training

Institution & Location	Degree	Year(S)	Field of Study
University of Toronto	B.A.	1962	Psychology
University of Toronto	Ph.D.	1983	Psychology
University of Toronto	Post-doc	1987	Psychology

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.

1. McFarland C and Glisky E. (2011) Implementation intentions and prospective memory among older adults: An investigation of the role of frontal lobe function. Aging, Neuropsychology, and Cognition, 18, 633-652.
2. Grilli, MD and Glisky EL. (2013) Imagining a better memory: Self-imagination in memory-impaired patients. Clinical Psychological Science, 1, 93-99.
3. Myhre JW, Mehl MR, and Glisky EL. (2016) Cognitive benefits of online social networking in healthy older adults. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences. doi:10.1093/geronb/gbw025.
4. Grilli MD, Woolverton CB, Crawford MS, and Glisky EL. (2017) Self-reference and emotional memory effects in older adults at increased genetic risk of Alzheimer's disease. Aging, Neuropsychology, and Cognition. doi: 10.1080/13825585.2016.1275508.

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, UA
2006 – 2019	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
2019	Professor Emerita, University of Arizona

Honors and Awards

1980 – 1981	Natural Sciences and Engineering Research Council Postgraduate Scholarship
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.

1. Glisky EL, Schacter DL, and Tulving E. (1986) Learning and retention of computer related vocabulary in memory impaired patients: Method of vanishing cues. Journal of Clinical and Experimental Neuropsychology, 8, 292 312.
2. Glisky EL and Schacter DL. (1987) Acquisition of domain specific knowledge in organic amnesia: Training for computer related work. Neuropsychologia, 25, 893 906.
3. Glisky EL. (1992) Acquisition and transfer of declarative and procedural knowledge by memory-impaired patients: A computer data-entry task. Neuropsychologia, 30, 899-910.
4. Glisky EL. (1995) Acquisition and transfer of word processing skill by an amnesic patient. Neuropsychological Rehabilitation, 5(4), 299-318.

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 neuro-psychological tests designed to measure memory function, dependent on the MTLs, and executive function, dependent on the MTLs, 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.

1. Glisky EL, Polster MR, and Routhieaux BC. (1995) Double dissociation between item and source memory. Neuropsychology, 9, 229-235.
2. Glisky EL, Rubin SR, and Davidson PSR. (2001) Source memory in older adults: An encoding or retrieval problem? Journal of Experimental Psychology: Learning, Memory, and Cognition, 27,1131-1146.
3. Glisky EL and Kong LL. (2008) Do young and older adults rely on different processes in source memory tasks? A neuropsychological study. Journal of Experimental Psychology: Learning, Memory, and Cognition, 34, 809-822.
4. Drag LL, Bieliauskas L, Kaszniak AW, Bohnen NI, and Glisky EL. (2009) Source memory and frontal functioning in Parkinson's disease. Journal of the International Neuropsychological Society, 15,399-406.

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.

1. Glisky EL. (1996) Prospective memory and the frontal lobes. In M. Brandimonte, G. Einstein & M. McDaniel (Eds.), Prospective memory: Theory and applications (pp. 249-266). Northvale, NJ: Lawrence Erlbaum Associates.
2. McDaniel MA, Glisky EL, Rubin SR, Guynn MJ, and Routhieaux BC. (1999) Prospective memory: A neuropsychological study. Neuropsychology, 13, 103-110.

3. McFarland CP and Glisky EL. (2009) Frontal lobe involvement in a task of time-based prospective memory. Neuropsychologia, 47, 1660-1669.
4. McFarland C and Glisky E. (2012) Implementation intentions and imagery: Individual and combined effects on prospective memory among young adults. Memory & Cognition, 40, 62-69.

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.

1. Glisky EL and Marquine MJ. (2009) Semantic and self-referential processing of positive and negative trait adjectives in older adults. Memory, 17, 144-157.
2. Grilli MD and Glisky EL. (2010) Self-imagining enhances recognition memory in memory-impaired individual with neurological damage. Neuropsychology, 24, 698-710.
3. Grilli MD and Glisky EL. (2011) The self-imagination effect: Benefits of a self-referential encoding strategy on cued recall in memory-impaired individuals with neurological damage. Journal of the International Neuropsychological Society, 17, 929-933.
4. Grilli MD and Glisky EL. (2013) Imagining a better memory: Self-imagination in memory-impaired patients. Clinical Psychological Science, 1, 93-99. doi: 10.1177/2167702612456464.

Biographical Sketch

Matthew D. Grilli, Ph.D.
Assistant Professor Psychology

Education/Training

Institution & Location	Degree	Year(s)	Field of Study
University of California, Irvine, CA	B.A.	2007	Psychology
University of Arizona, Tucson, AZ	M.A.	2009	Psychology
Brandeis University, Waltham, MA	Ph.D.	2013	Clinical Psychology
VA Boston Healthcare System, Boston, MA	Postdoc	2015	Clinical Neuropsychology

Personal Statement

I am an Assistant Professor in the Departments of Psychology and Neurology at University of Arizona. I am also Director of neuropsychology training for our clinical psychology PhD program and a licensed psychologist. As Principal Investigator of the Human Memory Lab at University of Arizona, my team's research is broadly focused on the clinical and cognitive neuroscience of autobiographical memory, which is memory for real world events. I utilize a combination of cognitive, neuropsychological, neuroimaging (magnetic resonance imaging), and genetic methods. For the past 10 years, I have studied older adults at varying levels of Alzheimer's disease (AD) risk, as well as individuals with medial temporal lobe lesions, to gain insights into the cognitive and neural bases of our ability to form and retrieve long-term memories. In my laboratory, we are developing new cognitive tasks of learning and memory, and we are exploring novel methods for assessing cognition (e.g., smartphone apps), with the goal of creating assessments for cognitive aging that are more accurate, ecologically valid, and better able to detect preclinical signs of AD.

1. Grilli MD, Wank, AA, Bercel, JJ, Ryan, L. Evidence for Reduced Autobiographical Memory Episodic Specificity in Cognitively Normal Middle-Aged and Older Individuals at Increased Risk for Alzheimer's Disease Dementia. Journal of the International Neuropsychological Society. J Int Neuropsychol Soc. 2018 Nov;24(10):1073-1083. doi: 10.1017/S1355617718000577. Epub 2018 Aug 23. PubMed PMID: 30136918; PubMed Central PMCID: PMC6237636.
2. Strikwerda-Brown C, Grilli MD, Andrews-Hanna J, Irish M. "All is not lost"-Rethinking the nature of memory and the self in dementia. Ageing Res Rev. 2019 Jun 22;54:100932. doi: 10.1016/j.arr.2019.100932. [Epub ahead of print] Review. PubMed PMID: 31238174.
3. Memel M, Wank AA, Ryan L, Grilli MD. The relationship between episodic detail generation and anterotemporal, posteromedial, and hippocampal white matter tracts. Cortex. 2020 Feb;123:124-140. doi: 10.1016/j.cortex.2019.10.010. Epub 2019 Nov 6. PubMed PMID: 31783222; PubMed Central PMCID: PMC6984983
4. Wank, AA, Mehl, MR, Andrews-Hanna, JR, Polsinelli, AJ, Moseley, Glisky, EL, & Grilli, MD. Eavesdropping on autobiographical memory: A naturalistic observation study of older adults' memory sharing in daily conversations. Frontiers in Human Neuroscience. 2020. https://doi.org/10.3389/fnhum.2020.00238

Positions

2012 – 2013	Psychology Intern, Boston Consortium in Clinical Psychology, Boston, MA
2012 – 2014	Teaching Fellow in Psychiatry, Boston University School of Medicine, Boston, MA
2012 – 2015	Clinical Fellow in Psychology, Harvard Medical School, Boston, MA

2014 – 2015	Assistant Professor, Boston University School of Medicine, Boston, MA (Promoted while completing postdoctoral fellowship)
2015 – Present	Assistant Professor, Department of Psychology, University of Arizona, Tucson, AZ; Director of Neuropsychology Track for the Clinical Psychology PhD Program
2016 – Present	Director of the Neuropsychology Clinic, Evelyn F. McKnight Brain Institute Affiliate, Department of Neurology, Evelyn F. McKnight Brain Institute, and Graduate Interdisciplinary Program – Cognitive Sciences

Honors

2007	Summa Cum Laude, University of California, Irvine
2007	Undergraduate Investigator Spotlight, University of California, Irvine
2007	Order of Merit Scholar-Athlete of the Year, University of California, Irvine
2007	Undergraduate Research Fellowship, University of California, Irvine
2008	Community Outreach Fellowship, University of Arizona, Tucson
2010	Human Development and Aging Fellowship, Heidelberg University, Germany
2012	College of Science Scholar of the Year, University of Arizona, Tucson
2008	Council of Graduate Schools Dissertation Nominee, Univ of Arizona, Tucson
2019	Junior Investigator Recognition, Arizona Alzheimer's Disease Core Center

Contribution to Science

Revealing normal age-related changes in autobiographical memory. Much of my work aims to understand why, relative to younger adults, cognitively unimpaired older adults seem to think about their past (and future) in a more "semantic" way – meaning relying on factual details and more general or extended event descriptions (e.g. details spanning several days). In our recent work, we have used a "think aloud" paradigm (Wank, Andrews-Hanna, & Grilli, in press, Memory & Cognition) to show that older age is associated with reduced efficiency in two episodic retrieval routes that have been linked to prefrontal and medial temporal lobe recollection. In addition, we (Acevedo-Molina, Matijevic, & Grilli, 2020, Memory) showed that when asked to describe life chapters, which are broad, conceptual periods of time (e.g., first job or living in Tucson), older adults generate more detail than younger adults, suggesting that this story-telling corresponds with older adults' retrieval style. I, along with my collaborators Dr. Jessica Andrews-Hanna and Dr. Matthias Mehl, have started to used smartphone applications to assess autobiographical memory. In one project (Wank, et al., Grilli, 2020, Frontiers in Human Neuroscience), we drew on evidence of fairly widespread age-related alterations to the default network of the brain, which has been implicated in both episodic and semantic autobiographical retrieval, to propose that reflecting on the past may become less common with advanced age – a finding that would be difficult to reveal in constrained, brief lab tasks. Using a smartphone app that records ambient sound, we showed that older age is associated with less sharing of autobiographical memories in daily conversations.

1. Acevedo-Molina MC, Matijevic S, Grilli MD. Beyond episodic remembering: elaborative retrieval of lifetime periods in young and older adults. Memory. 2020 Jan;28(1):83-93. doi: 10.1080/09658211.2019.1686152. Epub 2019 Oct 31. PubMed PMID: 31665972; PubMed Central PMCID: PMC6934901
2. Wank, AA, Andrews-Hanna, JR, & Grilli, MD (in press). Searching for the Past: Exploring the Dynamics of Direct and Generative Autobiographical Memory Search Among Young and Cognitively Normal Older Adults. Memory & Cognition. https://doi.org/10.31234/osf.io/hd749
3. Wank, AA, Mehl, MR, Andrews-Hanna, JR, Polsinelli, AJ, Moseley, Glisky, EL, & Grilli, MD. Eavesdropping on autobiographical memory: A naturalistic observation study of older adults' memory sharing in daily conversations. Frontiers in Human Neuroscience. 2020. https://doi.org/10.3389/fnhum.2020.00238

Uncovering early cognitive and brain markers of Alzheimer's disease risk in autobiographical memory and the default network. In addition to characterizing normal age-related cognitive outcomes, I am studying whether autobiographical memory might aid in the pre-clinical detection of Alzheimer's disease. I hypothesized that because autobiographical memory places a high burden on the core brain network affected by Alzheimer's disease, namely the default network, some of the earliest signs of this age-related disease may be found in the way middle-aged and older adults reflect on their personal past. We have shown that in cognitively unimpaired older adults, we can associate declines in autobiographical memory episodic specificity, meaning episodic memory retrieval or detail generation, with several risk factors for Alzheimer's disease, including advanced age (Wank et al., 2020, Frontiers in Human Neuroscience), the structural integrity of the fornix and cortical pathways vulnerable to aging and Alzheimer's disease (Memel, Wank, Ryan, & Grilli, 2020, Cortex), and the e4 allele of the APOE gene (Grilli et al., 2018, JINS; in prep). I, along with my collaborator Dr. Jessica Andrews-Hanna, have since extended our hypothesis to include other forms of autobiographical thought and to propose a more refined connection between autobiographical thought patterns and integrity of the default network (Andrews-Hanna et al., 2019, OREP).

1. Grilli MD, Wank, AA, Bercel, JJ, Ryan, L. Evidence for Reduced Autobiographical Memory Episodic Specificity in Cognitively Normal Middle-Aged and Older Individuals at Increased Risk for Alzheimer's Disease Dementia. J Int Neuropsychol Soc. 2018 Nov;24(10):1073-1083. doi: 10.1017/S1355617718000577. Epub 2018 Aug 23. PubMed PMID: 30136918; PubMed Central PMCID: PMC6237636.
2. Andrews-Hanna JR, Grilli MD, Irish M. A Review and Reappraisal of the Default Network in Normal Aging and Dementia. In Oxford Research Encyclopedia of Psychology. Oxford University Press. 2019 March; doi: 10.1093/acrefore/9780190236557.013.384
3. Memel M, Wank AA, Ryan L, Grilli MD. The relationship between episodic detail generation and anterotemporal, posteromedial, and hippocampal white matter tracts. Cortex. 2020 Feb;123:124-140. doi: 10.1016/j.cortex.2019.10.010. Epub 2019 Nov 6. PubMed PMID: 31783222; PubMed Central PMCID: PMC6984983

Elucidating the role of the medial temporal lobe in autobiographical memory. A longstanding view in my field is that there are two basic types of autobiographical memory: episodic memories, meaning memories of unique events, and personal semantics, which are facts/knowledge about the self. Until recently, far more attention was given to how these two types of autobiographical memory differed as opposed to how they might be similar. I have been particularly interested in revealing how the medial temporal lobe, a brain region long implicated in episodic memories, contributes to personal semantics. Through lesion-based work, we have shown that some personal semantics depend on the medial temporal lobe for retrieval, namely knowledge that describes the scene or timing of repeated events (e.g., family dinners) and extended events (e.g., college years) (Grilli & Verfaellie, 2014; 2016, Neuropsychologia). In contrast, we have found that conceptually-based personal semantics, such as abstract facts about one's life and one's personality, depend on anterior lateral temporal and medial prefrontal cortical regions, which are implicated in general semantics (Grilli, Bercel, Wank, & Rapcsak, 2018; Marquine, Grilli, et al., 2016, Neuropsychologia).

