Reducing Risk for Alzheimer's Disease in High-Risk Women through Yogic Meditation Training

Study Protocol

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INTRODUCTION AND SPECIFIC AIMS

Abstract:
Almost two thirds of individuals in the United States living with Alzheimer's disease (AD) are women (Snyder et al., 2016). Several factors may account for the increased risk of AD in women, including genetic susceptibility (Chêne et al., 2015; Snyder et al., 2016), increased rates of heart disease (K. A. Lin, Choudhury, Petrella, & Doraiswamy, 2015), stress and anxiety (Burke, Cadet, Alcide, O'Driscoll, & Maramaldi, 2017; McLean & Anderson, 2009), premature "wearing out" of brain connectivity (Snyder et al., 2016), hormonal factors (Manly et al., 2000; Viña & Lloret, 2010), as well as increased risk of insomnia (Burke et al., 2017; Ohayon, 2002), bereavement (Martikainen & Valkonen, 1996), and depression (Burke et al., 2017) in late life. Respiration is closely linked to cardiovascular health and has been found impaired in AD (Billinger, Vidoni, Honea, & Burns, 2011; Burns et al., 2008; Sasano et al., 2002). While conscious control of the heart is difficult to achieve, respiratory control combined with body movement can be used to modulate cardiac functioning (Bhavanani, Ramanathan, & Madanmohan, 2015). Preventative measures such as mind-body interventions may help to reduce risk in women at high risk of developing AD (i.e., those with high cerebrovascular risk and subjective memory complaints). Mind-body interventions may be particularly beneficial for improving quality of life, cognitive functioning, and cardiovascular health in women at risk for AD. Previous research in our lab has demonstrated the efficacy of mind-body interventions in improving cognition, mood, resilience, and quality of life in older adults with amnestic mild cognitive impairment (MCI) (B. P. Acevedo, Pospos, & Lavretsky, 2016; Eyre et al., 2016; Eyre et al., 2017; H. Yang et al., 2016). *To date, no such studies have targeted women with increased cardiovascular risk for AD.* We propose to investigate the efficacy and neurobiological mechanisms of response to a mind-body yogic meditation program for improving cognition, mood, cardiovascular and respiratory health, and overall quality of life in adult women at elevated risk for developing AD.

Specifically, we aim to investigate the neurobiological mechanistic response of women to memory enhancement training (MET) compared to combined Kundalini yoga (KY) and Kirtan Kriya (KK, *a Kundalini yoga meditation*) through a randomized study targeting women with high AD risk. For the purposes of this study, women with high risk for AD are defined as women with high cardiovascular risk (Ho, Pinsky, Kannel, & Levy, 1993; Truelsen, Lindenstrom, & Boysen, 1994) and subjective memory complaints. The methodology for this study is based on our study of individuals with MCI randomized to either combined KK+KY or to memory enhancement training (MET) (B. P. Acevedo et al., 2016; Eyre et al., 2016; Eyre et al., 2017; H. Yang et al., 2016). Compared to MET, KK+KY demonstrated short- and long-term benefits in executive functioning, as well as broader effects on depressed mood and resilience. The positive outcomes of this study suggest that KK+KY may be a promising intervention for reducing risk for AD in women. Our study sample will consist of 100 women over the age of 50 with high risk of developing AD. Participants will be randomized to 12 weeks of either KK+KY or MET. ***The primary outcome*** *is memory performance.* ***Secondary outcomes*** *include executive functioning, brain structure and connectivity. The benefit of interventions will be determined at 12 weeks and at 6- and 12- month follow-up.* The proposed study will test the mechanisms and efficacy of the proposed interventions to improve memory and cognitive performance, mood, resilience and quality of life in older women, with the purpose of reducing AD risk in this population. We will use the proposed model to develop preventive interventions for women at high-risk for developing AD.

Introduction:

Alzheimer disease (AD) is an increasingly widespread, fatal neurodegenerative disease that is largely resistant to current attempts to slow its progression. Substantial evidence points to a significant health disparity in rates of Alzheimer's disease (AD) in women, suggesting that female gender may be an inherent risk factor for the development of AD. Currently, nearly two-thirds of individuals within the United States living with AD are women. In her 60s, a woman's lifetime risk for developing AD is one in six, compared to a one in 11 risk for men. Furthermore, among adults with mild cognitive impairment, women's cognitive abilities appear to decline roughly twice as fast as those of their male counterparts (Chêne et al., 2015). As such, it is essential that we characterize specific risk factors unique to women and determine whether these factors are amenable to intervention. This

population-specific knowledge will improve our ability to target factors that place women at particularly high risk for AD.

Risk Factors
For years, the observation that women develop AD in disproportionate numbers to men was explained by women's longer (four to five years longer, on average), life spans - and that age is the number-one risk factor for the disease. As science progresses, several additional factors have been identified which likely contribute to this health disparity.

First, neuroanatomy research suggests that women have a higher ratio of white matter to grey matter volume compared to men, which may lead to greater susceptibility to cognitive impairment (van den Heuvel et al., 2004). Rate of accumulation of beta-amyloid, a brain plaque proposed to play a role in AD, also differs between sexes, and may also contribute to the increased rates of AD observed in women (Snyder et al., 2016). In addition, women may experience higher cardiovascular burden than men in older age, potentially leading to microstructural differences in women that make their brains more vulnerable to AD. Researchers further suggest that because men are more likely to die from heart disease in middle age than women, those who live past the age of 65 may have healthier hearts that offer protection against dementia (K. A. Lin et al., 2015). Indeed, the Framingham Heart Study suggests that sex differences in cardiovascular risk among men and women in late-life may in part explain the higher rates of AD among women (K. A. Lin et al., 2015). AD and cardiovascular disease share several risk factors, including obesity, diabetes, and high cholesterol.

Women may also have increased genetic risk for AD compared to men. In a study of more than 8,000 people, researchers at Stanford University found that women who carry the ApoE4 genetic variant, which increases AD risk (as well as risk for cardiovascular disease), were more than twice as likely to go on to develop the disease than women without the gene. They found that male carriers, on the other hand, only had a slightly increased risk when compared with men who didn't have the gene (Altmann, Tian, Henderson, & Greicius, 2014). Other studies have shown that not only does ApoE4 increase a woman's risk for developing AD, but that it also increases the severity of dementia in those who develop it (Snyder et al., 2016; van den Heuvel et al., 2004). On brain scans and tests of cognitive performance, women with the gene have shown greater brain atrophy and worse memory performances compared to men with the same gene (Snyder et al., 2016).

AD has further been associated with abnormal respiratory functioning. For example, multiple studies have found impaired blood pressure responses to the Valsalva maneuver and impaired heart rate responses to the handgrip task (challenges for the autonomic nervous system) in AD (Jensen-Dahm et al., 2015). Other impairments included inspiratory and expiratory pressure, increasing the risk for more severe respiratory complications, and exercise-related cardiorespiratory functioning, including oxygen consumption and minute ventilation (Billinger et al., 2011; Burns et al., 2008; Sanches et al., 2014). A 29-year longitudinal study in originally healthy women found that poorer respiratory functioning in midlife was associated with an increased risk of developing AD later in life (Guo et al., 2007). Moreover, studies in young, healthy participants have demonstrated that the presence of the APOE-e4 allele is associated with abnormal brain and neurovascular functioning, blood pressure, heart rate and end-tidal CO_2 (Filippini et al., 2009; Suri et al., 2015). Respiration is closely linked to, and can affect cardiovascular functioning (Sasano et al., 2002). For instance paced breathing at 5.5 breaths per minute can increase heart rate variability and enhance feelings of relaxation in healthy individuals (I. M. Lin, Tai, & Fan, 2014).

It's possible the APoE4 genetic variant may present an increased risk for AD in women because of how it interacts with estrogen. Researchers believe that estrogen may have neuroprotective properties, as well as provide protection in the context of AD, particularly when it comes to defending cells against amyloid-beta toxicity (Viña & Lloret, 2010). As women undergo menopause, they experience declines in their level of estradiol, a form of estrogen produced by the ovaries that may have an impact on the brain. As such, cognitive changes and declines are common complaints during this time in a woman's life (Mitchell & Woods, 2011). In fact, data suggests that nearly half of all postmenopausal women report noticeable symptoms of cognitive decline,

including difficulties with memory, attention, and concentration. Women also share cognitive complaints during the transition itself. And it is possible the loss of estrogen support at this time is responsible (Morrison, Brinton, Schmidt, & Gore, 2006).

One study, published in Neurology, looked specifically at the relationship between estradiol level and AD. It found that women with AD were four to six times more likely than women without AD to have estradiol levels less than 20 pg/mL. This finding suggests that estrogen levels decline more significantly for women in whom AD develops (Manly et al., 2000). Additional studies have looked at a more general connection between menopause and incidence of AD. For instance, a study of 31 postmenopausal women found that women with the most menopausal symptoms demonstrated reduced functional brain connectivity on fMRI (Vega et al., 2016). In another study involving more than 200 healthy women and men, women scored significantly higher on all categories of memory function in a series of tests, with one noticeable exception. Postmenopausal women performed on par with their male counterparts, and worse than the other women, on tests of information retrieval and initial learning. This suggests menopause, and the hormonal fluctuations associated with it, may impact the frontal areas of the brain involved in learning and executive function. Of note, women in this study who demonstrated the highest estradiol levels also had better memory performance (Henderson, Watt, & Galen Buckwalter, 1996; Tang et al., 1996).

In addition to health and biological factors, women tend to experience unique emotional stressors in late life. While the prevalence of anxiety and depression in women is disproportionately higher than in men across the lifespan, because women live longer than men, they are at greater risk of losing their spouse or partner. Becoming widowed is a risk factor for decreased physical health and depression (Newson, Boelen, Hek, Hofman, & Tiemeier, 2011; Wilcox et al., 2003), each of which in turn are risk factors for dementia. In addition, women are often the primary caregiver for a person with dementia. Women comprise around 60 percent of Alzheimer's caregivers and a third of female caregivers care report providing care around the clock. Importantly, nearly 40 percent of female caregivers say they had no choice in taking on the role, reporting a perceived lack of control which has been identified as an important predictor of depression. Nearly half of all female caregivers report high physical and emotional stress (Shriver). Indeed, research has demonstrated that caregiving has a significant impact on all levels of physical and mental health, cognition, and well-being, including increased risk for AD.

The unique emotional stressors to which women are exposed in late life may also make women more susceptible to cardiovascular events compared to men. One recent study of women with stable coronary heart disease found that women are more susceptible to mental stress-induced myocardial ischemia (Vaccarino et al., 2016). Another study showed that women appear to be at greater risk for blood clots under stress than men due to greater collagen-stimulated platelet aggregation responses after stress (Samad et al., 2014). In this same study, men were more likely than women to show changes in traditional physiological markers, such as blood pressure, suggesting that this added cardiovascular risk for women may not be captured by traditional screening measures.

Proposed Intervention

Enhancing cognitive function, especially memory in women with high AD risk (i.e., high cardiovascular risk, subjective memory complaints) may prevent or delay onset of AD. Numerous studies have observed that people who are physically active are less likely than sedentary persons to experience cognitive decline and dementia in later life. Weuve and authors (Weuve et al., 2004) reported that higher levels of physical activity over two years was associated with improved cognitive scores among the 18,766 women enrolled in the Nurses' Health Study. Similarly, Abbott and authors (Abbott, 2004) reported that men who walk at least 2 miles a day are 1.8 times less likely than sedentary men to develop dementia over a follow-up period of 6 years. Subsequent prospective studies have confirmed that physical activity is associated with reduced incidence of dementia (Larson et al., 2006; Podewils, 2005) and demonstrated an association between physical activity and cognitive function even when exercise is limited to later life (van Gelder et al., 2004).

Several epidemiological studies and randomized controlled trials have demonstrated the benefits of exercise to cognition (Baker et al., 2010; Hamer & Chida, 2009; A. F. Kramer et al., 1999; Lautenschlager et al., 2008;

Masley, Weaver, Peri, & Phillips, 2008; Okumiya et al., 1996; Scherder et al., 2005; van Uffelen, Chinapaw, van Mechelen, & Hopman-Rock, 2008; Weuve et al., 2004; Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001) and a meta-analysis reported that physical activity is associated with improvements in attention, processing speed, and executive function in older adults with or without cognitive impairments (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008; P. J. Smith et al., 2010; van Uffelen, Chinapaw, van Mechelen, & Hopman-Rock, 2008). RCTs have found that the benefits of physical activity on cognitive function in older adults with MCI include general cognitive function, executive function and glucometabolic and hypothalamic-pituitary-adrenal axis responses (Baker et al., 2010; Lautenschlager et al., 2008; Scherder et al., 2005; van Uffelen et al., 2008).

We designed the present randomized trial to test whether 12 weeks of supervised weekly Kundalini yoga class and a brief daily home meditation practice can improve cognitive function among older women with high AD risk compared to weekly classes of memory training with daily homework. Our choice of interventions is based on prior studies of mind-body exercise in older adults that revealed robust cognitive benefit, as well as our own studies of this intervention compared to cognitive memory training in older adults with MCI. Kundalini yoga has also been observed to impact the frontal lobes, likely due to increased cerebral blood flow (Lavretsky et al., 2013b).

The primary outcome will be memory performance at 12 weeks (i.e., immediately post-treatment).

Secondary outcomes include measures of executive functioning and changes in brain structure and connectivity.

Specific Aim 1: To evaluate effects of Kundalini Yoga+ Kirtan Kriya (KK+KY) and Memory Enhancement Training (MET) on memory performance in women with high AD risk.

Hypothesis 1: Improved memory performance will be observed in women receiving KK+KY and MET at 12 weeks compared to baseline.

Specific Aim 2: To test the efficacy of KK+KY vs. MET for improving executive functioning including working memory.

Hypothesis 2: KK+KY will improve performance in executive functioning to a greater extent than MET.

Exploratory Aim 3a: To test the effects of MET vs. KK+KY on structural and functional connectivity and task-related activation for working and episodic memory.

Hypothesis 3a: Compared to MET, KK+KY will be associated with greater improvement in connectivity in regions associated with working and episodic memory.

Exploratory Aim 3b*:* To test the effects of MET vs. KK+KY on levels of cellular and genomic markers of inflammation, telomerase activity level, and telomere length after 12 weeks and at 6 and 12 month follow-up.

Hypothesis 3b: Compared to MET, KK+KY will be associated with decreases in cellular and genomic markers of inflammation and increases in telomerase activity level and telomere length after 12 weeks and at 6 and 12 month follow-up.

Exploratory Aim 3c*:* To explore whether KK+KY results in reduced cardiovascular risk factors compared to MET, and whether this effect will correlate temporally with changes in fMRI measures and clinical outcomes.

Exploratory Aim 3d*:* To explore whether KK+KY results in greater subjective and objective interoceptive awareness (as assessed by breath counting accuracy) compared to MET, and whether these effects will correlate temporally with changes in fMRI measures.

Future directions of this work will include developing specific mind-body interventions for women at risk for AD to prevent or delay of conversion to dementia in this high- risk group.

Background and Rationale:

A look at current research makes it increasingly clear: the odds are stacked against women when it comes to risk for Alzheimer's disease (AD). With one in six women in her 60s developing Alzheimer's disease, identifying effective preventative interventions is increasingly important. In addition, while modern biomedicine has made great strides in defining and understanding disease, the objective characterization of healthy aging, particularly

among women, remains elusive. Health requires the integration – across multiple time and spatial scales – of control systems, feedback loops, and regulatory processes that enable an organism to function and adapt to the demands of everyday life. Aging can be associated with progressive multi-system declines, often leading to decreased physical and cognitive function and reduced adaptability to stress (J. D. Lipsitz, Gur, Albano, & Sherman, 2011; L. A. Lipsitz, 2006). Because of the complex nature of aging processes, present reductionistic methods may not be adequate for defining good health or healthy aging. Due to its capacity to characterize complex dynamics within and between physiological systems, the emerging field of complex systems biology and its array of quantitative tools show great promise for improving our understanding of aging, monitoring senescence, and providing biomarkers for evaluating novel interventions, including traditional mind–body exercises, that treat age-related disease and promote healthy aging (Goldberger, 2006).

