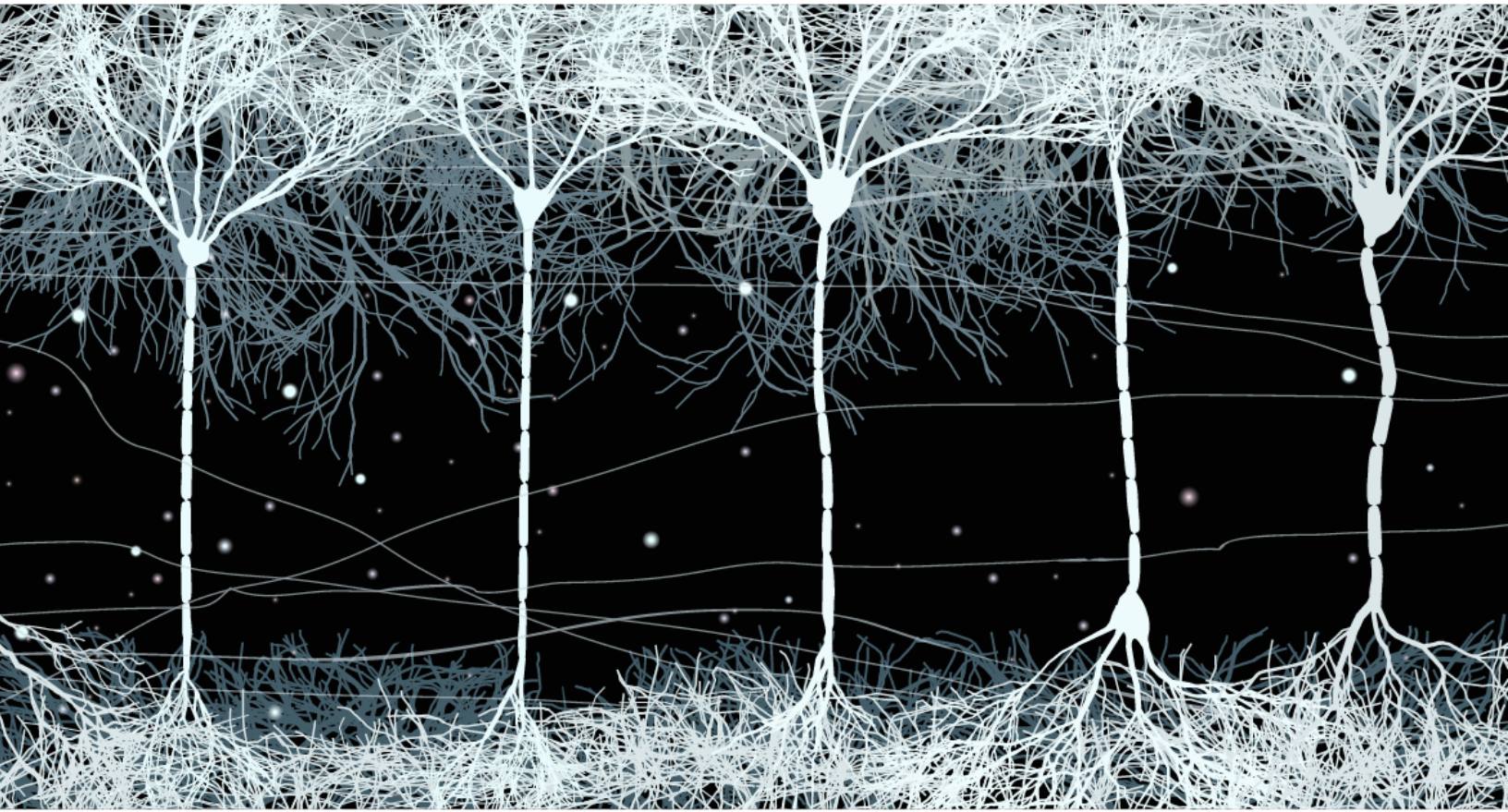




# **Evelyn F. McKnight Brain Institute**

**Full Lives Through Healthy Minds**

**Annual Report 2019**



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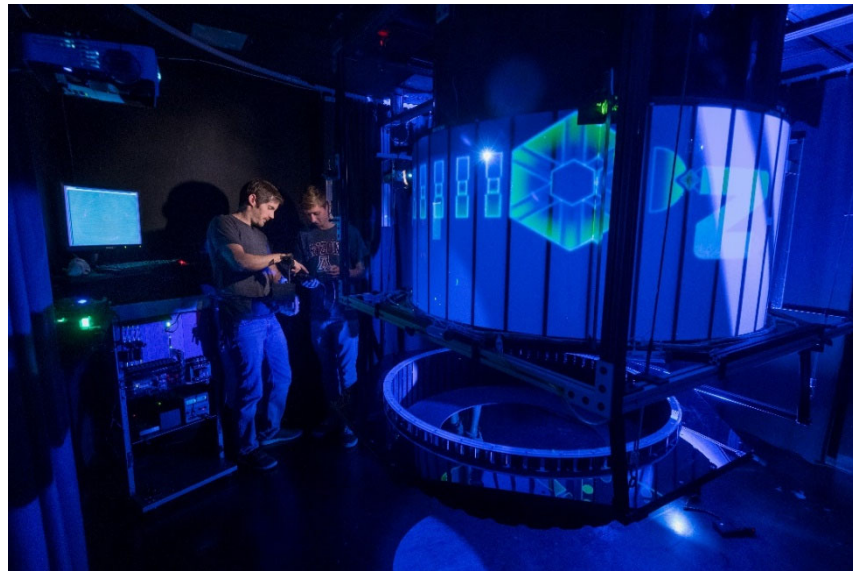
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## *Summary of scientific achievements since last report*

The director and other members of the Evelyn F. McKnight Brain Institute at the University of Arizona have had another productive year. The full list of publications can be found on pages 12 through 19. The following outlines some of these accomplishments that **directly relate to mechanisms of age-related memory loss**, first from the Director's and Associate Director's laboratories, and then from other Evelyn F. McKnight Brain Institute (EMBI) Affiliate Faculty laboratories.

### **Barnes**

The Barnes laboratory collaborated with four other EMBI Affiliate Faculty (Coleman, Trouard, Alexander and Huentelman) to examine the effect of gradual hypertension induction on cognition in a rat model of hypertension. While the impact of hypertension on the function of the renal and cardiovascular systems is well studied, its influence on brain regions important for cognition



has garnered less attention. Our collaborator Kenneth Mitchell (Tulane) generated a novel transgenic rat model (Cyp11a1 Ren2) in which hypertension could be induced by a xenobiotic compound at an age of choice. Renin-dependent hypertension was gradually induced over a 6 week period in middle aged rats, to mimic the age at which hypertension begins to be observed in human populations. Significant elevations in blood pressure was induced in the animals given the xenobiotic compound, while the transgenic rats not fed the compound maintained stable blood pressure. The hypertension was associated with cardiac, aortic and renal hypertrophy as well as increased collagen deposition in the left ventricle and kidney of the treated rats. Additionally, rats with hypertension showed reduced savings from prior spatial memory training on a hippocampus-dependent task, but they did not show deficits in sensory or motor tasks. These data indicate a profound effect of hypertension not only on the cardiovascular-renal axis, but also on brain systems critically important for learning and memory (**reported in Willeman et al. 2019**). This finding clearly warrants replication and further study.

Barnes collaborated with four other individuals (Stern, Grady, Jones and Raz) in writing a summary of the session in the Cognitive Aging Summit III on "Brain Reserve, Cognitive Reserve, Compensation and Maintenance" (**reported in Stern et al., 2019**). The goal of the session was to begin to operationalize, explore validity and mechanisms of cognitive resilience. Significant individual difference in the trajectories of cognitive aging and age-related changes of brain structure and function have been reported in the past half-century. In some individuals, significant pathological changes in the brain are observed in conjunction with relatively well-preserved cognitive performance. Multiple constructs have been invoked to explain this paradox of resilience, including brain and cognitive reserve, maintenance and compensation. We examine the overlap and distinction in definitions and measurement of these constructs. We proposed a continued dialog

among investigators as a means to help refine the language used across broad fields, so that faster progress can be made in understanding both the resistance and vulnerability to cognitive decline during aging.

Barnes and Gray from the Tucson EMBI authored an invited chapter describing results that Barnes presented for the Sackler Colloquium of the National Academy of Sciences, the topic being: “Using Monkey Models to Understand and Develop Treatments for Human Brain Disorders” (**reported in Gray and Barnes, 2019**). The use of animal models in brain aging research has led to numerous fundamental insights into the neurobiological processes that underlie changes in brain function associated with normative aging. The present review highlights how nonhuman primates provide a critical bridge between experiments conducted in rodents and development of therapeutics for humans. Several studies from the Barnes laboratory were discussed to illustrate how this work has been important for translating mechanistic implications derived from experiments conducted in rodents to human brain aging research.

The Barnes laboratory collaborated with Rapp (NIA Intramural) to examine the behavioral impact of long-term chronic implantation of neural recording devices in the monkey. While there is widespread use of invasive recording methods with animal models and in humans, little is known of their effect on behavior in healthy populations. We were able to quantify the effect of chronic electrode implantation that targeted the hippocampus on recognition memory performance in macaques ranging in age from 7 to 26 years. Memory on the delayed non-matching-to-sample task was not significantly affected by chronic electrode implants targeting the hippocampus in healthy monkeys (**reported in Kyle et al., 2019**). These data indicate that the tissue damage and subsequent foreign body response caused by hyperdrive implantation was not sufficient to disrupt hippocampal circuits and impair memory performance, even though small lesions have been shown to influence this behavior.

The Barnes laboratory and EMBI Affiliate Faculty member Ekstrom collaborated on the creation of a cytoarchitectonically-driven MRI atlas of the nonhuman primate hippocampus. Identification of human and nonhuman primate hippocampal subfields *in vivo* using structural MRI imaging relies on variable anatomical guidelines and signal intensity differences to differentiate between regions. Methods are currently being developed for human experiments to use *ex vivo* histology or MRI methods that have the potential to inform subfield demarcations of *in vivo* images. For optimal results, however, *ex vivo* and *in vivo* images should ideally be matched within the same brains with the goal to develop a neuroanatomically-driven basis for *in vivo* structural MRI images. We report here a novel method that uses Nissl stained histological sections in which we can identify the dentate gyrus, CA3, CA2, CA1, subiculum, presubiculum and parasubiculum guided by morphological cell properties. The histologically identified boundaries were merged with *in vivo* structural MRIs via iterative rigid and diffeomorphic registration resulting in probabilistic atlases of young and old rhesus macaques. Our results indicate stability in hippocampus subfield volumes over an age range of 13 to 32 years (**reported in Kyle et al., 2019**). Our approach has the potential to provide a ‘ground truth’ for more accurate identification of hippocampal subfield boundaries on human *in vivo* MRIs

The Barnes laboratory developed a new method to remove background autofluorescence from aging primate brain tissue. Age-related accumulation of molecules with autofluorescent properties such as lipofuscin, can possess spectral profiles that invade the typical emission range of fluorophores commonly utilized in fluorescent microscopy. The traditional method for dealing with native fluorescence is to apply lipophilic dyes that are able to sequester these unwanted signals. While effective, such dyes can present a range of problems including the obstruction of fluorescent probe emissions relevant to the experiment. This study compared the Sudan Black dye method to spectral imaging and linear unmixing methods. We found that the linear unmixing approach yielded significantly higher cell numbers counted than the dye-based Sudan black approach (**results in Pyon**

**et al., 2019**). These results suggest an alternative method for aging studies in which brain tissue accumulates large quantities of lipofuscin.

The Barnes laboratory along with the Trouard laboratory (EMBI Faculty Affiliate) has begun to examine the contribution that sensory system function plays in age-related cognitive decline. Recent evidence suggests that hearing-impaired individuals have a greater risk of developing cognitive impairment and dementia compared to people with intact auditory function. The neurobiological basis of this association is poorly understood. To begin to better understand this relationship we examined a colony of young and older bonnet macaques. They completed a battery of behavioral tests designed to probe frontal and temporal lobe-dependent cognition, were tested electrophysiologically for auditory brainstem responses and visual evoke potentials, and were imaged using structural and diffusion methods. Animals showing higher cognitive function had significantly better auditory processing capacities, and these associations were selectively observed with tasks that depend on temporal lobe brain structures. Tractography analyses revealed that fractional anisotropy of the fimbria-fornix and hippocampal commissure were associated with temporal lobe-dependent cognitive performance and auditory sensory function (**reported in Gray et al., 2019**). Frontal cortex white matter integrity, on the other hand, was not associated with frontal lobe-dependent memory or with sensory function. The visual sensory measures were not related to any of the cognitive tests given. This study demonstrates significant and selective relationships between auditory processing, white matter connectivity and higher-order cognitive ability.

Barnes was invited to contribute an opinion piece for *Trends in Neurosciences*. Along with EMBI Affiliate Faculty Matt Huentelman, and U19 Precision Aging Network grant participant Zhao Chen, they 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 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, they 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 (**reported in Huentelman et al., in press**).

## Ryan

Barnes, Ryan, Hay, Mehl and Huentelman from the Tucson EMBI collaborated with Levin and Rundek from the Miami EMBI, and colleagues participating in our U19 Precision Aging Network grant from Johns Hopkins (Solden and Pettigrew) and from Georgia Tech (Duarte) to co-author a review article on the importance of applying concepts from precision medicine to the field of cognitive aging (**reported in Ryan et al., 2019**). We contend in this article that the current “one size fits all” approach to our cognitive aging population is not adequate to close the gap between cognitive health span and human lifespan. We present a novel model for understanding, preventing and treating age-related cognitive impairment based on concepts borrowed from precision medicine. This Precision Aging model is meant as a starting point to guide future research. To that end, we discuss key risk categories, genetic risks, and brain drivers involved in setting cognitive trajectories across age and suggest steps needed to move the field forward.

The Ryan laboratory along with the Grilli laboratory (EMBI Faculty Affiliate) published a report on the impact of cardiovascular risk factors on cognition in Hispanic and non-Hispanic whites. Among non-Hispanic whites, cardiovascular risk factors are associated with increased mortality and poorer cognition. Prevalence of cardiovascular risk factors among aging Hispanics is also high. While Hispanics generally have poorer access to healthcare, they tend to have advantageous cardiovascular disease rates and outcomes and live longer than do non-Hispanic whites. This epidemiological phenomenon is commonly referred to as the Hispanic or Latino health paradox. Whether the

Hispanic paradox with respect to greater longevity with the disease extends to the impact of cardiovascular disease on cognition was not known. In this study Hispanics and non-Hispanic whites were matched on age, education, sex, cognitive status and apolipoprotein E4 status. History of hypertension and higher body mass index were associated with poorer executive functions among Hispanics. This relationship was not observed in non-Hispanic whites (**reported in Stickel et al., 2019**). These findings do not fit with the notion of a Hispanic health paradox for cognitive aging and suggest greater vulnerability to impairments in executive functions among Hispanics with hypertension and obesity.

## Alexander

The Alexander laboratory collaborated with the Raichlen lab to investigate the relationship between physical activity, cardiorespiratory fitness and brain volume in middle-aged to older adults. Two measures of exercise that might account for the benefits of aerobic exercise (time spent in moderate-to vigorous physical activity and cardiorespiratory fitness) were examined. Using the UK Biobank, 7,148 males and 4,086 females were studied and time spent in moderate-to-vigorous physical activity and cardiorespiratory fitness were measured along with neuroimaging. They found that moderate-to-vigorous physical activity was associated with overall gray matter volume, while cardiorespiratory fitness was associated with left and right hippocampal volumes (but not overall gray matter volume) (**reported in Raichlen et al., 2019**). This suggests that there are separable effects of specific kinds of exercise on brain health.

The Alexander and Raichlen laboratories collaborated on a study to examine best methods for analysis of accelerometer data that monitor and track physical activity for health-related applications. They examined the potential for fractal complexity of actigraphy data to serve as a clinical biomarker for mortality risk. The results suggest that fractal complexity of physical activity decreased significantly with age and was lower in women compared with men. Higher levels of moderate-to-vigorous physical activity in older adults were associated with greater fractal complexity. Lower fractal complexity of activity was associated with greater mortality (**reported in Raichlin et al., 2019**). These data suggest that wearable accelerometers can provide a noninvasive biomarker of physiological aging.

## Andrews-Hanna

The Andrews-Hanna laboratory has explored how age alters off-task, self-generated thought (mind-wandering) under conditions of low cognitive demand. They explored the frequency, temporal focus and self-referential/social content of spontaneous decoupled thought in younger and older adults in the Shape Expectations task. The participants also completed the daydreaming subscale of the Imaginal Process Inventory as a trait measure of mind-wandering propensity. Their findings indicate a distinct attenuation of off-task, self-generated thought processes with increasing age, and evidence for a shift in temporal focus and self-referential quality during periods of low cognitive demand (**reported in Irish et al., 2019**).

Andrews-Hanna and collaborators explored the neural correlates of mind wandering in normal older adults and adults with a behavioral variant of frontotemporal dementia (bvFTD) and Alzheimer's disease (AD). Relative to controls the bvFTD patients displayed significantly reduced mind wandering capacity, offset by a significant increase in stimulus-bound thought. In contrast, AD patients exhibited comparable levels of mind wandering as controls, but some increase in propensity towards stimulus-bound thought. The altered profiles of mind-wandering were associated with structural and functional brain changes in the hippocampus, default and frontoparietal networks (**reported in O'Callaghan et al., 2019**).

Andrews-Hanna and collaborators examined the long-held notion that memory and 'the self' are intertwined, and that a loss of memory in dementia results in a diminished sense of self. Their data

led them to propose a new framework for understanding and managing everyday functioning and behavior in dementia. They suggest that the temporally-extended self changes in healthy and pathological aging (but is not lost in neurodegenerative disease), and that this has important ramifications for development of person-centered care (**reported in Strikwerda-Brow et al., 2019**).

Andrews-Hanna and collaborators have explored mind-wandering in Parkinson's disease (PD) patients with hallucinations. In PD patients with visual hallucinations, they found abnormal activity within the default mode network, and altered pattern of connectivity patterns of this network to early visual regions. To test the hypothesis that individuals with hallucinations experience an increased frequency of mind-wandering, patients were compared to PD patients without hallucinations and controls. The results showed that patients with hallucinations exhibited significantly higher mind-wandering relative to non-hallucinators, who in turn had reduced levels of mind-wandering compared to controls (**reported in Walpola et al., 2019**). Taken together the data suggest that elevated mind-wandering and increased default-visual network coupling is a distinguishing feature of the hallucinatory phenotype. The data suggest that top-down influences over perception is involved in visual hallucinations.

## Brinton

The Brinton laboratory reported the results of a study that examined mechanisms responsible for neuroendocrine aging and perimenopause. Because age of perimenopause onset is only 47% heritable, they hypothesized that additional factors regulate this endocrine aging transition. They characterized transcriptional and epigenomic changes across endocrine aging using a rat model that recapitulates characteristics of the human perimenopause. RNA-seq analysis revealed that hypothalamic aging precedes onset of perimenopause. Epigenetic analysis revealed changes in DNA methylation in genes required for hormone signaling, glutamate signaling and melatonin and circadian pathways (**reported in Bacon et al., 2019**). When treatment with a DNA-methyltransferase inhibitor was given, this delayed the onset of perimenopause and endocrine aging, suggesting that there is a critical period of female neuroendocrine aging in brain that precedes ovarian failure, regulated by DNA methylation.