1. Grilli MD, Verfaellie M. Personal semantic memory: insights from neuropsychological research on amnesia. Neuropsychologia. 2014 Aug;61:56-64. PubMed PMID: 24949553.
2. Grilli MD, Verfaellie M. Experience-near but not experience-far autobiographical facts depend on the medial temporal lobe for retrieval: Evidence from amnesia. Neuropsychologia. 2016 Jan 29;81:180-5. PubMed PMID: 26721761; PubMed Central PMCID: PMC4738052.
3. Grilli MD, Bercel, JJ, Wank, AA, Rapcsak, SZ. The contribution of the left anterior ventrolateral temporal lobe to the retrieval of personal semantics Neuropsychologia. 2018 Aug;117:178-187. doi: 10.1016/j.neuropsychologia.2018.06.002. Epub 2018 Jun 4. PubMed PMID: 29879423.

4. Marquine MJ*, Grilli MD*, Rapcsak SZ, Kaszniak AW, Ryan L, Walther K, Glisky EL. Impaired personal trait knowledge, but spared other-person trait knowledge, in an individual with bilateral damage to the medial prefrontal cortex. Neuropsychologia. 2016;89:245-53. Epub 2016/06/21. doi: 10.1016/j.neuropsychologia.2016.06.021. PubMed PMID: 27342256; PMCID: PMC5119478. * Co-first authors.

Advancing understanding of how autobiographical memory is necessary for maintaining the self-concept. We have shown that despite profound episodic memory deficits, individuals with medial temporal lobe amnesia can turn to memory to reflect on their identity, contemplating what "defines them" and constructing the basic narrative of their life story (Grilli & Verfaellie, 2015, SCAN; Grilli & Verfaellie, 2016, Neuropsychologia; Grilli, Wank, & Verfaellie, 2018, Neuropsychologia; Grilli, Bercel, Wank, & Rapcsak, 2018, Neuropsychologia). Yet, whereas cognitively normal individuals tend to retrieve a rich combination of episodic and semantic memories from across the lifespan, individuals with medial temporal lobe amnesia rely on a limited set of facts, which seems to have consequences for how they describe their identity and life story. For instance, the sense of self in individuals with medial temporal lobe amnesia seems to be less robust, as these individuals tend to describe their identity with fewer traits and trait-supporting memories. The life stories of individuals with medial temporal lobe amnesia also appear to lack complexity, with less reference to themes (i.e., "chapters") and memories that overlap in time. Our results indicate that the medial temporal lobe has a role in forming and elaborating identity, which has implications for other clinical populations.

1. Grilli MD, Verfaellie M. Supporting the self-concept with memory: insight from amnesia. Soc Cogn Affect Neurosci. 2015 May 11;PubMed PMID: 25964501.
2. Grilli MD. The association of personal semantic memory to identity representations: insight into higher-order networks of autobiographical contents. Memory. 2017:1-9. Epub 2017/04/17. doi: 10.1080/09658211.2017.1315137. PubMed PMID: 28415908.
3. Strikwerda-Brown C, Grilli MD, Andrews-Hanna J, Irish M. "All is not lost"-Rethinking the nature of memory and the self in dementia. Ageing Res Rev. 2019 Jun 22;54:100932. doi: 10.1016/j.arr.2019.100932. [Epub ahead of print] Review. PubMed PMID: 31238174.
4. Grilli, M.D., & Ryan, L. (in press). Autobiographical memory and the self-concept. In R. Lane, L. Ryan, & L. Nadel (Eds.) The Neuroscience of Enduring Change: The Neural Basis of Talk Therapies. New York, NY: Oxford University Press U.S.A.

Investigating self-referential processing as a means for improving memory. Although much of my research has focused on advancing cognitive neuroscience models, I always consider how insights from basic research can inform new interventions for memory disorders. My first line of research merged two largely separate literatures on self-referential processing and imagination to establish a new cognitive strategy for improving episodic memory in individuals with acquired brain injury, which I referred to as self-imagination. In a series of studies, I have demonstrated that self-imagination is a highly effective cognitive intervention for individuals with traumatic brain injury and cognitively normal older adults, capable of enhancing recognition, cued recall, free recall, and prospective memory across various delays and over and above a variety of cognitive strategies.

1. Grilli MD, Glisky EL. Self-imagining enhances recognition memory in memory-impaired individuals with neurological damage. Neuropsychology. 2010 Nov;24(6):698-710. PubMed PMID: 20873930; PubMed Central PMCID: PMC2970672.
2. Hou M, Grilli MD, Glisky EL. Self-reference enhances relational memory in young and older adults. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2019 Jan;26(1):105-120. doi: 10.1080/13825585.2017.1409333. Epub 2017 Nov 27. PubMed PMID: 29179612.
3. Grilli MD, McFarland CP. Imagine that: self-imagination improves prospective memory in memory-impaired individuals with neurological damage. Neuropsychol Rehabil. 2011 Dec;21(6):847-59. PubMed PMID: 22150451; PubMed Central PMCID: PMC3296226.

4. Grilli MD, Glisky EL. Imagining a better memory: Self-imagination in memory-impaired patients. Clinical psychological science : a journal of the Association for Psychological Science. 2013; 1(1):93-99.

Complete list of published work in My Bibliography

https://www.ncbi.nlm.nih.gov/sites/myncbi/matthew.grilli.1/bibliography/48613144/public/?sort=date&direction=ascending

Research Support

RO3 AG060271 Grilli (PI) 4/15/19 – 3/31/21
NIH/NIA
The episodic autobiographical memory (EAM) hypothesis of preclinical Alzheimer's disease: Developing a new approach for early cognitive detection and measurement of Alzheimer's disease
The specific aims of this projects are to 1) To reveal that core EAM sub-components are disrupted in cognitively normal older ε4 carriers. 2) To demonstrate that EAM disruption is associated with altered RSFC in the DMN, indicating that disrupted EAM detects mild and/or severe preclinical AD.

R01 NS114913 Ekstrom & Yonelinas (MPIs) 6/15/20 – 5/31/25
NIH/NINDS
Precision and binding as two dimensions of medial temporal lobe amnesia
Specific aims: 1) to determine the impact of bilateral medial temporal lobe lesions on the precision and binding of memories. 2) To determine the neural mechanisms underlying compensatory recovery of cognitive function from unilateral surgical resection of the medial temporal lobe using the theoretical framework provided by PBM
Role on Project: co-investigator

McKnight Brain Research Foundation Grilli (MPI) 4/6/18 – 4/1/21
Uncovering Risk Profiles of Deception and Mitigating Susceptibility to Scamming in Midlife and Older Age: A Novel Intervention Tool
The specific aims of this project are to: 1) develop a prototype of MERLIN, an automated warning tool to support decision-making online; 2) develop the in-lab Scam Identification Task (SIT), a new behavioral task to effectively "scam people in the lab" and allow validation of the efficacy of MERLIN under controlled conditions; and 3) quantify the cognitive, physical, and socio-affective correlates of scam susceptibility to tailor MERLIN to age-specific user profiles.
Role on Project: PI (multi-PI)

Arizona Alzheimer's Consortium, DHS Grilli (PI) 7/1/20 -6/30/21
Autobiographical memory, future thinking, and neuropsychology in Hispanics.
The specific aims of this project are: 1) To reveal similarities and differences in themes and content of autobiographical memory and future thinking in Hispanic and White non-Hispanic adults.
Arizona Alzheimer's Consortium, DHS Grilli (PI) 7/1/19 -6/30/20\

Improving clinical neuropsychological assessment of subtle cognitive decline and mild cognitive impairment.
The specific aims of this project are to 1) To test everyday cognition in the context of subtle cognitive decline and mild cognitive impairment. 2) to begin longitudinal assessment of everyday cognition in these populations.

Biographical Sketch

Matthew J. Huentelman, Ph.D.
Professor of Neurogenomics

Education/Training

Institution & Location	Degree	Year(s)	Field of Study
Ohio University, Athens, OH	B.S.	1998	Biochemistry
University of Florida, Gainesville, FL	Ph.D..	2003	Physiology & Genomics
University of Florida, Gainesville, FL	Postdoc	2004	Physiology & Genomics
Translational Genomics Res. Inst., Phoenix, AZ	Postdoc	2006	Neuroscience & Genomics

Personal Statement

I have researched traits and diseases of the central nervous system for over twenty years, and I have extensive training in the physiology and molecular dissection of neuronal and glial cells. During the past fifteen years I have focused on the application of molecular genetic "-omics" technologies in the study of the basic characteristics of the brain as well as susceptibility to degenerative brain diseases. During my time at TGen, my laboratory has grown significant experience in the wet laboratory generation and bioinformatics assessment of next generation DNA and RNA sequencing data. My laboratory is split approximately 60:40 between wet laboratory (2 postdoctoral fellows, 1 graduate student, 1 Masters-level lab technician, and 1 Bachelors-level lab technician totaling over 17 years of experience in my lab) and bioinformatics (1 Research Assistant Professor, 1 Masters-level, and 1 Bachelors-level totaling over 15 years of experience in my lab) personnel and I have a demonstrable publication track record in both general areas of research.

Positions

06/98 – 08/98	Visiting Researcher, MV Lomonosov Moscow State University, Moscow, Russia
08/03 – 11/03	Visiting Postdoctoral Research Fellow, University of Bristol, United Kingdom
11/03 – 06/04	Postdoctoral Research Fellow, University of Florida, Gainesville, FL
07/04 – 08/06	Postdoctoral Research Fellow, Translational Genomics Research Institute, Phoenix, AZ
08/06 – 12/08	Assistant Professor, Translational Genomics Research Institute, Phoenix, AZ
12/08 – 02/16	Associate Professor, Translational Genomics Research Institute, Phoenix, AZ
06/10 – Present	Affiliate, Evelyn F. McKnight Brain Institute, University of Arizona, Tucson, AZ
08/11 – Present	Adjunct Faculty Member, Arizona State University SoLS, Tempe, Arizona
10/13 – Present	Scientific Director, Center for Rare Childhood Disorders, TGen, Phoenix, Arizona
05/14 – Present	Research Affiliate, Mayo Clinic, Scottsdale, Arizona
07/14 – Present	Research Associate Professor, Dept of Basic Medical Sciences, University of Arizona, Phoenix, AZ
02/16 – Present	Professor, Translational Genomics Research Institute, Phoenix, AZ

Honors

1994	Richard Eddy Service Award, Dept. of Chemistry, Ohio University, Athens, OH
1994	Hiram & Florence Wilson Scholarship, Dept. of Chemistry, Ohio Univ, Athens, OH
1998	Hamilton Community Foundation Award, Hamilton, OH

1998	Jeanette Grasseli-Brown Undergrad Research Award, Ohio Univ, Athens, OH
2000-2002	American Heart Assoc Predoctoral Fellowship, Florida/Puerto Rico Affiliate
2001	Proctor & Gamble Professional Opportunity Award, American Physiological Soc
2008	Young Investigator Award, The Arizona Alzheimer's Consortium, Phoenix, AZ
2009	Award for Research Excellence (nominee), Arizona Bioindustry Association
2013	40 Under 40 Awardee, Phoenix Business Journal
2014-2016	Board Member, Alzheimer's Association / Desert Southwest Chapter

Contribution to Science

Identification of the Genetic Basis of Human Disease – Rare Diseases in Children and Alzheimer's Disease: During the last 15 years my laboratory has focused on the use of multi-omics approaches [DNA, RNA, and protein analyses] to identify the genetic basis of rare and common human neurological diseases. Typically, these studies involve either a long-distance collaboration with other clinics and sequencing laboratories or large multi-laboratory collaborative efforts (this is especially true for our Alzheimer's disease work). In the last five years, we have reported on the identification of a new genetic basis for over 8 different neurological disorders.

In TGen's Center for Rare Childhood Disorders (C4RCD) clinic we have sequenced over 1,500 DNA samples in our attempts to identify the basis of disease in pediatric patients with neurological symptoms. Due to our focused efforts and extremely close collaboration with each treating neurologist we have identified the genetic cause in ~35% of our families. A particular focus of our Center is in the study of underserved individuals including over 60% of our families who are on Arizona's medical public assistance program (AHCCCS) and a partnership with a medical clinic in Hermosillo, Mexico in the cross-border Arizona-neighboring state of Sonora.

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

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

1. Arboleda-Velasquez JF, Lopera F, O'Hare M, Delgado-Tirado S, Marino C, Chmielewska N, Saez-Torres KL, Amarnani D, Schultz AP, Sperling RA, Leyton-Cifuentes D, Chen K, Baena A, Aguillon D, Rios-Romenets S, Giraldo M, Guzmán-Vélez E, Norton DJ, Pardilla-Delgado E, Artola A, Sanchez JS, Acosta-Uribe J, Lalli M, Kosik KS, Huentelman MJ, Zetterberg H, Blennow K, Reiman RA, Luo J, Chen Y, Thiyyagura P, Su Y, Jun GR, Naymik M, Gai X, Bootwalla M, Ji J, Shen L, Miller JB, Kim LA, Tariot PN, Johnson KA, Reiman EM, Quiroz YT. Resistance to autosomal dominant Alzheimer's disease in an APOE3 Christchurch homozygote: a case report. Nat Med. 2019 Nov;25(11):1680-1683.
2. Balak C, Benard M, Schaefer E, Iqbal S, Ramsey K, Ernoult-Lange M, Mattioli F, Llaci L, Geoffroy V, Courel M, Naymik M, Bachman KK, Pfundt R, Rump P, Ter Beest J, Wentzensen IM, Monaghan KG, McWalter K, Richholt R, Le Béchec A, Jepsen W, De Both M, Belnap N, Boland A, Piras IS, Deleuze JF, Szelinger S, Dollfus H, Chelly J, Muller J, Campbell A, Lal D, Rangasamy S, Mandel JL, Narayanan V, Huentelman M, Weil D, Piton A. Rare De Novo Missense Variants in RNA Helicase DDX6 Cause Intellectual Disability and Dysmorphic Features and Lead to P-Body Defects and RNA Dysregulation. Am J Hum Genet. 2019 Sep 5;105(3):509-525.

3. Schrauwen I, Szelinger S, Siniard AL, Kurdoglu A, Corneveaux JJ, Malenica I, Richholt R, Van Camp G, De Both M, Swaminathan S, Turk M, Ramsey K, Craig DW, Narayanan V, Huentelman MJ. A (2015) Frame-Shift Mutation in CAV1 Is Associated with a Severe Neonatal Progeroid and Lipodystrophy Syndrome. PLoS One. 10:e0131797. doi: 10.1371/journal.pone.0131797. eCollection.
4. Szelinger S, Malenica I, Corneveaux JJ, Siniard AL, Kurdoglu AA, Ramsey KM, Schrauwen I, Trent JM, Narayanan V, Huentelman MJ, Craig DW. (2014) Characterization of X chromosome inactivation using integrated analysis of whole-exome and mRNA sequencing. PLoS One. 9:e113036. doi: 10.1371/journal.pone.0113036.