Aging, cognition, and the use of mind-body interventions for prevention of cognitive decline in women. The general consensus that cognitive abilities decline with advancing age is supported by several studies that have delineated that older adults perform more poorly on multiple tests of cognitive performance as compared to younger adults (Prakash et al., 2012). These differences appear to be particularly large for tests that emphasize executive functioning, as well as speed of response and attention (Salthouse, 1996; West, 1996). To date, preventive measures against this cognitive decline have been mainly focused on dietary (Hughes et al., 2010; Krikorian et al., 2010; Scarmeas, Stern, Tang, Mayeux, & Luchsinger, 2006), physical (Colcombe et al., 2004; Kramer & Erickson, 2007), and lifestyle (Hultsch, Hertzog, Small, & Dixon, 1999; Lövdén, Ghisletta, & Lindenberger, 2005) behaviors which may increase the ability of adults to maintain their cognitive abilities into late life. However, little research has focused on evaluating mind-body interventions such as yoga and meditation. In the current study, we extend upon observational research demonstrating superior cognitive performance in yogic meditators vs. non-meditators.

Interventions such as yoga and meditation are multi-component mind-body exercises grounded in the holistic model of traditional Indian and Ayurvedic medicine. The explicit goals of targeting multiple physiological and cognitive processes and integrating their dynamics make yoga and meditation particularly well-suited for evaluating the effects on an intervention designed to enhance healthy aging within a systems biology framework. Prakash and colleagues (2011) demonstrated in a cross-sectional study comparing the cognitive performance of meditators (*N*=20) and non-meditators (*N*=20) older than 55 years old, using six neuropsychological tests for assessment of short-term memory, perceptual speed, attention, and executive functioning (Prakash et al., 2012). Vihangam Yoga meditators showed significantly better performances in all tests of attention ($p < .05$) except for the digit backward test, where a trend ($p = .08$) was observed compared to non-meditators.[47] In our pilot study of Kirtan Kriya for stress reduction in older dementia caregivers we found a robust cognitive benefit of meditation compared to relaxation (Black et al., 2013; Lavretsky et al., 2013b; Pomykala et al., 2012). Moss et al (2012) also used an 8-week 12 minute a day Kirtan Kriya meditation program in 15 older subjects with memory problems (Moss et al., 2012; A. B. Newberg, Wintering, Khalsa, Roggenkamp, & Waldman, 2010). The meditation training program resulted in notable improvement trends in mood, anxiety, tension, and fatigue, with some parameters reaching statistical significance. All major trends correlated with changes in cerebral blood flow (CBF). These preliminary efforts point toward potential of using yoga and meditation as cognition enhancing interventions for women who are at high risk for AD.

Kundalini yoga (KY) and Kirtan Kriya (KK) yogic meditation: Kundalini Yoga is a mind-body intervention that has been tested in several studies investigating effects on physical and mental health outcomes (Khalsa, Khalsa, Khalsa, & Khalsa, 2008; Krisanaprakornkit, Piyavhatkul, Kirkwood, Krisanaprakornkit, & Laopaiboon, 2004; Lynton, Kligler, & Shiflett, 2007; Pagnoni & Cekic, 2007; Shannahoff-Khalsa, 2004, 2005). Kirtan Kriya (KK) has been studied in older adults with memory complaints (Khalsa et al., 2008; Moss et al., 2012; A. B. Newberg et al., 2010). Our previous RCT demonstrated a significant effect of KK+KY on cognition and depression, *suggesting that this is a useful approach that may be readily incorporated into future clinical practice (Pagnoni & Cekic, 2007).* KY and KK have also been demonstrated to increase regional brain blood flow (Eyre et al., 2017; A. B. Newberg et al., 2010).

Memory Enhancement Training (MET): Memory training is based on the notion that cognition is plastic in older age (A. Acevedo & Loewenstein, 2007). Traditional memory training interventions facilitate plasticity by teaching people mnemonic techniques involving verbal association and visual imagery and practical strategies that boost encoding and retrieval (Gross et al., 2012; Verhaeghen, Marcoen, & Goossens, 1992). A meta-analysis of 33 clinical trials including data from over 1,500 older adults showed that gains on objective memory tests following memory training are large (i.e. on average, a standardized mean difference from pretest to posttest of .73) compared to the small-medium sized effects for control (.37) and placebo (.38) conditions. A more recent meta-analysis (Gross et al., 2012) of 35 studies reported that memory training effects remain significant after controlling for practice effect. The overall estimate of effect size (the mean standardized difference in pre-post change between memory-trained and control groups) was 0.31 standard deviations (SD); the pre-post training effect for memory-trained interventions was 0.43 SD and the practice effect for control groups was 0.06 SD. Effective mnemonic memory enhancement methods involved visual imagery, verbal associations, story mnemonics, organizational encoding strategies, and the use of multiple techniques, and no specific strategy is better than another (Bjorklund, Schneider, Cassel, & Ashley, 1994; Gross et al., 2012; Stigsdotter & Bäckman, 1989; Verhaeghen et al., 1992; Willis et al., 2006). Benefits from memory training may last from six months to five years (Verhaeghen et al., 1992; Willis et al., 2006). Memory training can transfer to daily life when participants are given homework practice and training in using techniques in daily life and novel situations (McDaniel & Bugg, 2012). Small group interventions, memory education, and relatively short sessions (e.g. 90 minutes or less) are other important components of training programs (Verhaeghen et al., 1992). Memory training also improves subjective memory functioning but effect sizes are smaller (.30) compared to the effect on objective test performance (Floyd & Scogin, 1997). *We chose to implement mnemonic methods over computerized memory training programs because the former have a longer history of implementation in aging populations and have more empirical evidence supporting their use in older adults. The MET program in the current proposal includes evidence-based techniques and approaches to facilitate transfer of new knowledge to participants' everyday lives.*

Telomerase as a biomarker of stress in women with high AD risk: Telomere length (TL) has recently been proposed as a useful 'psychobiomarker' linking stress and disease (E. Epel, Daubenmier, Moskowitz, Folkman, & Blackburn, 2009). Shortened TL and reduced telomerase (the cellular enzyme primarily responsible for telomere length and maintenance) predict a host of health risks and conditions (Blackburn, 2000; E. S. Epel et al., 2004; Serrano, 2004), and new findings suggest they may be regulated in part by psychological stress, stress appraisals, and well-being (E. Epel et al., 2009; E. S. Epel et al., 2004; Ornish et al., 2008). Prolonged psychological stress and depression are also likely to affect telomerase activity, considered a predictor of long-term cellular viability (E. S. Epel et al., 2004). For women in particular, recent stressors (such as the death of a partner, or ongoing caregiver-related distress), may have a strong impact on TL. One study (Putterman et al, 2015) which followed women over the period of one year found an incremental impact of stress on TL, such that for every major life stressor, there was a significantly greater decline in TL. In addition, this study found that health behaviors moderated this relationship, such that women who maintained higher levels of health behaviors appeared to be protected when exposed to stress. In addition, a recent study (Jacobs et al., 2011) linked meditation and positive psychological change to increased telomerase activity, suggesting improvement in TL and immune cell longevity. Additionally, our study of yogic meditation in caregivers over 8 weeks found increased levels of telomerase with yoga and meditation compared to passive listening to relaxing music. This evidence suggests that mind-body interventions may reduce the negative effects of stress on TL, a hypothesis that we will test in the current study.

A. Clinical translation. This project will be the first randomized clinical trial to test the effect of MET versus KK+KY for women who are at high risk for AD. Our behavioral interventions may also offer benefits of reducing polypharmacy, improving physical health, and increasing global well-being. We will investigate whether our interventions affect fMRI and cellular biomarkers of stress, inflammation and long-term cellular viability. Determining the mechanisms of response to KK+KY may easily translate into community care especially designed for older women.

Memory Enhancement Training (MET): As observed in our pilot studies (K. J. Miller et al., 2012), MET appears broadly beneficial for enhancing memory function in older adults with memory complaints and associated symptoms, and may readily be incorporated into future clinical practice. MET was well accepted by participants in our previous trial.

Image acquisition and analysis: We will employ advanced multimodal imaging methods to identify neuroimaging markers linked with disease and treatment outcome to KK+KY. Imaging data will be obtained on a Siemens 3T Prisma system using MRI sequences adapted from the NIH-sponsored Human Connectome Project (https://www.humanconnectome.org) designed for optimal trade-offs between acquisition time, spatial and temporal resolution, where each modality provides unique and complementary information to better evaluate the neurobiological bases of treatment response. Further, we will apply advanced and innovative computational image analysis approaches for integrating data in a novel way, focusing on the aging of the female brain, cognitive decline and plasticity, associations with biomarkers of stress and cognition, and the application of resting state fMRI to examine changes in functional connectivity. *The application of a comprehensive imaging protocol and biomarkers of stress/inflammation for evaluating treatment response may not only advance understanding of the unique mechanisms underlying high AD prevalence among women and intervention-based brain plasticity, but have substantial future impact on clinical practice by providing guidance in delineating biomarkers of treatment response.*

Timeliness: *The use of integrative medicine interventions will be shortly "in-demand" and highly beneficial for the rapidly growing large cohort of aging US "baby-boomers," most of whom are women (US Census Current Population Report-Baby Boomers, 2014, and who have high rates of MCI and dementia. Research has demonstrated that older women adhere to supervised exercise programs such as aerobic exercise and weight training. Thus, we expect that KK+KY may be well received in this population. Determining the efficacy of such interventions for improving cognitive performance in older women at high risk for AD is a research priority.*

B. Approach.

Overview: This proposal incorporates a multidisciplinary investigative team from several centers at UCLA including the Semel Institute (Dr. Lavretsky, PI), the Brain Mapping Center (Dr. Narr), and statistical expertise of other co-investigators from the UCLA Semel Institute (Dr. Siddarth). Below, we have incorporated preliminary data in areas germane to the proposed project: 1) cognition; 2) physical functioning; 3) inflammation; and 4) an fMRI study of the effects of KK in older stressed dementia caregivers.

Preliminary data:

1. Pilot study of KK found increased telomerase activity, increased efficiency of brain metabolism, and decreased gene expression in the inflammatory pathways compared to relaxation in dementia caregivers with mild depressive symptoms. In our pilot randomized controlled trial of 49 depressed family dementia caregivers (mean age 60.3 years (*SD*=10.2)), 39 completed either KK meditation or listening to relaxation music for 12 minutes per day for 8 weeks. Severity of insomnia, depressive and anxiety symptoms, caregiver burden, and coping were assessed at baseline and over the course of the study. The mean HAMD score at baseline was 11.6 (SD=4.1). Telomerase activity was examined in the monocytes before and after the study (Fig 2). Post-treatment, groups significantly differed on the health functioning outcomes (i.e., SF-36 role emotional and energy scale scores), global cognitive measure (MMSE) and measures of attention and executive function (Trails A/B) (p<.05), which was associated with decreased FDG-PET brain metabolism in right inferior frontal lobe (Fig 3).

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Table 1. Intervention effects in the meditation and relaxation study groups.

Change scores	Meditation (N=23) Mean (SD)	Relaxation (N=16) Mean (SD)	F (1,36)*	p-value*	Effect size Cohen's d
Sleep Hours of sleep	0.34 (1.2)	-0.3 (2.7)	3.9	0.05	0.6
PSQI	-2.7 (5.5)	-2.1 (5.1)	2.75	0.05	0.56
Mental health HAM-D	-7.4 (3.7)	-5.3 (4.5)	2.43	0.06	0.51
MCS of SF-36	12.8 (9.7)	6.3 (10.6)	3.87	0.03	0.64
Role emotional scale	33.3 (30.2)	-0.01 (47.2)	7.08	0.005	0.84
Energy scale	19.6 (20.6)	5.0 (16.7)	5.68	0.01	0.78
Cognition MMSE	0.2 (0.7)	-0.9(1.2)	13.79	0.0003	1.12
Trails A time (sec)	-3.6 (10.4)	-1.3 (18.7)	0.32	0.29	0.15
CVLT long delay cued recall	-0.6 (2.4)	-0.8 (2.5)	0.10	0.38	0.08

Figure 1

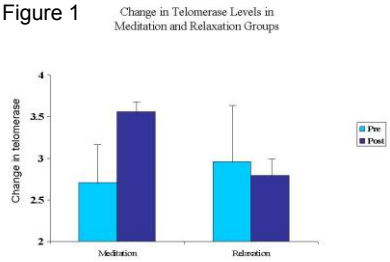
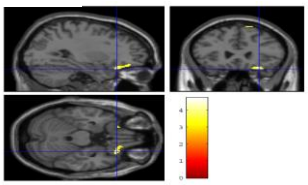


Figure 2



Improvement in coping and cognition correlated with increased telomerase activity in the meditation group (43%) compared the relaxation group (8%), which was significant after controlling for age and the duration of stress (*p*=0.03) (Fig 2). We also performed genome-wide transcriptional profiling in PBMC samples (microarrays) and observed the pattern of increased NF-kappa-B-related transcription of pro-inflammatory cytokines and decreased IRF-related transcription of innate antiviral response genes. *These findings suggest that KK can lead to improved coping and cognition compared to a relaxation intervention in distressed and mildly depressed caregivers. In addition, this effect was accompanied by increases in the levels of telomerase, down-regulation of inflammatory signaling pathways and cellular aging, and* decreased FDG-PET brain metabolism in right inferior frontal lobe (Lavretsky et al., 2013a). Based on our experience with scheduling follow up with caregivers in the pilot study, the emphasis will be on homework meditation time with additional 60 minute yoga classes provided weekly.

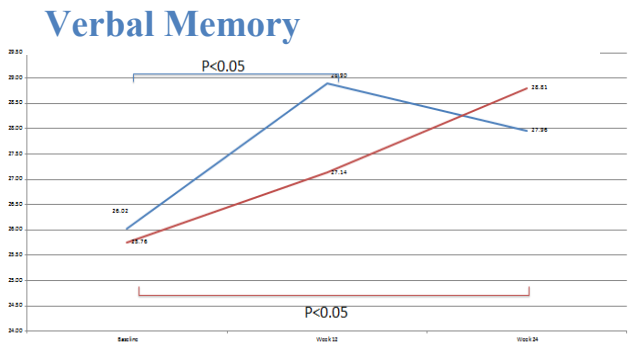
2. A randomized trial of Kundalini yoga in mild cognitive impairment. In our study investigating the effects of Kundalini yoga (KY) training, we randomized older participants (≥55 years of age) with MCI to 12 weeks of either KY or MET. Cognitive (i.e. memory and executive functioning) and mood (i.e. self-reported measures of depression, apathy, and resilience) assessments were administered at baseline, 12 weeks and 24 weeks. No significant baseline group differences were observed in clinical or demographic characteristics. At 12 weeks and 24 weeks, both KY and MET groups showed significant improvement in memory; however, only KY showed significant improvement in executive functioning. Further, only the KY group showed significant improvement in depressive symptoms and resilience (at week 12).