The Brinton laboratory reviewed what is known about autoimmune disease in women across the lifespan. Women have a higher incidence and prevalence of autoimmune disease than do men. Women also undergo dramatic endocrinological changes during lifetime, including puberty and menopause, and frequently also pregnancy. They provide evidence from human epidemiological data and animal studies that endocrine transitions exert profound impact on the development of autoimmune diseases through complex mechanisms, and suggest that a greater understanding of endocrine transitions could aid in prediction and prevention of autoimmune diseases in women (**reported in Desai and Brinton, 2019**).

The Brinton laboratory and collaborators reported an association of the apolipoprotein E4 genotype, metabolic profile and cognition in women. In a sample of 407 women, verbal memory was lower in the poor metabolic profile women, and performance in all cognitive domains was lowest in the APOE4 carriers in the poor metabolic cluster. Differences in executive functions were detected only in women carrying the APOE4 genotype (**reported in Karim et al., 2019**). Reduction in cognitive performance is more apparent in women who carry an APOE4 allele, especially in conjunction with a poor metabolic profile, suggesting a window of opportunity for interventions in postmenopausal women.

The Brinton laboratory has reported on the safety and feasibility of an estrogen receptor- $\beta$  targeted phytoSERM formulation for menopausal symptoms. The Phase 1b/2a randomized clinical trial suggested that the phytoSERM formulation was well tolerated at 50 and 100mg daily doses. Based on safety outcomes, vaginal bleeding at the 100mg dose and vasomotor symptoms and cognitive

outcomes at 12 weeks, a daily dose of 50mg was considered preferable for a Phase 2 efficacy trial (**reported in Schneider et al., 2019**).

The Brinton laboratory conducted a pilot study on the pharmacogenomic effects of mitochondrial haplogroup and APOE genotype on therapeutic efficacy of a phytoSERM. They conducted a retrospective analysis to identify potential responders to phytoSERM treatment, and to determine the optimal populations to pursue in a Phase 2 clinical trial of efficacy. The population was stratified by 2 genetic risk modulators for Alzheimer's disease – mitochondrial haplogroup and APOE genotype. When examined in this way, 50mg of daily phytoSERM for 12 weeks reduced hot flash frequency and preserved cognitive function in certain aspects of verbal learning and executive function (**reported in Wang et al., 2019**). They conclude that these data provide a reasonable rationale to extend analyses to a larger study set that is sufficiently powered statistically.

## **Chou**

The Chou laboratory and collaborators reviewed the impact of yoga as a form of advanced cognitive training. Specifically, they examined the neural effects and benefits of a yogic practice on the default mode network in post-traumatic stress disorder. Symptom severity in this disorder is related to decreased neural connectivity in the default mode network. The particular practice of Kirtan Kriya yoga involving a series of repetitive, sequential movements that are synchronized with a self-produced mantra in Kundalini yoga appears to be a powerful intervention for symptoms of this brain injury, and hold promise for neural repair (**as reported in Sales and Chou, 2019**).

The Chou laboratory conducted a systematic review and meta-analysis of repetitive transcranial magnetic stimulation (rTMS) effects on cognitive enhancement in mild cognitive impairment (MCI) and Alzheimer's disease (AD). The meta-analysis of thirteen studies focused on characterizing the effectiveness of various combinations of rTMS parameters on different cognitive domains in MCI and AD. There was an overall medium-to-large effect size favoring active rTMS over sham rTMS in the improvement of cognitive functions. Specific rTMS frequencies used over left dorsolateral prefrontal cortex and right dorsolateral prefrontal cortex significantly improved memory, while rTMS that targeted the right inferior frontal gyrus significantly improved executive functions. The effects of these treatments could last for 4-12 weeks, and they conclude could be effective for treatment of cognitive dysfunction (**reported in Chou et al., 2019**).

## **Cowen**

The Cowen laboratory collaborated with the Barnes laboratory to examine hippocampal sharp-wave ripples during waking states in young and aged rats. Several novel observations emerged from these studies, including the fact that aged rats express more ripples, but that young rats express higher ripple rates, and that while during periods of rest ripple frequencies were lower, aged rats could increase ripple rates during behavior to levels equivalent to young rats (**reported in Cowen et al., 2018**). The suggested role played by waking ripples in memory may indicate that slower movement speeds of aged rats may provide more opportunity to replay task-relevant information, and thus may result in some reduction of age-related declines in memory.

## **Ekstrom**

The Ekstrom laboratory conducted a study to examine the question of how we use environmental boundaries to anchor spatial representations during navigation. They conducted an experiment in which participants freely ambulated on an omnidirectional treadmill while viewing novel, town-sized environments in virtual reality on a head-mounted display. Participants performed interspersed judgments of relative direction to assay their spatial knowledge and to determine when during learning they employed environmental boundaries to anchor their spatial representations. Their results suggest that the use of spatial boundaries as an organizing schema during navigation of large-

scale space occurs in an experience-dependent fashion (**reported in Starrett et al., 2019**). These findings help bridge the gap between neurophysiological models of location-specific firing in rodents and human behavioral models of spatial navigation.

The Ekstrom laboratory published a study focusing on the networks that underlie the retrieval of large-scale spatial environments in the human brain. Recent breakthroughs in immersive virtual reality technology allowed examination of how body-based cues influence spatial representations of large-scale environments in humans. Availability of body-based cues were directly manipulated during navigation using an omnidirectional treadmill and a head-mounted display. The behavioral and neuroimaging results support the idea that there is a core, modality-independent network that supports spatial memory retrieval in the human brain (**reported in Huffman and Ekstrom, 2019**). This suggests that, at least in humans, primarily visual input may be sufficient for expression of complex representations of spatial environments.

The Ekstrom laboratory in collaboration with several other groups conducted a study on the role that the fornix plays in human navigation learning. Experiments in rodents have demonstrated that transecting the white matter fiber pathway linking the hippocampus with an array of cortical and subcortical structures (including the hippocampus) impairs flexible navigational learning in the Morris water maze. Human diffusion MRI methods have linked individual differences in fornix microstructure to episodic memory abilities, but the fornix had not been examined in relation to spatial memory. They found a statistically significant correlation between spatial learning rate and mean diffusivity of the fornix but not in another tract that links occipital and anterior temporal cortices (the inferior longitudinal fasciculus) (**reported in Hodgetts et al., 2019**). These findings extend previous animal studies by demonstrating the functional relevance of the fornix for human spatial learning in a virtual reality environment.

## Fernandez

The Fernandez laboratory completed a longitudinal study of sleep and diurnal rhythms in *Drosophila anassae*. In this study they used high-resolution monitors to track how circadian patterns of locomotor activity change in female flies as they enter mid-to-late life. Daily actograms were generated for each animal, along with a time series of activity across the observational period. Consistent with findings from older rodents and humans, older flies exhibited degraded patterns of wake and sleep that were fragmented – but still rhythmic – across the 24 hour cycle (**reported in Kaladchibachi et al., 2019**). Overall levels of daily activity declined with age, with particular loss of circadian arousal in the wake-maintenance zone a few hours before bedtime.

The Fernandez laboratory conducted a systematic study to examine the optimal parameters to use for adjusting the circadian pacemaker. Recent work suggests that the circadian pacemaker responds optimally to millisecond flashes of light, not continuous light exposure as has been historically believed. This study stimulated *Drosophila* with 8, 16 or 120 millisecond flashes, with the energy content for each duration being systematically varied. The results suggested that when considering per microjoule investment, the 8 msec flashes were more effective than flashes at 16 or 120 msec (**reported in Kaladchibachi et al., 2019**). This suggests that the circadian pacemaker's photosensitivity declines within milliseconds of light contact, and that very little light can optimize circadian responses.

Fernandez wrote a review on circadian responses to fragmented light, summarizing findings from a family of experiments conducted over two decades in the research wing of the Brigham and Women's Hospital that examined the human circadian pacemaker's responses to standardized changes in light patterns generated from overhead fluorescent lighting. Across several hundred days of laboratory recording, the research group observed phase-shifts in body temperature and melatonin rhythms that scaled with illuminance. Phase resetting was optimized, however when exposure occurred as a series of minute-long episodes separated by periods of intervening darkness.

These results suggest that ultra-short duration light pulses can elicit pacemaker responses rivaling those created by continuous hour-long stimulation, if those few seconds of light are evenly distributed across the hour as discreet 2 millisecond pulses (**as described in Fernandez, 2019**). He suggests that these findings have important potential application in future phototherapy techniques. The Fernandez laboratory and collaborators at the University of Arizona reviewed the data concerning the common denominators of sleep, obesity and psychopathology. The high comorbidity between sleep problems, obesity and mental illness suggest that common mechanisms are at work between them. While several variables – obstructive sleep apnea, food intake and inflammation – appear to covary as mechanisms underlying these relationships, there is actually little current experimental evidence to draw strong conclusions at the present time (**as reported in Tubbs et al., 2019**). They emphasize the importance of experiments aimed at a better understanding of the moderating/mediating influences between sleep, obesity and mental health.

## Glisky

The Glisky laboratory reported data that suggests that working memory predicts subsequent episodic memory decline during healthy cognitive aging. To assess the relationship between working memory and episodic memory during healthy cognitive aging, they performed neuropsychological assessments at multiple time points to understand how these cognitive processes interact over time. They demonstrated that working memory performance was able to predict later episodic free recall, suggesting that working memory may be a useful metric of future episodic memory decline (**reported in Memel et al., 2019**).

The Glisky and Grilli (EMBI Faculty Affiliate) laboratories investigated whether the strategy of self-reference can benefit memory for multi-element events. Young and older adults imagined different person-object-location events with reference to themselves or in reference to two famous others. They found that self-reference enhanced memory for object-location and person-object pairs in both age groups (**reported in Hou et al., 2019**). This suggests that self-reference can benefit multiple types of associations and is effective at improving memory in both younger and older adults.

## Grilli

The Grilli laboratory and Associate Director Ryan's laboratory explored the relationship between episodic detail generation and anterotemporal, posteromedial and hippocampal white matter tracts. In this study they combine an autobiographical interview and diffusion MRI to investigate the relationships of two types of episodic detail – details about entities of an event (people and objects) and details about spatiotemporal context. Specifically, the integrity of the uncinate fasciculus, cingulum bundle and fornix pathways were examined. They found that only episodic detail generation was significantly related to cortical and hippocampal pathways. The uncinate fasciculus was more strongly related to event element details than it was to spatiotemporal context detail. The cingulum bundle was also related to these details. The fornix was related to both types of episodic detail (**reported in Memel et al., 2019**). These findings suggest that anterotemporal cortical regions are related to the retrieval of episodic details about autobiographical events.

The Grilli laboratory conducted experiments that suggest that an “episodic mode of thinking” facilitates encoding of perceptually rich memories for naturalistic events. In a between-subjects design, participants were given an episodic mode of thinking task while encoding events. The control was a “gist mode of thinking” task. Participants who received the episodic-generated narrative that contained more perceptual details, encoded memories more effectively than did the gist-generated tasks (**reported in Grilli et al., 2019**). This suggests that an episodic mode of thinking facilitates encoding of perceptually rich memories for naturalistic events.

## Huentelman

The Huentelman laboratory collaborated with four other EMBI Affiliate Faculty (Barnes, Ryan, Glisky, Hay) and published the first report from the MindCrowd web-based cognitive testing study cohort. While it is known that a first-degree family history of dementia is a risk factor for Alzheimer's disease, the influence of family history on cognition across the lifespan is poorly understood. This study addresses this issue. An internet-based paired-associate learning task was developed and was used to test 59,571 participant between the ages of 18 and 85 years of age. We showed that family history was associated with lower memory performance in both males and females under 65 years of age. The modifiers of this effect of family history of Alzheimer's disease included age, sex, education and diabetes. The apolipoprotein E4 allele was also associated with lower paired-associate learning scores in family history-positive individuals. Perhaps the most surprising finding in this study is the fact that family history is associated with reduced memory performance four decades before the typical onset of Alzheimer's disease (**reported in Talboom et al., 2019**).

## Mehl

The Mehl laboratory, along with several others who are participating in the Precision Aging Network U19 grant (Sternberg, Najafi) reported findings on the health benefits of controlling relative humidity in the workplace. They examined the association between relative humidity and objective measures of stress responses, physical activity and sleep quality in a group of office workers from four federal buildings, who wore chest-mounted heart rate variability monitors for three consecutive days, while relative humidity and temperature were measured in their work places. Those who spend the majority of time at the office in conditions ranging from 30-60% relative humidity experienced 25% less stress and better sleep quality than those outside that range (**reported in Razjouyan et al., 2019**). The study also suggested that optimal values may reside in an even narrower range around 45%.

The Mehl laboratory in collaboration with Sbarra (EMBI Affiliate Faculty) examined the use of language in a depressed population. Depressive symptomatology is associated with greater first-person singular pronoun use (i.e., I-talk), but the extent to which this is specific to depression remains unclear. Using pooled data from 6 laboratories across 2 countries, they studied "I-talk" in 4,754 participants. There was a small but reliable positive correlation between depression and I-talk for both females and males, with no evidence of gender differences (**reported in Tackman et al., 2019**). There was also a significant contribution from negative emotionality, suggesting that the use of first-person singular pronouns may be better described as a linguistic marker of general distress proneness or negative emotionality rather than a marker of depression.

The Mehl laboratory studied the prevalence of gender-biased language in everyday language. They investigated two forms of gender bias – paternalism through use of the infantilizing label 'girl' to refer to women and androcentrism through a tendency to use more masculine (i.e., man, guy) than feminine (e.g., girl, woman) labels in everyday speech. They found that the label girl surpassed all other labels for women and also found evidence of masculine-label bias (**reported in MacArthur et al, 2019**). It will be interesting to conduct studies that take a lifespan perspective to determine whether the age of the person being labeled shows the same pattern of gender bias.

## O'Connor

The O'Connor laboratory examined the role of personal and communal religiosity in the context of bereavement. Interviews and questionnaires from 33 bereaved adults were collected and associations with self-reported religious coping and grief symptoms were assessed. Personal and communal religiosity predicted positive religious coping as well as negative religious coping and grief severity. The data suggest that after loss, personal religiosity by itself is not necessarily protective

(**reported in Stelzer et al., 2019**). The presence of personal and communal religiosity contributes to positive religious coping, and the absence of communal religiosity indicates vulnerability.

O'Connor and colleagues conducted a systematic review of the association between bereavement and biomarkers of immune function. A meta-analysis was conducted to synthesize 41 years of research, and 33 publications met inclusion criteria. The overall conclusions were that individual differences in psychological response to bereavement (e.g., depression, grief) influence the association between bereavement and immune function (**reported in Knowles et al., 2019**). Going forward, this research area would benefit from longitudinal design, larger sample sizes and inclusion of advanced immunological methods.

O'Connor reviewed the history of research on how body, mind and brain adapt to grief. Morbidity and mortality following the death of a loved one has long been a topic of research, and it has long been known that there are immune cell changes in the bereaved. Newer neuroimaging methods have suggested that the greatest impact of the death of a loved one is in those who have the most severe psychological grief reactions. Differences in rumination, inflammation and cortisol dysregulation are clear between those who adapt well and those who do not (**reported in O'Connor et al., 2019**).

## Rance

The Rance laboratory examined how the glutamatergic neurokinin 3 receptor neurons in the median preoptic nucleus modulate heat-defense pathways in female mice. To characterize the thermoregulatory role of median preoptic nucleus neurons and their role in producing hot flushes, these neurons were selectively ablated. This resulted in increasing the core temperature of these female mice during the light phase and was independent of ambient temperature or estrogen status (**reported in Krajewski-Hall et al., 2019**). They conclude that glutamatergic median preoptic nucleus neurons that express the neurokinin 3 receptor modulate thermosensory pathways for heat defense.

Rance and colleagues examined whether noise-induced sleep disruption increases weight gain and decreases energy metabolism in female rats. Inadequate sleep increases obesity and environmental noise contributes to poor sleep. Women may be more vulnerable to noise than men, and this study investigated this in female rats who were monitored for sleep quality, feeding behavior, weight gain and estrous cycle length. The results showed that noise exposure disrupted sleep and increased weight gain in females but did not alter the length of the estrous cycle (**reported in Coborn et al., 2019**).

## Sbarra

The Sbarra laboratory in collaboration with Mehl (EMBI Affiliate Faculty) examined the effect of a stressful life transition (divorce) on mental and physical health outcomes. To identify individual differences that may predict risk for adverse outcomes following divorce, they examined the association between DNA methylation across the serotonin transporter gene and self-reported emotional distress following marital separation. The results suggest that relatively greater methylation of this gene was associated with less subjective separation-related psychological distress, even when accounting for age, length of the relationship and time since separation (**reported in Sbarra et al., 2019**). These findings raises interesting research questions regarding the mechanisms of psychosocial adaptation to stressful life events.

Sbarra and Mehl examined psychological overinvolvement, emotional distress and daily affect following marital dissolution. In a sample of recently separated adults they examined rumination, language use and judge-rated recounting and reconstruing in relation to daily affect and psychological distress (**reported in Bourassa et al., 2019**). The results suggest that people's tendency

to become overinvolved in their psychological experience after divorce predicts increased risk for distress in the months following marital separation.

## Wilson

The Wilson laboratory have examined the reasons that humans and other animals exhibit biases in foraging and intertemporal choice tasks. Via extensive behavioral testing and quantitative modeling, they showed that rats exhibit similar time preferences in both cases: they prefer immediate versus delayed rewards and they are sensitive to opportunity costs of delays to future decisions (**reported in Kane et al., 2019**). The model appears to explain individual rats' time preferences across both contexts and provides evidence for a common mechanism for myopic behavior in foraging and intertemporal choice.

The Wilson laboratory has examined the reasons that humans and other animals integrate evidence over time to make decisions, but do so suboptimally. This could arise because of neuronal noise, weighting evidence unequally over time, previous trial effects or overall bias. Using an auditory evidence accumulation task in humans, they report that people exhibit all four suboptimalities (**reported in Keung et al., 2019**). Pupilometry shows that only noise and unequal evidence weighting are related to different aspects of the pupil responses, and these could be related to tonic and phasic norepinephrine activity.

The Wilson laboratory has suggested an approach to successful modeling of behavioral data, using ten simple rules. Such modeling of behavior has revolutionized psychology and neuroscience by allowing us to probe the algorithms underlying behavior. This makes it more likely that neural correlates of these behaviors will be discovered with more precision, to yield a better understanding of optimal and suboptimal behaviors and the effect of interventions on these. To do this they applied their rules to both the simplest and more advanced modeling techniques to share the power of these methods and to point out potential pitfalls (**reported in Wilson and Collins, 2019**).



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**Andrews-Hanna JR, Grilli MD, and Irish M** (2019). A review and reappraisal of the default network in normal aging and dementia. Oxford Research Encyclopedia of Psychology, Oxford University Press, 10.1093/acrefore/9780190236557.013.384

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**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.

**Andrews-Hanna JR, Fox KC, Irving Z, Spreng RN, and Christoff K.** (in press) The neuroscience of spontaneous thought: An evolving, interdisciplinary field. In: The Oxford Handbook of Spontaneous Thought: Mind-wandering, Creativity, & Dreaming. New York City: Oxford University Press.

**Barnes, C.A., Ryan, L., and Peterson, M.A.** (2019) Nadel Special Issue Introduction. In: Hippocampus, Wiley Periodicals, in press.

Carey A L, Rentscher K, and **Mehl MR** (in press) Naturalistic observation of social interactions. In: M. R. Robbins & Sweeny, K. (Eds.) Wiley Encyclopedia of Health Psychology.

