

# Rationale and Design of a Clinical Trial of Adapted Tango to Improve Negative Health Impacts in Middle Aged African-American Female Caregivers of Persons with Alzheimer's Disease (ACT Trial)

Madeleine E. Hackney<sup>a,b,c,\*</sup>, Lauren E. McCullough<sup>d</sup>, Allison A. Bay<sup>a</sup>, Hayley A. Silverstein<sup>a</sup>, Ariel R. Hart<sup>a</sup>, Ryan J. Shin<sup>e</sup> and Whitney Wharton<sup>f</sup>

<sup>a</sup>*Department of Medicine, Division of General Medicine and Geriatrics, Emory School of Medicine, Atlanta, GA, USA*

<sup>b</sup>*Atlanta VA Center for Visual and Neurocognitive Rehabilitation, Decatur, GA, USA*

<sup>c</sup>*Department of Rehabilitation Medicine, Emory School of Medicine, Atlanta, GA, USA*

<sup>d</sup>*Emory University Rollins School of Public Health, Atlanta, GA, USA*

<sup>e</sup>*Emory University College of Arts and Sciences, Atlanta, GA, USA*

<sup>f</sup>*Department of Neurology, Atlanta, Emory University School of Medicine, GA, USA*

Accepted 16 January 2019

**Abstract.** Alzheimer's disease (AD) is a devastating progressive neurodegenerative disease resulting in memory loss and a severe reduction in ability to perform activities of daily living. The role of caring for someone with AD frequently falls to female family members, often daughters. The burden of caregiving can increase stress and anxiety and cause health decline in the caregiver. The combination of ethnicity-related genetic factors promoting the development of dementias among African-Americans (AA) and the increased risk among women for developing AD means that AA women who are caregivers of a parent with AD are at great risk for developing dementias including AD. The proposed study would compare the cognitive, motor, and psychosocial benefits of a well-established 12 week, 20-lesson adapted Argentine Tango intervention (N = 30) to a no-contact control group (N = 10) in middle-aged (45–65 years) AA women who are caregivers of a parent with AD in the metro Atlanta area.

**Keywords:** African American, Alzheimer's disease, caregiver, clinical trial, dance, inflammation

## INTRODUCTION

As of 2018, 16.1 million Americans provide unpaid care for people with Alzheimer's disease (AD) and

other dementias [1]. Compared to non-caregivers, caregivers experience more depressive symptoms and anxiety, lower levels of perceived health, more sleep problems, and worse physical health. Overall, higher stress is reported by caregivers compared to non-caregivers, correlating to increased risk of negative health outcomes [2]. Furthermore, in an older population, simply being a familial caregiver who is experiencing physical or psychological strain has

---

\*Correspondence to: Dr. Madeleine E. Hackney, PhD, Division of General Medicine and Geriatrics, Department of Medicine, Emory School of Medicine, 1841 Clifton Rd NE, #553; Atlanta, GA 30307, USA. Tel.: +1 404 321 6111/Ext. 5006; E-mails: mehackn@emory.edu and E-mail: madeleine.hackney@va.gov.

been identified as an independent risk factor for mortality [3]. As such, caregivers often have considerable health needs and require interventions for reducing stress and improving health.

Dementia caregivers have increased risk for psychological and physiological illness including depression, hypertension, diabetes mellitus, diminished quality of life (QOL), disruption of profession, and increased mortality [4, 5]. AD caregiving has unique challenges including mood fluctuations, personality changes, agitation, impaired language and reasoning, poor safety awareness, and impaired memory, which interfere with activities of daily living [6]. Stress and depression are independent risk factors for developing AD [7–9], and caregivers are more prone to cognitive impairment than healthy controls [10]. As a result, caregivers of those with AD may be at greater risk for developing AD themselves due to the increased burden of caring for a person with these deficits.

Although the current literature on biomarkers of stress in caregivers is mixed, certain studies show that AD caregiving is associated with higher subjective levels of stress and higher quantitative levels of low-grade inflammation, as indicated by elevated plasma C-reactive protein (CRP) and inflammatory cytokines [11, 12]. Furthermore, lower satisfaction with leisure activities was associated with higher inflammation, pointing to the importance of interventions which improve quality of life [13]. Further research is needed to elucidate the biological consequences of caregiver stress. What we do know is that inflammation is crucial to the development of AD pathophysiology, as evidenced by reactive microglia on autopsy studies and elevated inflammatory-binding on positron emission tomography (PET) imaging in patients who progress from mild cognitive impairment (MCI) to AD [14]. Recent literature suggests that an initial inflammatory stimulus triggers activation of microglia and astrocytes which secrete inflammatory cytokines and chemokines which lead to further accumulation of amyloid and further production of pro-inflammatory cytokines [15]. Inflammation is thought to eventually lead to increased blood brain barrier permeability, hypoperfusion, and eventual neuronal damage [16].