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

1. Piras IS, Bleul C, Talboom JS, De Both MD, Schrauwen I, Halliday G, Myers AJ, Serrano GE, Beach TG, Huentelman MJ. ESHRD: deconvolution of brain homogenate RNA expression data to identify cell-type-specific alterations in Alzheimer's disease. Aging (Albany NY). 2020 Mar 2;12(5):4124-4162.
2. Craig DW, Pearson JV, Szelinger S, Sekar A, Redman M, Corneveaux JJ, Pawlowski TL, Laub T, Nunn G, Stephan DA, Homer N, Huentelman MJ. (2008) Identification of genetic variants using bar-coded multiplexed sequencing. Nat Methods, 5: 887-893.
3. Pearson JV, Huentelman MJ, Halperin RF, Tembe WD, Melquist S, Homer N, Brun M, Szelinger S, Coon KD, Zismann VL, Webster JA, Beach T, Sando SB, Aasly JO, Heun R, Jessen F, Kolsch H, Tsolaki M, Daniilidou M, Reiman EM, Papassotiropoulos A, Hutton ML, Stephan DA, Craig DW. (2007) Identification of the genetic basis for complex disorders by use of pooling-based genomewide single-nucleotide-polymorphism association studies. Am J Hum Genet, 80:126-a39. PMID: 17160900; PMCID: PMC1785308.
4. Coleman JE, Huentelman MJ, Kasparov S, Metcalfe BL, Paton JF, Katovich MJ, Semple-Rowland SL, Raizada MK. (2003) Efficient large-scale production and concentration of HIV-1-based lentiviral vectors for use in vivo. Physiol Genomics, ;12:221-228.

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

both the development of wet laboratory methods and informatics approaches for biomarker discovery and characterization.

1. Kalani MYS, Alsop E, Meechoovet B, Beecroft T, Agrawal K, Whitsett TG, Huentelman MJ, Spetzler RF, Nakaji P, Kim S, Van Keuren-Jensen K. Extracellular microRNAs in blood differentiate between ischaemic and haemorrhagic stroke subtypes. J Extracell Vesicles. 2020 Jan 24;9(1):1713540.
2. Huentelman M, De Both M, Jepsen W, Piras IS, Talboom JS, Willeman M, Reiman EM, Hardy J, Myers AJ. Common BACE2 Polymorphisms are Associated with Altered Risk for Alzheimer's Disease and CSF Amyloid Biomarkers in APOE ε4 Non-Carriers. Sci Rep. 2019 Jul 3;9(1):9640
3. Napolioni V, Ober-Reynolds B, Szelinger S, Corneveaux JJ, Pawlowski T, Ober-Reynolds S, Kirwan J, Persico AM, Melmed RD, Craig DW, Smith CJ, Huentelman MJ. (2013) Plasma cytokine profiling in sibling pairs discordant for autism spectrum disorder. J Neuroinflammation, 10:38.
4. Kim S, Swaminathan S, Shen L, Risacher SL, Nho K, Foroud T, Shaw LM, Trojanowski JQ, Potkin SG, Huentelman MJ, Craig DW, DeChairo BM, Aisen PS, Petersen RC, Weiner MW, Saykin AJ (2011) Alzheimer's Disease Neuroimaging Initiative. Genome-wide association study of CSF biomarkers Abeta1-42, t-tau, and p-tau181p in the ADNI cohort. Neurology, 76:69-79

Complete list of published work in My Bibliography

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

Research Support

Aging Foundation Grant 20170175 Padilla (PI) 9/1/17-11/20/20

Early Onset Alzheimer's Disease Genomic Study

Clinical genomic analysis will be conducted on blood samples from patients who have been diagnosed with early onset Alzheimer's Disease and are "outliers" with no risk factors or family history of the disease.

Role: Co-Principal Investigator

NIA R01 AG049465 Barnes (PI) 8/1/14-3/31/20

Neural System Dynamics and 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.

Role: Co-Investigator

R01 AG049464 Coleman/Barnes/Alexander (MPI) 8/1/14-7/31/20

Epigenetic, Neuroimaging and 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.

Role: Co-Investigator

NIA P30 AG019610 Reiman (PI) 7/1/16-6/30/21

Arizona Alzheimer's Disease Core Center

This grant supports the clinical and research investigation of Alzheimer's disease. Dr. Huentelman will contribute his expertise regarding aspects of next generation sequencing data generation, quality control, statistical analysis, storage/dissemination, and general project and personnel management.

Role: Co-Investigator

NIA P30 AG019610-20S1 Reiman 6/01/20 - 6/30/21

Arizona Alzheimer's Disease Core Center- (COVID-19 Supplement)

This project will investigator 100 or more consecutive autopsies spanning the pandemic period to examine the effects of SARS-CoV-2 infection on central nervous system tissue.

Role: Co-Investigator

NIH UG30D023313 Deoni (PI) 9/21/16-8/31/21
The Developing Brain: Influences and Outcomes
Dr. Huentelman will advise the research team on the collection and analysis of DAN samples collected from all participants. In addition to overseeing the specific analysis described in this proposal, he will also work closely with the ECHO Core on implementing and performed required standardized analyses and contributing this data back to the overall consortium.
Role: Co-Investigator

NIA R01 1AG054180 Kaczorowski (PI) 5/15/17-4/30/22
Systems Genetics of Cognitive Aging and Alzheimer's Disease
Dr. Huentelman will contribute his expertise in the curation, interpretation, and analysis of his own – as well as publicly available data – for Alzheimer's disease and aging.
Role: Co-Investigator

NIH R56HL141165 Hale (PI) 9/20/18-8/31/23
Identifying a Pathogenic Fibroblast Subpopulation to Target for Protection Against Cardiac Fibrosis
Dr. Huentelman will lead a team for this grant that will perform generation and analysis of single cell RNA sequencing data.
Role: Co-Investigator

AZ Alzheimer's Consortium (ADHS) Huentelman/Reiman 7/1/20-6/30/21
Common genetic polymorphisms associated with exceptional verbal memory performance in aging
The aim of this project is to identify the genetic factors that may be associated with exceptional age-related performance on a verbal learning task.
Role: Principal Investigator

DARPA HR001119S0021 Broderick (PI) 10/1/19- 8/31/21
Peerless Operator Biologic Aptitude (Peerless)
The goal is to deliver a disruptive selection and training platform that integrates revolutionary high-information density molecular expression circuits, predictive models and real-time in vivo sensors to increase the biologic aptitude of elite special forces operators and units.
Role: Co-Investigator

DOD W81XWH1910534 Schwedt (PI) 09/01/19 - 8/31/23
A multidisciplinary translational approach to investigate the mechanisms, predictors and prevention of persistent post traumatic headache
Dr. Huentelman and his team will collaborate with the other investigators to perform multi-omic analysis of human clinical blood specimens from migraine patients.
Role: Co-Investigator

NIMH R01 MH097803 Gallitano (PI) 09/01/23 - 08/31/24
Environmental Regulation of Cortical Gene Expression and Circuit Function
Dr. Huentelman and his team perform analyses of the RNA sequencing data for genes and pathways.
Role: Co-Investigator

NIA R01 AG067781 Rogalski (PI) 05/01/20 - 04/30/25
Cognitive SuperAging: A model to explore resilience and resistance to aging and Alzheimer's disease
Dr. Huentelman and his team will perform analysis of the RNA sequencing data for genes and pathways.
Role: Co-Investigator

Biographical Sketch

Matthias R. Mehl, Ph.D.
Professor, Psychology

Education/Training

Institution & Location	Degree	Year(S)	Field of Study
University of Erlangen, Germany	B.A./M.A.	1998	Psychology
University of Texas, Austin, TX	Ph.D.	2004	Psychology

Personal Statement

I am a social, personality, and health psychologist with broad interest and expertise in the conceptualization and measurement of how social processes affect health. Methodologically, I use subjective and objective ambulatory assessment methods to study social processes and have helped to pioneer novel methods of ecologically valid data collection. One of these methods involves the collection and coding of ambient sounds via recording device called the Electronically Activated Recorder (EAR). As the developer of the EAR, a naturalistic observation sampling method, I have extensive experience in the administration of the EAR, the coding of ambient sounds, and the management and analysis of naturalistic observation data. I also have experience developing new approaches to coding ambient sounds for the purpose of understanding social processes in distinct populations, e.g., postpartum women. Finally, as a trained social/personality and health psychologist, I have pertinent research expertise in the area of social processes and health. I joined the faculty of the Psychology Department of the University of Arizona in 2004 where I am now a tenured Full Professor. I am also an Affiliate Faculty in Family Studies and Human Development and the Department of Communication, and an Affiliated Investigator at the Arizona Cancer Center, the Evelyn F. McKnight Brain Institute, and the University of Arizona Institute on Place, Wellbeing & Performance. My prior collaborative research has been funded, among other sources, by the American Cancer Society, the National Science Foundation, the NIH (National Institute of Mental Health, National Cancer Institute, National Center for Complementary and Integrative Health, National Institute for Child Health and Human Development) and the Intelligence Advanced Research Projects Activity (IARPA).

Positions

1998 – 1999	Visiting Scholar, Department of Psychology, University of Texas at Austin
1999 – 2000	Research Assistant, Institute for Physiological Psychology, University of Düsseldorf
2004 – 2010	Assistant Professor, Department of Psychology, University of Arizona
2010 – 2016	Associate Professor, Department of Psychology, University of Arizona
2007 – Present	Adjunct Faculty, Department of Communication, University of Arizona
2007 – Present	Associate Investigator, Arizona Cancer Center, University of Arizona
2010 – Present	Affiliate Faculty, Department of Communication, University of Arizona
2011 – Present	Affiliate Faculty, Evelyn F. McKnight Brain Institute, University of Arizona
2016 – Present	Professor, Department of Psychology, University of Arizona
2017 – Present	Affiliate Faculty, Div of Family Studies & Human Development, Univ of Arizona
2017 – Present	Affiliate Faculty, Institute of Place, Wellbeing & Performance, Univ of Arizona

Honors

1996 – 1998	Undergraduate Fellowship, German National Academic Foundation
1998 – 1999	Postgraduate Fellowship for Studying Abroad, German National Academic Foundation
2003 – 2004	University Continuing Fellowship, University of Texas at Austin
2011	Rising Star Award, Association for Psychological Science
2015	Fellow, Society for Personality and Social Psychology
2015	Fellow, Association for Psychological Science
2018	Fellow, Collegium Helveticum & Digital Society Initiative, University of Zürich
2019	Miegunyah Distinguished Visiting Fellow, University of Melbourne

Contribution to Science

Development of a Methodology for Naturalistic Observation of Daily Social Behavior and Interactions. Despite the fact that psychology is the study of human behavior, naturalistic observation of social behavior has a remarkably thin history in the field. I have (co-)developed and psychometrically validated the Electronically Activated Recorder as an ecological momentary assessment method for tracking people's naturally occurring (acoustic) social lives. Technically, the EAR is a digital audio recorder that intermittently records snippets of ambient sounds while participants go about their normal lives. Conceptually, it is a naturalistic observation method that produces an acoustic log of a person's day as it unfolds. With the EAR, researchers can study how subtle, yet objective aspects of people's daily behaviors and interactions are related to core psychological processes. The EAR app is freely available on iTunes and the Google Playstore and is currently being used in research studies by more than two dozen investigator groups on three continents.

1. Mehl MR, Pennebaker JW, Crow MD, Dabbs J, and Price JH. (2001) The Electronically Activated Recorder (EAR): A device for sampling naturalistic daily activities and conversations. Behavior Research Methods, Instruments, and Computers, 33:517–523.
2. Mehl MR and Conner TS. (Eds.) (2012) Handbook of research methods for studying daily life. Guilford Press: New York, NY.
3. Mehl MR, Robbins ML, and Deters GF. (2012) Naturalistic observation of health-relevant social processes: The Electronically Activated Recorder (EAR) methodology in psychosomatics. Psychosomatic Medicine, 74:410-417.
4. Mehl MR. (2017) The Electronically Activated Recorder or EAR: A method for the naturalistic observation of daily social behavior. Current Directions in Psychological Science, 26:184-190.

Natural Word Use as Linguistic Marker of Psychological Processes. Despite the fact that verbal behavior is by far the most frequent human behavior (apart from sleep), verbal data sources, until recently, have been surprisingly neglected. We have found that computerized text analysis programs, despite their relative conceptual simplicity, can provide highly valuable information about patterns of word use. People's natural (written or spoken) word use shows clear associations with their personalities, social status, well-being and even mental and physical health. In my research, I have studied word use mostly in the context of personality and coping-related couple and family interactions.

1. Pennebaker JW, Mehl MR, and Niederhoffer K. (2003) Psychological aspects of natural language use: Our words, our selves. Annual Review of Psychology, 54:547–577.
2. Mehl MR, Vazire S, Ramírez-Esparza N, Slatcher RB, and Pennebaker JW. (2007) Are women really more talkative than men? Science, 317:82.

3. Carey AL, Brucks M, Küfner ACP, Holtzman N, Deters F, Back MD, Donnellan B, Pennebaker JW, and Mehl MR. (2015) Narcissism and the use of personal pronouns revisited. Journal of Personality and Social Psychology, 109, e1-e15. doi: 10.1037/pspp0000029.
4. Mehl MR, Raison CL, Pace TWW, Arevalo JMG, and Cole SW. (2017) Natural language indicators of differential gene regulation in the human immune system. Proceedings of the National Academy of Sciences, 114:12554-12559.

The Role of Everyday Social Interactions in Coping and Health. Critical life events can cause serious disruptions to people's social lives. In my research, I explore the role that people's daily social lives play in coping with and adjustment to personal and collective upheavals. Because self-reports are particularly susceptible to bias when material of high personal relevance and emotional intensity is assessed—the very material in which coping researchers are interested—I have pursued this question primarily from a behavioral observation perspective. This choice of method has led to a theoretical focus on the role that people's mundane, ordinary, everyday conversations play for coping and health (in contrast to direct coping conversations about the focal illness or critical life event).

1. Mehl MR and Pennebaker JW. (2003) The social dynamics of a cultural upheaval: Social interactions surrounding September 11, 2001. Psychological Science, 14:579–585.
2. Robbins ML, Focella ES, Kasle S, Weihs KL, Lopez AM, and Mehl MR. (2011) Naturalistically observed swearing, emotional support and depressive symptoms in women coping with illness. Health Psychology, 30:789-792.
3. Robbins ML, Mehl MR, Holleran SE, and Kasle S. (2011) Naturalistically observed sighing and depression in rheumatoid arthritis patients: A preliminary study. Health Psychology, 30:129-133.
4. Robbins ML, López AM, Weihs KL, and Mehl MR. (2014) Cancer conversations in context: Naturalistic observation of couples coping with breast cancer. Journal of Family Psychology,28:380-390.

Behavioral Manifestations of Personality in Everyday Life. Personality is an important predictor of personal and relational life outcomes. However, for a long time, the field of personality was largely built on questionnaire responses and was lacking an empirical grounding in observable social behavior which, conceptually, is the variable that should "carry" or mediate personality's effects on life outcomes. My research in this area has been aimed at identifying such behavioral manifestations of personality and other individual differences in daily life. Importantly, to really understand how personality can affect life outcomes through variability in daily behavior, shared method variance should be minimized and therefore daily behavior be assessed through direct observation rather than indirect (self-)reporting. Over the last years, we have made critical contributions to this field by identifying clear, observable behavioral markers of the Big Five personality domain, subclinical depression, and psychological well-being.