Demiray B, Luo M, Tejada-Padron A, and **Mehl, MR** (in press) Sounds of healthy aging: Assessing everyday social and cognitive activity from ecologically sampled ambient audio data. In: PL Hill and M Allemand (Eds.) Personality and Healthy Aging in Adulthood. New York: Springer

**Grilli MD and Ryan L.** (in press) Autobiographical memory and the self-concept. 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.

**Mehl MR** and Wrzus C (in press) Ecological sampling methods for studying personality in daily life. In: O P John and RW Robins (Eds.) The Handbook of Personality (4th edition). New York: Guilford Press.

Smith R, **Ahern GL**, and Lane RD. (2019) The Role of the Anterior and Midcingulate Cortex in Emotional Awareness: A Domain-General Processing Perspective. In: Handbook of Clinical Neurology, Vol 166, 3rd Series, B Vogt (Ed): Cingulate Cortex. Cambridge, Elsevier, pg. 89-101.

Tubbs AS, Dollish HK, **Fernandez F**, and Grandner MA (2019) The basics of sleep physiology and behavior. In: Sleep and Health, MA Grandner (Ed): Academic Press, pg. 3-10.

## ***Presentations at scientific meetings***

**Barnes CA.** Age-related cognitive decline in rodents and monkeys. Arthur M. Sackler Colloquia of the National Academy of Sciences – Using Monkey Models to Understand and Treat Human Brain Disorders, Arnold and Mabel Beckman Center, Irvine, CA, January 2019.

**Barnes CA.** Aging cognition across species. 2019 Dallas Aging and Cognition Conference, Center for Longevity, Dallas TX, January 2019.

**Barnes CA.** Session Lead: Immediate Early Genes, Arc and Beyond in Health and Disease. Winter Conference on Neural Plasticity, Moorea, French Polynesia, February 2019.

**Huentelman MJ.** Immediate Early Genes: Arc and Beyond in Health and Disease. Winter Conference on Neural Plasticity, Moorea, French Polynesia, February 2019.

**Brinton, RD.** Innovations in brain science for those who need a cure today (keynote address). College of Medicine Research Day, University of Arizona, Tucson, AZ, February 2019.

Acevedo-Molina M, Teposte M, Robertson A, and **Grilli MD.** Cognitively normal older adults show elevated semantic detail generation for multiple forms of autobiographical memory retrieval. Annual Meeting of the International Neuropsychological Society, New York City, NY, February 2019.

Memel M, Wank AA, **Ryan L,** and **Grilli MD.** The relationship between episodic autobiographical memory detail generation and the integrity of MTL-cortical white matter pathways in cognitively normal older adults. Annual Meeting of the International Neuropsychological Society, New York City, NY, February 2019.

Wank AA and **Grilli MD.** Relationship of inhibition ability to early versus later stages of episodic autobiographical memory retrieval in cognitively normal older adults. Annual Meeting of the International Neuropsychological Society, New York City, NY, February 2019.

Wank AA, Moseley S, Polsinelli AJ, **Mehl MR,** and **Grilli MD.** From laboratory to real-world: measuring autobiographical memory retrieval in naturalistic settings. Annual Meeting of the International Neuropsychological Society, New York City, NY, February 2019.

**Chou Y-H.** Effects of repetitive transcranial magnetic stimulation on cognitive function in Alzheimer's disease and mild cognitive impairment: A systematic review and meta-analysis. 3rd International Brain Stimulation Conference. Vancouver, Canada, February 2019.

Sundman M, Lim K., Mizell, J.-M, Ton That V, Mennie W, Ugonna C, Lindley M, **Fuglevand A.** Chen N-K, Wilson R, Huang Y-Z, and **Chou Y-H.** Divergent effects on cortical excitability observed in healthy older adults during active voluntary contraction following motor cortex iTBS Poster presented in the 3rd International Brain Stimulation Conference. Vancouver, Canada, February 2019.

**Andrews-Hanna JR.** The Dynamics of Thought: A Window into Wandering and Sticky Minds. 2019 Society of Experimental Psychologists Meeting, Rutgers University, NJ, March 2019.

**Andrews-Hanna JR.** Exploring Neurocognitive Links Between Alzheimer's Disease and Depression in Older Adults. 2019 Arizona Alzheimer's Consortium Retreat, Sedona, AZ, March 2019.

**Barnes CA.** Impact of age on neural circuits critical to memory. HKIAS Symposium on Advances in Neuroscience, City University of Hong Kong, March 2019.

**Brinton, RD.** From Bench to Bedside: Translational Medicine in Alzheimer's Disease Research. Arizona Alzheimer's Consortium Southern Arizona Annual Education Conference, Tucson Jewish Community Center, March 2019.

**Brinton, RD.** Celebration of women in STEM and efforts to diversify STEM fields (keynote address). 2019 Science and Engineering Excellence Banquet, University of Arizona, Tucson, AZ, March 2019.

**Chou, Y-H.** Transcranial magnetic stimulation for Parkinson's disease. College of Science Café Series, University of Arizona, Tucson, AZ, March 2019.

**Fernandez, F.** Impact of sleep on cognition and AD in DS. Alzheimer's and Down Syndrome Workshop, Bethesda, MD, March 2019.

Yordanova CY, Demiray B, **Mehl MR,** Martin M, Wolf M, and Horn AB. Automatic detection of everyday social behaviours and environments from verbatim transcripts of daily conversations. IEEE International Conference on Pervasive Computing and Communications, Kyoto, Japan, March 2019.

**Alexander GE.** Patterns of daily activity in the oldest old: Findings from the McKnight Brain Aging Registry. Eleventh McKnight Inter-Institutional Meeting, University of Florida, Gainesville FL, April 2019.

**Barnes CA.** Impact of age on neural circuits critical to memory. The Cold Spring Harbor-Asia Francis Crick Symposium Transforming Neurosciences: Questions & Experiments, Suzhou Dushu Lake Conference Center, Suzhou, China, April 2019.

**Barnes CA.** Memory and the Aging Brain, New Member Research Briefings, Class II, National Academy of Sciences, April 2019.

**Brinton, RD.** Reaction Panelist: Prevention vs Intervention, A debate featuring doctors Andrew Weil and Irving Kron, Centennial Hall, University of Arizona. April 2019.

**Chou, Y-H.** Introduction to Transcranial Magnetic Stimulation. Principles of Psychophysiology, University of Arizona, Tucson, AZ, April 2019.

**Chou, Y-H.** Brain Stimulation and Mind Wandering. : Cognitive Neuroscience Graduate Seminar, University of Arizona, Tucson, AZ, April 2019.

**Ekstrom AD.** Navigation deficits in aging: What we can learn from immersive virtual reality. Eleventh McKnight Inter-Institutional Meeting, University of Florida, Gainesville FL, April 2019.

**Alexander GE.** Why your brain needs exercise: Lessons from evolutionary neuroscience. American College of Sports Medicine Annual Meeting, Orlando, FL. May 2019.

**Alexander GE.** Measuring physical activity in older adults: Associations with brain atrophy and white matter hyperintensities. Arizona Alzheimer's Consortium 21<sup>st</sup> Annual Conference, Tempe Center for the Arts, Tempe, AZ. May 2019.

Andrews E, Raffaelli Q, **O'Connor M-F**, Wilcox R, **Mehl M**, Matijevic S, **Ryan L**, **Grilli M**, and **Andrews-Hanna J.** Using multi-method approaches to characterize Maladaptive Repetitive Thought in Older Adults. Poster presentation given at the Arizona Alzheimer's Consortium 21<sup>st</sup> Annual Conference, Tempe Center for the Arts, Tempe, AZ, May 2019.

**Barnes CA.** Memory and the Aging Brain, Annual Scientific Meeting of the European Society for Clinical Investigation (ESCI 2019), Coimbra, Portugal, May 2019.

Lindley M, Sundman M, Lim K, Mizell J-M, Ton That V, Mennie W, Ugonna C, Chen N-K, and **Chou, Y-H.** Functional impact of theta burst stimulation on motor cortex. 27th ISMRM Annual Meeting & Exhibition. Montreal, Canada, May 2019.

Lindley M, Berstein A, McKinnon A, Ugonna C, Bruck MD, Johnson K, Altbach M, **Ryan L**, Guzman G, Chen N-K, **Chou Y-H**, **Trouard T**, and Weinkauff C. Functional and microstructural changes in the brain after carotid endarterectomy. 27th ISMRM Annual Meeting & Exhibition. Montreal, Canada, May 2019.

**Barnes CA.** Behavioral consequences in brain aging (Keynote Address). International Behavioral Neuroscience 27<sup>th</sup> Annual Meeting, Cairns, Australia, June 2019.

Bock D. Hsu C-H, **Rapczak S**, **Chou S-H**, Williams M, and Zhou W Differential Effects of Cardiovascular Risk Factors on Cognitive Function in Patients with Severe Carotid Stenosis. Poster presented in the Vascular Annual Meeting. National Harbor, MD, June 2019.

**Brinton, RD.** Panel Speaker: Hot topics in the basic science of sex differences in the brain. International Forum on Women's Brain and Mental Health Zurich, Switzerland, June 2019.

**Brinton, RD.** Women and Alzheimer's disease: moving from risk to resistance. Access Circles Summer Forum, Watch Hill, RI, June 2019.

Cowen SL. Panel Speaker: Preparation for graduate admission for underrepresented students. Undergraduate Research Opportunities Consortium (UROC), University of Arizona, Tucson, AZ, June 2019.

**Brinton, RD.** Predictors of AD risk and resilience and responsiveness to treatment: sex differences and the rise of the microbiome. Engaging Precision Medicine for AD through Open Science, Los Angeles, CA, July 2019.

**Brinton, RD.** Innovations in brain science of the future for those who need a cure today. Grand Rounds, University of California, San Francisco, CA, September 2019.

**Brinton, RD.** Sex differences in onset of prodromal phase of Alzheimer's disease. BrightFocus Foundation Alzheimer's Fast Track Workshop, Chicago, IL, October 2019.

**Brinton, RD.** Innovations in brain science of the future for those who need a cure today. Faculty Showcase, University of Arizona, Tucson, AZ, October 2019.

Bharadwaj P, **Andrews-Hanna J**, Kuo P, **Alexander G.** Alzheimer's disease fluid biomarkers related gray matter covariance patterns in healthy older adults. Program No. 652.22, 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Epp S, Preibsch C, **Andrews-Hanna JR**, and Reidl, V. Towards a metabolic baseline for default mode network activations and deactivations. Poster presentation given at the 2019 Organization for Human Brain Mapping Conference, Rome, Italy, June 2019.

**Andrews-Hanna JR.** The Dynamics of Thought: A Window into Wandering and Sticky Minds. International Society for Behavioral Neuroscience Conference, Taormina, Italy, June 2019.

Han E, Schimanski LA, Ali K, **Barnes CA**, and Tatsuno M. Detection of hippocampal cell assemblies while rats learn a place-dependent eyeblink conditioning task. Undergraduate Neuroscience Symposium, University of Alberta, August 2019.

**Ekstrom AD.** Wireless scalp EEG and immersive virtual interfaces provide novel insight into the neural basis of human spatial navigation. 59<sup>th</sup> Annual Meeting of the Society for Psychophysiology Research, Washington, DC, September 2019.

Gray DT, Umapathy L, DeLaPena NM, **Burke SN**, Engle JR, **Trouard TP**, and **Barnes CA.** Auditory processing deficits are selectively associated with medial temporal lobe mnemonic function and white matter integrity in aging macaques. Arizona Postdoctoral Research Conference, University of Arizona Phoenix Campus, Phoenix, AZ., September 2019.

**Barnes CA.** Life trajectories for successful aging: evidence from animal models of aging. Life Trajectories and Interventions that Support Successful Neurocognitive Aging Meeting, Montreal Neurological Institute, McGill University, Montreal, Canada, September 2019.

**Andrews-Hanna JR.** Dynamic Regulation of Internal Thought: A Clinical Story. The Norms of Attention: A Conference in Interdisciplinary Cognitive Science, University of Virginia, Charlottesville, VA, October 2019.

**Ekstrom AD.** Testing the influence of enriched body-based cues on how we encode and retrieve space. Memory Disorders Research Society, New York City, NY, October 2019.

**Ekstrom AD.** Space and time involve partially overlapping and unique neural signatures. Symposium IV: Time-space cognition: examination of independent and shared cognitive and neural mechanisms in healthy and clinical populations. 2<sup>nd</sup> Conference of the Timing Research Forum, Querétaro, Mexico, October 2019.

**Ekstrom AD.** Decoding how we represent space when we navigate. Colloquium Series, Department of Psychology, University of Arizona, Tucson, AZ, October 2019.

**Rance N.** Brain circuits mediating the generation of menopausal hot flushes. Brain Research Initiative, Brigham and Women's Hospital, Boston, MA, October 2019.

Branigan GL, Whiteman L, Corenblum MJ, **Madhavan L**, and **Brinton RD**. Comprehensive phenotyping of patient-derived fibroblasts from patients with sporadic Alzheimer's disease. Program No. 651.24. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Chen S, Wang T, and **Brinton RD**. Allopregnanolone prevent the loss of neuronal differentiative capacity in 3xTgAD mice. Program No. 651.10. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Crown L, Gray DT, Schimanski LA, **Barnes CA**, and **Cowen SL**. Spatial eye-blink learning but not age predicts theta-gamma coupling in the CA1 region of the hippocampus, Program No. 600.09. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Chawla MK, Zempare M, Hruby V, **Barnes CA**, and Cai M. Age-related, specific changes in expression of several central melanocortin receptor subtypes in the rat, Program No. 600.15. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Eck R, Chawla MK, Bagevalu Siddegowda B, Carey NJ, Zempare M, Nguyen C, Billheimer D, **Barnes CA**, and Zarnescu DC. RNA stress granule components are dynamically expressed during aging and stress conditions in rats and fruit flies, Program No. 600.17. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Falk T, Bartlett MJ, Heien ML, Ye T, **Cowen SL**, Steece-Collier K, Sherman SJ. Mechanisms underlying the anti-dyskinetic effect of sub-anesthetic ketamine. 39th Blankenese Conference: Signaling in Health and Disease, Hamburg, Germany, March 2019.

Falk T, Ye T, Bartlett MJ, Sherman SJ, and **Cowen, SL**. Region-dependent cross-frequency interactions in a preclinical model of L-DOPA-induced dyskinesia after low-dose ketamine. Program No. 131.18. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Feng SF, Wang S, Zarnescu SC, and **Wilson RC**. The dynamics of explore-exploit decisions reveals a signal-to-noise mechanism for random exploration. Program No. 518.18. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Gray DT, Pyon W, De La Pena NM, Schwyhart R, Wallace E, Puchta J, Hartig W, and **Barnes CA**. Perineuronal nets in the cerebral cortex of cognitively-assessed aged macaque monkeys, Program No. 600.11. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Hernandez GD, Wang Y, Zhao L, Mack MJ, Schneider L, and **Brinton RD**. Safety and feasibility of PhytoSERM - A selective  $\beta$ -receptor phytoestrogen formulation - for menopausal symptoms and cognitive decline: Phase 1b/2a clinical trial. Program No. 208.12. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Hill DF, Olson Z, Bartlett BJ, Falk T, Heien ML, and **Cowen SL**. Simultaneous measurement of ventral tegmental area activity and nucleus accumbens dopamine release reveals patterns of neuron firing associated with dopamine release. Program No. 773.18. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Huffman DJ and **Ekstrom AD**. A modality-independent network underlies the retrieval of large-scale spatial environments in the human brain. Program No. 516.02. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Jepsen WM, Ramsey K, Szelinger S, Llaci L, Balak C, Belnap N, Bilagody C, De Both M, Gupta R, Naymik M, Pandey R, Piras IS, Sanchez-Castillo M, Rangasamy S, Narayanan V, and **Huentelman MJ**. Two additional males with X-linked, syndromic mental retardation carry de novo mutations in HNRNPH2.

Program No. 535.03, 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Kyle C, Stokes J, Meltzer J, Permenter MR, Vogt JA, **Ekstrom AD**, and **Barnes, CA**. Estimation of non-rigid warps during 3D serial-section histology reconstruction optimization increases accuracy, Program No. 600.12. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019. Emergence of an Alzheimer's disease bioenergetic endophenotype in mid-life: Preclinical model

Liang M, Harootonian K, Isham E, Drake K, and **Ekstrom AD**. Low-frequency neural oscillations code distance and temporal duration as measured with scalp EEG and hippocampal intracranial recordings. Program No. 272.03. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Lester AW, Kapellusch AJ, and **Barnes CA**. A computational model of aged head direction network updating in the presence of sudden spatial cue mismatch, Program No. 600.16. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Lewis CR, Sowards HA, Doane LD, Lemery-Chalfant K, **Huentelman MJ**. Sensitive period for epigenetic consequences of early attachment on immune genes. Program No. 451.07, 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Martin AB, Andersen KR, Morrow JK, Hillier EA, Cardenas MA, Lee S, **Cowen SL**, and **Gothard KM**. From discriminative to affective touch: A mesoscale perspective of the somatosensory pathway to the primate amygdala. Program No. 774.03. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Mao Z, Shang Y, Berghout J, Lussier Y, Yin F, and **Brinton RD**. Emergence of an Alzheimer's disease bioenergetic endophenotype in mid-life: Preclinical model. Program No. 651.18. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Matijevic S, Elias M, **Huentelman MJ**, and **Ryan L**. Interactive Effects of Sex and BDNF Val66Met Polymorphism on Cognition in Older Adults. Program No. 792.18. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Mishra A, Shang Y, Wang Y, Yin F, and **Brinton RD**. The immuno-metabolic crisis in the aging female brain: Implications for Alzheimer's disease. Program No. 651.17. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Monroe EJ, Crown LM, Barlett MJ, Wiegand J-P, Eby AJ, Falk T, and **Cowen SL**. Increased sleep spindle density in LRRK2 G2019S mice. Program No. 294.10. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, 2019, October 2019.