Family history of AD increases risk due to both overrepresentation of the apolipoprotein E type 4 (APOE  $\epsilon$ 4) allele and psychosocial variables such as caregiver-related stress [17]. Ethnicity also plays a role in the risk for developing AD. African-Americans (AA) are 1.6 times more likely than

Whites to develop dementia by age 85. Among relatives of White (CC) persons with AD, those with the APOE  $\epsilon$ 4 allele have twice the risk of developing AD, whereas those of AA ethnicity who have at least one APOE  $\epsilon$ 4 allele have triple the risk of developing AD. Thus, ethnicity may be very powerful in determining risk of AD [18]. Middle aged AA female family caregivers who are the children of AD patients are particularly at risk for developing AD due to ethnicity, gender, and age. According to a CDC report on depression in the U.S., minorities including non-Hispanic blacks, Hispanics, and non-Hispanics of other races experience higher levels of depression compared to non-Hispanic whites [19]. Females have an increased risk of AD due to menopause related hormonal changes, longer lifespan, and propensity for caregiving [20]. Adult children are commonly caught between caring for their children and/or grandchildren in addition to their parents, while also maintaining employment. These demands often leave little time for self-care, including exercise.

This situation is problematic, as exercise may be preventative to the development of AD secondary to its effects on inflammation and the pathophysiology of AD. Exercise has already been shown to improve cognitive performance and functionality in patients with AD [21]. Namely, exercise reduces resting heart rate and blood pressure, increases myocardial oxygen utilization, and in the case of long-term exercise, prevents endothelial dysfunction and oxidative damage, which contribute to neuronal degeneration in AD [22]. Reductions in blood pressure, particularly those that act on the renin-angiotensin system, have beneficial effects on cognition and can slow conversion from MCI to AD [23]. Similarly, mid-life hypertension and cardiovascular disease are linked to development of dementia in later life [24]. For the targeted population, lack of exercise may be an additional contributor to increased risk of developing AD.

Adapted tango is an adapted form of Argentine tango, and an intervention that has been researched in individuals with Parkinson's disease (PD), as well as in older adults [25–28]. Adapted tango is a challenging dual-tasking activity promoting social interaction, cognitive engagement, musical interpretation, and creative thinking along with the physical demands of coordination, timing of movement, and balance [28]. While the physical effects of a dance intervention have yet to be investigated in this population, it is known that music alone has some potential in improving anxiety and depression and in reducing caregiver burden [29].

Here we describe the design and rationale of a pilot clinical trial to evaluate whether AD risk factors can be mitigated using an adapted tango intervention versus control. The trial will determine whether adapted tango is efficacious in improving quality of life (QOL), mood, cognitive and physical function, plasma inflammatory cytokines, and blood pressure within AA caregivers. We hypothesize that adapted tango will be a safe, enjoyable, and effective intervention that will reduce stress, and improve quality of life, balance, walking, and mobility, with a positive effect on inflammation and blood pressure.

## STUDY DESIGN

This is a 12-week, randomized, placebo-controlled Phase I clinical trial. Thirty participants will be randomized in a 2:1 ratio to treatment ( $N=20$ ) and control ( $N=10$ ) conditions with controls frequency matched to cases based on two age stratifications (45–55 years and 56–65 years of age). Participants undergo blood biomarker, cognitive, physical/motor, and mood testing pre and post intervention or control conditions. Participants will attend two clinical visits (pre and post intervention/control). Clinic visits will last approximately 2 h and will entail: 1) a 1 h cognitive testing battery; 2) blood draw for inflammatory cytokines, rapid blood glucose level, homeostatic model assessment for insulin resistance (HOMA-IR), and ApoE4 genotyping; 3) height, weight, and blood pressure measurement. Cognitive testing includes a comprehensive pre/post battery in domains of memory [30, 31], spatial ability [32, 33], executive function [34–36], language [37], quantitative measures that assess mood, and positive and negative aspects of caregiving [38–42]; and 4) physical function testing includes a pre/post battery in the domains of balance [43, 44], walking [45, 46], and motor function [44, 47]. Details of the physiological and cognitive measures are described below.