1. Mehl MR and Pennebaker JW. (2003) The sounds of social life: A psychometric analysis of students' daily social environments and natural conversations. Journal of Personality and Social Psychology,84:857-870.
2. Mehl MR. (2006) The lay assessment of sub-clinical depression in daily life. Psychological Assessment, 18, 340-345.
3. Mehl MR, Gosling SD, and Pennebaker JW. (2006) Personality in its natural habitat: Manifestations and implicit folk theories of personality in daily life. Journal of Personality and Social Psychology,90:862-877.
4. Mehl MR, Vazire S, Holleran SE, and Clark CS. (2010) Eavesdropping on happiness: Well-being is related to having less small talk and more substantive conversations. Psychological Science, 21:539-541.

Complete list of published work in My Bibliography

https://www.ncbi.nlm.nih.gov/sites/myncbi/1TS90_ozwnkQD/bibliography/54270729/public/?sort=date&direction=ascending

Research Support

NIMHD RO1 HD099176 Dhand: PI 9/01/20 – 08/31/25
SocialBit: Establishing the accuracy of a wearable sensor to detect social interactions after stroke
This study will develop and validate a wearable sensor to measure everyday social interactions to predict feelings of social isolation and aspects of recovery among stroke patients.
Role on Project: Co-Investigator

NIA RO1 AG068098 Grilli & Andrews Hanna (PIs) 9/15/20 – 8/31/21
Tracking autobiographical thoughts: a smartphone-based approach to the detection of cognitive and neural markers of Alzheimer's disease risk
This study investigates whether assessments of autobiographical cognition in daily life can help detect Alzheimer's disease risk and predict health outcomes linked to the preclinical progression of AD.
Role on Project: Co-Investigator

NIMH RO1 MD008940 Stone: PI 9/25/14 – 5/31/21
Reducing Implicit Verbal and Nonverbal Bias toward Hispanic Patients
The goal of this project is to test (a) how doctor's implicit bias is related to how they talk to Hispanic patients, and (b) how an intervention aimed at reducing implicit bias changes the way doctors talk to Hispanic patients.
Role on Project: Co-Investigator

NIMH RO1 MH105379 Nugent: PI 3/1/15 – 2/28/21
Biomarkers, Social, and Affective Predictors of Suicidal Thoughts and Behaviors in Adolescents
The goal of this project is to examine adolescent in vivo emotion reactivity as related to social context in the real world during the high-risk post-discharge period.
Role on Project: Co-Investigator

NIMH RO1 MH108641 Nugent: PI 7/1/16 – 6/30/21
Understanding the Interplay of Social Context and Physiology on Psychological Outcomes in Trauma-Exposed Adolescents
The goal of this project is to examine real-world emotion and social context as risk and protective factors for adjustment in trauma-exposed adolescents.
Role on Project: Co-Investigator

IARPA MOSAIC Ziegler (LM-ATL; PI) 8/1/17 – 6/30/20
Rapid Automatic & Adaptive Model of Performance Prediction (RAAMP2)
The goal of this project is to design and evaluate a multimodal mobile sensing system for the assessment of psychological traits and states traits (e.g., personality, stress, affect, performance) in the workplace.
Role: Co-Investigator

Biographical Sketch

Mary-Frances O'Connor, Ph.D.
Associate Professor, Psychology

Education/Training

Institution & Location	Degree	Year(S)	Field of Study
Northwestern University, Evanston, IL	B.A.	1996	Psychology
University of Arizona, Tucson, AZ	M.A.	2000	Clinical Psychology
University of Arizona, Tucson, AZ	Ph.D.	2004	Clinical Psychology

Personal Statement

I am an Associate Professor of Clinical Psychology and Psychiatry at the University of Arizona, and the Director of Clinical Training. My research focuses on the physiological correlates of emotion, in particular the wide range of physical and emotional responses during bereavement, including yearning and isolation. I investigate the failure to adapt following the death of a loved one, termed Complicated Grief, included as an area of research in the DSM-5. To that end, I have studied the neurobiological, immune and autonomic parameters that vary between individual grief responses. Specifically, I have publications utilizing functional neuroimaging, immune and endocrine analysis of saliva and blood, and psychophysiological assessment of heart rate variability. Specifically, I have done seminal work on proinflammatory cytokines in response to the social stress of bereavement (a, b), and methodological work on best practices in research with inflammatory markers (c).
I have had the honor to serve as mentor for an NRSA and an NSF predoctoral fellow in my lab. I recently served on the council for the American Psychosomatic Society (APS), where I inaugurated the annual Health and Behavior International Collaborative Award for trainees (graduate students, residents, post-doctoral fellows) to attend international laboratories and gain technical skills not available at their home institution. We have also been awarded an R13 conference grant to bring scholars to our annual meeting, with an emphasis on underrepresented scholars (see Research Support below)

1. Schultze-Florey, C.R., Martínez-Maza, O., Magpantay, L., Breen, E.C., Irwin, M.R., Gündel, H., O'Connor, M.F. (2012). When grief makes you sick: Bereavement induced systemic inflammation is a question of genotype. Brain, Behavior, and Immunity, 26, 1066-71.
2. O'Connor, M.F., Wellisch, D.K., Irwin, M. (2009). When grief heats up: Proinflammatory cytokines predict regional brain activation. NeuroImage, 47, 891-896.
3. O'Connor, M.F., Bower, J., Cho, H.J., Creswell, J.D., Hoyt, M.A., Martin, J.L., Robles, T., Sloan, E., Thomas, K.S., Irwin, M. (2009). To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. Brain, Behavior and Immunity, 23, 887-897.
4. O'Connor, M.F., Arizmendi, B.J., Kaszniak, A.K. (2014). Virtually supportive: A feasibility pilot study of an online support group for dementia caregivers in a 3D virtual environment. Journal of Aging Studies, 30, 87-93. doi: 10.1016/j.jaging.2014.03.001.

Positions

2007 – 2011	Assistant Professor, Cousins Center for Psychoneuroimmunology, Semel Institute for Neuroscience and Human Behavior, UCLA
2012 – 2017	Assistant Professor, Department of Psychology, University of Arizona, Tucson
2013 – Present	Affiliated Faculty, Evelyn F. McKnight Brain Institute, Univ of Arizona, Tucson
2017 – Present	Associate Professor, Department of Psychology, University of Arizona, Tucson

Honors

2005	NIH Loan Repayment Program Award
2006	UCLA Semel Institute for Neuroscience Research Fellow
2008	NIA and OBSSR invitation to "Opportunities for Advancing Behavioral and Social Science Research on Aging" Workshop
2009	UCLA School of Medicine John H. Walsh Young Investigator Research Prize Nominee
2010	NSF/University of Arizona ADVANCE Junior Scientist Award
2011	RAND Summer Institute Workshop on Aging Invitee
2011	Advanced Research Institute in Geriatric Mental Health Scholar
2012	International Research Development Travel Grant from University of Arizona
2014	Undergraduate Biology Research Program Outstanding Mentor Award
2014	International Research Development Travel Grant from University of Arizona
2015	Anxiety & Depression Association of America Career Development Leadership Program
2017	American Psychosomatic Society 75th Anniversary Award

Contribution to Science

Neuroimaging correlates of grief. Scientific contributions from my research investigate the way the brain processing the changing reality after the death of a loved one. Notably, my research was the first to using neuroimaging to investigate typical grief (5) and has now been cited nearly 200 times. Later work demonstrated that those with Complicated Grief show differential activation from to those with Non-Complicated Grief (4), highlighting the uniqueness of the disorder. This latter article, from 2008, has been cited nearly 150 times. My work investigates the relationship between both brain and peripheral physiology (3), because of the impact of grief (recursively) on these systems. From my K award, I have recently published on the cognitive-affective dysregulation of Complicated Grief during the emotional Stroop task (2), and hallmark symptoms of the clinical disorder (1).

1. McConnell, M.H., Killgore, W.D.S., and O'Connor, M.F. (2018) Yearning predicts subgenual anterior cingulate activity in bereaved individuals. Heliyon, 4, e00852. doi: 10.1016/j.heliyon.2018.e00852. P
2. Arizmendi BJ, Kaszniak AW, and O'Connor M-F. (2015) Disrupted prefrontal activity during emotion regulation in Complicated Grief: An fMRI investigation. NeuroImage, 124:968-976.
3. O'Connor M-F, Wellisch DK, and Irwin M. (2009) When grief heats up: Proinflammatory cytokines predict regional brain activation. NeuroImage, 47:891-896.
4. O'Connor M-F, Wellisch DK, Stanton AL, Eisenberger NI, Irwin MR, and Lieberman MD. (2008)Craving love? Complicated grief activates brain's reward center. NeuroImage, 42:969-972.
5. Gündel H, O'Connor M-F, Littrell L, Fort C, and Lane R. (2003) Functional neuroanatomy of grief :An fMRI study. American Journal of Psychiatry, 160:1946-1953.

Bereavement: Immune system and stress physiology. Additional work from my laboratory has investigated the biomarkers of adaptation during grief, primarily in the stress response systems (sympathetic nervous system(3) and hypothalamic pituitary adrenal axis(2d)) and the immune system (1,2). Supporting the hypothesis that Complicated Grief is the clinical outcome of concern in bereavement, I have demonstrated the flattened diurnal slope of cortisol in Complicated compared to Non-Complicated Grief groups (4). In addition, I have extensively reviewed the work in this subfield (1).

1. Knowles, L.M., Ruiz, J.M., and O'Connor, M.F. (2019). A systematic review of the association between bereavement and biomarkers of immune function. Psychosomatic Medicine, 81:415-433.

2. O'Connor M-F, Schultze-Florey CR, Irwin MR, and Cole SW. (2014) Divergent gene expression responses to Complicated Grief and Non-complicated Grief. Brain, Behavior and Immunity, 37:78–83.
3. O'Connor M-F, Shear MK, Fox R, Skritskaya N, Campbell B, Ghesquiere A, and Glickman K. (2013) Catecholamine predictors of complicated grief treatment outcomes. International Journal of Psychophysiology, 88:349-352.
4. O'Connor M-F, Wellisch DK, Stanton AL, Olmstead R, and Irwin MR. (2012) Diurnal cortisol in Complicated and Non-Complicated Grief: Slope differences across the day. Psychoneuroendocrinology, 37:725-728.

Psychological outcomes in bereavement. A third area of my work includes the study of psychological outcomes in patient families after the death of a loved one. Specifically, I have contributed to understanding the psychological reaction to interpersonal loss, how adaptation happens in typical grief, and what factors lead to poor adaptation. These psychological factors include cognitive functioning, yearning and repetitive thought, and quality of life.

1. O'Connor M-F and Arizmendi B. (2014) Neuropsychological correlates of complicated grief in older spousally bereaved adults. Journals of Gerontology: Psychological Sciences, 69B:12-18.
2. Bourassa KJ, Knowles L, Sbarra DA, and O'Connor M. (2016) Absent, but not gone: Interdependence in couples' quality of life persists after a partner's death. Psychological Science,27:270-281.
3. Kaplan DM, Palitsky R, Carey AL, Crane TE, Havens CM, Medrano MR, Reznik SJ, Sbarra DA, and O'Connor MF. (2018) Maladaptive repetitive thought as a transdiagnostic phenomenon and treatment target: An integrative review. Journal of Clinical Psychology, 74:1126–1136.
4. Robinaugh DJ, Mauro C, Bui E, Stone L, Shah R, Wang Y, Skritskaya NA, Reynolds CF, Zisook S, O'Connor M-F, Shear K, and Simon NM. (2016) Yearning and its measurement in complicated grief. Journal of Loss and Trauma, 21:410-420.

Development of criteria for disordered grief. As part of a group of leaders in the fields of psychology and psychiatry, I contributed to the argument that under specific extreme conditions, poor adaptation should be considered a disorder. This argument persuaded the committee developing the DSM 5, and Persistent Complex Bereavement Disorder was included as a disorder for further research. This article has been cited almost 600 times. The inclusion of Prolonged Grief Disorder in the International Classification of Diseases (ICD-11) has made cultural considerations a critical topic in grief research.

1. Shear MK, Duan N, Reynolds C, Simon N, Zisook S, Lebowitz B, Sung S, Guesquierre A, Gorscak B, Clayton P, Ito M, Nakajima S, Konishi T, Brent D, Melhem N, Meert K, Schiff M, Neimeyer R, O'Connor M-F, First M, Sareen J, Bolton J, Skritskaya N, and Mancini A. (2011) Complicated Grief and related bereavement issues for DSM-5. Depression and Anxiety, 28:103–117.
2. Stelzer E, Zhou N, Maercker A, O'Connor M-F, & Killikelly C (2020) Prolonged grief disorder and the cultural crisis. Frontiers in Psychology, 10: 2982. https://doi.org/10.3389/fpsyg.2019.02982
3. O'Connor MF, Arizmendi BJ (2015) What is "normal" in grief? Australian Critical Care, 8, 58–62. doi:10.1016/j.aucc.2015.01.005

Complete list of published work in My Bibliography

https://www.ncbi.nlm.nih.gov/sites/myncbi/mary-frances.o'connor.1/bibliography/40699290/public/?sort=date&direction=descending

Research Support

R13 AG066368 O'Connor(PI) 9/1/19 – 8/31/21

Social Neuroscience of Grief: 2020 Vision and Social Neuroscience of Grief: Early Adversity and Later Life Reversibility

The major goal of this conference grant is to give researchers an opportunity to 1) obtain knowledge about state-of-the-art animal and human research on grief, and 2) interact with like-minded investigators and trainees to foster collaborations and develop a translational model of the social neuroscience of grief.

Role on Project: PI

R13 AG066393 O'Connor (PI) 9/1/19 – 8/31/21

Conference grant to support Social Neuroscience of Grief: 2020 Vision and Social Neuroscience of Grief: Early Adversity and Later Life Reversibility

The major goal of this conference grant is to give researchers an opportunity to 1) obtain knowledge about state-of-the-art animal and human research on grief, and 2) interact with like-minded investigators and trainees to foster collaborations and develop a translational model of the social neuroscience of grief.

R13 AG066393 O'Connor(PI) 9/1/19 – 8/31/21

Conference Grant to support American Psychosomatic Society's 78th and 79th Annual Scientific Meetings

The major goals of this conference grant to support for pre- and post-doctoral trainees to attend the 78th and 79th Annual Scientific Meeting of the American Psychosomatic Society (APS).

Role on Project: PI

Biographical Sketch

Naomi Rance, M.D., Ph.D.
Professor, Pathology

Education/Training

Institution & Location	Degree	Year(S)	Field Of Study
University of Maryland, College Park	B.S.	1973	Psychology
University of Maryland, Baltimore	Ph.D.	1981	Physiology
University of Maryland, Baltimore	M.D.	1983	Medicine
The Johns Hopkins Hospital	Fellowship	1989	Neuropathology
The Johns Hopkins Hospital	Residency	1983 – 1987	Pathology

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 hypogonadotropic 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.