Palmer JM, Lawrence AV, **Grilli MD**, **Huentelman MJ**, Talboom S, and **Ryan L**. Interactive Effects of Sex and BDNF Val66Met Polymorphism on Cognition in Older Adults. Program No. 792.09. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Postans M, Williams AN, Stefani M, Lissaman R, Kolarik BS, Yonelinas AP, **Ekstrom AD**, Lawrence AD, Zhan J, Graham KS, and Hodgetts CJ (2019) The role of the pre-commissural fornix in an extended neuroanatomical network for goal-directed navigation. Program No. 272.11. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Pyon W, Gray DT, Schwyhart R, Wallace E, De La Pena NM, and **Barnes CA**. Quantification of neuronal and astrocytic cells in the locus coeruleus of cognitively assessed, young and aged nonhuman primates, Program No. 600.10. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Qi G, Mi Y, Chen S, **Brinton RD**, Yin F. Apoe isoforms differentially regulate neuronal- and astrocytic mitochondrial bioenergetic capacity and fuel dependency. Program No. 651.04. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Palmer JM, Lawrence AV, **Huentelman MJ**, and **Ryan L**. Interactive Effects of Sex and BDNF Val66Met Polymorphism on Cognition in Older Adults. Program No. 792.09. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Raichlen D, Bharadwaj P, Franchetti M, Sims S, Rezaei R, Merritt S, Jessup C, Porges E, Geldmacher D, Hishaw G, Alperin N, **Trouard T**, **Wadley V**, **Levin B**, **Woods A**, **Rundek T**, **Visscher K**, **Cohen R**, **Alexander G**. Relation of daily activity patterns to cortical gray matter maps in the healthy oldest old: Findings from the McKnight Brain Aging Registry. Program No. 246.01, 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Seaton BT, Hill DF, **Cowen SL**, and Heien ML. Mitigating the effects of electrode biofouling for improved long-term measurement of dopaminergic signaling. Program No. 796.21. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Shang Y, Mishara A, Desai MK, Wang T, and **Brinton RD**. APOE and chromosomal sex shows significant effect on the lipid pathways from multiple scale analysis of aged mice. Program No. 651.05. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Srivathsa SV, Khattab SO, Lester AW, and **Barnes CA**. Role of prefrontal-hippocampal interactions in age-related deficits in spatial working memory, Program No. 600.08. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Talboom JS, **Haberg AK**, De Both MD, Naymik MA, Schrauwen I, Lewis CR, Siniard AL, Bertinelli SF, Hammersland C, Myers AJ, **Hay M**, **Barnes CA**, **Glisky E**, **Ryan L**, and **Huentelman MJ**. Physiological and Cognitive Factors Associated with Health Aging. Program No. 793.03. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Terrazas A, Pyon W, Zempare M, Young KF, Dalmendray A, Do L, David B, Bohne KM, Carey NJ, Chawla MK, **Trouard TP**, Worley PF, and **Barnes CA**. Effects of NPTX2 knockout on behavior, brain volume by MRI and CA1 hippocampal single unit properties, Program No. 600.14. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Van Etten E, Bharadwaj P, Hishaw G, **Trouard T**, **Alexander G**. Mediation of age and hippocampal volume by temporal lobe white matter hyperintensities differ in relation to APOE e4 status in healthy older adults. Program No. 792.15. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

**Visscher K**, Stewart P, Sims S, Bharadwaj PK, Franchetti M, Rezaei RF, Merritt S, Jessup C, Raichlen D, Porgess EC, **Geldmacher D**, Hishaw G, **Trouard T**, **Alpirin N**, **Wadley VG**, **Levin BE**, **Woods AJ**, **Rundek T**, **Cohen R**, **Alexander G**. Functional connectivity in the healthy oldest old: Findings from the McKnight brain aging registry. Program No. 246.02. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Wang S, Sadeghiyeh H, and **Wilson RC**. The influence of action on explore-exploit decisions. Program No. 518.20. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Wang T, Chen S, Mao Z, and Brinton RD. Allopregnanolone potentiates bioenergetic capacity and restructures mitochondrial reticulum in neurons and astrocytes. Program No. 651.01. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Wang Y, Shang Y, Mishra A, Bacon E, Yin F, and **Brinton RD**. Dynamic metabolic aging of the female brain during endocrinological and chronological aging. Program No. 651.16. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Wilhite C, Alvarez A, Burton A, Preston D, Mustachich A, **Fuglevand K**, **Gothard S**, **Cowen SL**, and Witte RSW. In vivo swine model for developing and validating acoustoelectric brain imaging: Towards noninvasive, real-time 4D electrical brain mapping. Program No. 616.13. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Wilhite C, Witte, RS, and **Cowen SL** Activation of hippocampal CA2 region precedes CA3 following perforant-path stimulation and spontaneously occurring dentate spikes. Program No. 242.16. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Ye, T, Bartlett J, Sexauer M, Sherman SJ, Falk T, **Cowen SL**. Oscillatory signatures of L-DOPA-induced dyskinesia are dependent on the LID induction protocol and L-DOPA dose. Program No. 131.12. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

Zempare M, Carey NJ, Dalmendray A, Young KF, Bohne, KM, Do L, **Trouard TP**, Mitchell, KD, Chawla MK, **Huentelman MJ**, and **Barnes CA**. Effects of induced hypertension in middle aged CYP1A1-REN2 transgenic rats, Program No. 600.13. 2019 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, October 2019.

**Andrews-Hanna JR**. Constructing and Deconstructing the Dynamics of Autobiographical Thought. 60th Annual Meeting Psychonomic Society, Montreal, Quebec, Canada, November 2019.

**Brinton, RD**. Regenerating the degenerated Alzheimer's brain: challenges and innovation opportunities. Alzheimer's Disease Therapeutics: Alternatives to Amyloid 2019, New York, NY, November 2019.

**Chou Y-H**. Transcranial Magnetic Stimulation for Alzheimer's Disease and Mild Cognitive Impairment. Neuroscience GDP Colloquium, University of Arizona, Tucson, AZ. November 12th, 2019

**Chou Y-H**. Integrating MRI with Transcranial Magnetic Stimulation. Arizona Research Institute for Biomedical Imaging (ARIBI) workshop, University of Arizona, Tucson, AZ. November 2019.

Du Y, **Ekstrom AD**, and Starrett MJ. Asymmetrical influence of visual gain changes on spatial representations during navigation. 60th Annual Meeting Psychonomic Society, Montreal, Quebec, Canada, November 2019.

**Grilli MD**. The cognitive and neural bases of personal semantics: Insights from individuals with medial temporal lobe amnesia. 60th Annual Meeting Psychonomic Society, Montreal, Quebec, Canada, November 2019.

Oyao AV, Forloines MR, Robertson A, **Grilli MD**, and **Ekstrom AD**. Older adults show impairments in learning new spatial environments compared to younger adult. 60th Annual Meeting Psychonomic Society, Montreal, Quebec, Canada, November 2019.

## ***Presentations at public (non-scientific) meetings or events***

**Cowen SL**. Your Brain on Dopamine. Tucson Community Science Café, Tucson, AZ, January 2019.

**Cowen SL**. How our brains learn and remember and the impact of age. Sun City Oro Valley (SCOV) Active Health Committee. Oro Valley, AZ, February 2019.

**Cowen SL**. Dopamine, Neuroscience, and Science Fiction, Tucson Science Fiction Writers Association., Tucson, AZ, February 2019.

**Barnes CA.** Effectively communicating your science to the public. Panel Discussion with R Isaacson, CA Barnes, J Bizon, L Anderson, M Jaffee. Eleventh McKnight Inter-Institutional Meeting, University of Florida, Gainesville FL, April 2019.

**Andrews-Hanna JR.** The Science of Imagination. Workshop Organizer and Speaker, College Academy for Parents Program, University of Arizona, Tucson, AZ, March 2019.

**Andrews-Hanna JR.** The Balancing Act of Work and Life in Science and Medicine. Women in Science and Medicine Undergraduate Club, University of Arizona, Tucson, AZ, April 2019.

**Cowen SL.** The Aging Mind and Brain. UA Retired Faculty Dinner, Tucson, AZ. July 2019.

**Ryan, L.** Aging Well, Work-Life Balance and the Aging Workforce. Cox Board Retreat, Tucson, AZ, May 2019.

**Ryan L.** Contributions of perirhinal and parahippocampal cortex to episodic memory: Implications for aging and Alzheimer's disease. Neurology Grand Rounds, University of Arizona. Tucson, AZ. August 2019.

**Ryan L.** Conversation on Personalized Aging Brain Health. Spirit of the Senses Art Salon, Phoenix, AZ. September 2019.

**Ryan L.** Healthy Minds, Healthy Brains, Healthy Lives. Tucson Cancer Conquerors, Tucson, AZ. September 2019.

**Ryan L.** Healthy Minds, Healthy Brains, Healthy Lives. Pima Canyon Estates, Tucson, AZ. November 2019.

## **Awards**

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

**Jessica Andrews-Hanna, Ph.D.,** Curie Award for Outstanding Research, University of Arizona (2019)

**Jessica Andrews-Hanna, Ph.D.,** Galileo Circle Curie Award for "Rising Star" in Academic Scholarship, University of Arizona (2019)

**Lynn Nadel, Ph.D.,** William James Fellow Award, Association of Psychological Societies (APS), 2019

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

**Matthias Mehl, Ph.D.,** Miegunyah Distinguished Visiting Fellow, University of Melbourne (2019)

**Mary Peterson, Ph.D.,** Clifford T. Morgan Leadership Award, Psychonomic Society (2019)

**Mary Peterson, Ph.D.,** Excellence in Mentoring Award, Office of Inclusion and Multicultural Engagement, UA Successful Scholars Faculty Mentoring Program (2019)

**Mary Peterson, Ph.D.,** Early Career Psychologist Champion Award, American Psychological Association (2019)

**Eric Reiman, M.D.,** Appointment to National Advisory Council on Aging

**Dave Sbarra, Ph.D.,** Graduate Teaching and Mentoring Award from the Graduate College

# *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 Emeritus, 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
- 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
- Steve Rapcsak, M.D., Professor, Neurology, Psychology and Speech, Hearing and Language Pathology, University of Arizona; Chief, Neurology Section, VA Medical Center
- Linda L. Restifo, M.D., Ph.D., Professor, Neurology, Neuroscience, Cell Biology and Anatomy, and BIO5 Institute, University of Arizona
- David A. Sbarra, Ph.D., Professor and Director of Clinical Training, Psychology, University of Arizona
- Anne C. Smith, Ph.D., Associate Research Scientist, Evelyn F. 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**

<b>Institution &amp; Location</b>	<b>Degree</b>	<b>Year(S)</b>	<b>Field Of Study</b>
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 will provide oversight in the acquisition of CSF and blood samples at the University of Arizona and will work with the nurse practitioners and with Drs. Alexander, Beach, and Blennow in helping to augment efforts in the coordination of the CSF and blood sample acquisition, processing, and analyses as part of the Fluid Biomarkers Workgroup for the BI-FB Core. I will work with Drs. Alexander and Caselli (Clinical Core leader) and BI-FB Core staff to help identify interested ADCC Clinical Core participants for inclusion in the neuroimaging and fluid biomarker standardization cohort. My extensive experience in performing LPs for CSF acquisition and storage for both clinical and research protocols make me well suited to be an investigator on this new core.

1. Beach TG, Adler CH, Sue SI, Serrano G, Shill HA, Walker DG, Lue LF, Roher AE, Dugger BN, Maarouf C, Birdsill AC, Intorcchia 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, Shi J, 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, Intorcchia 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, Kleeefield 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.

Hemispacial 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 hemispacial 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 hemispacial 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 hemispacial 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 hemispacial neglect during the intracarotid amytal procedure. *Journal of the International Neuropsychological Society*, 4:1-7.

## **Complete list of published work in MyBibliography**

<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).

2018-2019 A Randomized, Double-Blind, Placebo-Controlled, Two-Cohort Parallel Group Study to Evaluate the Efficacy of CAD106 and CNP520 in Participants at Risk for the Onset of Clinical Symptoms of Alzheimer's Disease. (Generation 1) Protocol # CAPI015A2201J. Novartis. Total grant: \$100,702 / patient. 2% salary support, 2% effort.

2018-2019 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 serve 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 Association's 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 20 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 cerebral atrophy 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  $\beta$ -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

1995 – Present	Ad Hoc Reviewer, more than 20 journals in Neuropsychology, Psychiatry, Neurology, and Neuroscience.
1996 – 1999	Staff Recognition Awards (annual), Laboratory of Neurosciences, IRP, NIA, NIH
2000 – Present	Reviewer, Alzheimer's Association Research Grant Program
2003 – 2007	Member, Study Section, Clinical Neuroscience and Disease, IRG, CSR, NIH
2003	Member, SEP, Women's Health Initiative Memory Study, Review Branch, NHLBI, NIH
2004	Member, Special Emphasis Panel, Alzheimer's Disease Center Grant Review, NIA, NIH
2004 – 2009	External Advisor, Aging Brain: Vasculature, Ischemia & Behavior Program Project, UCSF/Davis
2005 – 2007	Member, Specialist Review Committee, Psychology: Exp/Clinical, Fulbright Scholar Program
2006	Chair, SEP, Clinical Neuroscience & Disease, ZRG1 BDCN-E, IRG, CSR, NIH
2008	Member, SEP, Prog Project Review Group, Recovery from Illness, ZAG1 ZIJ-8 O1, NIA, NIH
2008	Member, Study Section, Brain Injury & Neurovascular Pathology, ZRB 1 BDCN-L (07), CSR, NIH
2008	Member, SEP, SPRINT Center Review, ZHL1 CCT-B C2 1, NHLBI, NIH
2008 – Present	Member, Neuroimaging Workgroup, International Conf. on Alzheimer's Disease/ISTAART
2009	Reviewer, SEP, Challenge Grant Panel #10, ZRG1 BDA-A 58 R, CSR, NIH
2009	Member, SEP, P30 Faculty Recruitment in Biomedical Research Core Centers, NIA, NIH
2009	Member, SEP, RC2 Grand Opportunity Grants in Genetics, Epigenetics & Genomics, NIA, NIH
2009	Member, SEP, Program Project Review Group, Brain Dopamine, ZAG1 ZIJ-8 J3, NIA, NIH
2009	Member, SEP, Prog. Project Review. Group, Neuroimaging and Aging, ZAG1 ZIJ-5 JF, NIA, NIH
2010	Member, Neurological Sciences & Disorders K Review Committee, NSD-K, NINDS, NIH
2010 – 2012	Member, Neuroscience of Aging Review Committee, NIA-N, NIA, NIH

2010	Member, SEP, Prog. Project Rev., Exercise, Motor Deficits, & Aging, ZAG1-ZIJ-9, NIA, NIH
2010	Member, SEP, Prog. Project Review, Dopaminergic Dysfunct. Aging, ZAG1 ZIJ-6 J3, NIA, NIH
2011	Chairperson, Member Special Emphasis Panel, ZAG1 ZIJ-7 (J1), NIA, NIH
2011 – 2014	Advisory Editor, Neurobiology of Aging, Elsevier
2011	Member, VA MHBB Merit Review Subcommittee, Veterans Administration
2011	Member, SEP, Biobehavioral Research Award Innovative New Scientists (BRAINS), ZMH1ERBL04, NIMH, NIH
2011 – Present	Reviewer, Alzheimer's Disease Pilot Grant Program, Arizona Alzheimer's Disease Center
2011 – Present	Fellow, Association for Psychological Science
2012	Member, Neurological Sciences & Disorders K Review Committee, NSD-K, NINDS, NIH
2012 – Present	Member, Cognitive Workgroup, Evelyn F. McKnight Brain Institute
2012 – Present	Member, MRI Standardization Workgroup, Evelyn F. McKnight Brain Institute
2012 – Present	Co-Director, Annual Conference on Successful Aging, University of Arizona
2013	Member, SEP, Neurodegenerative & Neurodevelopmental Disease, ZRG1BDCN-Y(02), NIA, NIH
2013	Member, SEP, Psychol. Health, Development & Aging, 10 ZRG1 BBBP-D (02), NIA, NIH
2013	Member, Alzheimer's Disease Research Centers Review, ZAG1ZIJ4J1, NIA, NIH
2013 – Present	Member, Neuroscience of Aging Review Committee, NIA-N, NIA, NIH
2014	Member and Chairperson, Biobehavioral & Behavior. Processes Review Group, ZRG1BBBPY04, CSR, NIH
2015 – Present	Guest Assoc. Editor, Neuroimaging Approaches to Cognitive Aging, Frontiers Aging Neuroscience
2015 – Present	Chair, Research Committee, Department of Psychology, University of Arizona
2016	Member, SEP, Alzheimer's Disease Center Review, ZAG1 ZIJ-1 M1, NIA, NIH
2016	Member, SEP, Prevention Trial Review, ZAG1 ZIJ-1 M2, NIA, NIH
2017 – Present	Fellow, American Psychological Association Division 40, Society for Clinical Neuropsychology
2019	Member, SEP, Alzheimer Network U19 Review Panel, ZAG1 ZIJ-U M1, NIA, NIH
2019	Member, AD Center Review Panel, ZAG1 ZIJ GJ1, NIA, NIH
2019	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 least 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, Debbs 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 MyBibliography

<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 RO1 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 – 3/31/20

### ***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 – 6/30/21

### ***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

McKnight Brain Research Foundation Bowers, Alexander, Woods (MPIs) 5/1/18 – 4/30/20

### ***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 – 12/31/18

### ***McKnight Inter-Institutional Cognitive Aging Assessment Core***

To provide standardized clinical and cognitive measures for multi-institutional brain aging research.

Role on Project: PI

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: Dr. Alexander is PI of the UA subcontract.

AZ Alzheimer's Consortium (ADHS) Alexander (PI) 7/1/18 – 6/30/19  
***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

AZ Alzheimer's Consortium (ADHS) Alexander (PI) 7/1/18 – 6/30/19  
***Influence of Health & Lifestyle Factors on Brain Aging and the Risk for Alzheimer's Disease***  
The goal is to study health and lifestyle factors that alter effects of brain aging and cognitive health.  
Role on Project: PI

NIA R03 AG055020 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 P30 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 and member of the Data Management and Statistics Core

NIH 3 R01 AG031581 Reiman, Caselli (MPIs) 4/1/14 – 3/31/20  
***Brain Imaging, APOE & the Preclinical Course of Alzheimer's disease***  
The goal is to characterize the brain changes in those at risk for Alzheimer's disease with the APOE ε4 allele.  
Role on Project: Co-Investigator and PI of the UA subcontract.

NIA R01 AG049465 Barnes (PI) 8/1/14 – 3/31/20  
***Neural System Dynamics and Gene Expression Supporting Successful Cognitive Aging***  
The goal is to use cognitive, neurobiological and molecular methods to test reserve in a rodent model of aging.  
Role on Project: Co-Investigator

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 is to use cognitive, neurobiological and molecular methods to test reserve in a rodent model of aging.  
Role on Project: Co-Investigator

## ***Biographical Sketch***

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

### **Education/Training**

<b>Institution &amp; Location</b>	<b>Degree</b>	<b>Year(S)</b>	<b>Field Of Study</b>
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**

Despite constant sensory input from our busy environment, the human mind has the capacity to overcome external constraints in favor of a different time, place, or perspective. By imagining what was or what might be, and by reflecting on our emotions and simulating the mental states of other people, we become better adapted to predict our future mental states and navigate our social world. My research seeks insight into the psychological and neural mechanisms underlying these internally guided processes and their top-down regulation. Related to this central theme, I am also passionate about exploring these questions across the lifespan and in a variety of mental health disorders and neurodegenerative diseases, with an ultimate 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 also an assistant professor in the Department of Psychology and the Interdisciplinary Cognitive Science Program. I have a strong record of collaboration and research funding and have received grant support as PI or Co-I on several neuroimaging grants examining the neural underpinnings of functional and dysfunctional memory, prospection, and other forms of internally guided cognition. I employ a multimodal approach in my research, combining methods spanning task-related functional MRI, resting state functional connectivity MRI (RSFC-MRI), fMRI meta-analyses, and laboratory and naturalistic behavioral assessments. I have particular expertise in RSFC-MRI and brain network analyses, including graph theory. Using these techniques, my research has revealed important insight into the functional-anatomic organization of the brain's default mode network (DMN) and the frontoparietal control network, delineated how these large-scale brain systems develop throughout adolescence and change in normal and pathological aging, pointed to hyperconnectivity of the DMN in the first meta-analysis of RSFC-MRI in depression, and applied dynamic RSFC-MRI to clinical populations.

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 JR, Reidler J, Poulin R, and Buckner RL. (2010) Functional-anatomic fractionation of the default network. *Neuron*, 65:550-562.
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.

## 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 Reuters 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	Fellow of the Psychonomics Society
2018	Early Investigator Award, Society of Experimental Psychologists
2018	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. Buckner RL, Andrews-Hanna JR, and Schacter DL. (2008) The brain's default network: Anatomy, function, and relevance to disease. *Annals of the NY Academy of Science, Special Issue: The Year*

in Cognitive Neuroscience (Invited Review), 1124:1-38.