### Participants

Informed consent will be obtained prior to randomization at the first clinic visit. Thirty AA women family caregivers (aged 45–65 years) from the Emory Alzheimer's Disease Research Center (ADRC) and Dr. Wharton's studies of AD caregivers will be asked to participate in the proposed trial. The participants' parents will have a diagnosis of probable AD as defined by National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and

Related Disorders Association (NINDS-ADRDA) criteria and will be verified using the validated Dementia Questionnaire [48] and medical records, when available. Participants with a parental diagnosis have increased risk for AD and overrepresentation of the ApoE4 allele, a genetic risk factor for AD. In Dr. Wharton's previous studies, we have reported that 50–67% of the AD adult child sample is ApoE4 positive [49, 50]. Participants will be compensated \$50 for their participation in the form of gift cards.

### Intervention

#### *Adapted tango dance intervention (N = 20)*

Participants randomized to the experimental group will take part in 20, 1.5 h long adapted tango dance sessions over 12 weeks. Participants will be encouraged to participate in classes two times per week. Dance interventions will take place at the Atlanta VA Medical Center in the Movement Studies Laboratory (MSL) of the Center for Visual and Neurocognitive Rehabilitation (CVNR), which Dr. Hackney (Co-PI, CVNR) has used in previous studies. We will use a program previously tested in people with PD, visual impairment and older adults with cognitive impairment: an adapted Argentine tango (adapted tango) program. Adapted tango has benefitted spatial cognition, gait, balance, and disease severity in PD [51]. Classes taught by trained and experienced instructors will be offered four times per week for a total of 12 weeks in a movement studies laboratory at the VA. Our prior studies showed offering 4 class times per week allowed schedule flexibility for the participants, which increased the likelihood of participants completing 20 classes. Therefore, classes in the current study will be offered at four times per week. The classes will follow methods outlined in an adapted tango manual, which has been developed empirically through several studies [27]. The manual delineates older adult motor impairments and challenges, fall risk and prevention, partnering enhancement exercises, rhythmic entrainment, and a structured syllabus and format. Classes will begin with a 20 min standing warm-up followed by partnering and rhythmic exercises. Next, novel step elements will be introduced and participants will be taught how to combine the new steps with previously learned steps via improvisational. Caregivers will dance with each other or student volunteers. Music will be played throughout classes. Artistic expression, i.e., attention to aesthetics, and improvisation, will be encouraged. Adapted tango classes improve spatial cognition in

PD patients [51] and motor-cognitive integration in older adults [28], which we reported can last up to 3 months post treatment. Adapted tango has been introduced in AA communities successfully: in 2012, 18 retired AA participants began a 20-lesson adapted tango program and 14 of these participants completed 20 lessons within 12 weeks and were satisfied. Our prior data show also that a 12-week intervention is an acceptable period to show cognitive benefits of adapted tango in an AA population. Moreover, 12-week dance interventions have successfully improved inflammatory, vascular, and subjective mood measures in younger populations [52].

#### *Non-intervention control group (N = 10)*

Ten participants will take part in the pre-assessment and blood draw followed by the post assessment and blood draw 12 weeks later. Participants in this group will be instructed not to change anything from their daily routine during the time between appointments.

#### *Trial description summary*

Figure 1 shows the timeline and detailed visit procedures.

### **STUDY VISIT SPECIFICS**

*Screening – performed as a phone screen.*

### **PRETEST AND POSTTEST PROCEDURE DESCRIPTIONS**

Inflammatory, cognitive, motor, and mood indices collected pre and post intervention:

#### *Biological and clinical data*

Participants will undergo blood draw for E4 status and inflammatory cytokines before and after the trial using well-established research procedures. All blood samples will be collected after an 8 h overnight fast by a member of the research team. Participants will complete medical and medication questionnaires, anthropometric measures, and 2 resting blood pressure reads. Biomarkers include targeted, inflammatory, and depression indices that have been linked to AD family caregiver stress [12] and have been shown to change over a 3-month period,

the same duration of this trial [53]. Moreover, these inflammatory and stress markers are easily obtained, affordable, and likely measurable at a large number of clinics and research institutions.