1. Rance NE. (2009) Menopause and the human hypothalamus: Role of kisspeptin/neurokinin B neurons in the regulation of estrogen negative feedback. Peptides, 30:111-22.
2. Rance NE, Krajewski SK, Smith MA, Cholanian M, and Dacks PA. (2010) Neurokinin B and the hypothalamic regulation of reproduction. Brain Research, special issue entitled “New Insights into the Neurobiology of Reproduction and Puberty,” 1364:116-128.
3. Mittelman-Smith MA, Williams H, Krajewski-Hall, McMullen NT, and Rance NE. (2012) Role for kisspeptin/neurokinin B/dynorphin (KNDy) neurons in cutaneous vasodilatation and the estrogen modulation of body temperature. Proceedings of the National Academy of Science, USA,109:19846-19841, PMCID: PMC3511761.
4. Rance NE, Dacks PA, Mittelman-Smith MA, Krajewski SK, Romanovsky AA. (2013) Modulation of body temperature and LH secretion by hypothalamic KNDy (kisspeptin, neurokinin Band dynorphin) neurons: A novel hypothesis on the mechanism of hot flushes. Frontiers in Neuroendocrinology, 34, 211-27, PMID: 23872331.

Positions

1976 – 1981	Predoctoral Fellow, Department of Physiology, University of Maryland
1983 – 1986	Resident, Anatomic Pathology, The Johns Hopkins Hospital
1986 – 1987	Chief Resident, Anatomic Pathology, The Johns Hopkins Hospital

1987 – 1989	Clinical and Research Fellow, Neuropathology Laboratory, The Johns Hopkins Hospital
1989 – 1995	Assistant Professor, Department of Pathology, University of Arizona College of Medicine
1989	Chief, Division of Neuropathology, University Medical Center, Tucson, Arizona
1989	Neuropathology Consultant, Forensic Science Center, Pima County, Arizona
1995 – 2000	Associate Professor, Department of Pathology, University of Arizona College of Medicine, Tucson
1996	Associate Head, Department of Pathology, University of Arizona College of Medicine, Tucson
2000	Professor, Department of Pathology, University of Arizona College of Medicine, Tucson

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.

1. Rance NE and Young WS III. (1991) Hypertrophy and increased gene expression of neurons containing neurokinin B and substance P messenger RNAs in the hypothalami of postmenopausal women. Endocrinology, 128:2239-2247.
2. Rance NE and Bruce TR. (1994) Neurokinin B gene expression is increased in the arcuate nucleus of ovariectomized rats. Neuroendocrinology, 60:337-345.
3. Abel TW, Voytko ML, and Rance NE. (1999) Effects of hormone replacement therapy on neuropeptide gene expression in a primate model of menopause. Journal of Clinical Endocrinology and Metabolism, 84:2111-2118.
4. Rometo AM, Sally J, Krajewski SJ, Voytko ML, and Rance NE. (2007) Hypertrophy and increased kisspeptin gene expression in the hypothalamic infundibular nucleus of postmenopausal women and ovariectomized monkeys. Journal of Clinical Endocrinology and Metabolism, 92:2744-2750.

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.

1. Sandoval-Guzmán T and Rance NE. (2004) Central injection of senktide, an NK3 receptor agonist, or neuropeptide Y inhibits LH secretion and induces different patterns of Fos expression in the rat hypothalamus. Brain Research, 1026:307-312.
2. Krajewski SJ, Anderson Miranda J, Iles-Shi L, Chen, Kyung J, Urbanski HF, and Rance NE. (2005)Morphological evidence that neurokinin B neurons modulate GnRH secretion via NK3 receptors in the rat median eminence. Journal of Comparative Neurology, 489:372-386.
3. Mittelman-Smith MA, Williams H, Krajewski-Hall SJ, Lai J, Ciofi P, McMullen NT, and Rance NE. (2012) Arcuate kisspeptin/neurokinin B/dynorphin (KNDy) neurons mediate the estrogen suppression of gonadotropin secretion and body weight. Endocrinology, 153:2800-2012. PMCID:PMC3359616.
4. Mittelman-Smith MA, Krajewski-Hall, McMullen NT, and Rance NE. (2016) Ablation of KNDy neurons results in hypogonadotropic hypogonadism and amplifies the steroid-induced LH surge in female rats. Endocrinology, 157:2015-2027.

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.

1. Krajewski SJ, Anderson, Miranda J, Iles-Shi L, Chen, Kyung J, Urbanski HF, and Rance NE. (2005)Morphological evidence that neurokinin B neurons modulate GnRH secretion via NK3 receptors in the rat median eminence. Journal of Comparative Neurology, 489:372-386.
2. Krajewski SJ, Burke MC, Anderson MJ, McMullen NT, and Rance NE. (2010) Forebrain projections of arcuate neurokinin B neurons demonstrated by anterograde tract-tracing and monosodium glutamate lesions in the rat. Neuroscience, 166:1187-1193. PMCID: PMC2823949.
3. Burke MC, Letts (Dacks) PA, Krajewski SJ, and Rance NE. (2006) Coexpression of dynorphin and neurokinin B immunoreactivity in the rat hypothalamus: Morphologic evidence of interrelated function within the arcuate nucleus. Journal of Comparative Neurology, 498, 712-726.
4. Cholanian M, Krajewski-Hall SJ, Levine RB, McMullen NT, and Rance N. (2015) Chronic oestradiol reduces the dendritic spine density of KNDy (kisspeptin/neurokinin B/dynorphin) neurons in the arcuate nucleus of ovariectomised Tac2-enhanced green fluorescent protein transgenic mice. Journal of Neuroendocrinology 27:253-263.

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.

1. Dacks PA, Krajewski SK, and Rance NE. (2011) Activation of neurokinin 3 receptors in the median preoptic nucleus decreases body temperature in the rat. Endocrinology, 152:4894-4905. PMCID:PMC3230049.

2. Mittelman-Smith MA, Williams H, Krajewski-Hall, McMullen NT, and Rance NE. (2012) Role for Kisspeptin/Neurokinin B/Dynorphin (KNDy) Neurons in Cutaneous Vasodilatation and the Estrogen Modulation of Body Temperature. Proceedings of the National Academy of Science, USA,109:19846-19841, PMCID: PMC3511761.
3. Rance NE, Dacks PA, Mittelman-Smith MA, Krajewski SK, Romanovsky AA. (2013) Modulation of body temperature and LH secretion by hypothalamic KNDy (kisspeptin, neurokinin Band dynorphin) neurons: A novel hypothesis on the mechanism of hot flushes. Frontiers in Neuroendocrinology, 34, 211-27, PMID: 23872331.
4. Mittelman-Smith MA, Williams H, Krajewski-Hall, McMullen NT, and Rance NE. (2015) Neurokinin 3receptor-expressing neurons in the median preoptic nucleus modulate heat-dissipation effectors in the female rat. Endocrinology, 156:2552-2562.

Biographical Sketch

Lee Ryan, Ph.D.
Professor, Psychology, Neurology and Neuroscience Program

Education/Training

Institution & Location	Degree	Year(S)	Field Of Study
University of Toronto, Canada	B.Mus.	1979	Music
University of Toronto, Canada	M.A.	1981	Music
University of Toronto, Canada	B.S.	1988	Psychology/Neuroscience
University of British Colombia, Vancouver, Canada	Ph.D.	1992	Clinical/Cognitive Psych
University of California, San Diego, CA	Postdoc	1993 - 1995	Neuropsychology

Personal Statement

I am a Professor and the Head of the Psychology Department 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 over 60 scholarly articles specifically 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 fMRI, morphometry, and diffusion imaging have investigated factors that influence individual differences in age-related cognitive function, including genetic markers, obesity, hypertension, and APOE status. As a clinical neuropsychologist, I work with individuals and families who are coping with chronic and progressive diseases that affect 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. I have been very active in mentoring programs at the University of Arizona, including mentoring of tenure-tracked junior faculty, postdoctoral fellows, and graduate students.

1. Lawrence, A.V., Cardoza, J., and Ryan, L. (2020). Medial temporal lobe regions mediate complex visual discriminations for both objects and scenes: A process-based view. Hippocampus. 30(8):879-891.
2. Memel, M., Wank, A.A., Ryan, L., Grilli, M.D. (2020). The relationship between episodic detail generation and anterotemporal, posteromedial, and hippocampal white matter tracts. Cortex. 123:124-140.
3. Memel M and Ryan L. (2017) Visual integration enhances associative memory equally for young and older adults without reducing hippocampal encoding activation. Neuropsychologia, 100, 195-206.
4. Ryan L, Cardoza JA, Barense MD, Kawa KH, Wallentin-Flores J, Arnold WT, and Alexander GE. (2012) Age-related impairment in a complex object discrimination task that engages perirhinal cortex. Hippocampus, 22(10), 1978-89.

Positions and Honors

1988 – 1992	National Science & Engineering Research Council of Canada Graduate Fellowships
1993 – 1995	National Science & Engineering Research Council of Canada Postdoctoral Fellowships
1992 – 1993	Clinical internship in Neuropsychology, VAMC, La Jolla, and UCSD, San Diego
1993 – 1996	Research Scientist, Department of Psychiatry, University of California, San Diego
1996 – 2003	Assistant Professor, Department of Psychology, University of Arizona, Tucson
1998	Participant in Summer Institute on Aging Research, National Institute on Aging
1998 – Present	Director, Cognition & Neuroimaging Laboratories, University of Arizona, Tucson
2000 – Present	Member, Memory Disorders Research Society
2003 – 2014	Associate Professor and Associate Head, Department of Psychology, University of Arizona, Tucson
2013 – Present	Associate Director, Evelyn F. McKnight Brain Institute
2014 – Present	Professor, Department of Psychology, University of Arizona, Tucson
2015 – Present	Head, Department of Psychology, University of Arizona, Tucson

Contribution to Science

I have published theoretical articles that combine evidence from human cognitive neuroscience and animal models that present integrated views of age-related cognitive changes. Two recent papers highlight the novel concept of 'Precision Aging' emphasized in the current grant submission – taking an individualized approach to understanding complex patterns of risk and resilience associated with age-related cognitive impairment and risk for Alzheimer's disease. Another paper describes the impact of aging on neural circuitry across subregions of the medial temporal lobe, and how these changes are responsible for the specific types of memory impairments associated with normal aging. In addition, the model makes strong predictions regarding the neuropathological changes associated with normal aging versus those that may provide early pre-clinical markers of Alzheimer's disease.

1. Ryan, L., Hay, M., Huentelman, M.J., Duarte, A., Rundek, T., Levin, B., Solda, A., Pettigrew, C., Mehl, M. R., and Barnes, C. A. (2019). Precision Aging: Applying precision medicine to the field of cognitive aging. Frontiers in Aging Neuroscience, 11:128.
2. Hay M, Barnes C, Huentelman M, Brinton R, and Ryan L. (2020). Hypertension and age-related cognitive impairment: common risk factors and a role for precision aging. Current Hypertension Reports, 22(10):80. Published 2020 Sep 3.
3. Burke, S.N., Gaynor, L.S., Barnes, C.A., Bauer, R.M., Bizon, J.L., Roberson, E.D., & Ryan, L. (2018). Shared functions of perirhinal and parahippocampal cortices: implications for cognitive aging. Trends in Neuroscience, 41(6):349-359.
4. Alexander, G.E., Ryan, L., Bowers, D., Foster, T.C., Bizon, J.L., Geldmacher, D.S., & Glisky, E.L. (2012). Characterizing cognitive aging in humans with links to animal models. Frontiers in Aging Neuroscience, 4:21.

My laboratory has shown that cardiovascular and genetic risk factors have a negative impact on both the function and structure 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 interventions that prevent the occurrence of cardiovascular disease and obesity may maintain brain health.

1. McKinnon, A., Stickel, A., and Ryan, L. (2020). Cardiovascular risk factors and APOE-ε4 status affect memory functioning in aging via changes to temporal stem diffusion. Journal of Neuroscience Research, [e-pub ahead of print]. DOI: 10.1002/jnr.24734

2. Talboom, J.S., Håberg, A.K., De Both, M.D., Naymik, M.A., Schrauwen, I., Lewis, C.R., Bertinelli, S.F., Hammersland, C., Fritz, M.A., Myers, A.J., Hay, M., Barnes, C.A., Glisky, E., Ryan, L., Huentelman, M.J. (2019). Family history of Alzheimer's disease alters cognition and is modified by medical and genetic factors. eLIFE Human Biology and Medicine, Neurosicence, 8:e46179. PubMed Central PMCID: PMC661585.
3. Ryan, L. & Walther, K. (2014). White matter integrity in older females is altered by increased body fat. Obesity, 22(9):2039-46.
4. Ryan, L., Walther, K., Bendlin, B.B., Lue L-F., Walker, D.G., & Glisky, E.L. (2011). Age-related differences in white matter integrity measured by diffusion tensor imaging and cognitive function are related to APOE status. NeuroImage, 54(2), 1565-77.

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.

1. Campbell, J., Nadel, L., Duke, D., & Ryan, L. (2011). Remembering all that and then some: recollection of autobiographical memories after a 1-year delay. *Memory*, 19(4), 406-15. PMCID: PMC3773369.
2. Nadel, L., Winocur, G., Ryan, L., & Moscovitch, M. (2007). Systems consolidation and hippocampus: two views. *Debates in Neuroscience,* 4, 55-66.
3. Nadel, L., Ryan, L., Hayes, S., Gilboa, A., & Moscovitch, M. (2003). The role of the hippocampal complex in episodic long-term memory. In T. Ono, G. Matsumoto, R.R. Lllinas, A. Berthoz, R. Norgren, H. Nishijo & R., Tamura (Eds), Limbic and Association Cortical Systems - Basic, Clinical and Computational Aspects, 7-12 October 2002. Excerpta Medica International Congress Series (ICS), Amsterdam, Elsevier Science.
4. Ryan, L., Nadel, L., Keil, K., Putnam, K., Schnyer, D., Trouard, T., & Moscovitch, M. (2001). Hippocampal complex and retrieval of recent and very remote autobiographical memories: Evidence from functional magnetic resonance imaging in neurologically intact people. *Hippocampus*, 11: 707-714.

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.

1. Lawrence, A.V., Cardoza, J., and Ryan, L. (2020). Medial temporal lobe regions mediate complex visual discriminations for both objects and scenes: A process-based view. Hippocampus, 30(8):879-891.
2. Memel, M., Wank, A.A., Ryan, L., Grilli, M.D. (2020). The relationship between episodic detail generation and anterotemporal, posteromedial, and hippocampal white matter tracts. Cortex, 123:124-140.
3. Ryan, L., Cox, C., Hayes, S., & Nadel, L. (2008). Hippocampal activation during episodic and semantic memory retrieval: category production and category cued recall. Neuropsychologia, 46, 2109-2121.