4. Raffaelli, Q., Wilcox, R., and Andrews-Hanna, J.R. (in press) The neuroscience of imaginative thought: An integrative framework. In A. Abraham (Ed.), *The Cambridge Handbook of Imagination*. Cambridge, U.K.: Cambridge University Press

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, N.P., and Andrews-Hanna, J.R. (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, Mar 26). 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 PMID: In Progress
3. O'Callaghan C, Shine JM, Lewis SJG, Andrews-Hanna JR, and Irish M. (2015) Shaped by our thoughts: A new task to assess spontaneous cognition and its associated neural correlates in the default network. *Brain and Cognition*, 93:1-10.
4. O'Callaghan, C., Shine, M., Andrews-Hanna, J.R., and Irish, M. (2019) Hippocampal atrophy and intrinsic brain network dysfunction relate to alterations in mind wandering in neurodegeneration. *PNAS*, 116(8), 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, J.R., Kaiser, R., Turner, A., Reineberg, A., Godinez, D., and Banich, M.T. (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, R.H., Andrews-Hanna, J.R., Wager, T.D., and Pizzagalli, D. (2015) Large-scale network dysfunction in Major Depressive Disorder: Meta-analysis of resting-state functional connectivity. *JAMA Psychiatry*, 72(6), 603-11.
3. Arch, J.J., Wilcox R, Ives, L., Sroloff, A., and Andrews-Hanna, J.R. (under review) Off-task thinking among adults with and without social anxiety disorder: An ecological momentary assessment study.
4. Pelletier-Baldelli, A., Andrews-Hanna, J.R., and Mittal, V. (2017) Resting state connectivity dynamics in individuals at risk for psychosis. *Journal of Abnormal Psychology*, 127(3):314-325. PMID: PMC5912697

## Complete list of published work in MyBibliography

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

## Research Support

NIA 1R03AG060271-01A1

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

NIA P30 AG019610 Reiman: PI 7/1/18 – 6/30/19

***Uncovering Neurocognitive Links between Alzheimer's Disease and Depression in Mid-Life to Early Aging***

Role on Project: Pilot Grant PI

NIA 1R01 AG043452 Bryan: PI 8/1/14 – 7/31/19

***Enhancing Function in Later Life: Exercise and Functional Network Connectivity***

Role on Project: Co-Investigator

NIMH 1R21 AG108848 Banich: PI 6/20/16 – 3/31/19

***Clearing the Contents of Working Memory: Mechanisms and Representations***

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 used 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 (274 total, H index 101), 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 in *Egr1* 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 MyBibliography

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

## Research Support

NIA R01 AG003376 Barnes (PI) 1/1/16 - 11/30/20

### ***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 - 5/31/20

### ***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 AG048907 Huentelman, Barnes (MPI) 9/30/14 - 5/31/19

### ***CATT: Development and Application of a Neuronal Cell Activity-Tagging Toolbox***

Our overall goal of this EUREKA award is to develop methods to label cells that were active during a defined temporal period and utilize a new approach to investigate the impact of aging on the circuit elements engaged by those behaviors as well as the transcriptional function of those behavior-driven labeled cells. The “Cell Activity-Tagging Toolbox” will provide a means to “permanently mark” the specific cells that were engaged in a defined behavioral experience. This is an extension of the catFISH methodology that can only labels cells for minutes to hours after a behavior.

Role: Principal Investigator (Multi-PI)

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 - 3/31/20

***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

Professor, Pharmacology and Neurology

### **Education/Training**

<b>Institution &amp; Location</b>	<b>Degree</b>	<b>Year(S)</b>	<b>Field Of Study</b>
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 inaugural director of the UA 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 mechanistically driven therapeutic development and translational research for age-associated neurodegenerative diseases (<https://cibs.uahs.arizona.edu/>). My research has focused broadly on the mechanisms underlying late onset Alzheimer's disease (AD) and developing therapeutics to prevent, delay, and cure the disease. Towards that goal, I lead three programs of discovery research and two programs of translational and clinical research. Our discovery research programs focus on systems biology of 1) mechanisms underlying risk of Alzheimer's during female brain aging, 2) sex differences in mechanisms underlying Alzheimer's, and 3) regeneration and repair mechanisms to regenerate the Alzheimer's brain. Fundamental insights that have emerged from our research indicate that the aging brain is dynamic and adaptive. The dynamic adaptive nature of the aging brain has led to an increasing focus on transition states of the aging brain, their plasticity, limits, and vulnerability. We have advanced our basic science discoveries into FDA IND-enabling translational programs and two early phase clinical trials. These programs of research are supported by the National Institute on Aging (R01, P01, U01, U54) and by philanthropic foundations. The breadth and depth of our research requires effective and collaborative team science that is mission focused. Teams that I lead include basic, translational, and clinical scientists and technology transfer professionals.

### **Positions**

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

## Honors

1999	Laboratory Named “The Norris Foundation Laboratory for Neuroscience Research”
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	Recipient: NIH MERIT (Method to Extend Research in Time) Award; for outstanding record of scientific achievement as principal investigator on National Institute of Aging (NIA) research projects.
2017	Alzheimer’s Drug Discovery Foundation, Melvin Goodes Prize for Excellence in Alzheimer’s Drug Discovery
2017	National Academy of Inventors

## Contribution to Science

The focus of my research has been to discover mechanisms leading to late-onset Alzheimer’s disease and to translate those insights into therapeutics to prevent, delay, and treat the disease. Results of my systems biology research programs have resulted in fundamental discoveries of steroid action in the brain that have been translated into two independent clinical trials targeting different receptor systems and mechanisms of action. Research endeavors in my laboratory are organized under three major themes: 1) Aging female brain and endocrine mechanisms of aging that increase risk of late onset Alzheimer’s disease, 2) Sex differences in mechanisms leading to late onset Alzheimer’s disease, and 3) Allopregnanolone regenerative systems neurobiology and regenerative therapeutic for Alzheimer’s disease.

The Aging female brain and endocrine mechanisms of aging that increase risk of late-onset Alzheimer’s disease program of research is devoted to understanding the mechanisms underlying the increased lifetime risk of Alzheimer’s in women. Outcomes of this pioneering research indicate that the female brain is highly dependent upon estrogen, which functions as a master regulator of the bioenergetic system of the brain. The perimenopausal transition, unique to the female, results in a bioenergetic shift in the brain from a glucose-dependent brain to a brain dependent on the alternative fuel ketone bodies. The adaptive bioenergetic shift to utilizing ketone bodies as an auxiliary fuel creates a risk for catabolizing brain lipids, myelin, to generate ketone bodies to fuel a starving brain. Based on our discovery science of estrogen action in the brain, we developed a GMP clinical grade estrogen receptor beta selective formulation that progressed into a NIA sponsored Phase 1b/2a clinical trial of PhytoSERMs for Menopause Symptoms and Age-Associated Memory Decline. Results of the PhytoSERM clinical trial are currently being analyzed.

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. Yin F, Yao J, Sancheti H, Feng T, Melcangi RC, Morgan TE, Finch CE, Pike CJ, Mack WJ, Cadenas E, and Brinton RD. (2015) The perimenopausal aging transition in the female rat brain: decline in bioenergetic systems and synaptic plasticity. *Neurobiol Aging*, 36:2282-2295.
3. Mosconi L, Berti V, Guyara-Quinn C, McHugh P, Petrongolo G, Osorio RS, Connaughty C, Pupi A, Vallabhajosula S, Isaacson RS, de Leon MJ, Swerdlow RH, and Brinton RD. (2017) Perimenopause

and emergence of an Alzheimer's bioenergetic phenotype in brain and periphery. PLoS One, Oct10;12(10): e0185926. doi: 10.1371/journal.pone.0185926.

4. Mosconi L, Berti V, Quinn C, McHugh P, Petrongolo G, Varsavsky I, Osorio RS, Pupi A, Vallabhajosula S, Isaacson RS, de Leon MJ, and Brinton RD. (2017) Sex differences in Alzheimer risk: Brain imaging of endocrine vs chronologic aging. *Neurology*, 89:1382-1390.

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. Zissimopoulos JM, Barthold D, Brinton RD, and Joyce G. (2016) Sex and race differences in the association between statin use and the incidence of Alzheimer disease. *JAMA Neurology*, 74:225-232.
2. Zhao L, Mao Z, Woody SK, and Brinton RD. (2016) Sex differences in metabolic aging of the brain: Insights into female susceptibility to Alzheimer's disease. *Neurobiology Aging*, 42:69-79.
3. Wang Y, and Brinton RD. (2016) Triad of Risk for Late Onset Alzheimer's: Mitochondrial Haplotype, APOE Genotype and Chromosomal Sex. *Frontiers in Aging Neuroscience*, 8:232 Riedel BC, Thompson PM, and Brinton RD. (2016) Age, APOE and sex: Triad of Risk of Alzheimer's disease. *J Steroid Biochem Mol Biol.*, 160:134-47.

The Allopregnanolone regenerative systems neurobiology and regenerative therapeutic for Alzheimer's disease programs of research are 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), and acquired an FDA IND to conduct a NIA sponsored Phase 1b clinical trial of allopregnanolone in persons with mild cognitive impairment or early Alzheimer's disease. The NIA-sponsored clinical trial Allopregnanolone for Mild Cognitive Impairment Due to Alzheimer's Disease or Mild AD is currently ongoing.

1. Brinton RD. (2013) Neurosteroids as regenerative agents in brain: Therapeutic implications. *Nature Rev. Endocrinol.*, 9:241-250.
2. Singh C, Liu L, Wang JM, Irwin RW, Yao J, Chen S, Henry S, Thompson RF, and Brinton RD. (2011) Allopregnanolone restores hippocampal-dependent learning and memory and neural progenitor survival in aging 3xTgAD and nonTg mice. *Neurobiol Aging*, 33:1493-506.
3. Chen S, Wang JM, Irwin RW, Yao J, Liu L, and Brinton RD. (2011) Allopregnanolone promotes regeneration and reduces β-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 MyBibliography**

<https://www.ncbi.nlm.nih.gov/sites/myncbi/roberta.brinton.1/bibliography/40443387/public/?sort=date&direction=ascending>

## Research Support

NIA R01 AG057931

Brinton (PI)

9/1/18 - 8/31/23

### ***Sex Differences in the Molecular Determinants of Alzheimer's Disease Risk: Prodromal Endophenotype***

The mission for the Sex Differences in the Molecular Determinants of Alzheimer's Disease Risk: Prodromal Endophenotype project is to determine the complex interaction between chromosomal sex and the major risk factors for late onset Alzheimer's (LOAD): age, APOE\*4 genotype and maternal history of AD. As LOAD accounts for the greatest incidence and prevalence of the disease, determining molecular mechanisms relevant to LOAD has the potential for greatest impact. Further, targeting early stage transitions of risk have the greatest potential for therapeutic efficacy. Thus, research proposed herein focuses on the prodromal / preclinical stage of LOAD and the sex differences that underlie early risks of LOAD progression. Elucidation of sex differences in the mechanisms driving prodromal LOAD will lead to identification of therapeutic targets to change the trajectory of the disease to prevent, delay and potentially reverse course of developing LOAD. Role: PI

NIA T32 AG061897

Brinton (PI)

9/1/18 - 8/31/23

### ***Translational Research in AD and related Dementias (TRADD)***

The University of Arizona (UA) Training Program to Advance Translational Research on Alzheimer's Disease and AD Related Dementias is designed to address knowledge and experience gaps in AD therapeutic discovery and preclinical translational development. To meet this challenge, the UA Translational Research in AD and related Dementias (TRADD) training program is designed as a problem based translational learning experience for predoctoral PhD and MD/PhD fellows. In alignment with the 2012, 2015 and 2018 NIH Alzheimer's Disease Research summits and the National Alzheimer's Project Act, the goal of the TRADD training program is to fill critical gaps that exist for AD translational research in academic graduate programs. To achieve this goal, the University of Arizona TRADD program will: 1) recruit trainees across multiple scientific disciplines; 2) employ problem-based learning approaches to solve challenges in AD therapeutic development with emerging tools **and techniques; and 3) equip TRADD trainees with career development and leadership skills necessary to conduct team science and manage multidisciplinary teams in the 21st century.**

**Role: PI**

NIA R37-AG053589

Brinton (PI)

3/15/17 - 2/28/22

### ***Aging and Estrogenic Control of The Bioenergetic System In Brain***

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

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

Role: PI

NIA P01 AG026572

Brinton (PI)

7/1/05 - 5/31/21

### ***Perimenopause in Brain Aging and Alzheimer's Disease***

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

interventions to prevent Alzheimer's disease in those at greatest lifetime risk, postmenopausal women.

Role: Program PI; PL Administrative Core A, Project 1 and Project 4

NIA U01 AG047222

Brinton (PI)

6/15/18- 6/30/19

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

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

Role: PI

Alzheimer's Association

Brinton (PI)

5/1/17 - 4/30/20

***Perimenopause In ApoE4 Brain: Accelerated Myelin Catabolism for Fuel***

Discovery of at-AD-risk phenotypes in women and the underlying mechanisms could potentially lead to early identification of those at greatest risk of developing AD and interventions to prevent the disease. Having established that the perimenopause is a neurological bioenergetic transition state that shifts the brain from utilizing glucose as its primary fuel to utilizing ketone bodies as an auxiliary fuel and that metabolic compromise is associated with compromised cognitive function in postmenopausal women [3], we advance a program wide three hit hypothesis for women positive for ApoE4: Females positive for ApoE4 gene experience three strikes that result in accelerated bioenergetic aging in brain and concomitant generation of three hallmarks of Alzheimer's disease in brain, hypometabolism, beta amyloid deposition and white matter (WM) degeneration. Strike one for ApoE4 positive females, is the genetic risk conferred by the ApoE4 genotype. Strike two is chronological aging. Strike three is the bioenergetic transformation of the perimenopause. Interestingly, all three of these strikes are independently associated with WM degeneration and we hypothesize that in combination they will lead to an accelerated AD-like WM degeneration phenotype.

NIA R01 AG059093

Kaddurah-Daouk (PI)

8/1/18 - 6/30/23

***Metabolic Networks and Pathways Predictive of Sex Differences in AD Risk and Responsiveness to Treatment***

In this study, we use global metabolomics approach to delineate biochemical differences in men and women across the trajectory of disease. We aim to define biochemical pathways and networks for greater vulnerability of disease in women and men that would enable discovery of more effective therapies for each of the sexes.

Role: Subaward PI

## 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 brain imaging and transcranial magnetic stimulation (TMS) techniques to 1) develop image-guided therapeutic TMS protocols and 2) explore TMS-derived and image-based biomarkers for early diagnosis and prediction of therapeutic outcomes for individuals with mild cognitive impairment as well as Parkinson's disease. For the past few years, I have been involved in a number of NIH-funded studies investigating brain function and its relation to cognitive performance. I am currently the Director of Brain Imaging and TMS Laboratory and teach undergraduate and graduate level courses in cognitive neuroscience, brain rehabilitation, and brain connectivity at the University of Arizona.

1. Chou YH, Ton That, V., Sundman, M. (in press) A systematic review and meta-analysis of rTMS effects on cognitive enhancement in mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging*.
2. 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.
3. Chou YH, Panych LP, Dickey CC, Petrella JR, Chen NK. Investigation of long-term reproducibility of intrinsic connectivity network mapping: A resting-state fMRI study. *Am J Neuroradiol.*, 33: 833-838.
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): 451-9.

### 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
2017	Scholar, CDC Arizona Healthy Brain Research Center

## 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 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. However, results evaluating the effectiveness of rTMS are mixed, mostly due to low statistical power or variety in individual rTMS protocols. Recently, we published a meta-analysis that included 13 studies with 293 patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD)<sup>a</sup>. The therapeutic effect of rTMS on overall cognitive function was significant (effect size = 0.77,  $p < .0001$ ). Subgroup analyses of the 13 studies revealed that 1) high-frequency or excitatory rTMS over the left DLPFC significantly improved memory function (effect size = 0.68,  $p < .005$ ), and the effects of 5-30 consecutive rTMS daily sessions were durable for 4-12 weeks. We conducted another meta-analysis examining differences in TMS-induced measures of cortical excitability between AD, MCI and cognitively normal older adults (CN)<sup>b</sup>. Findings of this meta-analysis suggest the existence of cortical hyper-excitability in AD and MCI, as well as reduced inhibition in AD. We are currently conducting 2 pilot TMS/MRI studies to 1) investigate differences in cortical excitability, meta-plasticity, and brain connectivity between MCI and CN (current  $N = 44$ ); and 2) develop an image-guided rTMS protocol to stimulate the hippocampus in MCI (current  $N = 9$ ).

In 2015, we published a meta-analysis of 20 clinical trials in 470 patients with Parkinson's disease, suggesting a significant medium effect size favoring active rTMS over sham rTMS for reducing motor

symptoms. In the same year, we published another article investigating the effects of high-frequency rTMS over the primary motor cortex on motor function and brain connectivity in individuals with multiple system atrophy. Findings of this clinical trial support the therapeutic effect of 10-session, high-frequency rTMS in improving motor symptoms in multiple system atrophy. Several functional links involving the default mode, cerebellar and limbic networks exhibited positive changes in functional connectivity. The positive changes in functional connectivity were associated with improvement in motor symptoms. The present findings suggest that rTMS may improve motor symptoms by modulating functional links connecting to the default mode, cerebellar and limbic networks, inferring a future therapeutic candidate for patients with multiple system atrophy.

1. Chou YH, Ton That V., Sundman M. (in press) A systematic review and meta-analysis of rTMS effects on cognitive enhancement in mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging*.
2. Chou YH., Rapcsak S., Chen N.-K., Sundman M., Lim K., Ugonna C., Lindley M., Fuglevand A., Mohler, J., Huang, Y.-Z. (2018) Cortical Excitability in Alzheimer's Disease and Mild Cognitive Impairment: A Systematic Review and Meta-analysis of Transcranial Magnetic Stimulation Studies. Oral presentation at the Arizona Alzheimer's Consortium 2018 Annual Scientific Conference, Phoenix, AZ.
3. 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.
4. 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.

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. PMID: 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 PMID: 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 2,000 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. PMID: 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. PMID: 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 MyBibliography

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

## Research Support

NIA NIBIB	Witte (PI)	9/30/19 – 9/29/20
<b><i>Transcranial Acoustoelectric Imaging for High Resolution Functional Mapping of Neuronal Currents</i></b>		
Role on Project: Co-Investigator		
NIA R56 AG061888	Wilson (PI)	9/30/18 - 8/31/23
<b><i>Evaluating the Neurocomputational Mechanisms of Explore Exploit Decision Making in Older Adults</i></b>		
Role on Project: Co-Investigator		
NIA P30 AG019610	Reiman(PI); Chou (Pilot PI)	7/01/17 - 06/30/19
<b><i>Use of TMS and fMRI Measures to Assess the Risk of Conversion of MCI to Dementia</i></b>		
In this pilot project, we propose probing cortical excitability and plasticity in individuals with MCI in order to assess the diagnostic potential of TMS-evoked responses.		
Role on Project: Pilot Project PI		
NIA P30 AG019610	Reiman (PI); (Wilson Pilot PI)	7/1/17 – 6/30/19
<b><i>The Neural Substrates of Explore-Exploit Decisions in Old Age</i></b>		
The purpose of this pilot study is to understand the neural systems underlying explore-exploit decisions and how these systems change in old age and with cognitive decline.		
Role on Project: co-investigator		
Arizona Alzheimer's Consortium, DHS	Chen (PI)	7/1/19 – 6/30/20
<b><i>Transcranial Magnetic Stimulation for Mild Cognitive Impairment</i></b>		

Role on Project: Project PI

Arizona Alzheimer's Consortium, DHS                      Chen (PI)                      7/1/18 – 6/30/19  
***High-resolution MR Imaging Technologies for Mapping Neuronal Connectivity Network to Subfields of Hippocampus and Amygdala: Application to Studies of Alzheimer's Disease***  
Role on Project: Project PI

Cancer Center, University of Arizona                      Kou (PI)                      7/1/18 - 6/30/20  
***Feasibility Study for the Treatment of Post-Chemotherapy Cognitive Impairment with Transcranial Magnetic Stimulation***  
Role on Project: Co-Investigator

BIO5 Institute, University of Arizona                      Chou (PI)                      7/1/18 - 6/30/19  
***Developing a Non-Invasive Magnetic Brain Stimulation Protocol for Mild Cognitive Impairment***  
Role on Project: PI

## Biographical Sketch

Stephen Cowen, Ph.D.