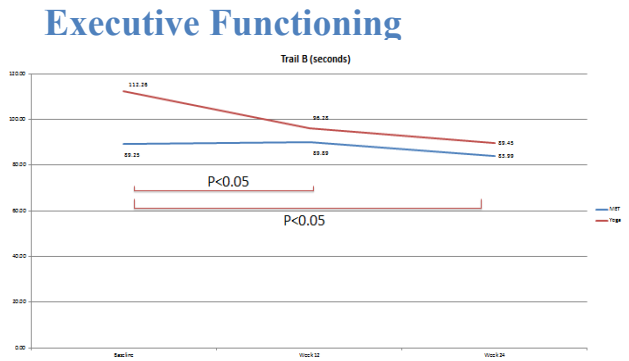
Demographic Characteristics

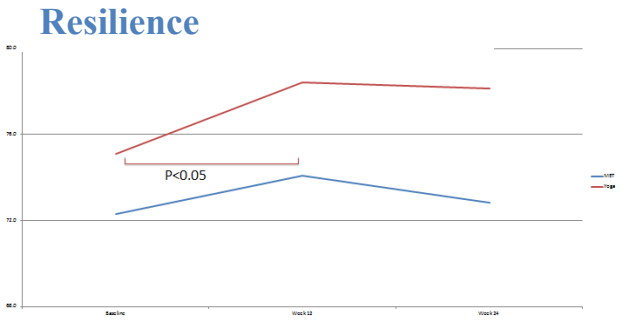
Variable	KY Group	MET Group
	(N=38)	(N=41)
Sex		
Female	25 (65.8%)	27 (65.9%)
Male	13 (34.2%)	14 (34.1%)
Race		
Caucasian	24 (63.2%)	30 (73.2%)
Non-Caucasian	14 (36.8%)	11 (26.8%)
Age (years)	68.1 (8.7)	67.6 (8.0)
Education (years)	17.4 (3.4)	16.7 (3.3)
BMI	26.7 (4.9)	25.1 (4.7)

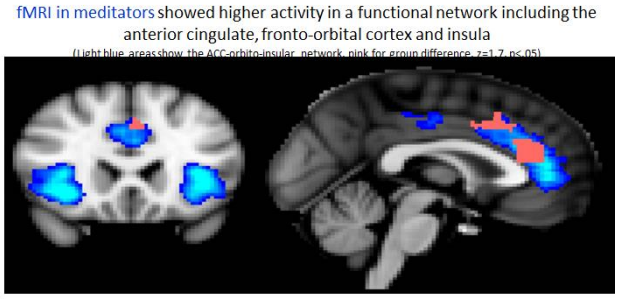
Table 2. Pilot Data: Cognitive Outcome Measures in the Kundalini Yoga and Memory Enhancement Training Groups

	KY Group			MET Group		
Measures	Baseline Mean (SD)	12-Weeks Mean (SD)	24-Weeks Mean (SD	Baseline Mean (SD)	12-Weeks Mean (SD)	24-Weeks Mean (SD
HVLT Total	25.76 (6.20)	27.14 (6.75)	28.81 (6.52)	26.02 (5.42)	28.90 (4.19)	27.96 (5.44)
HVLT Delayed	9.03 (2.70)	9.48 (1.86)	9.73 (2.22)	8.93 (2.26)	9.93 (2.08)	9.60 (2.74)
WMS Immediate Recall	17.19 (9.53)	22.28 (8.15)	23.35 (7.81)	18.27 (7.90)	24.00 (6.49)	24.72 (5.62)
WMS Delayed Recall	5.22 (2.88)	6.72 (1.85)	7.58 (4.30)	6.27 (2.39)	7.27 (1.17)	7.36 (1.47)
Rey-O 3-min	16.01 (5.93)	18.90 (6.85)	18.77 (8.48)	16.80 (5.29)	21.22 (6.76)	22.63 (7.19)
Rey-O 30-min	16.71 (6.36)	19.10 (7.65)	20.31 (7.11)	16.69 (5.34)	20.88 (7.38)	23.60 (6.92)









We also explored the relationship between performance on memory tests and resting-state functional connectivity before and after KY vs. MET. Resting-state (rs-) fMRI was used to map correlations between brain networks and memory performance changes over time. Default mode networks (DMN), language and superior parietal networks were chosen as networks of interest to analyze the association with changes in verbal and visuospatial memory performance. Fourteen KY and 11 MET participants completed the rs-fMRI portion of the study. We observed improved verbal memory performance correlated with increased connectivity between the DMN and frontal medial cortex, pregenual anterior cingulate cortex, right middle frontal cortex, posterior cingulate cortex, and left lateral occipital cortex (see figure on right). Improved verbal memory performance positively correlated with increased connectivity between the language processing network and the left inferior frontal gyrus. Improved visuospatial memory performance correlated inversely with connectivity between the superior

parietal network and the medial parietal cortex. Thus KY may be as effective as MET in improving functional connectivity in relation to verbal memory performance.

Study Design:

a) Rationale for duration of interventions and follow up:

We propose a randomized controlled design for this pilot 12-week trial of the behavioral intervention MET compared to KK+KY for improving cognitive performance and health in women at high risk of AD. We hope to control for nonspecific factors by using a gold standard active control condition that has demonstrated acceptability in this population.

The proposed study will to test whether KK+KY is superior to MET for improving cognitive functioning, health (including cardiovascular factors), and mood in women with high AD risk. All participants will be recruited from the UCLA Women's Cardiovascular Center, UCLA outpatient clinics and the UCLA Longevity Center Program. All participants will be identified as having high AD risk including subjective memory complaints and high cardiovascular risk based on the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (Goff et al., 2014). Follow up of all enrolled subjects at 6- and 12-months (52 weeks total) will allow detection of any continued cognitive or health benefits.

b) Methods for reducing risk of bias:

Participants will be informed prior to enrollment that they will receive one of two evidence-based interventions for improving memory. Descriptions of the study will be designed to minimize risk of possible between group differences resulting from differences in treatment expectancy. Differences in treatment expectancy/ credibility will be tested for at baseline, week 12, and week 24 as specified below. We will also control for the "instructor" effect if several instructors teach classes. The feasibility of weekly yoga/MET classes and homework time was assessed during previous studies and found reasonable for participants to complete (Eyre et al., 2016; H. Yang et al., 2016). Behavioral raters will be blind to group assignment.

1. Study Population: We anticipate screening about 250 subjects to recruit 100 women with subjective memory complaints and high cardiovascular risk based on the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. Participants will be recruited from the women's clinics and geriatric clinics at UCLA as well as the UCLA Longevity Center.

Screening Procedures: Potential participants will receive a telephone screening.. Only participants who are naïve to Kundalini Yoga and Kirtan Kriya or who have not practiced in the past year will be included in the study. Only participants currently not taking psychotropic medications prior to the initiation of the study will be enrolled. A research coordinator will assist with recruitment, screening, and scheduling.

A member of the research team will obtain informed consent from participants prior to the in-person screening. The in-person screening will include a questionnaire to collect demographic information, medications and medical and reproductive history. A physical exam and ECG for screening purposes will also take place at this time.

The baseline visit will include neuropsychiatric and physical examinations and laboratory tests. Though eligibility will be assessed at baseline, participation may be terminated if the subject stops meeting entry criteria. Dementia is an exclusion criterion. We will screen for possible incipient dementia and mild cognitive impairment of the amnestic subtype. This will include reviewing an extensive history and mental status exam together with corroborating information with regard to functional skills. A MMSE score of $\leq$ 23 or an established dementia diagnosis will mandate exclusion. The evaluation for dementia includes: 1) an interview by a trained study staff to identify physical and cognitive limitations; 2) a standard battery of hematologic studies; 3) neuropsychological examination (detailed below); and 4) psychiatric evaluation as detailed above. Adjudication of dementia is based on DSM-5 criteria (Knopman et al., 2001; Lyketsos et al., 2002).

Reducing Risk for Alzheimer's Disease in High-Risk Women through Yogic Meditation Training
Principal Investigator (PI): Helen Lavretsky, M.D., M.S.

Inclusion criteria are:
1) Current subjective memory complaints:
- Frequency of at least once per week
- Able to provide an example of a recent memory difficulty
- Self-reported decline in memory ability since 5-10 years ago
- Self-reported concern about memory problems

2) High cardiovascular risk defined as at least one of the following:
- 7.5 percentile risk or higher using ASCVD risk calculator
- Myocardial Infarction more than 6 months ago
- Diabetes
- Taking medication for blood pressure
- ≥140/90 blood pressure
- Taking medication for lyperlipidemia
- LDL≥160

3) Sufficient English proficiency and the 8th grade or higher reading level as determined by the word reading subtest of the Wide Range Achievement Test-IV (this criterion is necessary in order to ensure ability to participate in MET, which involves reading and writing and has a Flesch-Kinkaid school equivalency of 7th grade)
4) Capacity to provide informed consent

Exclusion criteria are:
1) History of psychosis, bipolar disorder, alcohol/ drug dependence, or neurological disorder
2) Clinically significant depressive symptoms as indicated by a BDI score >17
3) Recent (within three months) surgery, anticipated surgery within next year, or unstable medical condition
4) Any disability preventing participation in MET or KK+KY (e.g., severe visual or hearing impairment)
5) Insufficient English proficiency to participate in either MET or KK+KY
6) Diagnosis of dementia
7) Mini Mental Health Examination score of 23 or below
8) Currently taking any psychoactive medication (stable on antidepressant and not currently depressed is OK)
9) Participation in a psychotherapy that involves cognitive training
10) Current yoga practice (frequency of once/week or greater)
11) Myocardial Infarction within the past 6 months

Screening for dementia. We do not expect that demented patients will be referred for enrollment because referring physicians will be told that dementia is an exclusion criteria. However, in the course of screening, those with a Mini-Mental State Examination score of ≤ 23 or an established dementia diagnosis will be excluded. Adjudication of dementia is based on DSM-5 criteria, as recommended by Knopman and authors (Knopman et al., 2001) as well as Lyketsos and authors (Lyketsos et al., 2002). The PI will hold a consensus conference in cases where eligibility is unclear, where additional information will be reviewed. At the consensus conference, additional information will be reviewed (e.g., collateral information, family history, drug use). If there are clinical features suggestive of dementia, the patients will be referred back to their primary care doctors. We will screen for possible incipient dementia, as verified by assessments. This will include reviewing an extensive history and mental status exam together with corroborating information with regard to functional skills. The evaluation for dementia includes: (1) an interview by Dr. Lavretsky or Dr. Ercoli to identify cognitive limitations; (2) neurological examination (UPDRS); and (3) memory screening using two neuropsychological tests, as detailed below. Adjudication of dementia is based on DSM-5 criteria (Knopman et al., 2001; Lyketsos et al., 2002). If a diagnosis of dementia is discovered, we will refer subjects to the appropriate clinics for dementia care (i.e. geriatric psychiatry and Alzheimer's Disease Center at UCLA). We will offer to discuss the diagnosis with patients and their families, and will offer to discuss this with their physicians.

Screening for MCI. Sensitivity analyses will be conducted to explore whether the efficacy of our interventions is

significantly different in those participants MCI vs. those with only subjective memory complaints. MCI will be defined as follows:

- Clinical Dementia Rating Scale score of .5, OR
- MMSE score greater than 1 SD below age and education-corrected norms (Crum, Anthony, Bassett, & Folstein, 1993), OR
- MMSE score equal to 1 SD below age and education-corrected norms IF at least one of the items missed is a memory item

Measures and Outcomes: All instruments provide a comprehensive assessment of cognition, mood, quality of life, well-being, mindfulness and resilience. Diagnosis will be determined on study entry. *All outcome measures will be administered at baseline, week 12, and 6 and 12 months, or upon early termination. Primary and secondary outcome and safety measures will be administered at each assessment visit*.

The Hopkins Verbal Learning Test-Revised (HVLT-R)(Benedict, Schretlen, Groninger, & Brandt, 1998) delayed recall will be administered at baseline to identify memory impairment.

The Beck Depression Inventory will be used to rule out current clinically-significant depressive symptoms.

Inter-rater reliability for all instruments will be established at the beginning of the trial. Drs. Lavretsky and Ercoli will administer clinician-administered instruments and will be trained to reliability (current inter-rater correlation coefficient (ICC) ≥ 0.9.).

Assessment: Memory performance as determined by neuropsychological evaluation (described below) is the primary outcome of interest. Behavioral outcome assessments will be performed by raters blind to treatment assignment**.**

Table 3. Neuropsychological test battery

Domain	Test	Administration Time
Memory	HVLT (delayed recall)	30 min
	WMS-IV (Logical Memory II delayed recall)	30 min
	Rey-Osterreith Complex Figure 3-min Delay	5 min
Executive Function/ working memory	Stroop Interference	5 min (computerized)
	Trails B	5 min
Attention/ processing speed	Trails A	3 min
	Digit Span	5 min
	Stroop color and word	(no time added)
Language Fluency	CFL/FAS/PRW fluency	3 min
	Animal Fluency	1 min
	Boston Naming Test	15 min
Premorbid Cognitive Function	Wechsler TOPF	5 min

Neuropsychological tests will be administered at baseline and at the 6- and 12-month follow-up. We will use a focused test battery developed by Dr. Ercoli that is highly sensitive to memory deficits. Because memory function is the main target of MET interventions, this will be the primary outcome. Specifically, **the primary**

outcome will be an average of the participant's z-scores on three tests. Two of these tests will be of verbal memory tests: 1) the Hopkins Verbal Learning Test (HVLT) (total and delayed recall scores) (Shapiro et al., 1999), and (2) the Wechsler Memory Scale (WMS-IV) (immediate and delayed) and one will be of visual memory (the Rey-Osterreith Complex Figure 3-minute delay recall) . The secondary outcome measure of executive functioning will include Trail Making B and Stroop Color-Word Interference tests to estimate mental flexibility and inhibition/adjustment of behavior. Tests of language fluency will include Animal fluency and CFL Letter Fluency to assess strategic searching/organization of verbal knowledge, as well as the Boston Naming Test. The battery will also include measures of attention/ processing speed which are commonly impaired in the geriatric population according to prior research by our group (Schneider, Ercoli, Siddarth, & Lavretsky, 2012) and others (Alexopoulos, Kiosses, Klimstra, Kalayam, & Bruce, 2002; Bhalla et al., 2009; Butters, 2004; Favrod et al., 2015; Lockwood, Alexopoulos, & van Gorp, 2002). These tests place significant demand on mental operations that require speed, manipulation and monitoring of information that is in conscious awareness (Trail Making A; Digit Span; Stroop Color and Word). Most of the measures have 2 or 4 alternate forms so that unique forms may be administered to participants during repeat testing. We include both traditional, standardized tests and computerized tests for enhanced sensitivity of the battery to potential intervention effects and so that our results can also be compared with other findings in the literature. In addition to the cognitive outcome measures, we will include the TOPF to estimate pre-morbid cognitive functioning.

Secondary clinical outcome measures will include the Clinical Global Impression- Severity and Improvement scale (CGI)(Busner, Targum, & Miller, 2009) to quantify overall severity and clinical improvement over time (2 min). Subjective memory complaints will be assessed via the 10-item Memory Functioning Questionnaire scale. The Beck Depression Inventory (BDI) (Beck, Steer, & Brown, 1996; Beck, Steer, & Carbin, 1988), a self-assessment scale of depression (5 min), will also be administered, as will the Hamilton Anxiety scale.

Perceived stress will be assessed via the Perceived Stress Scale (PSS), a validated measure of the degree to which situations in one's life are appraised as stressful (5 min) (Cohen, Kamarck, & Mermelstein, 1994).

Resilience: the Connor-Davidson Resilience scale (CD-RISC), a measure of resilience (Connor & Davidson, 2003)(5 min) will be administered. We previously administered this measure in a sample of 337 adults over the age of 60 years; exploratory factor analyses identified the following four factors: grit, active coping self-efficacy, accommodative coping self-efficacy, and spirituality.

Emotion regulation will be assessed via the15-item Mindful Attention Awareness Scale (MAAS) which is designed to assess open or receptive awareness of and attention to what is taking place in the present (Brown, 2003), as well as a 5-item measure of self-kindness (Neff, 2003) and a 6-item measure of rumination (Trapnell & Campbell, 1999), both of which were found to significantly mediate the effects of 6week mindfulness intervention on depressive symptoms (Boyle, Stanton, Ganz, Crespi, & Bower, 2017) (5 min).

Health-Related quality of life will be determined using the Medical Outcomes Study Short Form 36-Item Health Survey (SF-36) (Ware & Gandek, 1994), which comprises 8 scales: physical functioning, role limitations – physical, role limitations – emotional, energy, emotional well-being, social functioning, pain, and general health (15 min).

The 11-item Duke Social Support Scale (Koenig et al., 1993) will be used to assess subjective support (7-item Subjective Support Subscale) and objective support (4-item Social Interaction Subscale). Both subjective and objective social support have been associated with mental and physical health symptoms (sleep disturbance, depressive symptoms, and fatigue) in older adults (Choi, Irwin, & Cho, 2015). Existing research evidence suggests that yoga increases oxytocin (Jayaram et al., 2013); thus, it might be reasonable to expect that women assigned to yoga may experience greater decreases in subjective social isolation than women assigned to MET.

Behavioral regulation/ impulsivity will be assessed via an abbreviated (9-item) version of the Monetary Choice Questionnaire developed by Kirby and Marakovic (Kirby & Maraković, 1995). Because yoga is proposed to increase self-regulation, we expect that the yoga group will improve on this measure to a greater extent than the MET group. A recent study found that older adults with MCI showed significantly greater delay discounting than healthy controls at the small reward magnitude, leading the authors to propose delay discounting as a candidate marker for early dementia (Lindbergh, Puente, Gray, Mackillop, & Miller, 2014). Because these results were only significant at the small reward magnitudes, we are only using the small reward magnitude items (i.e., items for which the delayed reward is less than or equal to $35).

Measures of medical comorbidity. Comprehensive assessment of vascular and nonvascular medical burden will be provided using screening ECG and medical assessments and the review of medical documentation and will include the Stroke Risk Factor Prediction Chart (SRF)(Ho et al., 1993; Truelsen et al., 1994) of the American Heart Association for rating cerebrovascular risk factors (5 min). This scale incorporates eight independent measures; age, presence and treatment of hypertension, diabetes, smoking, coronary vascular disease, atrial fibrillation and left ventricular hypertrophy and provides a score indicating overall risk for cerebrovascular disease and stroke. The Cumulative Illness Rating Scale-Geriatric (CIRS-G)(Salvi et al., 2008) is used for rating the severity of chronic medical illness and burden in 14 organ-systems (15 min).
Family History of Dementia. Because family history of dementia is a known risk factor, this will be assessed in the form of a yes/ no question during the in-person screening. This variable will be added as a covariate and investigated as a possible moderator of treatment effects.