Inflammatory and depression blood biomarkers will be batched and assayed at Emory University. Four panels of biomarkers will be measured in plasma using commercially available singleplex or multiplex assays in a Luminex 200 platform: Cytokines and chemokines (including interleukin-7, interleukin-8, interleukin-9, interleukin-10, interferon induced protein 10, macrophage derived chemokine, monocyte chemoattractant protein 1, transforming growth factor alpha, and tumor necrosis factor alpha); C-reactive protein and serum amyloid protein; stress-related cortisol; endothelial markers ICAM-1 and VCAM-1; metabolic variables including homeostasis model assessment for insulin resistance index (HOMA-IR) and rapid blood glucose homeostasis.

#### *Cognitive data*

Cognitive testing will last 1.5 h and will take place at the Memory Disorders Clinic at Emory University. To determine the extent to which the dance intervention affects cognition, we will use a comprehensive battery in cognitive domains of memory, spatial ability, executive function and language, with a focus on executive function. Testing will be conducted by a trained Research Coordinator during the same clinical visit that blood and vitals are collected. Tests include but are not limited to: the Montreal Cognitive Assessment [54], the Tower of London [55], the Stroop Color Word Interference test [56], Trails B [57], Digit Span [58], the Buschke Selective Reminding Test [59], the Reverse Corsi Blocks [33], the Brooks spatial memory test [60], and the body position spatial task [61].

#### *Motor and physical function data*

To determine the extent to which the dance intervention affects physical function, we will use a comprehensive battery in motor domains of balance, walking, and lower body strength. Motor and physical function testing will be conducted by a trained Research Coordinator during the same clinical visit that blood and vitals are collected. Tests include but are not limited to the 30 s chair stand [47], four-square step test [43], 6 min walk [46], Miniature Balance Evaluation Systems Test (mini-BEST) [44], and gait speed tests (preferred, fast, backward) [45].

TASK NAME	PURPOSE	START DAY	END Day
<b>Recruitment and Preparation</b>			
Phone Screening	Verify Eligibility	0	0
Eligibility Verified by Neuroscientist	Proceed to Enrollment	0	0
<b>Pre-Intervention</b>			
Inflammatory Indices Collected	Assess inflammatory cytokines	0	0
Cognitive Indices Collected	Assess memory, spatial ability, executive function and language	0	0
Mood Indices Collected	Assess positive and negative aspects of caregiving	0	0
Motor/Physical Function Indices Collected	Determine baseline function for balance, walking, and mobility	0	0
<b>Intervention</b>			
Caregiver Group (n=30): Adapted Tango Classes		1	84
Control Group (n=10)		1	84
<b>Post-Intervention</b>			
Inflammatory Indices Collected	Assess inflammatory cytokines	85	90
Cognitive Indices Collected	Assess memory, spatial ability, executive function and language	85	90
Mood Indices Collected	Assess positive and negative aspects of caregiving	85	90
Motor/Physical Function Indices Collected	Determine baseline function for balance, walking, and mobility	85	90

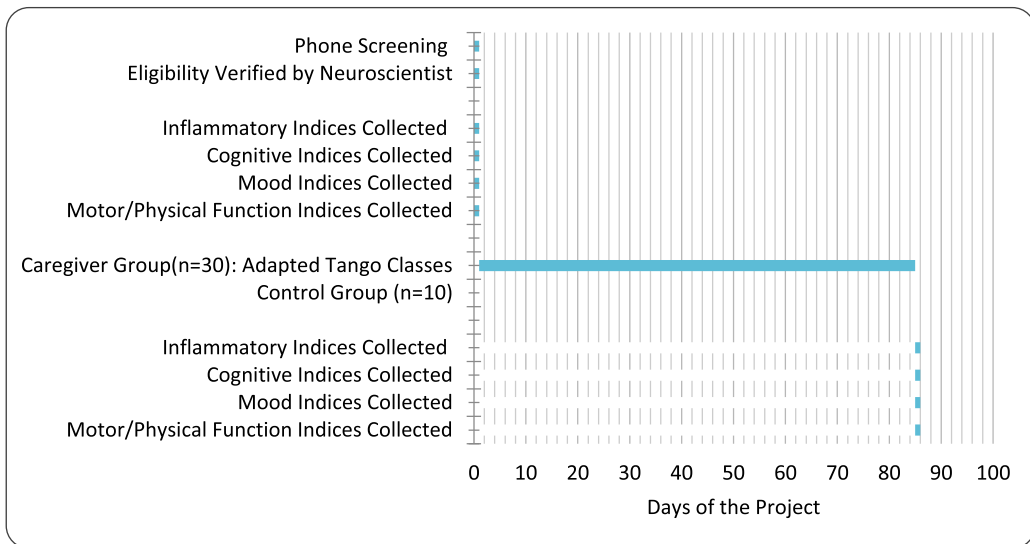


Fig. 1. Study tasks and timeline.