Assistant 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 activities of tens of billions of interconnected neurons become coordinated during learning, decision making, and sleep. Resolving this question is important as dysregulated neural coordination and communication contributes to age-associated cognitive decline, substance abuse, epilepsy, Parkinson's disease (PD), and depression. My research seeks to understand the mechanisms by which the timing of the activities of ensembles of neurons and dopamine release is organized during learning and sleep. 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 changes in dopamine release (Parent et al., 2017). My laboratory is using this tool to investigate the role that dopamine plays in regulating neuronal coordination and plasticity in anesthetized and behaving animals, and we are working towards testing this device in animal models of substance abuse and PD. The advanced sensing technologies described in the Research Enhancement Grant proposal would provide my laboratory with opportunities to directly expand and extend this research and would provide key preliminary data for NIDA R01 applications in the next 2 years.

Beyond technology development and the study of dopamine release, my lab also investigates the roles that brain oscillations play in learning, memory, disease, and aging. For example, we have found that normal aging is associated with a significant decrease in the frequency of oscillations in the hippocampus that are associated with memory formation (Wiegand et al., 2016; Cowen et al., 2018). With regard to disease, my laboratory is investigating how low to moderate doses of ketamine (a drug of abuse and anesthetic) alter brain oscillations in the dorsal and ventral striatum (Ye et al., 2018). Data collected in my laboratory now suggests that ketamine simultaneously enhances corticostriatal coherence at high-frequencies (~135 Hz) and reduces coherence at theta and beta frequencies (~8-30 Hz) – frequency ranges associated with Parkinsonian motor symptoms.

1. Ye T, Bartlett MJ, Schmit MB, Sherman SJ, Falk T, and Cowen SL. (2018) Ten-Hour Exposure to Low-Dose Ketamine Enhances Corticostriatal Cross-Frequency Coupling and Hippocampal Broad-BandGamma Oscillations. *Front. Neural Circuits*, 12, 61. doi: 10.3389/fncir.2018.00061
2. 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. doi: 10.1097/j.pain.0000000000001226. (Editor's Choice article)
3. 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.
4. 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.

## 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 – Present	Assistant Professor	Department of Psychology, University of Arizona Graduate Interdisciplinary Program in Neuroscience Graduate Interdisciplinary Program in Cognitive Science Graduate Interdisciplinary Program in Phys. Sciences

## 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.
2. 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 through 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.

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

- Ultrasound measurement of electrical brain activity. I am a collaborator on Brain Initiative R24(Lead PI: Russel Witte, UA) to develop a non-invasive ultrasound system for the measurement of electrical activity in the brain. The system capitalizes on the acoustoelectric effect, and my role is to validate the system’s effectiveness by comparing in vivo measurements obtained from the ultrasound system with measurements obtained from traditional electrophysiology.
- Simultaneous dopamine and single-unit/local-field measurement. Awarded a 2014 NSF BRAINEAGER grant to develop technologies for the simultaneous recording of the activities of ensembles of neurons and real-time measurement of dopamine release. Since receiving support, we have produced working versions of this device and successfully tested the device in anesthetized and awake and behaving rats (methods paper under review). The next stage of development will be to improve the hardware and software to improve robustness and ease of use.
- To better characterize fine body movements in animals as they perform decision-making behaviors, I developed a novel 9-axis head-mounted inertial measurement system. Prototypes of this system are being developed for three laboratories for the investigation of brain-body interactions in the hippocampus, parietal cortex, and prefrontal cortex.
- Designed and built numerous automated maze systems for the training and testing of decision-making and memory-driven behaviors. The design and required software is freely available. I helped set up these systems in the laboratories of three collaborators and they continue to be used.
- Produced an interactive graphical system for real-time and off-line spike sorting (Waveform Cutter, Cowen 2002). This tool became an integral part of MClust (David Redish, U. Michigan), one of the most popular open-source spike-sorting systems.

## Complete list of published work in MyBibliography

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

## Research Support

LuMind Foundation

PI: Elgin

1/1/17 - present

***Brain Development, Sleep & Learning in Down Syndrome***

Objective: Identify neural signatures of sleep dysfunction in Down-syndrome subjects (EEG).  
Role on Project: Co-Investigator

Michael J. Fox PI: Cowen 8/1/17 - 7/31/19

***Identification of Network and Oscillatory Signatures Of The LRRK2 Mutation***

Objective: Identify neural biomarkers that distinguish the LRRK2 genetic form of Parkinson's disease from healthy controls and idiopathic Parkinson's disease.

Role on Project: Principal Investigator

R44 MH114776 PI: Hedlin 8/1/19 – 1/1/20

***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 – 8/1/20

***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

NIA NIBIB Witte (PI) 9/30/19 – 9/29/20

***Transcranial Acoustoelectric Imaging for High Resolution Functional Mapping of Neuronal Currents***

Role on Project: Co-Investigator

## ***Biographical Sketch***

Arne Ekstrom., Ph.D.

Associate Professor, Psychology,

### **Education/Training**

<b>Institution &amp; Location</b>	<b>Degree</b>	<b>Year(S)</b>	<b>Field Of Study</b>
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 – Present	Associate 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**

Multivariate approaches to the fMRI of human episodic memory and navigation. In the work cited below, 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. 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.
2. 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.
3. 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.

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 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 AJ, Tandon N, Connor C, Pieters T, and Ekstrom AD. (2013) Frequency-specific increases in network connectivity underlie successful spatiotemporal memory retrieval. *Nature Neuroscience*, 16:349-56. PMID: 23354333.
2. Schedlbauer A, Copara MS, Watrous AJ, and Ekstrom AD. (2014) Multiple interacting brain areas underlie successful spatiotemporal memory retrieval in humans. *Scientific Reports*, 4:6431.
3. Ekstrom AD, Huffman D, and Starrett MJ. (2017) Interacting networks of brain regions underlie human spatial navigation: A review and novel synthesis of the literature. *Journal of Neurophysiology*, 118:3328-3344.

Behavioral and neural correlates of human spatial navigation. In the work cited below, we employ patients with focal lesions, fMRI, and behavioral methods to better understand the neural basis of human spatial navigation. Prior to this work, the exact contribution of the human hippocampus versus extra-hippocampal cortical areas to encoding and retrieval spatial locations was unclear. Based on our findings, we propose that allocentric spatial memory (memory for object locations referenced to external cues in the environment rather than the self) depends primarily on extra-hippocampal network contributions, with the hippocampus primarily contributing to the precision of such spatial memories. Together, these findings argue for the importance of hippocampal and extra-hippocampal cortical areas to spatial navigation and provide novel paradigms for understanding human spatial navigation.

1. Kolarik BS, Baer T, Shahlaie K, Yonelinas AP, and Ekstrom AD. (2018) 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.

2. Kolarik BS, Shahlaie K, Hassan B, Borders AA, Kaufman K, Gurkoff G, Yonelinas AP, and Ekstrom AD. (2016) Impairments in precision, rather than spatial strategy, characterize performance on the virtual Morris Water Maze: A case study. *Neuropsychologia*, 80:90-101.
3. Zhang H and Ekstrom AD. (2013) Human neural systems underlying rigid and flexible forms of allocentric spatial representation. *Human Brain mapping*, 34(5):1070-87.
4. Arnold AE, Iaria G, and Ekstrom AD. (2016) Mental simulation of routes during navigation involves adaptive temporal compression. *Cognition*, 157:14-23.

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.

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 AD. (2010) How and when the fMRI BOLD signal relates to underlying neural activity: The danger in dissociation. *Brain Research Reviews*, 62(2):233-44. PMID: 20026191.
2. Ekstrom AD, Bazih AJ, Suthana NA, Al-Hakim R, Ogura K, Zeineh M, and Bookheimer SY. (2009) Advances in high-resolution imaging and computational unfolding of the human hippocampus. *Neuroimage*, 47, 42-49. PMID: 19303448.
3. Ekstrom AD, Suthana NA, Millett D, Fried I, and Bookheimer SY. (2009) Correlation Between BOLD fMRI and Theta-band Local Field Potentials in the Human Hippocampal Area. *Journal of Neurophysiology*, 101, 2668-2678. PMID: 19244353.
4. Ekstrom AD, Suthana NA, Behnke E, Salamon N, Bookheimer SY, and Fried I. (2008) High-resolution depth electrode localization and imaging in patients with pharmacologically intractable epilepsy. *Technical Note. Journal of Neurosurgery*, 108, 812-5. PMID: 18377264.

## Research Support

NINDS R01 NS076856

PI: Ekstrom

7/1/12 – 6/30/22

### ***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.

Role on Project: PI

NSF BCS-1630296

PI: Ekstrom

9/1/16 – 8/31/20

### ***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.

Role on Project: PI

NIA R01 AG003376

PI: Barnes

10/1/15 – 9/30/20

### ***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

NINDS R01 NS08402

PI: Gurkoff

2/1/14– 1/30/19

### ***Restoring Connectivity Following Traumatic Brain Injury***

The goal of this grant is to assess how traumatic brain injury alters oscillations, particularly phase coherence across distal neural networks, during performance of cognitive tasks and to determine whether deep brain stimulation can be utilized to improve coherence and restore function. 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**

<b>Institution &amp; Location</b>	<b>Degree</b>	<b>Year(S)</b>	<b>Field Of Study</b>
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**

I see many parallels between running a laboratory and operating a technology startup. My vision is to use the lab as a vehicle to identify promising basic research that—if strategically rounded out with a little more investment—could have a disproportionate impact on the way diseases of the nervous system are conceptualized and treated. This perspective informs my current work on circadian rhythms and aging, as well as a previous project I led concerning the design of a treatment for intellectual disability in people with Down syndrome (please see Fernandez et al., *Nature Neuroscience*, 2007, Jamie Edgin & Fabian Fernandez, *New York Times*, “The Truth about Down Syndrome,” and item 1 in Publications and Career Contributions).

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

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

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

## Positions

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 Garner CC. (2007) Object recognition memory is conserved in Ts1Cje, a mouse model of Down syndrome. *Neuroscience Letters*, 421: 137-141.
3. Fernandez F and Garner CC. Over-inhibition: a model for developmental intellectual disability. *Trends in Neurosciences*, 30: 497-503, 2007.
4. Fernandez F and Garner CC. (2008) Episodic-like memory in Ts65Dn, a mouse model of Down syndrome. *Behavioural Brain Research*, 188: 233-237.
5. Fernandez F, Trinidad JC, Blank M, Feng DD, Burlingame AL, and Garner CC. (2009) Normal protein composition of synapses in Ts65Dn mice, a mouse model of Down syndrome. *Journal of Neurochemistry*, 110: 157-169.
6. 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 Pentylene tetrazole. *Journal of Biological Rhythms*, 25: 63-66.
7. Fernandez F, Torres V, and Zamorano P.\* (2010) An evolutionarily conserved mechanism for presynaptic trapping. *Cellular and Molecular Life Sciences*, 67: 1751-1754.
8. Zampieri BL, Fernandez F\*, Pearson JN, Stasko MR, and Costa ACS. (2014) Ultrasonic vocalizations during male-female interaction in the mouse model of Down syndrome Ts65Dn. *Physiology & Behavior*, 128: 119-125.
9. Fernandez F and Reeves RH. (2015) Assessing cognitive improvement in people with Down syndrome: Important considerations for drug efficacy trials. *Handbook of Experimental Pharmacology*, 228: 335-380.
10. Fernandez F and Edgin JO. (2016) Pharmacotherapy in Down syndrome: Which way forward? *Lancet Neurology*, 15: 776-777.
11. Clark CAC, Fernandez F, et al. (2017) The medial temporal memory system in Down syndrome: Translating animal models of hippocampal compromise. *Hippocampus*, 27: 683-691.
12. 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 60 months of life. *Sleep Medicine*, 33: 134-144.

Since 2005, my colleague, Dr. Norman Ruby, and I have explored how circadian arrhythmia impairs memory function using a novel animal model, the Siberian hamster (*Phodopus sungorus*) (PNAS 2008; PLoS 2013; Science, 2014). Circadian misalignment due to shift work or jet-lag is well-known to impair memory in humans. However, circadian arrhythmia in rodents induced by clock gene knockouts or surgical lesion of the suprachiasmatic nucleus (SCN), the brain's clock, is reported to have very little effect on memory. Dr. Ruby and I reasoned that this long-held disconnect occurred because the SCN remains developmentally and structurally intact in humans but not in these rodent models. What if the impairments brought on by circadian dysfunction resulted, not from the loss of a "good-functional" SCN (i.e., degeneration), but from the gain of a "bad-defective" SCN that was now sending error signals to memory systems in the medial temporal lobe? What if the proper phenotypic expression of arrhythmia in the brain – and its effects on behavior – require preservation of circuitry from "malfunctioning" SCN areas to their downstream targets? What if key aspects of this expression are lost upon severing SCN connections? We addressed these issues in the Siberian hamster, a species that can be rendered circadian arrhythmic by a simple, one-time photic treatment that does

not interfere with SCN structure or development/genetics. We found that hamsters with persistent light-induced arrhythmia actually have severe deficits in spatial and object recognition memory that can be rescued by subsequent ablation of the SCN. These data suggest that chronic arrhythmia per se does not cause memory impairments in animals – or presumably humans – as has been historically believed. Rather, in line with our hypothesis, an intact, but dysrhythmic SCN is necessary to realize these deficits (Fernandez et al., Science, 2014).

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. Lewis SA, Negelspach DC, Kaladchibachi S, Cowen SL, and Fernandez F.\* (2017) Spontaneous alternation: A potential gateway to spatial working memory in *Drosophila*. *Neurobiology of Learning and Memory*, 142: 230-235. \*Corresponding Author
4. 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.
5. Kaladchibachi S and Fernandez F. (2018) Precision light for the treatment of psychiatric disorders. *Neural Plasticity*, 5868570, 1-16.
6. Kaladchibachi S, Negelspach DC, and Fernandez F.\* (2018) Circadian phase-shifting by light: Beyond photons. *Neurobiology of Sleep and Circadian Rhythms*, 5: 8-14. \*Corresponding Author
7. Negelspach DC, 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.

## Research Support

Velux Stiftung

PI: Fernandez

2019 - 2021

Programming the Circadian Clock with Precision Flashes of LED Light

Role on Project: Project PI

## ***Biographical Sketch***

Elizabeth L. Glisky., Ph.D.  
Professor, Psychology

### **Education/Training**

<b>Institution &amp; Location</b>	<b>Degree</b>	<b>Year(S)</b>	<b>Field Of Study</b>
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 FLs, to look at individual differences in older adults. I normed a battery of tests on 227 older adults yielding two composite measures: one that tapped fundamental memory functions dependent on the MTLs and one that measured executive function, depending on the FLs. These composite measures were then used to predict performance on item and source memory tasks respectively, and later on other kinds of memory tasks, including prospective memory. The idea was picked up by several other researchers to explore brain-behavior relations in older adults, and the use of neuropsychological tests in older adults has now become quite commonplace.

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.

## Research Support

Arizona Alzheimer's Consortium, DHS

PI: Glisky

7/1/18 -6/30/19

### ***Memory and executive function in normally-aging older adults: Completion, analyses, and publication of two projects***

The goals are to document changes over time in episodic memory and executive function in normally aging older adults aged 65+; identify specific demographic, health, genetic, and neurocognitive variables that are associated with differential change; and validate an executive function test battery for older adults incorporating specific sub-components of executive function.

Role on Project: PI

## ***Biographical Sketch***

Matthew D. Grilli, Ph.D.

Assistant Professor Psychology

### **Education/Training**

<b>Institution &amp; Location</b>	<b>Degree</b>	<b>Year(s)</b>	<b>Field Of Study</b>
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 Early Stage Investigator and 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 young and older adults, 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 the past 4 years, my lab has focused intensively on the relationship between Alzheimer's disease (AD) risk and autobiographical memory, combining novel cognitive testing with genetics and brain imaging. Much of this work has been done in collaboration with Dr. Jessica Andrews-Hanna, Director of the Neuroscience of Emotion and Thought Lab. My initial work in this area has gained national attention, as I was recently recognized as an Alzheimer's Disease Core Center Junior Investigator. This R01 application, which builds on our currently funded R03 from NIH/NIA (PI: Grilli, Co-I: Andrews-Hanna) and a grant from the Arizona Alzheimer's Consortium (PI: Andrews-Hanna, Co-I: Grilli), extends our theoretical and empirical approach to studying autobiographical thought and the default network as cognitive and neural markers of Alzheimer's disease risk among cognitively unimpaired adults. In addition to the invaluable expertise of MPI Andrews-Hanna (see Biosketch), I believe that my expertise in clinical neuropsychology, aging, and AD risk ensures that the proposed research has the potential to be translated to improved assessment and intervention, and potentially new cognitive tests for neuropsychologists. Our active collaboration and experience executing studies of this magnitude and complexity demonstrates that we are prepared for this R01, especially given our support from Co-Is Dr. Matthias Mehl and Dr. Matthew Huentelman, Other Significant Contributor Dr. Eric Reiman, Other Significant Contributor Dr. Edward Bedrick, and the unique resources of GeneMatch and MindCrowd (see Facilities and Resources).

1. Grilli MD, Wank, AA, Berceel, 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. Grilli MD, Woolverton CB, Crawford M, Glisky EL. Self-reference and emotional memory effects in older adults at increased genetic risk of Alzheimer's disease. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2018 Mar;25(2):186-199. doi: 10.1080/13825585.2016.1275508. Epub 2017 Jan 3. PubMed PMID: 28044474.
4. Wank AA, Moseley S, Polsinelli AJ, Glisky EL, Mehl MR, Grilli MD. Real-world memories in everyday life: Replication of some, but not all, laboratory-based episodic specificity findings in ecological contexts. *PsyArXiv*. [Preprint] June 25, 2019. available from <https://psyarxiv.com/v34tm/>

## 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, University of Arizona, Tucson, AZ
2015 – Present	Director of Neuropsychology Track for the Clinical Psychology PhD Program
2015 – Present	Director of the Neuropsychology Clinic, Evelyn F. McKnight Brain Institute
2015 – Present	Affiliate, Department of Neurology, Evelyn F. McKnight Brain Institute, 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

Introduced the episodic autobiographical memory hypothesis of preclinical AD cognitive detection. My colleagues and I recently proposed that disrupted retrieval of detailed episodic autobiographical memories may be a sensitive indicator of subtle cognitive decline from AD, because this type of memory taxes a neural network associated with this disease. Our initial findings support the notion that disrupted episodic autobiographical memory may be a marker of AD risk. In regard to my role, with my collaborator MPI Andrews-Hanna's, we 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. I have also served as a Co-I on Dr. Andrews-Hanna's work on depressive symptoms, autobiographical thought, and the default network, and I collaborated on a review paper that Dr. Andrews-Hanna led on normal and abnormal aging, autobiographical thought, and the default network. I was the lead researcher and first author for the first publication on our novel hypothesis, and I was the PI of several small grants that supported this work.

1. Grilli MD, Wank AA, Bercel JJ and Ryan L. (2018) 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*, doi: 10.1017/S1355617718000577.