Physical Activity and Meditation Practice. Degree of physical activity and meditation practice will be assessed and used as covariates in analyses of treatment effects. For physical activity assessment, we will be using the short International Physical Activity Questionnaire modified for the elderly (IPAQ-E) (Hurtig-Wennlöf, Hagströmer, & Olsson, 2010).

Pain will be assessed via the Brief Pain Inventory (BPI) Short Form, a validated scale for rapidly assessing the severity of pain and its impact on functioning (Cleeland, 1989).

Safety Evaluations: All participants will be interviewed about their recent history of psychiatric and medical illnesses, psychosocial stressors, and current medications. We will use the UKU Side Effect Rating Scale (Lingjærde, Ahlfors, Bech, Dencker, & Elgen, 1987), a rating scale for monitoring adverse events which will be completed at each assessment visit.

Table 4. Assessment schedule.

Domains of Assessment	Screen	Baseline	Week 6 (after class)	Week 12	Week 24	Week 48
Cognitive						
Clinical Dementia Rating	X					
MMSE	X			X	X	X
Neuropsychological battery		X			X	X
Memory Functioning	X			X	X	X
Psychosocial						
Beck Depression Inventory	X			X	X	X
Hamilton Anxiety	X			X	X	X
Perceived Stress Scale	X			X	X	X

Resilience (CD-RISC Scale)	X			X	X	X
Emotion Regulation	X		X	X	X	X
SF-36 (QOL)	X			X	X	X
Duke Social Support	X			X	X	X
Monetary Choice	X			X	X	X
Medical						
CIRS-G	X			X		
Stroke Risk	X			X		
Clinical ECG	X					
Brief Pain Inventory	X			X	X	
Other						
Demographics / medical and reproductive history and medications	X					
Monitoring for new treatments		X	X	X	X	X
Treatment credibility		X (wk 2)		X		
Clinical Global Improvement				X	X	X
Family history of dementia	X					
Physical Activity and Meditation Practice	X			X	X	X
Adverse reactions		X	X	X	X	X
Cellular Biomarkers						
Telomerase levels		X		X	X	
Telomere length		X		X	X	
Cardiac Biomarkers						
Lipid panel, hsCRP, HbA1c, TSH, electrolytes, CBC		X		X	X	
BP, HR, weight		X		X	X	X
Molecular Biomarkers						
Cytokine gene polymorphisms		X		X	X	
Microarrays (GWAS expression)		X		X	X	
Imaging Biomarkers						
Structural MRI		X		X		
fMRI		X		X		
ANS Biomarkers						

Breathing rate		X		X	X	
End-tidal CO_2		X		X	X	
ECG		X		X	X	
Continuous blood pressure		X		X	X	
Skin face temperature		X		X	X	
Electromyogram		X		X	X	
Spirometry		X		X	X	
Galvanic skin response		X		X	X	
ANS challenges		X		X	X	

Inflammatory biomarkers: Inflammatory signaling will be measured by assay of activation of NF-κB using intranuclear staining and flow cytometric analyses, given its associations with mood (Koo, Russo, Ferguson, Nestler, & Duman, 2010; Pace & Miller, 2009).

Microarray-based genome-wide transcriptional analyses will be used identify the molecular inflammation-related signaling pathways that are plausible candidates for molecular mediators of inflammation (e.g., NF-B) (Cole, 2010; Irwin, Olmstead, & Motivala, 2008; Irwin, Wang, Campomayor, Collado-Hidalgo, & Cole, 2006) and glucocorticoid receptor-related signaling pathways that may underlie increased inflammatory signaling (Cole et al., 2007; G. E. Miller et al., 2008) with measures performed at baseline, week 12, and at 6-months, as described previously (Cole et al., 2007; G. E. Miller et al., 2008). Expression data will be subject to quantile normalization, with differentially expressed genes identified based on False Discovery Rate analyses controlling false positive errors at 5%, and subsequent TELiS bioinformatics analysis of GR target motifs within the promoters of genes up-regulated in KK+KY vs. MET. Confirmatory RT-PCR analyses will be conducted on a subset of 12 differentially expressed transcripts to confirm microarray indications (Cole et al., 2007; G. E. Miller et al., 2008). We will assess the activity **of telomerase level and TL at baseline**, weeks 12 and 6-month follow-up to monitor changes. The protocol will be the same as the one used previously by Jacobs and colleagues (Jacobs et al., 2011). Quantification of telomerase activity will be measured from the extract using the telomeric repeat amplification protocol (TRAP) as previously described (Kim & Wu, 1997) with a commercial kit (TRAPeze®, Chemicon, Temecula, CA). We will assess **other factors related to inflammation** during our baseline assessment and throughout the trial (e.g., alcohol, smoking, BMI, physical activity; use of NSAIDs, and recent infections when samples are collected). This will require 8 tablespoons of blood to be drawn at 3 time points (baseline, 12 weeks, and 6-month follow up).

Sequence #	Sequence type	Acquisition time	Protocol type
1. Localizer			
1.1	Localizer	0:00:09	HCP
1.2	AAHScout	0:00:14	HCP
1.3	Localizer_aligned	0:00:21	HCP
2. T1-weighted image			
2.1	T1w_setter	0:00:02	HCP
2.2	T1w_MPR_vNav_4e	0:08:22	HCP
3. T2-weighted image			
3.1	T2w_setter	0:00:03	HCP
3.2	T2w_SPC_vNav	0:06:35	HCP
4. Resting state fMRI			
4.1	SpinEchoFieldMap_AP	0:00:09	HCP
4.1	SpinEchoFieldMap_PA	0:00:09	HCP
4.3	Cal_800TR	0:00:30	HCP
4.4	rfMRI_REST_AP	0:06:41	HCP
4.5	rfMRI_REST_PA	0:06:41	HCP
5. tfMRI N-back task			
5.1	task fMRI N-back	010:00	HCP
5.2	SpinEchoFieldMap_AP	0:00:09	HCP
5.3	SpinEchoFieldMap_PA	0:00:09	HCP
6. task fMRI face naming			
6.1	task fMRI face naming	0:05:25	HCP
6.2	SpinEchoFieldMap_AP	0:00:09	HCP
6.3	SpinEchoFieldMap_PA	0:00:09	HCP
7. Diffusion-weighted image			
7.1	dMRI_dir98_AP	0:05:38	HCP
7.2	dMRI_dir98_PA	0:05:38	HCP
8. Arterial spin labeling			
8.1	PCASLhr_SpinEchoFieldMap_AP	0:00:09	HCP
8.2	PCASLhr_SpinEchoFieldMap_PA	0:00:09	HCP
8.3	mbPCASL_PA	0:05:29	HCP
9. Magnetic resonance spectroscopy (optional)			
9.1	svs_edit_859G_WS	0:08:40	Siemens
9.2	svs_edit_859G_NWS	0:00:14	Siemens
10. High-resolution hippocampus structure (optional)			
10.1	TSE_HiResHp	0:03:31	HCP
Total time (excluding shimming and set-up)		**1:05:25**	

Imaging Biomarkers: Imaging data will be acquired from each subject **at baseline and at 12- weeks post-randomization** on a Siemens 3T Prisma system using a 32-channel head coil. Each scanning session will last 60 minutes and include 1) high-resolution T1- and T2 weighted structural scans (0.8 mm^3 voxel size) using protocols developed for the Human Connectome Project (HCP) Lifespan Project (www.humanconnectome.org), which will be used for registration and to measure morphometric features as may be included as covariates and used for the detection and quantification of WMHs and CSF; and 2) three separate multiband EPI sequences with enhanced spatial (2 mm^3) and temporal (TR: 720 ms) resolution and anterior-posterior/posterior-anterior (AP/PA) phase encoding to correct for anatomic distortions for the acquisition of rs- and task-related fMRI data used for the examination of working memory processing and functional connectivity. In addition, localizers and

field maps to correct for EPI anatomic distortions will be acquired. The morphometry sequences are optimized for determining brain tissue contrast with reduced distortion (van der Kouwe, Benner, Salat, & Fischl, 2008).

Functional Imaging: *Analysis of rs-fMRI data will determine whether KK+KY leads to plasticity in brain network activity*. To address our hypothesis that *KK+KY versus MET will result in improved executive functioning (working memory)* we will employ the N-back task. During resting periods and tasks, we will also assess physiological measures, including respiratory rate (respiration belt around the chest), GSR (electrodes on the hand), heart rate (pulse-ox), and end-tidal CO2 (nasal cannula).

Working Memory Task. We will use a well-established 2-back version of the N-back task detailed by Barch and colleagues (Barch, Burgess, Harms, Petersen, Schlaggar, Corbetta, Glasser, Curtiss, Dixit, & Feldt, 2013) to elicit neural activation linked with working memory. Participants indicate whether a stimulus presented in the center of the screen is the same or different from the stimulus two trials ago. Button presses record accuracy and response time. This task elicits activation in lateral fronto-parietal cortex and anterior cingulate (ACC) (Barch, Burgess, Harms, Petersen, Schlaggar, Corbetta, Glasser, Curtiss, Dixit, Feldt, et al., 2013), regions implicated in emotion regulation and cognitive control. Though emotion regulation is not directly assessed in this task, activated regions may nevertheless be used as seed regions or reference points for subsequent connectivity analyses.

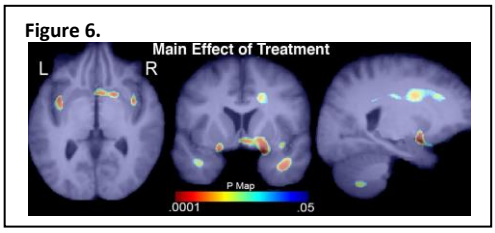
Face-name Association Memory Test. This task is a paired-associates memory task assessing verbal and non-verbal memory (Zeineh, Engel, Thompson, & Bookheimer, 2003). A sequence of faces is presented on the screen together with names. Participants are asked to encode the names of the different face identities in a study period and mentally recall them in later blocks. During the recall blocks, each face is presented together with a name. The subject is asked to indicate by pressing a button whether the association of face and name has been presented during the study period or whether the current presentation constitutes a novel pairing. Both encoding- and retrieval-related neural processes can be investigated using fMRI (Klamer et al., 2017).

Breath Counting Task. The breath counting task will be used to assess interoceptive attention. During this task, participants are instructed to attend to their breathing by counting the number of inhales within a one-minute timeframe. The accuracy of the report has been used as an indicator of interoceptive attention {Herrero, 2017 #3478}. This task will involve 5 trials of one minute each. Previous studies have found that greater accuracy during interoceptive tasks is associated with increased activity in the right anterior insular/ opercular cortex {Critchley, 2004 #3514}.

Resting State-fMRI: During acquisition of rsfMRI data, participants will be asked to remain awake with their eyes open, viewing a static fixation cross. Though resting state connectivity is highly reproducible over time in healthy participants (Damoiseaux et al., 2006), experience-based neural plasticity in resting state connectivity has been shown to occur over periods as short as 2-9 days. To measure cardiac and respiratory signals, a pulse oximeter and respiratory bellows will be fitted to participants prior to the fMRI sessions. Non-neuronal physiological artefacts (including cardiac and respiratory effects) will be eliminated.

Preprocessing and Analysis: Preprocessing of all fMRI data will follow similar workflows using adapted HCP minimal processing pipelines (www.humanconnectome.org). Specifically, preprocessing steps incorporating FSL (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; S. M. Smith et al., 2004; Woolrich et al., 2009) and custom processing modules will include: a) removal of non-brain tissue; b) rigid-body head motion correction; c) spatial smoothing (5-6 mm FWHM); d) demising and high pass filtering using FSL's MELODIC; and d) co-registration of the BOLD and T1 images using the matched bandwidth EPI images for intermediate registration. First-level analysis will include the modeling of activation between task conditions (e.g. 0-back vs. 2-back). Temporal derivatives and the 6 motion parameters will be included as covariates of no interest to improve statistical sensitivity. Second-level (fixed effects) and third-level (mixed effects) analyses will average runs within participants and between groups, respectively. *Longitudinal analysis:* In addition to subtracting changes in

activation between baseline and follow-up scans within individuals for subsequent group comparisons, we will represent fMRI maps as statistical change maps in time. These maps will be presented against the structural template, to determine the effects of structural change, functional change, and their interaction. One sample t-tests will determine whether activation for each individual changes significantly over time. *Task-related connectivity analysis:* To investigate effective "functional" connectivity, we will determine differences in task-dependent functional connectivity between regions-of-interest (ROIs). Using seeds for the hippocampus, ACC and DLPFC, we will investigate within-ROI activity and seed-based connectivity across the brain for working memory load compared to no load (2-back vs. 0-back). Similarly, we will contrast ROI activity and functional connectivity of learned with novel face-name associations. Additionally, encoding-related activity/connectivity will be investigated while subjects study face-name pairs. Group-level FSL FEAT analyses will produce statistical maps indicating voxels throughout the brain showing significantly correlated task-dependent activity with the ROI. Regressors include the ROI (e.g., hippocampus activity), the cognitive variable (0-back vs. 2-back condition and learned vs. novel face-name associations), and their interaction. Higher-level analyses will determine the degree of functional coupling among treatment groups. *Resting state analysis:* After applying preprocessing steps similar to the described above, widely documented independent components analysis (ICA) (De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006; Greicius et al., 2007) using FSL's MELODIC, will estimate the optimal number of components for each subject and to remove components representing artifacts. After low pass filtering (0.1-0.01 Hz) and transformation into atlas space, the best-fit DMN, executive and salience, and fronto-parietal and dorsal attention networks implicated in working memory and cognitive attention network components for a subject will be selected for higher-level group analysis. We will explore components of other networks (Damoiseaux et al., 2006; De Luca et al., 2006). We will also examine voxel correlation within particular networks in follow-up analyses of ROIs (Bluhm et al., 2009; Di Martino et al., 2008; Greicius et al., 2007). Changes in functional connectivity will be quantified by comparing Fisher z-transformed correlation coefficients between ROIs.



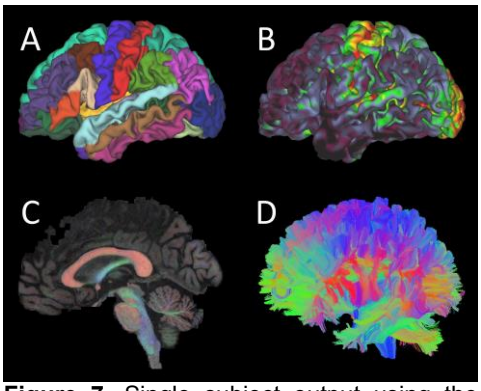


Figure 7. Single subject output using the HCP Minimal Preprocessing Pipelines and BIDS-App as modified for our project. A. Cortical segmentation, B. Myelin maps on reconstructed cortical surfaces, and C. Color-direction FA map and D. Fiber tracking.

Fig 6. ECT-related brain changes with FDR-corrected p-values overlaid on the group-derived MDT.

Structural Imaging. Structural image analysis will incorporate methods refined and validated by project co-investigators and include: 1) volumetric/cortical thickness analysis using automated and manual segmentation, and 2) refined shape/surface structure analyses. In brief, widely used freesurfer (http://surfer.nmr.mgh.harvard.edu/) processing streams that include a) correction for magnetic field inhomogeneities; b) removal of non-brain tissue; c) tissue segmentation; d) separation of the hemispheres and subcortical structures; e) extraction of the white/gray and pial cortical surface and f) initial segmentation of cortical and subcortical ROIs (with manual correction of errors, Figure 7 A) will be used to estimate regional tissue volumes for comparison across treatment groups and time. These analyses will be followed by more refined morphometric analysis to reveal very local changes in the shape/surface structure of the hippocampus and other ROIs as informed by the volumetric results (see below). Procedures include manual segmentation and the use of surface-based mesh modeling and skeletonization methods that have been used to assess local changes in the morphology of the hippocampus, the ACC, and others in the fronto-striatal-limbic system (e.g. amygdala, striatum, DLPFC) and in several clinical groups including and across time in our prior studies (Ballmaier et al.,

2008; Narr et al., 2004; Y. Yang, Raine, Narr, Colletti, & Toga, 2009).