### *Mood and stress data*

In light of recent literature linking caregiver stress to increased inflammation and cognitive decline, we have compiled a battery of stress measures that assess both positive and negative aspects of caregiving. We also include measures to assess the physical and cognitive status of the care recipient, which likely contributes to caregiver stress. Measures include: Positive Aspects of Caregiving Scale (11 item) [38, 39], Pearlin Caregiver Stress Scale [62], The Zarit Burden Interview [40], Center for Epidemiologic Studies Depression Scale (CES-D) [41], Dementia Quality of Life measure (DEMQOL) (Carer v4) [42].

### *Evaluations and data collection timelines*

Figure 1 shows the timeline and detailed visit procedures.

## **ANALYSES**

We will assess the biological, cognitive, and mood outcomes pre and post intervention for both experimental and control groups. All tests will be two-tailed and use a 0.05 significance level. Models will be adjusted for age, education, and other covariates, as appropriate, based on *a priori* knowledge, and directed acyclic graph analyses. While we will use inferential statistics to compare function before treatment with after treatment, this pilot trial has been primarily designed to provide information about the feasibility of a dance intervention among AA female caregivers, appropriate clinical and patient reported outcomes, as well as clinically meaningful effect sizes. Feasibility will be determined by a conservative estimate of attrition rate less than 30% in both groups based on Dr. Wharton's and Hackney's previous studies and documented adherence tendencies in caregiver interventions which literature suggests may be as high as 70% in a similar population after 15 months [63]. Appropriateness of clinical and patient-reported outcomes will be determined by number of refusals to perform the tests, all of which will be documented. This population, which consists of AA female caregivers, has an overrepresentation of diabetes and high blood pressure, symptoms which are exacerbated by caregiver physiological and psychological stress, all of which will be measured and assessed in this trial. We will also observe all tests for ceiling effects in determining appropriateness.

Literature has shown that interventions and pharmaceutical therapies have made clinically meaningful reductions on inflammation and blood pressure in less than 12 weeks; therefore, the data we gather related to the effect of the dance intervention will be compared to these studies' findings and effect sizes.

## **DISCUSSION**

Several studies have examined the relationship between caregiving and cognitive, motor, and psychosocial measures. A comprehensive literature review by Vitaliano et al. found that people who are caregivers of a spouse with dementia are at an increased risk for cognitive impairment than non-caregivers [64]. Similarly, Caswell et al. (2003) found evidence that caregivers of spouses with dementia may also have negative impacts on cognitive and psycho-social health as a result of caregiving [65]. Another study by Canonici et al. (2012) found evidence that motor interventions for people with probable AD improved motor function for AD patients and decreased caregiver burden among the caregivers of the patients involved in the motor intervention [66]. The body of previous literature suggests that caregiving increases risk for negative cognitive, mood, and psycho-social indicators among caregivers, while motor interventions improve cognition among individuals with cognitive impairment including dementias. However, no study has examined the impact of a neuro-cognitive intervention on a population consisting of AA women who are also caregivers for a parent with probable AD, and therefore at greater risk for developing AD themselves. Given the multi-faceted nature of the increased risk for cognitive impairment in this population, our proposed study would fill a gap in existing knowledge about the relationship between caregiving and AD.

With the increasing incidence and prevalence of AD, research efforts should target high-risk groups to prevent or slow disease progression in tandem with cure-driven research directives in established disease. Interventions that may impart physiological, cognitive, physical and mood related benefits, including adapted tango intervention, is a cost-effective way of slowing AD, particularly in high-risk individuals, and allow for more rapid research trajectories over conventional drug discovery approaches [67]. While longer interventions are optimal, early intervention is critical and assessing the impact on biomarkers in addition to cognitive changes is also of great

importance. Because we know that inflammation and vascular health are implicated in AD neuropathology, and exercise is beneficial in preventing AD, research should clinically investigate the extent to which adapted tango interventions could confer AD-related benefits in African Americans at high risk for AD, during middle age. This pilot clinical trial will provide data to address these issues.