Complete list of published work in My Bibliography

https://www.ncbi.nlm.nih.gov/sites/myncbi/lee.ryan.1/bibliography/44215085/public/?sort=date&direction=descending

Research Support

NIA R01 AG062543 Chou (PI) 5/01/20 – 1/31/25

Enhancement of hippocampal plasticity using repetitive transcranial magnetic stimulation

The goal of this project is to utilize MRI-based neuronal connectivity maps as a guide to precisely propagate the neuronal excitation elicited by the superficial repetitive transcranial magnetic stimulation to the hippocampus in individuals with amnestic mild cognitive impairment.

Role: Co-Investigator

NIA R03 AG060271 Grilli (PI) 4/15/19 – 3/31/21

The episodic autobiographical memory hypothesis of preclinical Alzheimer's disease: Developing a new approach for early cognitive detection and measurement of Alzheimer's disease

This grant uses experimental lab-based tasks to examine whether multiple sub-components of episodic autobiographical memory are sensitive to APOE4 status, and functional connectivity of the default network, in cognitively normal older individuals.

Role: Co-Investigator

Arizona Alzheimer's Consortium, ADHS Ryan (PI) 7/1/20 – 6/30/21

Assessing medial temporal lobe network integrity using high resolution fMRI

This project is designed to improve the assessment of age-related cognitive alterations that are linked to risk factors for AD including APOE e4 status.

Role: Principal Investigator

Arizona Alzheimer's Consortium, ADHS Ryan (PI) 7/1/20 – 6/30/21

Assessing the Impact of COVID-19 on Cognitive Functions

This project studies an existing cognitively characterized cohort (called MindCrowd) of over 50,000 individuals that span the aging spectrum (18-90+) to study the cognitive effects of past SARS-CoV-2 infection.

Role: Principal Investigator

Arizona Alzheimer's Consortium, ADHS Ryan (PI) 7/1/19 – 12/31/20

Contextual retrieval impairment in self-defining autobiographical memories as an early indicator of risk for AD

This project studies medial temporal lobe functions in a group of older adults using functional MRI.

Role: Principal Investigator

Biographical Sketch

Robert C. Wilson, Ph.D.
Assistant Professor, Psychology and Cognitive Science

Education/Training

Institution & Location	Degree	Year(S)	Field of Study
University of Cambridge	B.A.	2002	Natural Sciences
University of Cambridge	M.Sci.	2002	Chemistry
University of Pennsylvania	M.S.E.	2003	Bioengineering
University of Pennsylvania	Ph.D.	2009	Bioengineering
Princeton University	Postdoc	2014	Psychology and Neuroscience

Personal Statement

I am an expert in the computational neuroscience and mathematical psychology. I have modeled learning and decision making at a variety of levels – from low level neural networks to high level Bayesian inference – and have extensive experience linking theoretical models to experimental data. Most relevant to the current proposal is my work developing explore-exploit experiments (1), my work building cognitive models of complex tasks (2), my work linking models to behavioral and neural data (3) and my work on the effects of TMS on explore-exploit behavior (4).

1. Wilson RC, Geana A, White JM, Ludvig EA, and Cohen JD. (2014) Humans use directed and random exploration to solve the explore-exploit dilemma. JEP: General, 143 (6) 2074-2081.
2. Wilson RC and Niv Y. (2012) Inferring relevance in a changing world. Front Hum Neurosci, 5:189.
3. Wilson RC, Takahashi YK, Schoenbaum G, and Niv Y. (2014) Orbitofrontal cortex as a cognitive map of task space. Neuron, 81(2) 267-279.
4. Zajkowski WK, Kossut M, and Wilson, R. C. (2017) A causal role for right frontopolar cortex in directed, but not random, exploration. eLife, 6.

Positions

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

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.

1. Wilson RC, Geana A, White JM, Ludvig EA, and Cohen JD. (2014) Humans use directed and random exploration to solve the explore-exploit dilemma. JEP: General, 143 (6), 2074-2081.
2. Somerville LH, Sasse SF, Garrad MC, Drysdale AT, Abi Akar N, Insel C, and Wilson RC. (accepted)Charting the Expansion of Strategic Exploratory Behavior During Adolescence. JEP: General.
3. Krueger PK, Wilson RC, and Cohen JD. (2017) Strategies for exploration in the domain of losses. Judgment and Decision Making, 12(2), 104.
4. Zajkowski W, Kossut M, and Wilson RC. (2017) A causal role for right frontopolar cortex in directed, but not random, exploration. eLife, 6.

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.

1. Wilson RC and Finkel LH. (2009) A neural implementation of the Kalman filter. Advances in Neural Information Processing Systems, 22, 2062-2070.
2. Wilson RC, Nassar, MR, and Gold JI. (2010) Bayesian online learning of the hazard rate in change-point problems. Neural Computation, 22(9), 2452-2476.
3. Wilson RC and Niv Y. (2012) Inferring relevance in a changing world. Front Hum Neurosci, 5:189.
4. Wilson RC, Nassar MR, and Gold JI. (2013) A Delta-rule approximation to Bayesian inference in change-point problems. PLoS Comp Biol, 9(7), e1003150.

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 over 100 times in just over two years.

1. Takahashi YK, Roesch MR, Wilson RC, Toreson K, O'Donnell P, Niv Y, and Schoenbaum G. (2011)Expectancy-related firing of midbrain dopamine neurons depends on orbitofrontal cortex. Nature Neuroscience, 14, 1590-1597.
2 Wilson RC, Takahashi YK, Schoenbaum G, and Niv Y. (2014) Orbitofrontal cortex as a cognitive map of task space. Neuron, 81 (2) 267-279.

Complete list of published work in My Bibliography

http://www.ncbi.nlm.nih.gov/sites/myncbi/robert.wilson.3/bibliography/48037481/public/?sort=date&direction=ascending

Research Support

NIA R56 AG06188 Wilson (PI) 9/30/18 – 8/31/20

Evaluating the Neurocomputational Mechanisms of Explore-Exploit Decision Making in Older Adults

This grant uses behavioral, neuroimaging, and neurostimulation experiments to investigate explore-exploit behavior in younger and older adults.

Role on Project: PI

McKnight Brain Research Foundation Wilson (UA PI; multi-PI) 7/1/17 – 4/30/20

Evaluating the Neurocomputational Mechanisms of Explore-Exploit Decision Making in Older Adults

This grant uses behavioral, neuroimaging, and neurostimulation experiments to investigate explore-exploit behavior in younger and older adults.

Role on Project: Multi-PI: Wilson, Grilli, Levin, Ebner, Oliveira, Getz

Trainees

Postdoctoral

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

Alexander Danvers, Ph.D. (Mehl)
Area of Interest: Mobile-phone and wearable sensor-based assessment of social and emotional processes in daily life; dynamic systems modeling of emotion dynamics

Yu (Karen) Du, Ph.D. (Ekstrom)
Area of Interest: Virtual reality, scalp EEG, and fMR

Daniel Gray, Ph.D. (Barnes)
Area of Interest: Circuits and synapses involved in cognitive decline in a non-human primate model of aging

Derek Huffman, Ph.D. (Ekstrom; currently Assistant Professor, Psychology, Colby College, Main)
Area of Interest: Decoding body-based neural codes underlying human spatial navigation using fMRI

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

Candace Lewis, Ph.D. (Huentelman)
Area of Interest: Understanding how genetics and epigenetics is associated with differential human development from the aspect of behavior and cognition.

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

Erin Maresh, Ph.D. (Andrews-Hanna)
Area of Interest: Neural underpinnings and health relevance of social cognition

Irina Sinakevitch, Ph.D. (Barnes)

Area of Interest: Understanding the role of different subcomponents of the locus coeruleus to cognitive changes that occur in an aging nonhuman primate model

Joshua Talboom, Ph.D. (Huentelman)
Area of Interest: Massive internet-based cohort recruitment for a better understanding of factors associated with cognitive performance across the aging spectrum.

Jiah Yoo, Ph.D. (O'Connor)
Area of Interest: Role of culture and emotion beliefs in caregivers

Li Zheng, Ph.D. (Ekstrom)
Area of Interest: Temporal interval representation during human episodic memory and navigation using high-resolution fMRI.

Predoctoral

Mónica Acevedo-Molina (Grilli)
Area of Interest: Self-referential cognition and emotional changes associated with normal aging and Alzheimer's disease

Eric Andrews (Andrews-Hanna)
Area of Interest: App-based momentary assessments of emotion and well-being

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

Greg Branigan (Diaz Brinton)
Area of Interest: Impact of estrogen therapies on Alzheimer's disease pathways

Yu-Chin Chen (Chou)
Area of Interest: Repetitive TMS treatment for people with MCI

Patricia Chilton (Grilli)
Area of Interest: Cognitive aging and wisdom

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

Andrea Coppola (Andrews-Hanna)
Area of Interest: The neuroscience of empathy and social well-being

Lindsey Crown (Cowen) – Ph.D. received May 2020
Area of Interest: Neural basis of Parkinson's disease and Neural synchrony involved in memory functions

Hannah Dollish (Fernandez
Area of Interest: Seasonality of circadian photo-responses

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

Sydney Friedman (O'Conner)
Affective science and psychophysiology in bereaved individuals

Nathaniel Gallegos (Ryan)
Area of Interest: Genetic family history in ad

Gabriel Holguin (Cowen,)
Area of Interest: Neural basis of Parkinson's disease and Neural synchrony involved in memory functions and spatial navigation in the hippocampus

Wayne Jepsen (Huentelman)
Area of Interest: Genomics of Alzheimer's disease and normative aging with a focus on interesting or unique families our cognitive performance outliers.

Gianna Jordan (Cowen)
Area of Interest: Biomedical engineering and automated control and monitoring of complex motor function in rodents

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

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

Mingli Liang (Ekstrom)
Area of Interest: Human spatial navigation and wireless scalp EEG

Yilin Liu (Chou)
Area of Interest: Brain Imaging and Transcardial Magnetic Stimulations

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

Mairead McConnell (O'Conner)
Area of Interest: The impact of emotion on physical health, mediated through brain mechanisms, and clinical interventions improving emotional expression

Kelsey McDermott (Barnes)

Area of interest: Understanding how the locus coeruleus contributes to age-related cognitive deficits in an aging nonhuman primate model.

Katie McVeigh (Grilli)
Area of Interest: Cognitive aging, social interaction, and loneliness.

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

Alana Muller (Ekstrom)
Area of Interest: Understanding the cognitive processes involved in spatial navigation using EEG and virtual reality

David Negelspach (Fernandez)
Area of Interest: Scaling circadian responses to millisecond administration of FED light

Justin Palmer (Ryan)
Area of Interest: Cognitive and neurobiological changes with normal and abnormal aging trajectories

Alma Tejeda Padron (Mehl)
Area of Interest: Psychological aspects of natural language use; linguistic markers of aging

Quentin Raffaelli (Andrews-Hanna)
Area of Interest: Cognitive neuroscience of memory, creativity, and spontaneous thought

Eva Robinson (Ekstrom)
Area of Interest: Neural basis or navigation and decision making.

Saren Seeley (O'Conner)
Area of Interest: Relationships between cognition and emotion, and neural and psychophysiological mechanisms through which these factors give rise to distress and impairment

Samantha Smith (Alexander)
Area of Interest: Actigraphy and cognition in normal and pathological aging

Hyun Song (Alexander)
Area of Interest: Neural mechanisms of individual differences in cognitive aging

Sahana Srivathsa (Barnes)
Area of Interest: Age-related changes of signals involved in spatial memory and decision making

Michael Starrett (Ekstrom)
Area of interest: Human spatial navigation and scales of space

Eva-Maria Stelzer (O'Conner)
Area of Interest: The cultural (collectivist vs. individualist) effects of major life stressors, such as bereavement, on mental and physical health

Mark Sundman (Chou)
Area of Interest: Development of image-guided rTMS protocols

Colin Tidwell (Mehl and O'Conner)
Area of Interest: Naturalistic study of how everyday behaviors and social interactions impact health and well-being (focusing on LGBTQ mental health.

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

Hannah Van Rossum (Brinton)
Areas of Interest: Alzheimer's Disease, Neuroinflammation, Epigenetics, Perimenopause

Abhilasha Vishwanath (Cowen)
Area of Interest: Neural basis of Parkinson's disease and Neural synchrony involved in memory functions.

Siyu Wang (Wilson) Ph.D. received May 2020
Area of Interest: The neural correlates of exploration and exploitation

Aubrey Wank (Grilli)
Area of Interest: Brain and autobiographical memory changes associated with normal aging and Alzheimer's disease

Da'Mere Wilson (O'Conner)
Area of Interest: The role of discrimination, grief, and other stressors on the development of cardiovascular disease within the African American and Latinx community

Cindy Woolverton (Glisky) – Ph.D. received July 2020
Area of Interest: Effects of intergenerational interactions in young and older adults

Marc Zempare (Barnes)
Area of Interest: Understanding the role of NPTX2 as a resilience factor in the aging rat brain

Clinical / translational programs

Dr. Roberta Brinton (EMBI Affiliate Faculty) has been conducting studies to evaluate allopregnanolone as a therapeutic agent to treat age-associated memory deficits. Part of the goal is to complete collecting data in a translational therapeutic development project, required for an Investigational New Drug application to the FDA. The goal is 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. Brinton has received a $37.5 million federal grant to study a potential regenerative therapy for Alzheimer's disease. With the initiation of this five-year grant from the National Institute on Aging, Dr. Brinton will lead a nationwide Phase 2 clinical trial that will study the effectiveness of allopregnanolone in early-stage patients, rather than late stage, and hope to determine whether allopregnanolone will be effective as a therapy. She is taking a precision medicine approach for Alzheimer's disease, designed to treat the right person at the right time.

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 trial:
2018-2024 A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of CNP520 in Participants at Risk for the Onset of Clinical Symptoms of Alzheimer's Disease. (Generation 2) Protocol # CCNP520A2202J. Novartis.

Technology transfer

Nothing to report

Budget update

Last years' budget and actual results - July 1, 2019 to June 30, 2020

Evelyn F. McKnight Brain Institute	Budget	Expenditures
Personnel	$500,000	$426,407
Operations	$250,000	$144,649
Total	$750,000	$571,056

Cowen Recruitment Account	Budget	Expenditures
Cowen Start-up	$27,420	$27,420

(a) Status of matching funds (to 11/30/20)

See the University of Arizona Foundation Endowment Investment Report on pages 112 - 115 for full value.