Diffusion tensor imaging: The acquisition of DTI data will be used to measure structural connectivity of white matter within brain networks relating to emotion regulation and stress. We will use HARDI (High Angular Resolution Diffusion Imaging) with anterior-posterior and posterior-anterior phase encoding and 2 different b-values (1500 and 3000) to correct for anatomic distortion and provide greater precision for mapping crossing fibers respectively (see Figure 7 B-D). These sequences will improve reliability and sensitivity for probabilistic tractography to estimate fiber trajectories from regions defined with our other imaging modalities (structural, resting state or task fMRI).

DTI processing: The diffusion preprocessing pipeline performs standard steps for DTI data using FSL, including equalizing intensity of b0s across runs, removing EPI and eddy-current distortions, correcting for motion and gradient nonlinearities, and registration to T1w images. Tractography and other DTI post-processing including tensor fitting (to obtain global and tract-specific measures of fractional anisotropy (FA) and mean, axial and radial diffusivity (MD, AD and RD)) will occur separately, according to published protocols developed by our group (Lyden et al., 2014; Phillips et al., 2009; Reavis et al., 2017)(Lyden et al., 2014; Phillips et al., 2009; Reavis et al., 2017) (Lyden et al., 2014; Phillips et al., 2009; Reavis et al., 2017) and others (Sotiropoulos et al., 2013). For quality control of DTI data, we will utilize custom protocols that include automatic identification of signal drop out due to motion; each individual gradient map will also be inspected to flag other imaging artifacts and noise, and as for structural MRI data will be assigned a 1-4 quality rating. If >10 gradients are assigned a poor quality rating, data will be determined as unusable and if possible, reacquisition will be scheduled.

Arterial Spin Labeling (ASL): A state-of-the-art Simultaneous Multislice echo-planar imaging pseudo-continuous ASL (SMS EPI pcASL) will be used to acquire whole-brain regional cerebral blood flow (rCBF) and arterial transit time (ATT) maps. RCBF is a marker of regional brain function and consists of non-invasive labeling of blood water using the magnetic properties of hydrogen protons to investigate blood volume flow (ml/min) and blood perfusion (ml/100mg of tissue/min). ATT denotes the time it takes for the blood to flow from the labeling region (in the neck area) to the region of interest. rCBF and ATT will be used here as markers for the antidepressant and cognitive enhancement effects of yoga vs. memory training. In particular, since patients exhibit cardiovascular risk factors and cognitive problems, the efficiency of arterial blood supply will be highly informative, both as a biomarker at baseline, and a marker of treatment change. The SMS EPI pCASL sequence will constitute five post-label-delays (PLDs) with the following parameters: TR/TE = 3594/19ms, 60 slices (thickness = 2.3mm with 0.2mm gap in between), FOV = 215 x 215mm, voxel size = 2.5 x 2.5 x 2.5mm , matrix size = 86 x 86, slice acceleration factor=6, PLDs= 200, 700, 1200, 1700, 2200ms. Total scan time = 5min30s.

ASL Processing: Image preprocessing involves motion correction with rigid head alignment and frame-wise displacement (FD) to identify and discard frames reflecting severe motion (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). Subjects with >= 20% of images discarded will be excluded. A principal component analysis (PCA)-based algorithm will be performed to further remove residual motion artifacts and physiological noise in the remaining images. RCBF and ATT will be computed using two methods; weighted-delay (WD) and parameter fitting, described in detail by Wang and colleagues (Wang et al., 2013). The formula (Dai, Robson, Shankaranarayanan, & Alsop, 2012) to compute ATT(δ) from WD using WD is:
1. Weighted-delay (WD):

$$WD = \left[\sum_{i=1}^{5} w(i)\Delta M(i)\right] / \left[\sum_{i=1}^{5} \Delta M(i)\right]$$

Whereby w(i) refers to the PLDs.

2. Parameter fitting method:

$$f(i) = \frac{\lambda \Delta M(i) R_{1a}}{2\alpha M_0 [exp((min(\delta - w(i), 0) - \delta)R_{1a}) - exp(-(\tau + w(i))R_{1a})]}$$

In the fitting method, f(i) is CBF at each individual delay and the final CBF is the mean of the estimated CBF per PLD. The 5 PLDs allow us to estimate CBF and ATT simultaneously using parameters fitting (2). Resulting rCBF and ATT maps will then be co-registered with the T1-weighted structural scan and normalized to the MNI standard space template with subsequent spatial smoothing.

WM Hyperintensities (WMH). The 3D T2-space images will be used to visualize WMHs by employing a semi-automated WMH identifier (Schwarz, Fletcher, DeCarli, & Carmichael). Briefly, WMH burden will be assessed based on the signal intensities of co-registered 3D MEMPR and T2-SPACE images, and population statistics on the spatial distribution and neighborhood structure of WM lesions. With every unit increase in WM burden, we will estimate % reduction in local brain tissue volume. GLM and multiple regression analyses will determine links between WM burden, clinical measures and vascular risk factors in each treatment group that may need to be controlled for.

Integration with Mood and Neurocognitive Measures. To test hypotheses about the relationships between imaging metrics and change in mood and cognition, we will derive domain summary scores for the 3 domains of interest – i.e., mood, memory, and executive functioning. Percent change in the mean Z scores will be calculated for each domain score and entered into analysis. We will first test the specific hypotheses described in the aims using separate GLMs for each MRI method. *Integration of Predictive Variables.* After analysis is complete on the predictive validity of each MRI measure, those that significantly predict remission/relapse or cognitive decline at follow-up will be combined for regression analysis. We will use the best single predictor in each modality. The final analysis will include a step-wise multiple regression analysis of clinical outcomes.

Autonomic nervous system (ANS) and respiratory measures. In order to link genotype and neuroimaging data with respiratory and ANS functioning, we will perform a series of five tests: 1) rest; 2) paced breathing; 3) breath hold; 4) Valsalva maneuver; 5) hand grip. These tasks will provide detailed information about cardiorespiratory functioning. Continuous blood pressure will be assessed using a probe attached to two fingers of the same hand. An additional finger probe will be used to measure the Galvanic skin response (GSR) and chest electrodes will be applied for the electrocardiogram (ECG) and on the hand for an electromyogram (EMG). A respiratory belt around the patient's chest will provide breath rate data and a small probe attached to the cheek will measure changes in face skin temperature. End-tidal CO2 will be measured using a capnometer and spirometry will be used to investigate pulmonary capacity. Verbal instructions will be provided and a computerized task will indicate to the subjects when to begin and end each challenge, for example when to prepare for the breath hold (deep inhale followed by deep exhale and then hold at the top of the next deep inhale). Data will be recorded and time-locked using a BioPac system and associated software, which will also be used to process the data.

Randomization and treatment schedule:
After all screening and baseline test results are reviewed and eligibility criteria are confirmed, patients will sign the informed consent form. Next, participants will be randomized to either MET or KK+KY groups using a computer-generated random assignment scheme, which assigns participants in a 1:1 ratio to each group using a customized module built into the centralized data system. All behavioral raters will be blind to the group assignment, and participants will be asked not to disclose their group assignment to the raters.

Study intervention procedures:
Participants will be randomized to: (1) MET class for 60 minutes per week plus daily homework; or (2) KY class for 60 minutes per week plus daily KK homework. Participants will complete a questionnaire about their treatment expectations after their second class. Follow-up assessments immediately after the intervention (12 weeks) as well as at 24 and 48 weeks will test the effect of the interventions at both short- and long-term follow-up.

Memory Enhancement Training Intervention. Patients will be informed that MET teaches specific memory strategies and has been shown to improve memory in adults with mild cognitive impairment. The standard detailed protocol for MET program is based on evidence based techniques that use verbal and visual association strategies and practical strategies for memory compensation (Gross et al., 2012; Verhaeghen et al., 1992). The MET program is manualized and includes components adapted from other effective memory training programs (Verhaeghen et al., 1992) such as: (1) Education about memory; (2) Preliminary instruction in the basic elements of memory strategies (i.e. "pre-training"); (3) Instruction in specific memory strategies; (4) Home practice with logs to track activity; (5) Addressing non-cognitive factors such as self-confidence, anxiety, and negative expectations; (6) Small (i.e. 10 persons) groups and short (60 min) sessions. The curriculum is divided into 12 weekly sessions which are organized in the same way in which trainers: (1) Document attendance, collect homework completion logs and assess engagement in alternative treatments; (2) Review the previous session's homework in order to reinforce home practice; (3) teach new techniques, reviews, and conduct in-class exercises, (4) assign homework for the upcoming week. Overall, in each session, roughly 15 minutes are devoted to reviewing the homework and 45 minutes is devoted to learning and practicing techniques. Specific techniques include: Visual associative learning strategies for learning faces and names (adapted from McCarty,1980)(McCarty, 1980), verbal associative techniques such as the use of stories to remember lists; organizational strategies (categorizing items on a grocery list); forming good memory habits to recall where one places items, what one has done in the recent past (e.g. locking doors, turning off appliances); and how to remember future tasks (i.e., appointments). Dr. Ercoli, a postdoctoral fellow supervised by Dr. Ercoli, or a masters-level trainee supervised by Dr. Ercoli will teach the MET intervention.

KK+KY intervention:

Kundalini yoga (KY) class will be scheduled for 60 minutes weekly and will be conducted by a certified yoga teacher. The content and structure of the class will be similar across weeks: 1) Tuning in (5 minutes); 2) Warm up (10 minutes); 3) Pranayam (10 minutes); 3) Kriya (20 minutes); 4) Meditation (12 minutes) 5) Shavasana (3 minutes).

Kirtan Kriya (KK). Participants will be asked to engage in 12 minutes of daily KK meditation. Meditations will be guided by standardized CDs distributed to participants that can be practiced at home. The protocol for KK is a standard ancient chanting meditation for the Kundalini Yoga practice as taught by Yogi Bhajan and as utilized in previous studies in older adults (Andrew B. Newberg, Wintering, Khalsa, Roggenkamp, & Waldmanb, 2012). The meditation involves repetitive finger movements or mudras, as well as chanting of the mantra "Saa, Taa, Naa, Maa," meaning "Birth, Life, Death, and Rebirth" first chanted aloud, then in a whisper, and silently for the total of 11 minutes with 1 minute allocated to "tuning in" at the beginning and the final deep breathing relaxation accompanied by the visualization of light.

Alternate treatments. All participants will be medically stable prior to entry into the study protocol. However, if participants engage in alternate treatments, they will be advised to inform the PI. Upon completion of the research procedures, yoga classes will be offered to participants who participated in MET and vice versa.

Treatment expectancy/ credibility. Our study has been designed to promote equal perception of treatment expectancy/ credibility between groups. We will evaluate treatment credibility, expectation for change, and satisfaction after the 2nd session of treatment and at post-intervention using a 10-point Likert scale, as we have done in our pilot study.

Dosing effects. We will distribute and collect home practice logs to determine the relationship between practice and outcomes. The extent to which participants continue to practice skills learned during the intervention period will also be assessed at 6-month and 12-month follow up. As in previous studies, we will also ask participants in both intervention groups to keep a brief weekly journal about any changes they have noticed that they attribute to the intervention. This data will be analyze through qualitative analysis at the completion of the study. **Data analysis.** Primary analyses will be carried out on an intent-to-treat basis; additional analyses considering dropout or other observable post-randomization outcomes will make use of an instrumental-variable analysis framework.

Data will be analyzed using the SAS (v9.4) statistical package. Data will be examined initially to identify issues such as departures from normality, which might suggest the need for transformation (e.g., logarithmic). Demographic variables (e.g., age, gender, etc.) will be compared by treatment group and examined in relation to outcome variables; this would define one possible set of appropriate covariates, if needed. Correlations (a) among outcome measures and (b) among potential covariates will be examined to eliminate redundancy via possible data reduction, e.g., formation of composite scores or selection of single measures from sets of highly inter-correlated variables. Cognitive domain scores will be obtained as follows: for each neuropsychological test, raw scores will be converted to standardized (Z) scores with a mean of 0 and a SD of 1, based on all participants combined. Then, for each of the tests in a cognitive domain, the Z scores will be averaged to create a single Z score per cognitive domain.

The independent samples *t*-test or Chi-square test will be used to compare the demographic characteristics between the MET and KK+KY control group. The effect of intervention over time on the cognitive functions will be investigated in intention-to-treat (ITT) analyses. Measurements will be analyzed using linear mixed models; analyses will assume missing at random with missingness allowed. All models will include random intercepts to account for correlations between the repeated measures for each participant. The fixed components of the models will include effects of group and time and a group X time interaction, with post hoc analyses between times and groups. All statistical significance tests will be two-sided, and an alpha-level of 0.05 will be considered statistically significant for primary analyses and Bonferroni correction will be employed for post hoc analyses.

Primary outcome: The analyses for the memory domain Z scores will use general linear mixed model (GLMM) analysis (e.g., SAS PROC MIXED). The two treatment groups will be compared for time course of cognitive domain z scores the initial endpoint EOT at 12 weeks and 6- and 12-months. Covariates may be included in the model as noted above. As noted above, the primary cognitive domain of interest for this proposal is memory. A separate GLMM as above will be estimated using memory domain z-scores as dependent variables. Executive Function will be examined as secondary outcome measure. Supplementary analyses of the follow-up period will look at the cognitive domain scores by treatment group controlling for values at EOT (post-treatment changes). Objective memory measures will be examined using a similar GLMM.

Exploratory Hypotheses: GLMM models as described above will be used to examine telomerase activity (overall level and TL) and inflammatory measures separately. Relationships between changes in markers of inflammation and telomerase activity to changes in cognitive scores, cognitive domain scores and fMRI measures will be examined using regression models within each group. Transformations of the measures will be performed as necessary.

Power analysis: The power analysis is focused on the primary aim of the study to assess whether the KK+KY and MET groups demonstrate comparable improvement in memory performance. We plan to enroll a total of 100 women in the study, anticipating an attrition rate of at most 10% based on our previous studies. Thus, we will most likely have a total of 90 completers. With a sample size of 45 per group, we achieve 80% power to detect equivalence within a margin of equivalence of 0.62, when the true difference between the means is assumed to be zero. In the PI's previous study using similar interventions on older adults with MCI, a between-group effect size of 0.3-0.4 was observed for the memory measures. In the proposed study, the target population is women with high risk for AD, hence we believe that the proposed sample size will have sufficient power to address the primary hypothesis of the study. With this sample size, we can also expect to detect an effect size of 0.60 at a significance level of 0.05 and 80% power for the secondary outcome measure (executive functioning). We intend to test the secondary outcomes adjusting for multiple comparisons using the Benjamini-Hochberg false discovery rate approach (which is more powerful than the simple Bonferroni correction). Further, we will report results of all proposed analyses and conclusions will be based on the pattern of results.

Data management: Data management and analysis support will be provided by the UCLA Semel Institute Statistical Core (SI-Stat) (Dr. Siddarth). The SI-Stat will provide needed software and technical support with a data manager operating under the supervision of Dr. Siddarth. The SI-Stat has a Dell PC computer network with

automated CD R/W backup and is set up for medium to large-scale data processing and analysis using available commercial database and statistical software. **1. Randomization.** Randomization schedules will be prepared in a masked manner by the statistician. **2. Data submission and quality control.** Data forms will be delivered from the originating location to the central data unit within one week of being generated. When errors, omissions, or unclear information is detected on the paper forms, a copy will be returned for corrections. The data manager will generate monthly reports summarizing missing and incorrect data will be sent to the PI.

Upon receipt of the data, each form will be visually scanned for obvious errors and logged in. The data clerk will perform the data entry and generate a daily and monthly report, and a quarterly patient accrual report. Data entry will be facilitated by 1) having visual screen formats similar to the actual forms; 2) having range boundaries on each field, where appropriate, to be checked automatically as data is entered; 3) having default values incorporated into the data entry system to minimize typing. **3. Data confidentiality.** All data including patient information will be carefully handled and securely stored. Patient study forms will be stored in locked file cabinets and will be accessible only to authorized personnel. A shredder will be used to discard all unwanted study documents. A single computer will be dedicated to this study. Access to the system will be password protected with only authorized persons having knowledge of the password.