## ACKNOWLEDGMENTS

A Department of Veterans Affairs Career Development award supported ME Hackney (N0780W). W Wharton is supported by NIH-NIA grants: K01AG042498. This trial is supported by the Emory Goizueta Alzheimer's Disease Research Center and the Atlanta VA Center for Visual and Neurocognitive Rehabilitation.

Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/18-1130r1>).

## REFERENCES

- [1] Alzheimer's Association (2018) 2018 Alzheimer's disease facts and figures. *Alzheimers Dement* **14**, 367-429.
- [2] DeFries EL, McGuire LC, Andresen EM, Brumback BA, Anderson LA (2009) Caregivers of older adults with cognitive impairment. *Prev Chronic Dis* **6**, A46.
- [3] Schulz R, Beach SR (1999) Caregiving as a risk factor for mortality: The Caregiver Health Effects Study. *JAMA* **282**, 2215-2219.
- [4] Gonzalez EW, Polansky M, Lippa CF, Gitlin LN, Zauszniewski JA (2014) Enhancing resourcefulness to improve outcomes in family caregivers and persons with Alzheimer's disease: A pilot randomized trial. *Int J Alzheimers Dis* **2014**, 323478.
- [5] Goren A, Montgomery W, Kahle-Wroblewski K, Nakamura T, Ueda K (2016) Impact of caring for persons with Alzheimer's disease or dementia on caregivers' health outcomes: Findings from a community based survey in Japan. *BMC Geriatr* **16**, 122.
- [6] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr., Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269.
- [7] Pinquart M, Sorensen S (2003) Differences between caregivers and noncaregivers in psychological health and physical health: A meta-analysis. *Psychol Aging* **18**, 250-267.
- [8] Ory MG, Hoffman RR, 3rd, Yee JL, Tennstedt S, Schulz R (1999) Prevalence and impact of caregiving: A detailed comparison between dementia and nondementia caregivers. *Gerontologist* **39**, 177-185.
- [9] Vitaliano PP, Zhang J, Scanlan JM (2003) Is caregiving hazardous to one's physical health? A meta-analysis. *Psychol Bull* **129**, 946-972.
- [10] Corrêa MS, Giacobbo BL, Vedovelli K, Lima DB, Ferrari P, Argimon II, Walz JC, Bromberg E (2016) Age effects on cognitive and physiological parameters in familial caregivers of Alzheimer's disease patients. *PLoS One* **11**, e0162619.
- [11] Aschbacher K, von Kanel R, Mills PJ, Hong S, Roepke SK, Mausbach BT, Patterson TL, Ziegler MG, Dimsdale JE, Ancoli-Israel S, Grant I (2007) Combination of caregiving stress and hormone replacement therapy is associated with prolonged platelet activation to acute stress among postmenopausal women. *Psychosom Med* **69**, 910-917.
- [12] Gouin JP, Glaser R, Malarkey WB, Beversdorf D, Kiecolt-Glaser J (2012) Chronic stress, daily stressors, and circulating inflammatory markers. *Health Psychol* **31**, 264-268.
- [13] von Kanel R, Mausbach BT, Mills PJ, Dimsdale JE, Patterson TL, Ancoli-Israel S, Ziegler MG, Allison M, Chattillion EA, Grant I (2014) Longitudinal relationship of low leisure satisfaction but not depressive symptoms with systemic low-grade inflammation in dementia caregivers. *J Gerontol B Psychol Sci Soc Sci* **69**, 397-407.
- [14] Yasuno F, Kosaka J, Ota M, Higuchi M, Ito H, Fujimura Y, Nozaki S, Takahashi S, Mizukami K, Asada T, Suhara T (2012) Increased binding of peripheral benzodiazepine receptor in mild cognitive impairment-dementia converters measured by positron emission tomography with [<sup>11</sup>C]DAA1106. *Psychiatry Res* **203**, 67-74.
- [15] Minter MR, Taylor JM, Crack PJ (2016) The contribution of neuroinflammation to amyloid toxicity in Alzheimer's disease. *J Neurochem* **136**, 457-474.
- [16] Park KW, Yoon HJ, Kang DY, Kim BC, Kim S, Kim JW (2012) Regional cerebral blood flow differences in patients with mild cognitive impairment between those who did and did not develop Alzheimer's disease. *Psychiatry Res* **203**, 201-206.
- [17] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* **261**, 921-923.
- [18] Green RC, Cupples LA, Go R, Benke KS, Edeki T, Griffith PA, Williams M, Hipps Y, Graff-Radford N, Bachman D, Farrer LA, MIRAGE Study Group (2002) Risk of dementia among white and African American relatives of patients with Alzheimer disease. *JAMA* **287**, 329-336.
- [19] Gonzalez O, Berry JT, McKnight-Eily LR, Strine T, Edwards VJ, Lu H, Croft JB (2010) Current Depression Among Adults—United States, 2006 and 2008. *MMWR* **59**, 1229-1235.
- [20] Paganini-Hill A, Henderson VW (1994) Estrogen deficiency and risk of Alzheimer's disease in women. *Am J Epidemiol* **140**, 256-261.
- [21] Hernández SS, Sandreschi PF, da Silva FC, Arancibia BA, da Silva R, Gutierrez PJ, Andrade A (2015) What are the benefits of exercise for Alzheimer's disease? A systematic review of the past 10 years. *J Aging Phys Act* **23**, 659-668.
- [22] Lange-Asschenfeldt C, Kojda G (2008) Alzheimer's disease, cerebrovascular dysfunction and the benefits of exercise: From vessels to neurons. *Exp Gerontol* **43**, 499-504.
- [23] Wharton W, Goldstein FC, Zhao L, Steenland K, Levey AI, Hajjar I (2015) Modulation of renin-angiotensin system