	MBRF Gift	Match
Permanent Endowment	$5,000,000	$2,331,336

(b) Projected budget – July 1, 2020 – June 30, 2021

Evelyn F. McKnight Brain Institute	Budget
Personnel	$500,000
Operations	$250,000
Total	$750,000

Budget update

(c) Extramural funding

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)

Subcontract PI:	Alexander, Gene E. (Multi-PI: Alexander, Bowers, Woods)
Project:	Revitalizing Cognition in Older Adults at Risk for Alzheimer's Disease with Near-Infrared Photobiomodulation (R01 AG064587)
Sponsor:	National Institute on Aging
Project Dates:	August 2019 – April 2024
Subaward Amount:	$330,833 (current year)

Subcontract PI:	Alexander, Gene E. (PI: Reiman)
Project:	Brain Imaging and Fluid Biomarkers Core (R01 AG019610)
Sponsor:	National Institute on Aging
Project Dates:	August 2018 – June 2021
Subaward Amount:	$304,037 (current year)

Subcontract 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 2020
Subaward Amount:	$39,297 (current year)

PI:	Alexander, Gene E. (Multi-PI: Cohen, Woods, Marsaki, Alexander)
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:	$244,773 (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)

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 – April 2020
Award Amount:	$85,653 / year

Univ Arizona PI: Alexander, Gene E. (Multi-PI: Bowers, Alexander, Woods)
Project: A Pilot Intervention with Near Infrared Stimulation: Revitalizing Cognition in Older Adults
Sponsor: McKnight Brain Research Foundation
Project Dates: May 2018 – April 2021
Award Amount: $60,000 (project period)

Univ Arizona PI: Alexander, Gene E. (PI: Williamson)
Project: Transcutaneous Vagal Nerve Stimulation and Cognitive Training to Enhance Cognitive Performance in Healthy Older Adults
Sponsor: McKnight Brain Research Foundation
Project Dates: October 2019 – September 2021
Subaward Amount: $60,000 (project period)

Univ Arizona PI: Alexander, Gene E. (Multi-PI: Cohen, Levin, Wadley))
Project: McKnight Inter-Institutional Cognitive Aging Assessment Core
Sponsor: McKnight Brain Research Foundation
Project Dates: September 2015 – December 2022
Award Amount: $180,000 (project period)

Univ Arizona PI: Alexander, Gene E. (Multi-PI: Cohen, Visscher, Wright)
Project: McKnight Inter-Institutional Neuroimaging Core and Brain Imaging Registry
Sponsor: McKnight Brain Research Foundation
Project Dates: September 2015 – December 2022
Award Amount: $180,000 (project period)

Univ Arizona Co-PI: Alexander, Gene E. (PI: MacLean)
Project: Development of Cognitive and Physical Activity Biomarkers for a Companion Dog Model of Alzheimer's Disease (U19 AG057377)
Sponsor: University of Washington (NIA Prime)
Project Dates: July 2020 – June 2021
Subaward Amount: $60,115 (current year)

Univ Arizona Co-PI: Alexander, Gene E. (PI: MacLean)
Project: Physical Activity Predictors of Cognitive and Brain Health in the Risk for Alzheimer's Disease (R56 AG067200
Sponsor: National Institute on Aging
Project Dates: September 2020 – August 2021
Subaward Amount: $306,993 (current year)

Univ Arizona PI: Alexander, Gene E. (co'I's: Hischaw, Raichlen, Simpson, Trouard)
Project: Neuroinflammation, Aging, and Cognition: An Intervention Study
Sponsor: Arizona Alzheimer's Consortium, state of Arizona, DHS
Project Dates: July 2019 – June 2020
Award Amount: $57,463(project period)

Univ Arizona PI: Alexander, Gene E.
Project: Behavioral Biomarkers in Brain Aging and Alzheimer's Disease Risk
Sponsor: Arizona Alzheimer's Consortium, state of Arizona, DHS
Project Dates: July 2020 – June 2021

Award Amount:	$30,000(project period)
Univ Arizona PI:	Andrews-Hanna, Jessica
Project:	Real-world markers and neural mechanisms of Alzheimer's disease risk in cognitively normal older adults
Sponsor:	Arizona Alzheimer's Consortium, state of Arizona, DHS
Project Dates:	July 2019 – June 2020
Award Amount:	$22,143 (project period)
Univ Arizona PI:	Andrews-Hanna, Jessica
Project:	Why is the glass half-full? Sources of the positivity effect in healthy aging and AD risk
Sponsor:	Arizona Alzheimer's Consortium, state of Arizona, DHS
Project Dates:	July 2020 – June 2021
Award Amount:	$20,000 (project period)
PI:	Barnes, Carol A. (co-I: Ekstrom)
Project:	Neurobehavioral Relations in Senescent Hippocampus (R01 AG003376)
Sponsor:	National Institute on Aging
Project Dates:	January 2016 – November 2021
Award Amount:	$736,431 / 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 2021
Award Amount:	$516,626 / year
PI:	Barnes, Carol A. (co-I's: Alexander, Billheimer, Huentelman, Trouard)
Project:	Neural System Dynamics & Gene Expression Supporting Successful Cognitive Aging (RO1 AG049465)
Sponsor:	National Institute on Aging
Project Dates:	August 2014 – March 2020
Award Amount:	$734,165 / year
Subcontract PI:	Barnes, Carol A. (PI: Stern)
Project:	Collaboratory on Research for Cognitive Reserve and Resilience (P30 AG061421)
Sponsor:	Columbia University Subcontract, National Institute on Aging
Project Dates:	October 2018 – September 2021
Subaward Amount:	$18,945 / year
Subcontract PI:	Barnes, Carol A. (PI: Reiman)
Project:	Arizona Alzheimer's Disease Core Center Ad Hoc Review (P30 AG019610)
Sponsor:	National Institute on Aging
Project Dates:	July 2016 – June 2021
Subaward Amount:	$24,476 / year
PI:	Barnes, Carol A. (co-I's: Bimonte-Nelson, Coleman, Huentelman, Reiman)
Project:	Postdoctoral Training, Neurobiology of Aging and Alzheimer's Disease (T32 AG044402)

Sponsor: National Institute on Aging
Project Dates: May 2016 – April 2021
Award Amount: $260,293 / year

PI: Barnes, Carol A. (Mentor for Pilot Award to Daniel Gray)
Project: A test of the hypothesis that factors acting to protect synapse function will lead to an understanding of the biological basis on cognitive reserve (P30 AG061421)
Sponsor: Columbia University Subcontract, National Institute on Aging
Project Dates: September 2020 – February 2022
Award Amount: $47,510 / year

Univ Arizona PI: Barnes, Carol A.
Project: Age-related specific changes in expression of several central melanocortin receptor subtypes and their localization in rat brain
Sponsor: Arizona Alzheimer's Consortium, state of Arizona, DHS
Project Dates: July 2019 – June 2020
Award Amount: $18,079 (project period)

Univ Arizona PI: Barnes, Carol A.
Project: Neuroinflammation, Aging, and Cognition: An Intervention Study
Sponsor: Arizona Alzheimer's Consortium, state of Arizona, DHS
Project Dates: July 2019 – June 2020
Award Amount: $24,922 (project period)

Univ Arizona PI: Barnes, Carol A.
Project: Combining high resolution ex vivo magnetic resonance imaging with immunohistochemical labelling of neurovascular function in aged macaque monkey brains
Sponsor: Arizona Alzheimer's Consortium, state of Arizona, DHS
Project Dates: July 2020 – June 2021
Award Amount: $30,000 (project period)

PI: Brinton, Roberta (co-I's: Chang, Yin)
Project: Sex Differences in the Molecular Determinants of Alzheimer's Disease Risk: Prodromal Endophenotype (R01 AG057931)
Sponsor: National Institute on Aging
Project Dates: September 2018 – August 2023
Award Amount: $1,192,861 (current year)

PI: Brinton, Roberta
Project: Translational Research in AD and related Dementias (TRADD) (T32 AG057931)
Sponsor: National Institute on Aging
Project Dates: September 2018 – August 2023
Award Amount: $300,250 (current year)

PI: Brinton, Roberta
Project: Aging & Estrogenic Control of the Bioenergetic System in Brain (R01 AG053589)
Sponsor: National Institute on Aging
Project Dates: March 2017 – February 2022
Award Amount: $308,930 (current year)

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:	$2,496,919 (current year)

Subaward PI:	Brinton, Roberta (co-I: Yin)
Project:	Metabolic Networks and Pathways Predictive of Sex Differences in AD Risk and Responsiveness to Treatment (R01 AG059093)
Sponsor:	Duke University (National Institute on Aging Prime)
Project Dates:	August 2018 – June 2023
Award Amount:	$153,500 (current year)

PI:	Brinton, Roberta (co-I: Rodgers)
Project:	Allopregnanolone a Regenerative Therapy for Alzheimer's: FDA-Required Toxicology (U01 AG047222)
Sponsor:	National Institute on Aging
Project Dates:	June 2018 – June 2021
Award Amount:	$234,775 (current year)

PI:	Brinton, Roberta (co-I's: Hernandez, Rodgers)
Project:	Allopregnanolone as Regenerative Therapeutic for Alzheimer's: Phase II Clinical Trial (RO1 AG063826)
Sponsor:	National Institute on Aging
Project Dates:	August 2019 – April 2024
Award Amount:	$8,410,912 (current year)

Co-PI:	Brinton, Roberta (PI: Rodgers)
Project:	Undergraduate Readying for Burgeoning Research for American Indian Neuroscientists y (R25 NS107185)
Sponsor:	National Institute on Neurological Diseases and Stroke
Project Dates:	July 2019 – June 2024
Award Amount:	$123,261 (current year)

Co-Investigator:	Brinton, Roberta (PI: Rodgers)
Project:	IND Enabling Studies for RASRx 1902, a Novel Mas Receptor Agonist, for Treatment of Cognitive Impairment in Patients at Risk for Alzheimer's Disease
Sponsor:	National Institute on Aging
Project Dates:	May 2020 – April 2024
Award Amount:	$1,533,089 (current year)

PI:	Chou, Ying-hui (co-I's: Alexander, Barnes, Bedrick, Chen, Mohler, Rapcsak, Ryan(
Project:	Enhancement of hippocampal plasticity using repetitive transcranial magnetic stimulation (R01 AG062543)
Sponsor:	National Institute on Aging
Project Dates:	May 2020 – January 2025
Subaward Amount:	$735,125 (current year)

Co-Investigator:	Chou, Ying-hui (PI: Killgore)
Project:	Transcranial Magnetic Stimulation of the Default Mode Network to Improve Sleep (DOD)
Sponsor:	United States Army Medical Research Acquisition Activity
Project Dates:	September 2020 – August 2022
Amount:	$30,699 / project period (Chou component)

Univ Arizona PI:	Chou, Ying-hui
Project:	Transcranial Magnetic Stimulation for Mild Cognitive Impairment
Sponsor:	Arizona Alzheimer's Consortium, state of Arizona, DHS
Project Dates:	July 2019 – June 2021
Award Amount:	$45,115 (project period)

Co-Investigator:	Chou, Ying-hui (PI: Witte)
Project:	4D Transcranial Acoustoelectric Imaging for High Resolution Functional Mapping of Neuronal Currents (U01 EB029834)
Sponsor:	National Institute of Biomedical Imaging and Bioengineering
Project Dates:	September 2020 – June 2025
Amount:	$6,880 / year (Chou component)

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 – May 2021
Award Amount:	$458,236 / year

Co-Investigator:	Cowen, Stephen (PI: Witte)
Project:	4D Transcranial Acoustoelectric Imaging for High Resolution Functional Mapping of Neuronal Currents (U01 EB029834)
Sponsor:	National Institute of Biomedical Imaging and Bioengineering
Project Dates:	September 2020 – June 2025
Amount:	$27,523 / year (Cowen component)

Co-Investigator:	Cowen, Stephen (PI: Falk)
Project:	Mechanisms of Low-Dose Ketamine Treatment for Parkinson's Disease (R56 NS109608)
Sponsor:	National Institute on Aging
Project Dates:	August 2019 – August 2021
Amount:	$115,541 (Cowen component)

Subcontract PI:	Cowen, Stephen, L.
Project:	High Density, Miniaturized, Zero Switching, Stimulation and Recording Headstage for Small Animals (R44 MH114776)
Sponsor:	Advanced Medical Electronics Corp (NINDS Prime)
Project Dates:	August 2019 February 2021
Award Amount:	$50,683 (project period)

PI:	Ekstrom, Arne (co-I's: Andrews-Hanna, Drake, Grilli)
Project:	Precision and Binding as Two Dimensions of Medial Temporal Lobe Amnesia (R01 NS109819)
Sponsor:	National Institute of Neurological Disorders and Stroke
Project Dates:	June 2020 – May 2025
Award Amount:	$613,429 (current year)

PI:	Ekstrom, Arne
Project:	Volumetric and Connectivity Measures of Navigation and Memory Skill Acquisition
Sponsor:	National Institute of Neurological Disorders and Stroke
Project Dates:	September 2020 – August 2022
Award Amount:	$434,125 (current year)

Subcontract PI:	Ekstrom, Arne (co-I's: Drake, Isham)
Project:	Representation of Spatiotemporal Information in Human Episodic Memory and Navigation (R01 NS07856)
Sponsor:	National Institute of Neurological Disorders and Stroke
Project Dates:	July 2012 – April 2023
Award Amount:	$347,985 (current year)

PI:	Ekstrom, Arne
Project:	The Neural Basis of Human Spatial Navigation in Large-scale Virtual Spaces with Vestibular Input (NSF BCS-1630296)
Sponsor:	National Science Foundation
Project Dates:	July 2016 – August 2021
Award Amount:	$347,985 / year

PI:	Fernandez, Fabian
Project:	Programming the Circadian Clock with Precision Flashes of LED Light
Sponsor:	Velux Stiftung (Switzerland)
Project Dates:	January 2020 – December 2022
Award Amount:	$275,000 (project period)

PI:	Grilli, Matthew (co-I's: Andrews-Hanna, Ryan)
Project:	The Episodic Autobiographical Memory Hypothesis of Preclinical Alzheimer's Disease: Developing a New Approach for Early Cognitive Detection and Measurement of Alzheimer's Disease (R03 AG060271)
Sponsor:	National Institute on Aging
Project Dates:	April 2019 – March 2022
Award Amount:	$76,750 (project period)

PI:	Grilli, Matthew (co-I's: Andrews-Hanna, Mehl)
Project:	Tracking Autobiographical Thoughts: A Smartphone-Based Approach to the Detection of Cognitive and Neural Markers of Alzheimer's Disease Risk (R03 AG060271)
Sponsor:	National Institute on Aging
Project Dates:	September 2020 – August 2021
Award Amount:	$642,211 (project period)

Univ Arizona PI:	Grilli, Matthew
Project:	Improving clinical neuropsychological assessment of subtle cognitive decline and mild cognitive impairment
Sponsor:	Arizona Alzheimer's Consortium, state of Arizona, DHS
Project Dates:	July 2019 – June 2020
Award Amount:	$22,412 (project period)

Univ Arizona PI:	Grilli, Matthew
Project:	Autobiographical memory, future thinking, and neuropsychology in Hispanics
Sponsor:	Arizona Alzheimer's Consortium, state of Arizona, DHS
Project Dates:	July 2020 – June 2021
Award Amount:	$20,000 (project period)