Data Sharing and Future Research:
Data from this study will be used for other ongoing or future research projects in the following ways:
-To perform the research
-Share it with researchers in the U.S. or other countries for data analyses
-Use it to improve the design of future studies
-Share it with the sponsor, business partners of the sponsor or
-File applications with U.S. or foreign government agencies to get approval for new drugs or health care products

HUMAN SUBJECTS:

Availability. Participants will be recruited from several settings in order to obtain a representative sample. For previous clinical studies we have successfully targeted recruitment efforts toward elderly patients presenting at geriatric ambulatory care settings with an interdisciplinary focus and community dwelling patients who respond to our community outreach efforts. The vast majority of elderly participants receive care for their mental and physical health in ambulatory care clinics: 1) Geriatric Medicine-Psychiatry clinics within the UCLA Medical Center; 2) UCLA Women's Cardiovascular Health Center 3) The UCLA Memory and Aging Center and the Longevity Center. In addition, we will conduct community outreach efforts and recruitment through advertising in newsletters and local newspapers.

Each of these methods has significantly contributed to ongoing recruitment for other studies in our laboratory. Dr. Lavretsky also has links to the local community of care providers for the elderly and to mental health professionals who could serve as a source of referrals. We anticipate having no competition with other studies for the same study population (i.e., those 50 years and older).

Recruitment. Participants will be recruited, assessed and randomized according to the scientific protocol and the consent procedures approved by the UCLA Institutional Review Board and the Office of Protection of Research Subjects. We project a recruitment period of two years to achieve recruitment of 100 participants. Our current rate of recruitment into antidepressant clinical trials for participants 55 years or older averages about 4-5 participants/month. We anticipate that the incentive to participate will be sufficient since participation includes free MET and KK-KY classes. Data analysis will be performed in year 2. We anticipate the dropout to be about **10% (45 completers per group) in the first 12 weeks, and additional 10% at 6 months and 12 months, leading to 35-36 completers per group at 12 months**.

Table 6. Timeline.

Years of the project	***Activities***
Year 1,	Review assessment instruments; Inter-rater reliability sessions. Develop patient schedule with

Years of the project	*Activities*
months 1-4	the UCLA CRC. Develop patient database with P. Siddarth and research assistants. Start subject recruitment at month 4.
Year 1, months 4-12	Continue recruitment (50 participants).
Year 2	Continue recruitment (50 participants). Conduct inter-rater reliability sessions.

Retention of participants. We have developed several successful strategies for retention of elderly participants. These include an ongoing and continuous process of consent to study procedures, involvement of family members whenever possible, and use of concerned and empathic clinicians and staff. However, it is important to note that our data analytic approach is robust to attrition.

Cohort maintenance. The comprehensive evaluation of participants prior to randomization and entry into the treatment trial is designed to minimize attrition. The evaluation of weekly compliance questionnaires will also alert the PI to potential attrition problems.

Protection of human subjects and other human subject considerations. The procedures involve minimal potential risks. One of the potential findings may be dementia. If dementia is documented during this study, one of the PI's will counsel patients and their families about its significance and prognosis. Additionally, appropriate referrals for counseling and follow up will be made (e.g., UCLA Alzheimer's Center and the local chapter of the Alzheimer's Association). If participants continue to demonstrate significant cognitive impairment despite successful treatment, we will refer them for a more complete neuropsychological evaluation to the UCLA Geriatric Evaluation Clinic (Director Gary Small), or the UCLA Alzheimer's Disease Center (Dr. David Teplow), or other qualified providers in the community in order to rule out the diagnosis of dementia. If a new physical illness is diagnosed, the participants will be informed and their primary physicians will be contacted, or an appropriate referral in the community will be made. If the PI feels that the treatment has been inadequate or adverse effects occur, the primary physicians and/or psychiatrists will be contacted and appropriate recommendations will be made.

Potential benefits for participants include diagnosis and treatment for memory dysfunction. For society, this study may provide a new strategy for improving memory dysfunction in women and may improve our understanding of the impact of other variables (e.g., medical burden and cerebrovascular risk factors) on treatment response.

The MET program will offer the additional benefits of giving participants instruction in and tools for memory enhancement, which may improve their memory functioning. KK+KY will provide benefits of mindful exercise and socialization, which is usually appreciated by our older patients.

Testing procedures also involve minimal potential risks. Blood drawing, though a routine part of general medical examinations, entails a small possibility of such discomforts as bleeding, bruising, lightheadedness, fainting – or, rarely – infection. Neuropsychological testing may induce feelings of failure, frustration, or anxiety. However, our psychometrist is highly experienced in assessing persons with memory impairment and conveys a relaxed and confident attitude. A minority of participants experience anxiety and claustrophobia during MRI scanning. A potential risk of MRI scanning is if the patient has a non-magnet compatible device or if MR unsafe objects are brought into the scanner room. The UCLA Brain Mapping Center is fully compliant with the recommendations of the American College of Radiology standards, screening with an approved questionnaire, dual screening, and strict adherence to safety guidelines regarding devices. Another issue concerns how participants are informed if their MRI scans show an unexpected abnormality. The Brain Mapping Center has a

uniform policy with regard to this which is included in our IRB materials. If an abnormality is detected, a full report is generated, the patient will be individually counseled by Dr. Narr or by Dr. Lavretsky, and the patient will be recommended to follow-up with their physician.

The responsibility for medical, psychiatric, nursing, and social care of participants will remain with the individual's primary physician and psychiatrist. All patients will be followed by a psychiatrist. Should the participant not have a physician in the area, a referral will be made to one in the patient's geographic area. With the subject's consent, the results of their evaluation will be shared with the psychiatrist and primary physician. Subject identities will not be disclosed by publication or any other means.

COVID-19 Restrictions – Enacting March 2020. As of March 2020, UCLA has enacted several restrictions on our campus to prevent COVID-19 contraction and spread. In order to align with these standards, we are giving participants the option to participate virtually through web-based and telephone meetings. This will be offered for any appointment that is able to be completed remotely, as well as for both interventions the study is testing. All remaining portions that are not possible to obtain remotely (e.g., MRI, venipuncture) will be obtained as close to the proposed visit date as possible.

COVID-19 Questionnaire and Assessment. We will also instill a COVID-19 Questionnaire to all active participants to ensure optimal safety reporting and to correlate with current psychiatric measures. This will be administered as a survey, with the responses coming verbatim from the participant. We will also remotely administer HAMA and BDI at the same time point. This visit will only be administered once, but will happen as soon as possible once approved.

Compensation. Because the procedures are time-consuming, participants will receive a $100.00 honorarium for their participation in the trial, which will be disbursed after completion of the 6-month follow-up assessment. Participants will receive an additional $50 for completing the 12-month follow-up. Participants completing fMRI scans will receive $50 per scan. Thus, the maximum amount a participant will be paid for her participation in the trial is $250. In addition, we will offer reimbursement for parking up to $234.00 for 18 visits, including classes.

All files will be kept in locked cabinets, as will copies of the signed informed consent forms to maintain the anonymity of participants and to bar any unauthorized access. The computerized database will be protected through the use of entry codes available only to authorized personnel.

In conjunction with the UCLA-NPI Human Subject Protection Committees (HSPC), as well as with the HSPC in all participating institutions, all legal and ethical safeguards for participants will be implemented. All participants will receive a copy of the Subject's Bill of Rights prior to giving consent to participate and will sign the Informed Consent form approved by the HSPC of UCLA-NPIH and affiliated institutions. They will receive a copy of the consent form.

Potential adverse effects of neuropsychological testing. Some study participants may experience mild frustration or boredom during testing. Clinicians administering neuropsychological tests are experienced in helping participants relax and feel comfortable during testing.

Discontinuation procedures. Discontinuation from the study will be considered if participants experience severe side-effects (rating of 3 or greater on the UKU Side Effect Rating scale). **All severe adverse events will be reported to the participants, their psychiatrist and to their primary physicians and the UCLA IRB within one week of PI's awareness, and within two weeks to the funder.**

All dropouts will be analyzed by the reason for termination and the reasons will be classified as:

1. a) Lack of efficacy; b) Side-effects; c) Lost to follow-up; d) Hospitalization; e) Death; f) Other
2. Relation to the study intervention: a) likely; b) probable; c) unlikely.

Risk/benefit ratio. Benefits from the proposed study outweigh its risks by providing a low-risk behavioral intervention for women with high AD risk factors. We will monitor participants for side-effects. Neuropsychiatric tests carry minimal risk.

The risk of breach of confidentiality is reduced by the following aspects of our protocol: 1) storing records in a locked file, with access available only to the PI and designated project staff; 2) removing identifying information from all data during the data analysis phase of the project; and 3) removing identifying information from all data presented publicly in lectures, seminars, or publications.

Data and Safety Monitoring plan. We will assess safety in each individual case during each visit. The patients will be under continued care of their own physician for monitoring cardiovascular health, mood and medication. In addition, ongoing monitoring of mood and cardiovascular health will be monitored by Dr. Lavretsky and Dr. Horwich, respectively.

The PI will review study progress and ensure that consent documentation is properly obtained and stored. She will also ensure that study coordinators and research assistants are collecting, storing, and disposing of data properly. Key personnel will provide progress reports to facilitate this review. The PI will also review any recent research relevant to the study. The summary reports will provide data on enrollment and adverse events. Adverse events will be monitored using the UCLA Adverse Event and/or Incident Reporting forms (Forms HS-5 & HS-6).

Inclusion of women and minorities.

This study will selectively recruit women as a population of interest. Women are adequately represented in the Memory Clinic population and usually outnumber men (60%). Most participants will not be minority members due to the composition of the population out of which our sample will be drawn. Patients of the Memory Clinic are primarily Caucasian (75%), followed by a minority of African-American (25%), Latino, and other ethnicities. The proportion of minority participants recruited into our previous studies is as follows: African-Americans, 9%; Hispanic, 6%; Asian, 3%; other, 4%. Recently, Dr. Lavretsky has been active in providing outreach lectures, consultations, and advertising to the African-American and Hispanic communities in Los Angeles through the events by the LA County DMH and local publications. At this time, we are confident in our ability to recruit 25% minority participants.

Justification for including women only.

Multiple factors lead us to conclude that a women-only participant pool will be ideal for the current pilot research:

1) As previously mentioned, women are at a significantly greater risk for AD than men.
2) Our experience conducting previous trial suggests that women may be more comfortable participating in women-only yoga classes.
3) Our previous study found that women were more interested in participating in a trial of yoga vs. memory enhancement training (our previous sample was 66% female).
4) fMRI data will be more interpretable if we limit our sample to one sex.
5) The sponsor of study is interested in focusing on women.

References

Abbott, R. D. (2004). Walking and Dementia in Physically Capable Elderly Men. *Jama, 292*(12), 1447. doi:10.1001/jama.292.12.1447

Acevedo, A., & Loewenstein, D. A. (2007). Nonpharmacological Cognitive Interventions in Aging and Dementia. *Journal of Geriatric Psychiatry and Neurology, 20*(4), 239-249. doi:10.1177/0891988707308808

Acevedo, B. P., Pospos, S., & Lavretsky, H. (2016). The neural mechanisms of meditative practices: novel approaches for healthy aging. *Current behavioral neuroscience reports, 3*(4), 328-339.

Alexopoulos, G. S., Kiosses, D. N., Klimstra, S., Kalayam, B., & Bruce, M. L. (2002). Clinical Presentation of the "Depression–Executive Dysfunction Syndrome" of Late Life. *The American Journal of Geriatric Psychiatry, 10*(1), 98-106. doi:10.1097/00019442-200201000-00012

Altmann, A., Tian, L., Henderson, V. W., & Greicius, M. D. (2014). Sex modifies theAPOE-related risk of developing Alzheimer disease. *Annals of neurology, 75*(4), 563-573. doi:10.1002/ana.24135

Angevaren, M., Aufdemkampe, G., Verhaar, H. J., Aleman, A., & Vanhees, L. (2008). Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev, 3*(3).

Baker, L. D., Frank, L. L., Foster-Schubert, K., Green, P. S., Wilkinson, C. W., McTiernan, A., . . . Craft, S. (2010). Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch Neurol, 67*(20065132), 71-79.

Ballmaier, M., Narr, K. L., Toga, A. W., Elderkin-Thompson, V., Thompson, P. M., Hamilton, L., . . . Kumar, A. (2008). Hippocampal morphology and distinguishing late-onset from early-onset elderly depression. *American Journal of Psychiatry, 165*(2), 229-237.

Barch, D. M., Burgess, G. C., Harms, M. P., Petersen, S. E., Schlaggar, B. L., Corbetta, M., . . . Feldt, C. (2013). Function in the human connectome: task-fMRI and individual differences in behavior. *NeuroImage, 80*, 169-189.

Barch, D. M., Burgess, G. C., Harms, M. P., Petersen, S. E., Schlaggar, B. L., Corbetta, M., . . . Van Essen, D. C. (2013). Function in the Human Connectome: Task-fMRI and Individual Differences in Behavior. *Neuroimage, 80*, 169-189. doi:10.1016/j.neuroimage.2013.05.033

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Beck depression inventory-II. *San Antonio, 78*(2), 490-498.

Beck, A. T., Steer, R. A., & Carbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clin Psychol Rev, 8*(1), 77-100.

Benedict, R. H. B., Schretlen, D., Groninger, L., & Brandt, J. (1998). Hopkins Verbal Learning Test Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability. *The Clinical Neuropsychologist (Neuropsychology, Development and Cognition: Section D), 12*(1), 43-55. doi:10.1076/clin.12.1.43.1726

Bhalla, R. K., Butters, M. A., Becker, J. T., Houck, P. R., Snitz, B. E., Lopez, O. L., . . . Reynolds, C. F. (2009). Patterns of Mild Cognitive Impairment After Treatment of Depression in the Elderly. *The American Journal of Geriatric Psychiatry, 17*(4), 308-316. doi:10.1097/jgp.0b013e318190b8d8

Bhavanani, A. B., Ramanathan, M., & Madanmohan. (2015). Single session of integrated "silver yoga" program improves cardiovascular parameters in senior citizens. *J Intercult Ethnopharmacol, 4*(2), 134-137. doi:10.5455/jice.20141228065658

Billinger, S. A., Vidoni, E. D., Honea, R. A., & Burns, J. M. (2011). Cardiorespiratory response to exercise testing in individuals with Alzheimer's disease. *Arch Phys Med Rehabil, 92*(12), 2000-2005. doi:10.1016/j.apmr.2011.07.194

Bjorklund, D. F., Schneider, W., Cassel, W. S., & Ashley, E. (1994). Training and Extension of a Memory Strategy: Evidence for Utilization Deficiencies in the Acquisition of an Organizational Strategy in High- and Low-IQ Children. *Child Development, 65*(3), 951-965. doi:10.1111/j.1467-8624.1994.tb00795.x

Black, D. S., Cole, S. W., Irwin, M. R., Breen, E., St Cyr, N. M., Nazarian, N., . . . Lavretsky, H. (2013). Yogic meditation reverses NF-kappaB and IRF-related transcriptome dynamics in leukocytes of family

dementia caregivers in a randomized controlled trial. *Psychoneuroendocrinology, 38*(3), 348-355. doi:10.1016/j.psyneuen.2012.06.011

Blackburn, E. H. (2000). Telomere states and fates. *Nature, 408*(6808), 53-56. doi:10.1038/35040500

Bluhm, R., Williamson, P., Lanius, R., Théberge, J., Densmore, M., Bartha, R., . . . Osuch, E. (2009). Resting state default-mode network connectivity in early depression using a seed region-of-interest analysis: Decreased connectivity with caudate nucleus. *Psychiatry and clinical neurosciences, 63*(6), 754-761.

Boyle, C. C., Stanton, A. L., Ganz, P. A., Crespi, C. M., & Bower, J. E. (2017). Improvements in emotion regulation following mindfulness meditation: Effects on depressive symptoms and perceived stress in younger breast cancer survivors. *Journal of Consulting and Clinical Psychology, 85*(4), 397.

Brown, K.W. & Ryan, R.M. (2003). The benefits of being present: Mindfulness and its role in psychological well-being. Journal of Personality and Social Psychology, 84, 822-848

Burke, S. L., Cadet, T., Alcide, A., O'Driscoll, J., & Maramaldi, P. (2017). Psychosocial risk factors and Alzheimer's disease: the associative effect of depression, sleep disturbance, and anxiety. *Aging & mental health*, 1-8.