2. Andrews-Hanna JR, Grilli MD and Irish M. (2019) 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 and Grilli MD (under review). The relationship between episodic detail generation and anterotemporal, posteromedial, and hippocampal white matter tracts.

Developed a novel cognitive neuroscience model of how personal semantics are stored and retrieved. Much of one's autobiographical memory is composed of personal semantics, which is knowledge about the self that contextualizes experiences and adds meaning to the life story. Despite the importance of personal semantics to one's sense of self, how such knowledge is organized and retrieved remains underspecified. I have attempted to close this gap in knowledge by studying personal semantics in individuals with lesions to core regions of the autobiographical memory neural network. I have proposed that personal semantics can be viewed as consisting of subtypes of content that place distinct computational demands on regions in the autobiographical memory network. Personal semantics can be bound to events, in which case they are supported by bilateral medial temporal lobe structures (Grilli & Verfaellie, 2014; 2016). They also can be associated with personally known people, places, and objects and critically depend on the left anterior ventrolateral temporal lobe (Grilli et al., 2018). Or, they can represent categorical knowledge about the self, such as personality traits or social roles, in which case they are supported by neural regions that are implicated in basic level categorical knowledge or schema-like knowledge, including the medial prefrontal cortex (Marquine, Grilli, et al., 2016). This cognitive neuroscience model reflects a comprehensive attempt to explain the neural bases of personal semantics. For my role, I was the lead researcher and first author (or co-first author) of the publications that have come from my work on this topic, including key theory pieces (Grilli & Verfaellie, 2016; Grilli et al., 2018).

1. Grilli MD and Verfaellie M. (2014) Personal semantic memory: insights from neuropsychological research on amnesia. *Neuropsychologia*, 61:56-64.
2. Grilli MD and Verfaellie M. (2016) Experience-near but not experience-far autobiographical facts depend on the medial temporal lobe for retrieval: Evidence from amnesia. *Neuropsychologia*, 81:180-185.
3. Grilli MD, Bercl JJ, Wank AA, and Rapcsak SZ. (in press) The contribution of the left anterior ventrolateral temporal lobe to the retrieval of personal semantics. *Neuropsychologia*.
4. Marquine M, Grilli MD, Rapcsak SZ, Kaszniak AW, Ryan L, Walther K, and Glisky EL. (2016) Impaired personal trait knowledge, but spared other-person trait knowledge, in an individual with bilateral damage to the medial prefrontal cortex. *Neuropsychologia*, 89:245-53.

Advanced understanding of how autobiographical memory is necessary for maintaining the self-concept. Autobiographical memory, which is the repository of experiences and facts that are unique to each person, has long been thought to ground one's conceptualization of the self. My research has supported this idea. First, in a neuropsychological study, I demonstrated that MTL amnesics rely entirely on abstract personal semantic memories to ground their identity, which comes at a cost: they cannot retrieve as many self-defining traits as healthy controls do. This indicates that episodic autobiographical memories serve a necessary role in grounding the self-concept. Second, I showed that the relative importance of episodic autobiographical memory and personal semantic memory depends on the stability of one's traits and roles. Specifically, I found that whereas healthy adults primarily rely on episodic and episodic-like autobiographical memories to ground recently formed traits and roles, they tend to ground remotely formed traits and roles with abstract personal semantic memories more than other autobiographical contents. These studies provide important insight into the self-supporting function of autobiographical memory.

1. Grilli MD and Verfaellie M. (2015) Supporting the self-concept with memory: insight from amnesia. *Social Cognition and Affective Neuroscience*, 10:1684-1692.
2. Grilli MD. (2017) The association of personal semantic memory to identity representations: insight into higher-order networks of autobiographical contents. *Memory*, 25:1435-1443.
3. Strikwerda-Brown C, Grilli MD, Andrews-Hanna J, and Irish M. (2019) "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]
4. Grilli, M.D., and 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.

Developed a novel cognitive strategy 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, capable of enhancing recognition, cued recall, free recall, and prospective memory across various delays and over and above a variety of cognitive strategies. In regard to my role, I was the lead researcher and first-author on most of this work.

1. Grilli MD and Glisky EL. (2010) Self-imagining enhances recognition memory in memory-impaired individuals with neurological damage. *Neuropsychology*, 24:698-710.
2. 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 Neuropsychology Society*, 17:929-933.
3. Grilli MD and McFarland CP. (2011) Imagine that: Self-imagination improves prospective memory in memory-impaired individuals with neurological damage. *Neuropsychology Rehabilitation*, 21:847-59.
4. Grilli MD and Glisky EL. (2013) Imagining a better memory: Self-imagination in memory-impaired patients. *Clinical Psychological Science*, 1:93-99.

## Complete list of published work in MyBibliography

<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  $\epsilon 4$  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.

McKnight Brain Research Foundation

Grilli (MPI)

4/6/18 – 9/1/20

***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)      7/1/19 -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.

Arizona Alzheimer’s Consortium, DHS      Grilli (PI)      7/1/18 -6/30/19

***The Status of Personal Semantic Memory Among Cognitively Healthy Older Adults and Individuals with Mild Cognitive Impairment.***

The specific aims of this project are: 1) to identify patterns of spared versus impaired personal semantic memory (PSM) among cognitively normal older adults relative to young adults, as well as in comparison to individuals with mild cognitive impairment (MCI), and 2) to reveal that PSM status is related to neural markers of the integrity of the medial temporal and ventrolateral temporal lobes, as measured with MRI methods.

NIA P30 AG019610      Reiman(PI); Andrews-Hanna (Pilot PI)      7/1/17 - 6/30/19

***Uncovering Neurocognitive Links between Alzheimer’s Disease and Depression in Mid-Life to Early Aging***

The specific aims of this project are: 1) to compare symptoms of depression and characteristics of internally oriented thought across middle-aged adults with and without a first-degree family history of late-onset AD, and 2) to develop novel, dynamic neurocognitive markers of depressive symptoms in cognitively healthy middle aged to early older-aged adults.

Role on Project: co-investigator

## ***Biographical Sketch***

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

### **Education/Training**

<b>Institution &amp; Location</b>	<b>Degree</b>	<b>Year(s)</b>	<b>Field Of Study</b>
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, live cell imaging, 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 aging brain as well as Alzheimer’s disease. The focus of my lab is on the molecular genetic association and biomarker discoveries linked to neurodegenerative diseases as well as cognitive performance in healthy aging individuals. 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 (5 full-time employees; 2 postdoctoral fellows, 1 graduate student, 1 Masters-level lab technician, and 1 Bachelors-level lab technician totaling over 15 years of experience in my laboratory) and bioinformatics (3 full-time employees; 1 Research Assistant Professor, 1 Masters-level, and 1 Bachelors-level totaling over 13 years of experience in my laboratory) personnel and I have a demonstrable publication track record in both general areas of research. My laboratory has current expertise in the techniques and approaches required for successful execution of the proposed work as well as experience in multidisciplinary team-based science.

### **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. Balak C, Belnap N, Ramsey K, Joss S, Devriendt K, Naymik M, Jepsen W, Siniard AL, Szelinger S, Parker ME, Richholt R, Izatt T, LaFleur M, Terraf P, Llaci L, De Both M, Piras IS, Rangasamy S, Schrauwen I, Craig DW, Huentelman M, Narayanan V. (2018) A novel FBXO28 frameshift mutation in a child with developmental delay, dysmorphic features, and intractable epilepsy: A second gene that may contribute to the 1q41-q42 deletion phenotype. *Am J Med Genet A*. 176:1549-1558.
2. Lessel D, Schob C, Küry S, Reijnders MRF, Harel T, Eldomery MK, Coban-Akdemir Z, Denecke J, Edvardson S, Colin E, Stegmann APA, Gerkes EH, Tessarech M, Bonneau D, Barth M, Besnard T, Cogné B, Revah-Politi A, Strom TM, Rosenfeld JA, Yang Y, Posey JE, Immken L, Oundjian N, Helbig KL, Meeks N, Zegar K, Morton J, The Ddd Study, Schieving JH, Claasen A, Huentelman M,

- Narayanan V, Ramsey K; C4RCD Research Group, Brunner HG, Elpeleg O, Mercier S, Bézieau S, Kubisch C, Kleefstra T, Kindler S, Lupski JR, Kreienkamp HJ. (2018) De Novo Missense Mutations in DHX30 Impair Global Translation and Cause a Neurodevelopmental Disorder. *Am J Hum Genet.* 102:196. doi: 10.1016/j.ajhg.2017.12.016.
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  $1 \times 10^{10}$  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 iPSC 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. 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.
2. 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.
3. Hua J, Craig DW, Brun M, Webster J, Zismann V, Tembe W, Joshipura K, Huentelman MJ, Dougherty ER, Stephan DA. SNIPer-HD: improved genotype calling accuracy by an expectation-maximization algorithm for high-density SNP arrays. *Bioinformatics*. 2007 Jan 1;23(1):57-63.
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. Quinn JF, Patel T, Wong D, Das S, Freedman JE, Laurent LC, Carter BS, Hochberg F, Van Keuren-Jensen K, Huentelman M, Spetzler R, Kalani MY, Arango J, Adelson PD, Weiner HL, Gandhi R, Goilav B, Putterman C, Saugstad JA. (2015) Extracellular RNAs: development as biomarkers of human disease. *J Extracell Vesicles*, 4:27495.
2. Laurent LC, Abdel-Mageed AB, Adelson PD, Arango J, Balaj L, Breakefield X, Carlson E, Carter BS, Majem B, Chen CC, Cocucci E, Danielson K, Courtright A, Das S, Abd Elmageed ZY, Enderle D, Ezrin A, Ferrer M, Freedman J, Galas D, Gandhi R, Huentelman MJ, Van Keuren-Jensen K, Kalani Y, Kim Y, Krichevsky AM, Lai C, Lal-Nag M, Laurent CD, Leonardo T, Li F, Malenica I, Mondal D, Nejad P, Patel T, Raffai RL, Rubio R, Skog J, Spetzler R, Sun J, Tanriverdi K, Vickers K, Wang L, Wang Y, Wei Z, Weiner HL, Wong D, Yan IK, Yeri A, Gould S. (2015) Meeting report: discussions and preliminary findings on extracellular RNA measurement methods from laboratories in the NIH Extracellular RNA Communication Consortium. *J Extracell Vesicles*, ;4:26533.
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 MyBibliography

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

## Research Support

Aging Foundation Grant 20170175                      Padilla (PI)                      9/1/17-11/20/19

### ***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 AG031581                      Reiman (PI)                      5/1/28-3/31/19

### ***Brain Imaging, APOE & Preclinical Course of Alzheimer's Disease***

Dr. Huentelman will lead a team for this grant that will perform generation and analysis of exome sequencing and hypothesis-driven SNP genotyping data.

Role: Co-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

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 Consortium (ADHS) Huentelman/Reiman 7/1/18-6/30/20

***AARC FY 19 & 20: Alzheimer's Projects***

This grant is a collection of collaborative research projects focused on the better understanding and earlier diagnosis of Alzheimer's disease.

Role: Principal Investigator

***Necroptosis as a novel mechanism of neurodegeneration in Alzheimer's disease***

The ultimate aim of this project is the discovery of novel candidate risk factor genes using a multi-omic approach, determining relationships among genetic epigenetic modifications, and expression of specific transcripts Alzheimer's disease.

Role: Co-Investigator

FA8650-11-C-6159 Broderick (PI) 7/1/18-12/31/19

Wright State Applied Research Corporation

***RFP WSARC-17-00751 Revolutionary Intelligence***

Role: Co-Investigator

1UH2/UH3TR000891 Huentelman/Jensen (PI) 8/1/13-7/31/19

***exRNA signatures Predict Outcomes after brain injury***

Role: Principal Investigator (Multi

## ***Biographical Sketch***

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

### **Education/Training**

<b>Institution &amp; Location</b>	<b>Degree</b>	<b>Year(S)</b>	<b>Field Of Study</b>
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 a recording device called the Electronically Activated Recorder (EAR). As the developer of the EAR method, a naturalistic observation sampling method, I have extensive experience in the administration of the EAR, the coding of the sound files, and the management and analysis of the EAR data. Further, I have extensively published about and given workshops on the method. I joined the faculty of the Psychology Department of the University of Arizona in 2004 and I am now a tenured full professor. I am also an adjunct faculty in Family Studies and Human Development and the Department of Communication and an affiliated investigator at the Arizona Cancer Center and the Evelyn F. McKnight Brain Institute. My prior collaborative EAR research has been funded by, among other sources, the American Cancer Society and 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).

### **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 MyBibliography**

[https://www.ncbi.nlm.nih.gov/sites/myncbi/1TS90\\_ozwnkQD/bibliography/54270729/public/?sort=date&direction=ascending](https://www.ncbi.nlm.nih.gov/sites/myncbi/1TS90_ozwnkQD/bibliography/54270729/public/?sort=date&direction=ascending)

## Research Support

NIMH RO1 MD008940

Stone: PI

9/25/14 – 5/31/19

***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 – 2/28/20

***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
University of California, Los Angeles, CA	Postdoc	2007	Psychoneuroimmunology

### Personal Statement

I am an Associate Professor of Clinical Psychology at the University of Arizona, and I began in Fall, 2019 as 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. 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. Currently, I mentor or co-mentor 7 graduate students, 3 international MD/PhDs, and 1 postdoctoral scholar in my lab. I serve as the mentor an F31 NRSA award to my graduate student, and as co-mentor for several NIA K awards (subsequent to my own prior K award). Service to my academic department, as well as national and international professional societies, has been largely focused on mentoring and training. I recently served on the Council for the American Psychosomatic Society (APS), where I inaugurated the annual Health and Behavior International Collaborative Award, to enable trainees (graduate students, residents, post-doctoral fellows) to attend international laboratories and gain skills not available at their home institution. Additionally, I organize the Cousin's Center Global Outreach Award, which assists an applicant residing in a developing nation to attend the APS Annual Meeting each year. In addition to pending grant funding (see below), I am author of a forthcoming popular press book by HarperCollins, *The Grieving Brain*.

### 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 (a).

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.

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.

## Complete list of published work in MyBibliography

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

[frances.o'connor.1/bibliography/40699290/public/?sort=date&direction=descending](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 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 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 B and 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. PMID: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. PMID: 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. PMID: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, PMID: 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 B and 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 3 receptor-expressing neurons in the median preoptic nucleus modulate heat-dissipation effectors in the female rat. *Endocrinology*, 156:2552-2562.

## Research Support

NIA RO1 AG047887

Rance (PI)

8/15/14 – 4/30/19

### ***Role of Preoptic NK3R Neurons in the Estrogen Modulation of Body Temperature***

This grant explores how preoptic neurons that express the neurokinin 3 receptor participate in the neural circuits regulating body temperature. Our goal is to provide information related to mechanism of menopausal flushes. \$1.5 million total award.

Role on Project: PI

NIA R21 NS099468

Teske (PI)

2017 - 2019

### ***Pre-clinic model for sleep deprivation-induced obesity and hedonic intake due to noise exposure***

Role on Project: co-investigator

## 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 utilizing various MRI methods including functional MRI, ASL perfusion, voxel-based morphometry, and high resolution diffusion tensor imaging. My research on the neural basis of memory has focused on understanding the hippocampal processes mediating autobiographical and semantic memory, how memory changes across the adult lifespan, how those changes relate to brain structure and function, and the early prediction of Alzheimer's Disease. Recent studies using morphometric analyses and diffusion imaging have investigated factors that influence individual differences in age-related cognitive function, including genetic markers, obesity, hypertension, and anti-inflammatory drug use. As a clinical neuropsychologist, I work with individuals and families who are coping with chronic and progressive diseases that effect cognitive functioning, including multiple sclerosis, Parkinson's disease, and Alzheimer's disease. I teach undergraduate and graduate level courses in memory, neuropsychology, neuroanatomy, cognitive neuroscience, and MRI methods. I have been very active in mentoring programs at the University of Arizona

1. 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.
2. Ryan L, Walther K, Bendlin BB, Lue L-F, Walker DG, and Glisky EL. (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.
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(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

Recently, my colleagues and I published a theoretical article that combines evidence from human cognitive neuroscience and animal models to build an integrative model of age-related memory changes. The model 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. Burke SN, Gaynor LS, Barnes CA, Bauer RM, Bizon JL, Roberson ED, and Ryan L. (2018). Shared Functions of Perirhinal and Parahippocampal Cortices: Implications for Cognitive Aging. *Trends Neurosci.* 41(6):349-359.

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, and Ryan L. (2011) Remembering all that and then some: Recollection of autobiographical memories after a 1-year delay. *Memory* 19(4), 406-15.
2. Nadel L, Winocur G, Ryan L, and Moscovitch M. (2007) Systems consolidation and hippocampus: Two views. *Debates in Neuroscience*, 4, 55-66.
3. Nadel L, Ryan L, Hayes S, Gilboa A, and Moscovitch M. (2003) The role of the hippocampal complex in episodic long-term memory. In T Ono, G Matsumoto, R Llinas, A Berthoz, R Norgren, H Nishijo, and 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, and 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. Ryan L, Lin CY, Ketcham K, and Nadel L. (2010) The role of medial temporal lobe in retrieving spatial and nonspatial relations from episodic and semantic memory. *Hippocampus*, 20(1),11-8.
2. Greenberg DL, Keane MM, Ryan L, and Verfaillie M. (2009) Impaired category fluency in medial temporal lobe amnesia: The role of episodic memory. *Journal of Neuroscience*, 29(35), 10900-10908. PMID: PMC2761020.
3. Ryan L, Hoscheidt S, and Nadel L. (2008) Time, space, and episodic memory. In E Dere, A Easton, J Huston, and L Nadel (Eds.). *Handbook of Episodic Memory Research*.
4. Ryan L, Cox C, Hayes S, and Nadel L. (2008) Hippocampal activation during episodic and semantic memory retrieval: Category production and category cued recall. *Neuropsychologia*, 46, 2109-2121.

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

1. Ryan L and Walther K. (2014) White matter integrity in older females is altered by increased bodyfat. *Obesity (Silver Spring)*, 22(9):2039-46.
2. Ryan L, Walther K, Bendlin BB, Lue L-F, Walker DG, and Glisky EL. (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.
3. Walther K, Bendlin BB, Glisky EL, Trouard TP, Lisse JR, Posever JO, and Ryan L. (2011) Anti-inflammatory drugs reduce age-related decreases in brain volume in cognitively normal older adults. *Neurobiology of Aging*, 32(3), 497-505.
4. Walther K, Birdsill AC, Glisky EL, and Ryan L. (2010) Structural brain differences and cognitive functioning related to body mass index in older females. *Human Brain Mapping*, 31(7), 1052-64.

## Complete list of published work in MyBibliography

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

## Research Support

Arizona Alzheimer's Consortium, ADHS

Ryan (PI)

7/1/19 – 6/30/20

### ***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 on Project: PI

Arizona Alzheimer's Consortium, ADHS

Ryan (PI)

7/1/18 – 6/30/19

### ***A Novel Model of Medial Temporal Lobe Functions: Implications for Aging and Memory***

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

Role on Project: PI

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

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 W, Kossut M, and Wilson RC. (In revision) A causal role for right frontopolar cortex in directed, but not random, exploration. eLife.

### 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.

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

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.

## Research Support

NIA R56 AG06188

Runyon (PI)

7/1/19 – 6/30/20

### ***Thinking About Sweat: Sweat biomarker correlates of physical and mental effort***

This grant uses infrared imaging of sweat pores in combination with mass spectroscopy of sweat to probe the effect of physical and mental effort on sweat processes

Role on Project: co-PI

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 – 4/30/19

### ***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)

NIA P30 AG019610

Reiman (PI); (Wilson Pilot Project PI) 7/1/17 – 6/30/19

### ***The Neural Substrates of Explore-Exploit Decisions in Old Age***

The purpose of this pilot study is to understand the neural systems underlying explore-exploit decisions and how these systems change in old age and with cognitive decline.