Subcontract PI:	Mehl, Matthias (PI: Nugent)
Project:	Understanding the Interplay of Social Context and Physiology on Psychological Outcomes in Trauma-Exposed Adolescents (R01 MH108641)
Sponsor:	National Institutes of Mental Health
Project Dates:	July 2016 – June 2021
Award Amount:	$59,078 / year

Subcontract PI:	Mehl, Matthias (PI: Nugent)
Project:	Biomarkers, Social, and Affective Predictors of Suicidal Thoughts and Behaviors in Adolescents (R01 MH105379)
Sponsor:	National Institutes of Mental Health
Project Dates:	July 2019 – June 2021
Award Amount:	$104,321 (project period)

PI:	O'Connor, Mary-Francis
Project:	Social Neuroscience of Grief: 2020 Vision and Social Neuroscience of Grief: Early Adversity and Later Life Reversibility
Sponsor:	National Institute on Aging
Project Dates:	September 2019 – November 2021
Award Amount:	$14,100 (current year)

Univ Arizona PI:	Ryan, Lee
Project:	Contextual retrieval impairment in self-defining autobiographical memories as an early indicator of risk for AD
Sponsor:	Arizona Alzheimer's Consortium, state of Arizona, DHS
Project Dates:	July 2019 – June 2020
Award Amount:	$60,150 (project period)

Univ Arizona PI:	Ryan, Lee
Project:	Establishing pipelines data sharing and image analysis for cognitively healthy older adults at the University of Arizona
Sponsor:	Arizona Alzheimer's Consortium, state of Arizona, DHS
Project Dates:	July 2019 – June 2020
Award Amount:	$60,282 (project period)

Univ Arizona PI:	Ryan, Lee
Project:	Assessing medial temporal lobe network integrity using high resolution fMRI
Sponsor:	Arizona Alzheimer's Consortium, state of Arizona, DHS
Project Dates:	July 2020 – June 2021
Award Amount:	$38,225 (project period)

PI	Wilson, Robert C. (co-I's Alexander, Andrews-Hanna, Chou, Ekstrom)
Project:	Evaluating the Neurocomputational Mechanisms of Explore-Exploit Decision Making in Older Adults (R01 AG061888)
Sponsor:	National Institute on Aging
Project Dates:	September 2018 – August 2020
Award Amount:	$345,375 (project period)

UA PI:	Wilson, Robert (Multi-PI: Wilson, Grilli, Levin, Ebner, Oliveira, Getz)
Project:	Vulnerability of Older Adults to Financial Deception Schemes
Sponsor:	McKnight Brain Research Foundation
Date:	April 2018 September 2020
Amount:	$110,000 (project period)

Educational programs focusing on age-related memory loss

The 19th Annual Retreat of the Arizona Alzheimer's Consortium was held on Friday, January 24 to Sunday, January 26 at the Nautical Beach Resort in Lake Havasu, Arizona. The retreat was attended by ~ 50 scientists across to state who shared their work on broad topics involving Alzheimer's disease, as well as memory and aging. Due to COVID-19, all additional face-to-face educational programs were cancelled in 2020

Collaborative programs

with 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. As I discussed in the 'most important achievement section' we resubmitted the U19 Precision Aging Network grant to NIA in September 2020. If funded, the Miami EMBI (**Rundek, Levin, Sacco**) is directly involved as an important experimental site in the project, and we hope to eventually engage the other two EMBI sites to participate in our efforts towards making a Precision Aging Network a reality. Peer-reviewed examples of collaboration between the Tucson EMBI and other sites are listed below. EMBI faculty participating in the work mentioned are listed in bold, the full citations can be found in the publication section.

The McKnight Brain Aging Registry project has led to several publications in 2020. Two of these studies examined age-related differences in dorsolateral prefrontal cortex (DLPFC) structure and function, specifically to clarify how the structure and function of DLPFC contributed to working memory function in healthy older adults. The results revealed that the left DLPFC surface area significantly predicted the probability of being in the higher performing group, while the DLPFC BOLD signal did not. This suggests BOLD signal and surface area may independently contribute to working memory performance in healthy older adults (**DeKosky, Alexander, Marsiske, Cohen, Woods**). Another study confirmed previous research suggesting that bilateral hippocampal volume is associated with episodic memory performance, but further suggests that the left hippocampus volume may be associated with both episodic and working memory performance in aging. They conclude that investigations of lateralized hippocampus function could lead to more accurate identification of predictors of cognitive aging (**Porges, Dekosky, Marsiske, Cohen, Alexander, Woods**).

There has been some concern about older adults falling victim to "phishing" emails, which attempt to deceive a person into identity theft and fraud. One study investigated whether older age is associated with differences in perceived suspiciousness of phishing emails. They found that while older age was not related to a shift in overall perception of email safety, older age was related to worse discrimination between genuine and phishing emails, according to perceived suspiciousness. Thus, older adults may be at particular risk for online fraud because of an age-associated reduction in their sensitivity to the credibility of emails (**Grilli, Levin, Ebner,** Wilson). Another study examined cortical volume by MRI and speed of processing on the POSIT Double Decision task in a healthy older adult population. They found that less cortical thickness in right temporal, posterior frontal, parietal and occipital lobe structures were significantly associated with poorer Double Decision scores. These

findings suggest that changes in speed of processing performance in aging is associated with a wide array of cortical regions (**Marsiske, Cohen, Alexander, Woods**).

with non-McKnight institutions and research programs

In addition to inter-institutional collaborations among EMBI faculty, we also have extensive collaborations with other faculty inside the University of Arizona, across the state, across the country, and around the world. I mention examples of some of these interactions relevant to the aging brain and memory below.

Besides faculty from Miami and Tucson EMBIs, the U19 Precision Aging Network proposal that I described under 'important scientific achievements' includes two other clinical sites participating in the grant – one at Emory University (Allan Levey, Jim Lah), and one at Johns Hopkins University (Marilyn Albert). The collaborators on the RO1 grant that I mentioned in the 'important scientific achievements' section include Matt Huentelman (Arizona EMBI) but also Paul Worley from Johns Hopkins. In that grant, we will define the position of NPTX2 (an important 'resilience factor') in the connection between "brain healthspan" and "cognitive healthspan" and will test a compelling mechanisms and regulatory pathways that may provide therapeutic targets to mitigate cognitive decline in normative aging and AD.

Another important collaborative project that myself and Tom Foster (Gainesville EMBI) are participating in is a P30 grant from NIA entitled Collaboratory on Research for Cognitive Reserve and Resilience. Yaakov Stern is the PI, who leads a group of 5 individuals (myself, Rapp, intramural NIA; Albert, Johns Hopkins; Cabeza, Duke; and Pascual-Leone, Harvard) as an executive committee. Our goal is to build the infrastructure to organize workshops, databases, and facilitate award of pilot grants that will guide efforts to reach consensus on the most effective operational definitions for brain and cognitive reserve so that experiments can be directed at understanding underlying mechanism of these concepts. The idea for the RFA that went out to the community to apply for was a direct result of one of the Cognitive Aging Summits that the MBRF co-sponsored. In 2020 we held the second Reserve and Resilience Workshop, virtually. A working group emerged from this workshop who have published a whitepaper on the potential of longitudinal studies in nonhuman aging research on which Barnes and Foster were authors (see publication section.

Plans for future research

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 RO1 grants and one postdoctoral training grant. She is likely to receive a new RO1 (was scored very well), and submitted a renewal of another RO1 in 2020 that will be reviewed in February 2021. She also resubmitted a U19 grant entitled "Precision Aging Network: Closing the Gap between Cognitive Healthspan, Human Lifespan" in September that will also be reviewed in February. Through these funding sources we hope to make great strides in understanding how the brain changes during normative aging, how this impacts cognition. These efforts will lead to a better understanding of how to implement interventions for cognitive decline that are individually effective.

Investment report

Endowed Chair

Summary for 12 months ending June 30, 2020

Account Name: Evelyn F. McKnight Chair for Learning and Memory in Aging

A.	Beginning Balance on July 1, 2019	$ 897,715
B.	Investment Growth	$ (49,778)
C.	Distributions (to Endowed Chair Expendable)	$ (35,005)
D.	Additional Contributions	$
E.	Ending Balance on June 30, 2019	$ 812,932

Institute – Quasi Endowment

Summary for 12 months ending June 30, 2020

Account Name: Evelyn F. McKnight Brain Institute

A.	Beginning Balance on July 1, 2018	$ 1,385,461
B.	Investment Growth	$ (89,845)
C.	Distributions (to Endowed Chair Expendable)	$ (400,000)
D.	Additional Contributions	$
E.	Ending Balance on June 30, 2019	$ 895,616

Institute – Permanent Endowment

Summary for period ending November 30, 2020

Account Name: Evelyn F. McKnight Brain Institute

See full report from the University of Arizona Foundation on following pages

January 11, 2021

Trustees
The McKnight Brain Research Foundation
P.O. Box 620005
Orlando, FL 32862

Dear McKnight Brain Research Foundation Trustees,

It was a pleasure to catch up with Dr. Lee Dockery shortly before Thanksgiving on the latest happenings at the McKnight Brain Research Foundation and the McKnight endowment held here at the University of Arizona Foundation, and to express my thanks to the Trustees.

The McKnight Trustees have made investments for the long term through endowed gifts to promote research and investigation of the brain in the fundamental mechanisms that underlie the neurobiology of memory and cognitive changes that occur during the process of aging, to accomplish alleviations of age-related memory loss. We are extremely grateful for this support and very proud of the high-level scientific contributions produced by Dr. Barnes and her colleagues at the University of Arizona Evelyn F. McKnight Brain Institute (EMBI). At the University of Arizona Foundation, we are also working to build up our half of the endowment so it will be there for the long term.

Despite the many challenges of the last year, I am very pleased to share significant progress on the match in 2020.

- Last calendar year, starting on January 1, 2020 and *reporting through November 30, 2020, the endowed fund has received $2,144,332 in new gifts*.
- From the inception of the fund through November 30, 2020 *the total matched amount is $2,331,336*.

Completing the match is a high priority, and we will continue to find funds to fulfill the match as quickly as possible. In fact, we anticipate near-term additions to the fund of approximately $35,000, and we will continue to solicit funds and identify resources to achieve the match.

Not only do we have good news to report on matching gifts, but also a very positive investment return in the latter half of 2020, as detailed in the attached endowment summary for the period July 1, 2020 – November 30, 2020 for Fund Number 40-10-4500. This fiscal year, *as of November 30, 2020, the fund earned $852,066.56* from a beginning market value on July 1, 2020 of $5,794,304.72. *The ending market value of the fund as of November 30, 2020 is $7,878,167.36.*

As you can imagine, 2020 presented unusual circumstances for both fundraising and investment management. The Investment Committee of the University of Arizona Foundation board has met monthly during the Covid period, including with our new outsourced Chief Investment Officer (CIO), the Fund Evaluation Group (FEG). FEG provides services to

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institutions with approximately $65 billion in assets, with significant expertise in managing university endowments. We first engaged FEG in 2013 in an advisory/consulting capacity to serve as an extension of our staff. In 2020, the University of Arizona Foundation Board of Trustees and I decided to deepen our engagement with FEG to serve as outsourced CIO to assist us with navigating uncertain times.

On behalf of the University of Arizona and the University of Arizona Foundation, I also can confirm that the university has fulfilled its commitment to the Trustees to provide the payout to the EMBI as if the match had been completed. Please note that the commitment has been fulfilled by transferring funds under the direction of University of Arizona Research, Innovation and Impact to a separate university account under the direction of, and available for spending by, EMBI. Please further note that the transfer of funds in the amount of $132,418 is for the period 7/1/19 – 8/31/20.

Our entire team at the University of Arizona Foundation is always grateful to be able to support the mission of Dr. Barnes and her team and colleagues, as well as that of the McKnight Brain Research Foundation.

Sincerely,

John-Paul Roczniak
President & CEO

JPR/jf

Attachment

E.F. McKnight Brain Institute Endowment

Financial Report for the 2021 Fiscal Year

Activity for the Period July 1, 2020 – November 30, 2020

Fund Number: 40-10-4500

Fund Purpose

The purpose of the 2014 gift is to promote research and investigation of the brain in the fundamental mechanisms that underlie the neurobiology of memory and cognitive changes that occur during the process of aging, principally intended for clinical application, to accomplish alleviations of age-related memory loss.

Fund Performance

Beginning Market Value at 7/1/2020	$	5,794,304.72
New gifts and additions		1,382,769.25
Investment performance		852,066.56
Endowment Payout		-116,586.46
Endowment Fee		-34,386.71
Ending Market Value at 11/30/2020	**$**	**7,878,167.36**
Historic gift value at 11/30/2020	$	7,018,698.73

Social Media Outreach

What social media platforms are you active on and how many followers do you have?

- Facebook: 575 likes, 641 follows
- Instagram: 479 followers
- LinkedIn: 454 followers

Number of media impressions and placements secured mentioning the MBI and/or your leadership/researchers

See below.

Number of monthly visitors to your website and any peak areas of interest or engagement

These data were not tracked through the Psychology/EMBI websites in 2020, however, tracking has been initiated, and data will be available going forward for future annual reports.

2020 Press and articles

Alexander, Gene

- Featured on the cover of the January 2020 issue of Scientific American. January 2020 - Scientific American https://www.scientificamerican.com/magazine/sa/2020/01-01/
- Feed your head: Science shows that exercise can improve your brain as you age. Costco Connection. https://www.costcoconnection.com/connection/202006/MobilePagedReplica.action?pm=1&folio=48#pg51

Andrews-Hanna, Jessica

- App Unlocks Mysteries of the Mind. University of Arizona News https://news.arizona.edu/story/app-unlocks-mysteries-mind

Barnes, Carol and Huentelman, Matt

- Diversity in Science: Making a Difference on Aging Brain Research. Red Shoe Movement https://redshoemovement.com/diversity-in-science-making-a-difference-on-aging-brain-research/

Grilli, Matt

- Older Adults Share Fewer Memories as They Age. UA News. https://news.arizona.edu/story/older-adults-share-fewer-memories-they-age

Mehl, Matthias

- Can Conversation Add 15 Years to Your Life? The Science Says Yes. Forbes. https://www.forbes.com/sites/dianatsai/2020/07/31/can-conversations-add-15-years-to-your-life-the-science-says-yes/?sh=6aab77f639d2

Ryan, Lee

- Virtual fatigue, what it is and how to combat it. KGUN 9 News. https://www.bing.com/videos/search?q=kgun+9+news+Virtual+fatigue%2c+what+it+is+and+how+to+combat+it&view=detail&mid=1D8711545FF8CB909F531D8711545FF8CB909F53&FORM=VIRE
- Researchers Investigate How COVID-19 Impacts the Brain. UA News. https://news.arizona.edu/story/researchers-investigate-how-covid19-impacts-brain

Additional notes

Where 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

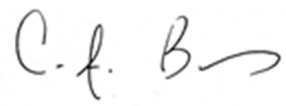
Did all activities during the report period further the Purpose?

Yes

Negative Events

N/A

Respectfully Submitted,



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