Burns, J. M., Cronk, B. B., Anderson, H. S., Donnelly, J. E., Thomas, G. P., Harsha, A., . . . Swerdlow, R. H. (2008). Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. *Neurology, 71*(3), 210-216. doi:10.1212/01.wnl.0000317094.86209.cb

Busner, J., Targum, S. D., & Miller, D. S. (2009). The Clinical Global Impressions scale: errors in understanding and use. *Comprehensive Psychiatry, 50*(3), 257-262. doi:10.1016/j.comppsych.2008.08.005

Butters, M. A. (2004). Executive Functioning, Illness Course, and Relapse/Recurrence in Continuation and Maintenance Treatment of Late-Life Depression: Is There a Relationship? *American Journal of Geriatric Psychiatry, 12*(4), 387-394. doi:10.1176/appi.ajgp.12.4.387

Chêne, G., Beiser, A., Au, R., Preis, S. R., Wolf, P. A., Dufouil, C., & Seshadri, S. (2015). Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. *Alzheimer's & dementia, 11*(3), 310-320. doi:10.1016/j.jalz.2013.10.005

Choi, H., Irwin, M. R., & Cho, H. J. (2015). Impact of social isolation on behavioral health in elderly: Systematic review. *World journal of psychiatry, 5*(4), 432.

Cleeland, C. S. (1989). Measurement of pain by subjective report. *Advances in pain research and therapy, 12*, 391-403.

Cohen, S., Kamarck, T., & Mermelstein, R. (1994). Perceived stress scale. *Measuring stress: A guide for health and social scientists*.

Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., Cohen, N. J., . . . Elavsky, S. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proceedings of the National Academy of Sciences, 101*(9), 3316-3321. doi:10.1073/pnas.0400266101

Cole, S. W. (2010). Elevating the perspective on human stress genomics. *Psychoneuroendocrinology, 35*(7), 955-962. doi:10.1016/j.psyneuen.2010.06.008

Cole, S. W., Hawkley, L. C., Arevalo, J. M., Sung, C. Y., Rose, R. M., & Cacioppo, J. T. (2007). Social regulation of gene expression in human leukocytes. *Genome Biology, 8*(9), R189. doi:10.1186/gb-2007-8-9-r189

Connor, K. M., & Davidson, J. R. (2003). Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). *Depress Anxiety, 18*(2), 76-82.

Crum, R. M., Anthony, J. C., Bassett, S. S., & Folstein, M. F. (1993). Population-based norms for the Mini-Mental State Examination by age and educational level. *Jama, 269*(18), 2386-2391.

Dai, W., Robson, P. M., Shankaranarayanan, A., & Alsop, D. C. (2012). Reduced resolution transit delay prescan for quantitative continuous arterial spin labeling perfusion imaging. *Magnetic resonance in medicine, 67*(5), 1252-1265.

Damoiseaux, J. S., Rombouts, S., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences, 103*(37), 13848-13853.

De Luca, M., Beckmann, C. F., De Stefano, N., Matthews, P. M., & Smith, S. M. (2006). fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *NeuroImage, 29*(4), 1359-1367.

Di Martino, A., Scheres, A., Margulies, D. S., Kelly, A. M. C., Uddin, L. Q., Shehzad, Z., . . . Milham, M. P. (2008). Functional connectivity of human striatum: a resting state FMRI study. *Cerebral cortex, 18*(12), 2735-2747.

Epel, E., Daubenmier, J., Moskowitz, J. T., Folkman, S., & Blackburn, E. (2009). Can Meditation Slow Rate of Cellular Aging? Cognitive Stress, Mindfulness, and Telomeres. *Ann N Y Acad Sci, 1172*(1), 34-53. doi:10.1111/j.1749-6632.2009.04414.x

Epel, E. S., Blackburn, E. H., Lin, J., Dhabhar, F. S., Adler, N. E., Morrow, J. D., & Cawthon, R. M. (2004). Accelerated telomere shortening in response to life stress. *Proceedings of the National Academy of Sciences, 101*(49), 17312-17315. doi:10.1073/pnas.0407162101

Eyre, H. A., Acevedo, B., Yang, H., Siddarth, P., Van Dyk, K., Ercoli, L., . . . Baune, B. T. (2016). Changes in neural connectivity and memory following a yoga intervention for older adults: a pilot study. *Journal of Alzheimer's Disease, 52*(2), 673-684.

Eyre, H. A., Siddarth, P., Acevedo, B., Van Dyk, K., Paholpak, P., Ercoli, L., . . . Lavretsky, H. (2017). A randomized controlled trial of Kundalini yoga in mild cognitive impairment. *International psychogeriatrics, 29*(4), 557-567.

Favrod, J., Nguyen, A., Fankhauser, C., Ismailaj, A., Hasler, J.-D., Ringuet, A., . . . Bonsack, C. (2015). Positive Emotions Program for Schizophrenia (PEPS): a pilot intervention to reduce anhedonia and apathy. *BMC Psychiatry, 15*(1). doi:10.1186/s12888-015-0610-y

Filippini, N., MacIntosh, B. J., Hough, M. G., Goodwin, G. M., Frisoni, G. B., Smith, S. M., . . . Mackay, C. E. (2009). Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. *Proc Natl Acad Sci U S A, 106*(17), 7209-7214. doi:10.1073/pnas.0811879106

Floyd, M., & Scogin, F. (1997). Effects of memory training on the subjective memory functioning and mental health of older adults: A meta-analysis. *Psychology and Aging, 12*(1), 150-161. doi:10.1037//0882-7974.12.1.150

Goff, D. C., Lloyd-Jones, D. M., Bennett, G., Coady, S., D'Agostino, R. B., Gibbons, R., . . . O'Donnell, C. J. (2014). 2013 ACC/AHA guideline on the assessment of cardiovascular risk. *Circulation, 129*(25 suppl 2), S49-S73.

Goldberger, A. L. (2006). Giles F. Filley Lecture. Complex Systems. *Proceedings of the American Thoracic Society, 3*(6), 467-471. doi:10.1513/pats.200603-028ms

Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., . . . Schatzberg, A. F. (2007). Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biological Psychiatry, 62*(5), 429-437.

Gross, A. L., Parisi, J. M., Spira, A. P., Kueider, A. M., Ko, J. Y., Saczynski, J. S., . . . Rebok, G. W. (2012). Memory training interventions for older adults: A meta-analysis. *Aging & mental health, 16*(6), 722-734. doi:10.1080/13607863.2012.667783

Guo, X., Waern, M., Sjogren, K., Lissner, L., Bengtsson, C., Bjorkelund, C., . . . Skoog, I. (2007). Midlife respiratory function and Incidence of Alzheimer's disease: a 29-year longitudinal study in women. *Neurobiol Aging, 28*(3), 343-350. doi:10.1016/j.neurobiolaging.2006.01.008

Henderson, V. W., Watt, L., & Galen Buckwalter, J. (1996). Cognitive skills associated with estrogen replacement in women with Alzheimer's disease. *Psychoneuroendocrinology, 21*(4), 421-430. doi:10.1016/0306-4530(95)00060-7

Ho, K. K. L., Pinsky, J. L., Kannel, W. B., & Levy, D. (1993). The epidemiology of heart failure: The Framingham Study. *J Am Coll Cardiol, 22*(4), A6-A13. doi:10.1016/0735-1097(93)90455-a

Hughes, T. F., Andel, R., Small, B. J., Borenstein, A. R., Mortimer, J. A., Wolk, A., . . . Gatz, M. (2010). Midlife Fruit and Vegetable Consumption and Risk of Dementia in Later Life in Swedish Twins. *The American Journal of Geriatric Psychiatry, 18*(5), 413-420. doi:10.1097/jgp.0b013e3181c65250

Hultsch, D. F., Hertzog, C., Small, B. J., & Dixon, R. A. (1999). Use it or lose it: Engaged lifestyle as a buffer of cognitive decline in aging? *Psychology and Aging, 14*(2), 245-263. doi:10.1037/0882-7974.14.2.245

Hurtig-Wennlöf, A., Hagströmer, M., & Olsson, L. A. (2010). The International Physical Activity Questionnaire modified for the elderly: aspects of validity and feasibility. *Public health nutrition, 13*(11), 1847-1854.

Irwin, M. R., Olmstead, R., & Motivala, S. J. (2008). Improving sleep quality in older adults with moderate sleep complaints: A randomized controlled trial of Tai Chi Chih. *Sleep, 31*(7), 1001-1008.

Irwin, M. R., Wang, M., Campomayor, C. O., Collado-Hidalgo, A., & Cole, S. (2006). Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Archives of internal medicine, 166*(16), 1756-1762.

Jacobs, T. L., Epel, E. S., Lin, J., Blackburn, E. H., Wolkowitz, O. M., Bridwell, D. A., . . . MacLean, K. A. (2011). Intensive meditation training, immune cell telomerase activity, and psychological mediators. *Psychoneuroendocrinology, 36*(5), 664-681.

Jayaram, N., Varambally, S., Behere, R. V., Venkatasubramanian, G., Arasappa, R., Christopher, R., & Gangadhar, B. N. (2013). Effect of yoga therapy on plasma oxytocin and facial emotion recognition deficits in patients of schizophrenia. *Indian journal of psychiatry, 55*(Suppl 3), S409.

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). FSL. *NeuroImage, 62*(2), 782-790. doi:10.1016/j.neuroimage.2011.09.015

Jensen-Dahm, C., Waldemar, G., Staehelin Jensen, T., Malmqvist, L., Moeller, M. M., Andersen, B. B., . . . Ballegaard, M. (2015). Autonomic Dysfunction in Patients with Mild to Moderate Alzheimer's Disease. *J Alzheimers Dis, 47*(3), 681-689. doi:10.3233/jad-150169

Khalsa, S. B., Khalsa, G. S., Khalsa, H. K., & Khalsa, M. K. (2008). Evaluation of a residential Kundalini yoga lifestyle pilot program for addiction in India. *J Ethn Subst Abuse, 7*(1), 67-79. doi:10.1080/15332640802081968

Kim, N. W., & Wu, F. (1997). Advances in quantification and characterization of telomerase activity by the telomeric repeat amplification protocol (TRAP). *Nucleic Acids Res, 25*(13), 2595-2597.

Kirby, K. N., & Maraković, N. N. (1995). Modeling myopic decisions: Evidence for hyperbolic delay-discounting within subjects and amounts. *Organizational Behavior and Human decision processes, 64*(1), 22-30.

Klamer, S., Milian, M., Erb, M., Rona, S., Lerche, H., & Ethofer, T. (2017). Face-name association task reveals memory networks in patients with left and right hippocampal sclerosis. *NeuroImage: Clinical, 14*, 174-182.

Knopman, D. S., DeKosky, S. T., Cummings, J. L., Chui, H., Corey-Bloom, J., Relkin, N., . . . Stevens, J. C. (2001). Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology, 56*(9), 1143-1153.

Koenig, H. G., Westlund, R. E., George, L. K., Hughes, D. C., Blazer, D. G., & Hybels, C. (1993). Abbreviating the Duke Social Support Index for use in chronically ill elderly individuals. *Psychosomatics, 34*(1), 61-69.

Koo, J. W., Russo, S. J., Ferguson, D., Nestler, E. J., & Duman, R. S. (2010). Nuclear factor- B is a critical mediator of stress-impaired neurogenesis and depressive behavior. *Proceedings of the National Academy of Sciences, 107*(6), 2669-2674. doi:10.1073/pnas.0910658107

Kramer, A. F., & Erickson, K. I. (2007). Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. *Trends in cognitive sciences, 11*(8), 342-348. doi:10.1016/j.tics.2007.06.009

Krikorian, R., Shidler, M. D., Nash, T. A., Kalt, W., Vinqvist-Tymchuk, M. R., Shukitt-Hale, B., & Joseph, J. A. (2010). Blueberry Supplementation Improves Memory in Older Adults†. *Journal of Agricultural and Food Chemistry, 58*(7), 3996-4000. doi:10.1021/jf9029332

Krisanaprakornkit, T., Piyavhatkul, N., Kirkwood, G., Krisanaprakornkit, W., & Laopaiboon, M. (2004). Meditation therapy for anxiety disorders. In *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd.

Larson, E. B., Wang, L., Bowen, J. D., McCormick, W. C., Teri, L., Crane, P., & Kukull, W. (2006). Exercise Is Associated with Reduced Risk for Incident Dementia among Persons 65 Years of Age and Older. *Annals of Internal Medicine, 144*(2), 73. doi:10.7326/0003-4819-144-2-200601170-00004

Lau, M. A., Bishop, S. R., Segal, Z. V., Buis, T., Anderson, N. D., Carlson, L., . . . Devins, G. (2006). The Toronto mindfulness scale: Development and validation. *Journal of Clinical Psychology, 62*(12), 1445-1467.

Lautenschlager, N. T., Cox, K. L., Flicker, L., Foster, J. K., van Bockxmeer, F. M., Xiao, J., . . . Almeida, O. P. (2008). Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *Jama, 300*(18768414), 1027-1037.

Lavretsky, H., Epel, E. S., Siddarth, P., Nazarian, N., Cyr, N. S., Khalsa, D. S., . . . Irwin, M. R. (2013a). A pilot study of yogic meditation for family dementia caregivers with depressive symptoms: effects on mental health, cognition, and telomerase activity. *Int J Geriatr Psychiatry, 28*(1), 57-65. doi:10.1002/gps.3790

Lavretsky, H., Epel, E. S., Siddarth, P., Nazarian, N., Cyr, N. S., Khalsa, D. S., . . . Irwin, M. R. (2013b). A pilot study of yogic meditation for family dementia caregivers with depressive symptoms: effects on mental health, cognition, and telomerase activity. *International journal of geriatric psychiatry, 28*(1), 57-65.

Lin, I. M., Tai, L. Y., & Fan, S. Y. (2014). Breathing at a rate of 5.5breaths per minute with equal inhalation-to-exhalation ratio increases heart rate variability. *International Journal of Psychophysiology, 91*(3), 206-211. doi:https://doi.org/10.1016/j.ijpsycho.2013.12.006

Lin, K. A., Choudhury, K. R., Petrella, J. R., & Doraiswamy, P. M. (2015). Marked gender differences in rate of cognitive decline in subjects at risk for Alzheimer's disease. *Alzheimer's & dementia, 11*(7), P817. doi:10.1016/j.jalz.2015.06.1814

Lindbergh, C. A., Puente, A. N., Gray, J. C., Mackillop, J., & Miller, L. S. (2014). Delay and probability discounting as candidate markers for dementia: an initial investigation. *Archives of clinical neuropsychology, 29*(7), 651-662.

Lingjærde, O., Ahlfors, U. G., Bech, P., Dencker, S. J., & Elgen, K. (1987). The UKU side effect rating scale: A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatrica Scandinavica, 76*(s334), 1-100. doi:10.1111/j.1600-0447.1987.tb10566.x

Lipsitz, J. D., Gur, M., Albano, A. M., & Sherman, B. (2011). A psychological intervention for pediatric chest pain: development and open trial. *J Dev Behav Pediatr, 32*(2), 153-157.

Lipsitz, L. A. (2006). Aging as a process of complexity loss. *Complex systems science in biomedicine*, 641-654.

Lockwood, K. A., Alexopoulos, G. S., & van Gorp, W. G. (2002). Executive Dysfunction in Geriatric Depression. *American Journal of Psychiatry, 159*(7), 1119-1126. doi:10.1176/appi.ajp.159.7.1119

Lövdén, M., Ghisletta, P., & Lindenberger, U. (2005). Social Participation Attenuates Decline in Perceptual Speed in Old and Very Old Age. *Psychology and Aging, 20*(3), 423-434. doi:10.1037/0882-7974.20.3.423

Lyden, H., Espinoza, R. T., Pirnia, T., Clark, K., Joshi, S. H., Leaver, A. M., . . . Narr, K. L. (2014). Electroconvulsive therapy mediates neuroplasticity of white matter microstructure in major depression. *Transl Psychiatry, 4*, e380. doi:10.1038/tp.2014.21

Lyketsos, C. G., Lopez, O., Jones, B., Fitzpatrick, A. L., Breitner, J., & DeKosky, S. (2002). Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *Jama, 288*(12), 1475-1483.

Lynton, H., Kligler, B., & Shiflett, S. (2007). Yoga in Stroke Rehabilitation: A Systematic Review and Results of a Pilot Study. *Topics in Stroke Rehabilitation, 14*(4), 1-8. doi:10.1310/tsr1404-1

Manly, J. J., Merchant, C. A., Jacobs, D. M., Small, S. A., Bell, K., Ferin, M., & Mayeux, R. (2000). Endogenous estrogen levels and Alzheimer's disease among postmenopausal women. *Neurology, 54*(4), 833-837. doi:10.1212/wnl.54.4.833

Martikainen, P., & Valkonen, T. (1996). Mortality after the death of a spouse: rates and causes of death in a large Finnish cohort. *American journal of public health, 86*(8_Pt_1), 1087-1093.