Role on Project: PI

## ***Trainees***

### **Postdoctoral**

Monica Chawla, Ph.D. (Barnes)

Area of Interest: Immediate early gene expression in aging in the rat

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 involved in working memory and their decline with age in a non-human primate model of aging

Derek Huffman, Ph.D. (Ekstrom)

Area of Interest: Decoding body-based neural codes underlying human spatial navigation using fMRI

Waitsang (Jane) Keung, Ph.D. (Wilson)

Area of Interest: Age-related changes in exploration and exploitation

Adam Lester, Ph.D. (Barnes)

Area of Interest: Spatial computations made by the entorhinal cortex and how this changes in aging rats (Ph.D. received fall 2018)

Candice 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

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.

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 and Allen)

Area of Interest: Brain network underpinnings of emotion and cognition, and relevance to aging and mental health

Pradyumna Bharadwaj (Alexander)

Area of Interest: Applications of multimodal brain imaging in the study of cognitive aging

Yu-Chin Chen (Chou)

Area of Interest: Repetitive TMS treatment for people with MCI

Sarah Cook (Wilson)

Area of Interest: The effect of top-down processing on perceptual decision making

Andrea Coppola (Andrews-Hanna, Sbarra)

Area of Interest: Intersection between healthy relationships and healthy minds

Lindsey Crown (Cowen)

Area of Interest: Neural basis of Parkinson's disease and Neural synchrony involved in memory functions

Mary Katherine Franchetti (Alexander)

Area of Interest: Effects of physical activity and sleep on cognitive and brain aging

Nathaniel Gallegos (Ryan )

Area of Interest: Genetic family history in ad

Dan Hill (Cowen)

Area of Interest: How the frontal cortex alters dopamine release in aging (PhD received January 2019)

Deanna Kaplan (Mehl and O'Connor)

Area of Interest: Naturalistic study of how everyday behaviors and social interactions impact health and well-being.

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.

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

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

Quentin Raffaelli (Andrews-Hanna)

Area of Interest: Cognitive neuroscience of memory, creativity, and spontaneous thought

Eva Robinson (Ekstrom)

Area of Interest: Neural basis of 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

Ariana Stickel (Ryan)

Area of Interest: Brain imaging, genetics, and cognitive changes in normal older adults (Ph.D received 2019)

Mark Sundman (Chou)

Area of Interest: Development of image-guided rTMS protocols

Alma Tejeda (Mehl)

Area of Interest: Psychological aspects of natural language use; linguistic markers of aging

Emily Van Etten (Alexander)

Area of Interest: Effects of healthy aging on memory and brain structure

Siyu Wang (Wilson)

Area of Interest: The neural correlates of exploration and exploitation

Aubrey Wank (Grilli)

Area of Interest: Brain and autobiographical memory changes associated with normal aging and Alzheimer's disease (Master's degree received 2018)

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)

Area of Interest: Effects of intergenerational interactions in young and older adults

## *Clinical / translational programs*

Drs. Meredith Hay and Lee Ryan (both EMBI Affiliate Faculty) are conducting a study to evaluate the safety and efficacy of angiotensin 1-7 to enhance cognitive function in participants undergoing coronary artery bypass graft surgery. Many older individuals undergo this surgical procedure and report negative effects on their cognition as a result. The hypothesis is that this drug will result in a decrease in brain inflammation and microglia activation in these individuals, which was predicted on the basis of preclinical animal experiments conducted at the UA. If the hypothesis is supported in this trial, the researchers will apply to conduct further tests and extend this type of trial for additional indications.

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 recently received notification that The University of Arizona Center for Innovation in Brain Science has received a \$37.5 million federal grant to research 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 trials:

2018-2019      A Randomized, Double-Blind, Placebo-Controlled, Two-Cohort Parallel Group Study to Evaluate the Efficacy of CAD106 and CNP520 in Participants at Risk for the Onset of Clinical Symptoms of Alzheimer's Disease. (Generation 1) Protocol # CAPI015A2201J. Novartis. Total grant: \$100,702 / patient. 2% salary support, 2% effort.

2018-2019      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.

# 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: \$378,525 (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 (R01 AG031581)  
Sponsor: National Institute on Aging  
Project Dates: May 2014 – March 2020  
Subaward Amount: \$14,630 (current year)

PI: Alexander, Gene E. (Multi-PI: Cohen, Woods, Marsaki, Alexander)  
Project: Augmenting Cognitive Training in Older Adults – The ACT Grant (R01 AG054077)  
Sponsor: National Institute on Aging  
Project Dates: July 2016 – June 2021  
Subaward Amount: \$255,352 (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 (current 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:	October 2019 – September 2021
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:	May 2018 – April 2020
Subaward Amount:	\$60,000 (project period)
Univ. Arizona PI:	Andrews-Hanna, Jessica (PI: Bryan)
Project:	Enhancing Function in Later Life: Exercise and Function Network Connectivity
Sponsor:	National Institutes of Health
Project Dates:	July 2017 – June 2019
Subaward Amount:	\$15,232 (current year)
Pilot PI:	Andrews-Hanna, Jessica (co-I: Grilli)
Project:	Uncovering Neurocognitive Links between Alzheimer’s Disease and Depression in Mid-Life to Early Aging (P30 AG019610)
Sponsor:	National Institutes of Health (ADC Pilot Award)
Project Dates:	July 2018 – June 2019
Subaward Amount:	\$46,050 (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 2020
Award Amount:	\$736,431 (current year)
PI:	Barnes, Carol A.
Project:	Cell Assemblies, Brain Adaptation and Cognitive Aging (R01 AG050548)
Sponsor:	National Institute on Aging
Project Dates:	September 2015 – May 2020
Award Amount:	\$516,626 (current 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 (current year)
PI’s:	Barnes, Carol A. and Huentelman, Matt J. (co-I: Okuno)
Project:	CATT: Development and Application of a Neuronal Cell Activity-Tagging Toolbox (RO1 AG049464)
Sponsor:	National Institute on Aging
Project Dates:	September 2014 – May 2019
Award Amount:	\$300,969 (current year)

Subcontract PI: Barnes, Carol A. (PI: Stern)  
Project: Collaboratory on Research for Cognitive Reserve and Resilience (P30 AG061421)  
Sponsor: National Institute on Aging  
Project Dates: October 2018 – September 2021  
Subaward Amount: \$18,945 (current 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 (current 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 (current year)

PI: Brinton, Roberta  
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: \$146,898 (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: \$309,287 (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: \$2,070,810 (current year)

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

PI:	Brinton, Roberta
Project:	Allopregnanolone a Regenerative Therapy for Alzheimer's: FDA-Required Toxicology (U01 AG047222)
Sponsor:	National Institute on Aging
Project Dates:	June 2018 – June 2019
Award Amount:	\$215,348 (current year)
PI:	Brinton, Roberta
Project:	Perimenopause in APOE4 Brain: Accelerated Myelin Catabolism for Fuel
Sponsor:	Alzheimer's Association
Project Dates:	May 2017 – April 2020
Award Amount:	\$249,280 (current year)
Pilot PI:	Chou, Ying-hui
Project:	Use of TMS and fMRI Measures to Assess the Risk of Conversion of MCI to Dementia (P30 AG019610)
Sponsor:	National Institute on Aging (ADC Pilot Award)
Project Dates:	July 2017 – June 2019
Subaward Amount:	\$46,050 (project period)
Co-Investigator:	Chou, Ying-hui (PI: Witte)
Project:	Transcranial Acoustoelectric Imaging for High Resolution Functional Mapping of Neuronal Currents (R56 AG061888)
Sponsor:	National Institute on Aging
Project Dates:	September 2019 – September 2020
Amount:	\$8,566 (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 2020
Award Amount:	\$458,236 (current year)
Co-Investigator:	Cowen, Stephen (PI: Witte)
Project:	Transcranial Acoustoelectric Imaging for High Resolution Functional Mapping of Neuronal Currents (R56 AG061888)
Sponsor:	National Institute on Aging
Project Dates:	September 2019 – September 2020
Amount:	\$12,849 (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 2020
Amount:	\$115,541 (Cowen component)

Subcontract PI: Cowen, Stephen, L.  
 Project: Restoring Functional Connectivity Following TBI (R01 NS084026)  
 Sponsor: National Institute of Neurological Disorders and Stroke  
 Project Dates: February 2014 – January 2019  
 Award Amount: \$20,413 (current year)

Subcontract PI: Cowen, Stephen, L.  
 Project: High Density, Miniaturized, Zero Switching, Stimulation and Recording Headstage for Small Animals (R44 MH114776)  
 Sponsor: National Institute of Neurological Disorders and Stroke  
 Project Dates: August 2019 February 2020  
 Award Amount: \$50,683 (current year)

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

Subcontract PI: Ekstrom, Arne  
 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 – June 2022  
 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 2020  
 Award Amount: \$347,985 (current year)

PI: Fernandez, Fabian  
 Project: Programming the Aged Circadian Clock with Flashes of Precision Light  
 Sponsor: Science Foundation Arizona  
 Project Dates: November 2019 – November 2022  
 Award Amount: \$297,000 (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 AG06027)  
 Sponsor: National Institute on Aging  
 Project Dates: April 2019 – March 2021  
 Award Amount: \$76,750 (project period)

Co-investigator:	Mehl, Matthias (PI: Stone)
Project:	Reducing Implicit Verbal and Nonverbal Bias toward Hispanic Patients (R01 MD008940)
Sponsor:	National Institute on Minority Health and Health Disparities
Project Dates:	September 2014 – May 2019
Award Amount:	\$90,000 (current year)
Subcontract PI:	Mehl, Matthias (PI: Nugent)
Project:	Reducing Implicit Verbal and Nonverbal Bias toward Hispanic Patients (R01 MD008940)
Sponsor:	National Institute on Minority Health and Health Disparities
Project Dates:	September 2014 – May 2019
Award Amount:	\$90,000 (current year)
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 (current year)
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 – August 2021
Award Amount:	\$14,100 (current year)
Co-investigator:	O'Connor, Mary-Francis (PI: Palitsky)
Project:	Untangling the Health Influence of Religion in Bereavement: The Role of Affect (R13 AG066368)
Sponsor:	Society for Scientific Study of Religion
Project Dates:	July 2018 – September 2019
Award Amount:	\$3,000 (project period)
PI:	Rance, Naomi E.
Project:	Role of Preoptic NK3R Neurons in the Estrogen Modulation of Body Temperature (R01 AAG047887)
Sponsor:	National Institute on Aging
Project Dates:	August 2014 – April 2019
Award Amount:	\$302,094 (current year)
Co-I:	Rance, Naomi E. (PI: Teske)
Project:	Pre-Clinical Model for Sleep Deprivation-Induced Obesity and Hedonic Intake Due to Noise Exposure
Sponsor:	National Institute of Neurological Disorders and Stroke
Project Dates:	July 2017 – June 2019
Award Amount:	\$169,601 (current year)

Co-investigator: Ryan, Lee (PI: Sweitzer; co-I's: Bedrick, Hay, Khalpey, Konhilas, Ryan)  
Project: Evaluation of the Safety and Efficacy of Angiotensin 1-7 to Enhance Cognitive Function in Participants Undergoing Coronary Artery Bypass Graft (CABG) Surgery (UO1 HL131014)

Sponsor: National Heart, Lung, and Blood Institute  
Project Dates: March 2017 – February 2021  
Award Amount: \$546,197 (current year)

PI: Ryan, Lee (co-I's: Alexander, Andrews-Hanna, Arce, Barnes, Chen, Chou, Gaffney, Grilli, Khanna, Rodgers, Saranathan, Weinkauff, Zhou)  
Project: Arizona Alzheimer's Consortium State-Funded Projects  
Sponsor: State of Arizona, DHS  
Date: July 2019 – June 2020  
Amount: \$600,000 (project period)

PI: Ryan, Lee (co-I's: Alexander, Barnes, Brinton, Chen, Edgin, Gaffney, Glisky, Grilli, Guzman-Perez, Khanna, Saranathan, Su, Trouard, Yin)  
Project: Arizona Alzheimer's Consortium State-Funded Projects  
Sponsor: State of Arizona, DHS  
Date: July 2018 – June 2019  
Amount: \$600,000 (project period)

PI: Wilson, Robert C. (co-I's Alexander, Andrews-Hanna, Chou)  
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: \$339,230 (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)

Pilot PI: Wilson, Robert C. (co-I: Chou)  
Project: The Neural Substrates of Explore-Exploit Decisions in Old Age (P30 AG019610)  
Sponsor: National Institute on Aging (ADC Pilot Award)  
Date: 7/1/17 – 6/30/19  
Award Amount: \$46,041 (project period)

## ***Educational programs focusing on age-related memory loss***

Barnes was probably the first person in the United States (and the world) to develop a ‘true Gerontology’ course that covered the entire spectrum of this discipline. The course was designed for senior undergraduates and graduate students from many disciplines – with the first class being taught when she was at the University of Colorado, Boulder in 1984. Barnes has taught this course almost yearly since then, and still teaches this course at the University of Arizona – it has had the same name for these 35 years – “Gerontology: A Multidisciplinary Perspective”.

Barnes, together with other University of Arizona faculty in the Department of Psychology began to develop in 2018 an on-line on Gerontology Certificate program focused on “Best Practices for Caregivers: Providing Quality Care and quality of Life for Older Adults”. The Fundamental “first course” in this program will be fashioned after Barnes’ upper level course in terms of content areas covered, and then there will be a number of other courses to follow, to allow students to customize their learning experience to best suit their interests, or professional specialty.

**Graduate Certificate Program:** The graduate certificate in Gerontology is designed to provide a broad overview of the field of aging, while offering targeted information directly applicable to individuals working with an aging population. In this series of courses, the University of Arizona’s renowned scientists and clinicians will discuss research-supported principles and information that are translated into practical applications for anyone working with older adults, in order to enhance the quality of life for older adults and caregivers alike.

The certificate program consists of a minimum of five courses taught in an enhanced interactive online format that gives students an exceptional educational experience with the freedom to work from anywhere, on your own schedule. Each course requires approximately 40 hours to complete. Students begin the program with an introductory core course, Fundamentals of Gerontology. The remaining four courses can be selected from the list of available options listed below.

### **Fundamentals of Gerontology**

This course provides a broad overview of the social, cultural, psychological, cognitive, and biological aspects of aging, as well as a look into the challenges faced by aging adults, their families, their caregivers, and their communities.

### **Cognitive and Psychological Aspects of Healthy Aging**

This course explores healthy aging with an emphasis on understanding how aging affects the quality of life for older adults through changes in cognitive functioning, mental health, personality, and adjustment. Students will learn facts and myths about aging and how caregivers can help optimize well-being among older adults.

### **Relationships and Aging in a Social-Cultural Context**

In this course, students will discuss social and cultural influences on aging, including social support, sexuality, and family dynamics, as well as the impact of an increasingly older population for society.

### **Dementias and Chronic Conditions in Older Adults**

This course focuses on dementias and other chronic conditions commonly experienced by older adults, how these disorders impact daily functioning, and the warning signs that an individual may need additional care. Students will learn about the most recent advances in the assessment and treatment of cognitive and mental health disorders among the elderly.

### **Caring for Aging Adults and their Caregivers**

This course covers basic concepts in the therapeutic care of aging adults with an emphasis on self-care and stress-management for older adults and caregivers alike. Topics include therapeutic

communication, managing depression and stress, and coping with death and loss.

### **Elder Care: Law, Policy, and Elder Mistreatment**

The course explores the intersection of law, policy, and elder abuse and neglect. Students will discuss legal and ethical issues relating to older adults. They will also learn about risk factors of abuse, perpetrator profiles, current approaches to elder abuse prevention, and legal responsibilities for reporting suspected abuse.

## ***Collaborative programs***

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

The Director, Associate Director, and Affiliate Faculty of the Evelyn F. McKnight Brain Institute at the University of Arizona have many collaborative interactions among themselves and other Institute faculty in Tucson and with other McKnight Brain Institutes. In addition, we have extensive collaborations with faculty inside the University of Arizona, across the state, across the country, and around the world. Some of these interactions have resulted in publications. These are listed in the summary of scientific achievements since last year section at the beginning of this report. I have explicitly included only those publications that have direct or potential relevance to the aging brain and memory. From the review of our progress in that section, it is evident that we are extremely collaborative, as well as extremely productive. We will resubmit the U19 Precision Aging Network grant to NIA in the coming year. 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.

## ***Most important scientific achievements this year***

There were many significant findings published this year, each of which contributes to our understanding of the aging brain and memory loss that occurs during the aging process. I have reviewed a selection of the accomplishments of the Director and Associate Director's laboratories, as well as those of our affiliate members in the synopsis found under the section "Summary of scientific achievements since last report".

## ***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 five RO1 grants and one postdoctoral training grant. She submitted two new RO1s last year and is submitting two competitive renewals in the coming year that will support her rodent and nonhuman primate work on the biological basis of memory decline in aging.

During the past year Barnes submitted a proposal for a U19 grant entitled "Precision Aging Network: Closing the Cognitive Healthspan, Human Lifespan Gap" for the submission deadline. The proposal was an enormous undertaking, with ~40 individuals participating. It did get reviewed, but it did not quite meet the pay line. Barnes is the PI of this U19 grant, and the Associate Directors of the grant are all Tucson EMBI Affiliate Faculty (Brinton, Hay, Huentelman and Ryan). The five of us, plus Paul Worley (our collaborator from Johns Hopkins) met with Molly Wagster, Jonathan King and Dallas Anderson at NIA last November to discuss strategies for a resubmission. They encouraged us to go forward with the revision and have helped us focus on areas that were of concern to the reviewers.

The most challenging issue was one of feasibility of recruiting the diverse set of participants into the face-to-face experiments – it was simply not possible to conduct pilot experiments on the main study before we received funding.

We received extremely exciting news from the University of Arizona President's office last summer that notified us that we could apply for pilot support from his Strategic Initiative fund to mount a study to collect preliminary data for our U19 resubmission. Our proposal was positively reviewed last year, the funds are just now being released, and we have begun to hire Program and Project coordinators, get our protocols finalized and IRB approvals in place to begin recruiting participants in Tucson beginning February 1, 2020. Barnes has also applied to the McKnight Brain Research Foundation to request support for a pilot study at the Miami U19 site, that is under consideration. If we had preliminary data from two locations, the resubmission will be even stronger.

The U19 resubmission date is September 25, 2020. We are already working very hard on revisions, and this will continue over the next year as we collect the preliminary data necessary to prove feasibility and improve the clarity of our written document. We are anticipating a positive outcome for this important effort.

## ***Additional notes***

**Were any funds used for a Prohibited Purpose during the report period?**

No

**Do you recommend any modification to the Purpose or mandates in the Gift Agreement?**

No

**Did all activities during the report period further the Purpose?**

Yes

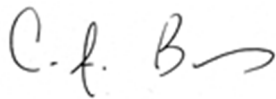
### **Negative Events**

N/A

### **Technology transfer**

Nothing to report

Respectfully Submitted,

A handwritten signature in black ink, appearing to read "C.A. Barnes", with a stylized flourish at the end.

C.A. Barnes, Ph.D.

Regents' Professor, Psychology, Neurology and Neuroscience

Evelyn F. McKnight Chair for Learning and Memory in Aging

Director, Evelyn F. McKnight Brain Institute

Director, Division of Neural Systems, Memory and Aging