McCarty, D. L. (1980). Investigation of a visual imagery mnemonic device for acquiring face-name associations. *Journal of Experimental Psychology: Human Learning & Memory, 6*(2), 145-155. doi:10.1037//0278-7393.6.2.145

McDaniel, M. A., & Bugg, J. M. (2012). Memory training interventions: What has been forgotten? *Journal of Applied Research in Memory and Cognition, 1*(1), 45-50. doi:10.1016/j.jarmac.2011.11.002

McLean, C. P., & Anderson, E. R. (2009). Brave men and timid women? A review of the gender differences in fear and anxiety. *Clin Psychol Rev, 29*(6), 496-505.

Miller, G. E., Chen, E., Sze, J., Marin, T., Arevalo, J. M. G., Doll, R., . . . Cole, S. W. (2008). A Functional Genomic Fingerprint of Chronic Stress in Humans: Blunted Glucocorticoid and Increased NF-κB Signaling. *Biological Psychiatry, 64*(4), 266-272. doi:10.1016/j.biopsych.2008.03.017

Miller, K. J., Siddarth, P., Gaines, J. M., Parrish, J. M., Ercoli, L. M., Marx, K., . . . Small, G. W. (2012). The Memory Fitness Program: Cognitive Effects of a Healthy Aging Intervention. *The American Journal of Geriatric Psychiatry, 20*(6), 514-523. doi:10.1097/jgp.0b013e318227f821

Mitchell, E. S., & Woods, N. F. (2011). Cognitive symptoms during the menopausal transition and early postmenopause. *Climacteric, 14*(2), 252-261. doi:10.3109/13697137.2010.516848

Morrison, J. H., Brinton, R. D., Schmidt, P. J., & Gore, A. C. (2006). Estrogen, Menopause, and the Aging Brain: How Basic Neuroscience Can Inform Hormone Therapy in Women. *Journal of Neuroscience, 26*(41), 10332-10348. doi:10.1523/jneurosci.3369-06.2006

Moss, A. S., Wintering, N., Roggenkamp, H., Khalsa, D. S., Waldman, M. R., Monti, D., & Newberg, A. B. (2012). Effects of an 8-week meditation program on mood and anxiety in patients with memory loss. *J Altern Complement Med, 18*(1), 48-53. doi:10.1089/acm.2011.0051

Narr, K. L., Thompson, P. M., Szeszko, P., Robinson, D., Jang, S., Woods, R. P., . . . Toga, A. W. (2004). Regional specificity of hippocampal volume reductions in first-episode schizophrenia. *NeuroImage, 21*(4), 1563-1575.

Neff, K. D. (2003). The development and validation of a scale to measure self-compassion. *Self and identity, 2*(3), 223-250.

Newberg, A. B., Wintering, N., Khalsa, D. S., Roggenkamp, H., & Waldman, M. R. (2010). Meditation effects on cognitive function and cerebral blood flow in subjects with memory loss: a preliminary study. *J Alzheimers Dis, 20*(2), 517-526. doi:10.3233/JAD-2010-1391

Newberg, A. B., Wintering, N., Khalsa, D. S., Roggenkamp, H., & Waldmanb, M. R. (2012). Meditation effects on cognitive function and cerebral blood flow in subjects with memory loss: a preliminary study. *Annals of Neurosciences, 19*(2). doi:10.5214/ans.0972.7531.12190207

Newson, R. S., Boelen, P. A., Hek, K., Hofman, A., & Tiemeier, H. (2011). The prevalence and characteristics of complicated grief in older adults. *Journal of affective disorders, 132*(1-2), 231-238. doi:10.1016/j.jad.2011.02.021

Ohayon, M. M. (2002). Epidemiology of insomnia: what we know and what we still need to learn. *Sleep medicine reviews, 6*(2), 97-111.

Ornish, D., Lin, J., Daubenmier, J., Weidner, G., Epel, E., Kemp, C., . . . Blackburn, E. H. (2008). Increased telomerase activity and comprehensive lifestyle changes: a pilot study. *The Lancet Oncology, 9*(11), 1048-1057. doi:10.1016/s1470-2045(08)70234-1

Pace, T. W. W., & Miller, A. H. (2009). Cytokines and Glucocorticoid Receptor Signaling. *Ann N Y Acad Sci, 1179*(1), 86-105. doi:10.1111/j.1749-6632.2009.04984.x

Pagnoni, G., & Cekic, M. (2007). Age effects on gray matter volume and attentional performance in Zen meditation. *Neurobiology of Aging, 28*(10), 1623-1627. doi:10.1016/j.neurobiolaging.2007.06.008

Phillips, O. R., Nuechterlein, K. H., Clark, K. A., Hamilton, L. S., Asarnow, R. F., Hageman, N. S., . . . Narr, K. L. (2009). Fiber tractography reveals disruption of temporal lobe white matter tracts in schizophrenia. *Schizophr Res, 107*(1), 30-38. doi:10.1016/j.schres.2008.10.019

Podewils, L. J. (2005). Physical Activity, APOE Genotype, and Dementia Risk: Findings from the Cardiovascular Health Cognition Study. *American Journal of Epidemiology, 161*(7), 639-651. doi:10.1093/aje/kwi092

Pomykala, K. L., Silverman, D. H. S., Geist, C. L., Voege, P., Siddarth, P., Nazarian, N., . . . Lavretsky, H. (2012). A pilot study of the effects of meditation on regional brain metabolism in distressed dementia caregivers. *Aging Health, 8*(5), 509-516. doi:10.2217/ahe.12.46

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage, 59*(3), 2142-2154.

Prakash, R., Rastogi, P., Dubey, I., Abhishek, P., Chaudhury, S., & Small, B. J. (2012). Long-term concentrative meditation and cognitive performance among older adults. *Aging, Neuropsychology, and Cognition, 19*(4), 479-494. doi:10.1080/13825585.2011.630932

Reavis, E. A., Lee, J., Wynn, J. K., Narr, K. L., Njau, S. N., Engel, S. A., & Green, M. F. (2017). Linking optic radiation volume to visual perception in schizophrenia and bipolar disorder. *Schizophr Res*. doi:10.1016/j.schres.2017.03.027

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological review, 103*(3), 403-428. doi:10.1037//0033-295x.103.3.403

Salvi, F., Miller, M. D., Grilli, A., Giorgi, R., Towers, A. L., Morichi, V., . . . DessÃ¬-Fulgheri, P. (2008). A Manual of Guidelines to Score the Modified Cumulative Illness Rating Scale and Its Validation in Acute Hospitalized Elderly Patients. *Journal of the American Geriatrics Society, 56*(10), 1926-1931. doi:10.1111/j.1532-5415.2008.01935.x

Samad, Z., Boyle, S., Ersboll, M., Vora, A. N., Zhang, Y., Becker, R. C., . . . Jiang, W. (2014). Sex Differences in Platelet Reactivity and Cardiovascular and Psychological Response to Mental Stress in Patients With Stable Ischemic Heart Disease. *J Am Coll Cardiol, 64*(16), 1669-1678. doi:10.1016/j.jacc.2014.04.087

Sanches, V. S., Santos, F. M., Fernandes, J. M., Santos, M. L., Muller, P. T., & Christofoletti, G. (2014). Neurodegenerative disorders increase decline in respiratory muscle strength in older adults. *Respir Care, 59*(12), 1838-1845. doi:10.4187/respcare.03063

Sasano, N., Vesely, A. E., Hayano, J., Sasano, H., Somogyi, R., Preiss, D., . . . Fisher, J. A. (2002). Direct effect of Pa(CO2) on respiratory sinus arrhythmia in conscious humans. *Am J Physiol Heart Circ Physiol, 282*(3), H973-976. doi:10.1152/ajpheart.00554.2001

Scarmeas, N., Stern, Y., Tang, M.-X., Mayeux, R., & Luchsinger, J. A. (2006). Mediterranean diet and risk for Alzheimer's disease. *Annals of neurology, 59*(6), 912-921. doi:10.1002/ana.20854

Scherder, E. J. A., Van Paasschen, J., Deijen, J. B., Van Der Knokke, S., Orlebeke, J. F. K., Burgers, I., . . . Sergeant, J. A. (2005). Physical activity and executive functions in the elderly with mild cognitive impairment. *Aging Ment Health, 9*(16019281), 272-280.

Schneider, B., Ercoli, L., Siddarth, P., & Lavretsky, H. (2012). Vascular burden and cognitive functioning in depressed older adults. *The American Journal of Geriatric Psychiatry, 20*(8), 673-681.

Schwarz, C., Fletcher, E., DeCarli, C., & Carmichael, O. (2009). *Fully-automated white matter hyperintensity detection with anatomical prior knowledge and without FLAIR*.

Serrano, A. L. (2004). Telomeres and Cardiovascular Disease: Does Size Matter? *Circulation Research, 94*(5), 575-584. doi:10.1161/01.res.0000122141.18795.9c

Shannahoff-Khalsa, D. S. (2004). An Introduction to Kundalini Yoga Meditation Techniques That Are Specific for the Treatment of Psychiatric Disorders. *The Journal of Alternative and Complementary Medicine, 10*(1), 91-101. doi:10.1089/107555304322849011

Shannahoff-Khalsa, D. S. (2005). Patient Perspectives. *Integrative Cancer Therapies, 4*(1), 87-100. doi:10.1177/1534735404273841

Shriver, S. *Address (Sargent Shriver)*. Retrieved from: http://dx.doi.org/10.1037/e590042009-017

Smith, P. J., Blumenthal, J. A., Hoffman, B. M., Cooper, H., Strauman, T. A., Welsh-Bohmer, K., . . . Sherwood, A. (2010). Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosomatic Medicine, 72*(3), 239.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., . . . Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage, 23*, S208-S219. doi:10.1016/j.neuroimage.2004.07.051

Snyder, H. M., Asthana, S., Bain, L., Brinton, R., Craft, S., Dubal, D. B., . . . Raber, J. (2016). Sex biology contributions to vulnerability to Alzheimer's disease: A think tank convened by the Women's Alzheimer's Research Initiative. *Alzheimer's & dementia, 12*(11), 1186-1196.

Sotiropoulos, S. N., Jbabdi, S., Xu, J., Andersson, J. L., Moeller, S., Auerbach, E. J., . . . Jenkinson, M. (2013). Advances in diffusion MRI acquisition and processing in the Human Connectome Project. *NeuroImage, 80*, 125-143.

Stigsdotter, A., & Bäckman, L. (1989). Multifactorial Memory Training with Older Adults: How to Foster Maintenance of Improved Performance. *Gerontology, 35*(5-6), 260-267. doi:10.1159/000213035

Suri, S., Mackay, C. E., Kelly, M. E., Germuska, M., Tunbridge, E. M., Frisoni, G. B., . . . Filippini, N. (2015). Reduced cerebrovascular reactivity in young adults carrying the APOE ε4 allele. *Alzheimer's & Dementia, 11*(6), 648-657.e641. doi:https://doi.org/10.1016/j.jalz.2014.05.1755

Tang, M.-X., Jacobs, D., Stern, Y., Marder, K., Schofield, P., Gurland, B., . . . Mayeux, R. (1996). Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. *The Lancet, 348*(9025), 429-432. doi:10.1016/s0140-6736(96)03356-9

Trapnell, P. D., & Campbell, J. D. (1999). Private self-consciousness and the five-factor model of personality: distinguishing rumination from reflection. *Journal of Personality and Social Psychology, 76*(2), 284.

Truelsen, T., Lindenstrom, E., & Boysen, G. (1994). Comparison of probability of stroke between the Copenhagen City Heart Study and the Framingham Study. *Stroke, 25*(4), 802-807.

Vaccarino, V., Wilmot, K., Mheid, I. A., Ramadan, R., Pimple, P., Shah, A. J., . . . Quyyumi, A. A. (2016). Sex Differences in Mental Stress-Induced Myocardial Ischemia in Patients With Coronary Heart Disease. *Journal of the American Heart Association, 5*(9), e003630. doi:10.1161/jaha.116.003630

van den Heuvel, D. M. J., Admiraal-Behloul, F., ten Dam, V. H., Olofsen, H., Bollen, E. L. E. M., Murray, H. M., . . . van Buchem, M. A. (2004). Different progression rates for deep white matter hyperintensities in elderly men and women. *Neurology, 63*(9), 1699-1701. doi:10.1212/01.wnl.0000143058.40388.44

van der Kouwe, A. J. W., Benner, T., Salat, D. H., & Fischl, B. (2008). Brain morphometry with multiecho MPRAGE. *NeuroImage, 40*(2), 559-569. doi:10.1016/j.neuroimage.2007.12.025

van Gelder, B. M., Tijhuis, M. A. R., Kalmijn, S., Giampaoli, S., Nissinen, A., & Kromhout, D. (2004). Physical activity in relation to cognitive decline in elderly men: The FINE Study. *Neurology, 63*(12), 2316-2321. doi:10.1212/01.wnl.0000147474.29994.35

van Uffelen, J. G. Z., Chinapaw, M. J. M., van Mechelen, W., & Hopman-Rock, M. (2008). Walking or vitamin B for cognition in older adults with mild cognitive impairment? A randomised controlled trial. *Br J Sports Med, 42*(18308888), 344-351.

Vega, J. N., Zurkovsky, L., Albert, K., Melo, A., Boyd, B., Dumas, J., . . . Newhouse, P. A. (2016). Altered Brain Connectivity in Early Postmenopausal Women with Subjective Cognitive Impairment. *Frontiers in Neuroscience, 10*. doi:10.3389/fnins.2016.00433

Verhaeghen, P., Marcoen, A., & Goossens, L. (1992). Improving memory performance in the aged through mnemonic training: A meta-analytic study. *Psychology and Aging, 7*(2), 242-251. doi:10.1037/0882-7974.7.2.242

Viña, J., & Lloret, A. (2010). Why Women Have More Alzheimer's Disease Than Men: Gender and Mitochondrial Toxicity of Amyloid-β Peptide. *Journal of Alzheimer's Disease, 20*(s2), S527-S533. doi:10.3233/jad-2010-100501

Wang, D. J. J., Alger, J. R., Qiao, J. X., Gunther, M., Pope, W. B., Saver, J. L., . . . Investigators, U. S. (2013). Multi-delay multi-parametric arterial spin-labeled perfusion MRI in acute ischemic stroke—comparison with dynamic susceptibility contrast enhanced perfusion imaging. *NeuroImage: Clinical, 3*, 1-7.

Ware, J. E., & Gandek, B. (1994). The SF-36 Health Survey: development and use in mental health research and the IQOLA Project. *International Journal of Mental Health, 23*, 49-73.

West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychological Bulletin, 120*(2), 272-292. doi:10.1037/0033-2909.120.2.272

Weuve, J., Kang, J. H., Manson, J. E., Breteler, M. M. B., Ware, J. H., & Grodstein, F. (2004). Physical activity, including walking, and cognitive function in older women. *Jama, 292*(15383516), 1454-1461.

Wilcox, S., Evenson, K. R., Aragaki, A., Wassertheil-Smoller, S., Mouton, C. P., & Loevinger, B. L. (2003). The effects of widowhood on physical and mental health, health behaviors, and health outcomes: The Women's Health Initiative. *Health Psychology, 22*(5), 513-522. doi:10.1037/0278-6133.22.5.513

Willis, S. L., Tennstedt, S. L., Marsiske, M., Ball, K., Elias, J., Koepke, K. M., . . . Active Study Group, f. t. (2006). Long-term Effects of Cognitive Training on Everyday Functional Outcomes in Older Adults. *Jama, 296*(23), 2805. doi:10.1001/jama.296.23.2805

Woolrich, M. W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., . . . Smith, S. M. (2009). Bayesian analysis of neuroimaging data in FSL. *NeuroImage, 45*(1), S173-S186. doi:10.1016/j.neuroimage.2008.10.055

Yang, H., Leaver, A. M., Siddarth, P., Paholpak, P., Ercoli, L., St. Cyr, N. M., . . . Lavretsky, H. (2016). Neurochemical and Neuroanatomical Plasticity Following Memory Training and Yoga Interventions in Older Adults with Mild Cognitive Impairment. *Frontiers in Aging Neuroscience, 8*. doi:10.3389/fnagi.2016.00277

Yang, Y., Raine, A., Narr, K. L., Colletti, P., & Toga, A. W. (2009). Localization of deformations within the amygdala in individuals with psychopathy. *Archives of General Psychiatry, 66*(9), 986-994.

Zeineh, M. M., Engel, S. A., Thompson, P. M., & Bookheimer, S. Y. (2003). Dynamics of the hippocampus during encoding and retrieval of face-name pairs. *Science, 299*(5606), 577-580.