- may slow conversion from mild cognitive impairment to Alzheimer's disease. *J Am Geriatr Soc* **63**, 1749-1756.
- [24] Bendlin BB, Carlsson CM, Gleason CE, Johnson SC, Sodhi A, Gallagher CL, Puglielli L, Engelman CD, Ries ML, Xu G, Wharton W, Asthana S (2010) Midlife predictors of Alzheimer's disease. *Maturitas* **65**, 131-137.
- [25] Hackney ME, Kantorovich S, Levin R, Earhart GM (2007) Effects of tango on functional mobility in Parkinson's disease: A preliminary study. *J Neurol Phys Ther* **31**, 173-179.
- [26] Hackney ME, Earhart GM (2010) Effects of dance on gait and balance in Parkinson's disease: A comparison of partnered and nonpartnered dance movement. *Neurorehabil Neural Repair* **24**, 384-392.
- [27] Hackney ME, McKee K (2014) Community-based adapted tango dancing for individuals with Parkinson's disease and older adults. *J Vis Exp*, doi: 10.3791/52066
- [28] Hackney ME, Byers C, Butler G, Sweeney M, Rossbach L, Bozzorg A (2015) Adapted Tango improves mobility, motor-cognitive function, and gait but not cognition in older adults in independent living. *J Am Geriatr Soc* **63**, 2105-2113.
- [29] Guetin S, Portet F, Picot MC, Defez C, Pose C, Blayac JP, Touchon J (2009) [Impact of music therapy on anxiety and depression for patients with Alzheimer's disease and on the burden felt by the main caregiver (feasibility study)]. *Encephale* **35**, 57-65.
- [30] Possin KL, Laluz VR, Alcantar OZ, Miller BL, Kramer JH (2011) Distinct neuroanatomical substrates and cognitive mechanisms of figure copy performance in Alzheimer's disease and behavioral variant frontotemporal dementia. *Neuropsychologia* **49**, 43-48.
- [31] Buschke H, Fuld PA (1974) Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology* **24**, 1019-1025.
- [32] Vandenberg SG, Kuse AR (1978) Mental rotations, a group test of three-dimensional spatial visualization. *Percept Mot Skills* **47**, 599-604.
- [33] Kessels RP, van den Berg E, Ruis C, Brands AM (2008) The backward span of the Corsi Block-Tapping Task and its association with the WAIS-III Digit Span. *Assessment* **15**, 426-434.
- [34] Krueger CE, Rosen HJ, Taylor HG, Espy KA, Schatz J, Rey-Casserly C, Kramer JH (2011) Know thyself: Real-world behavioral correlates of self-appraisal accuracy. *Clin Neuropsychol* **25**, 741-756.
- [35] Krueger CE, Bird AC, Growdon ME, Jang JY, Miller BL, Kramer JH (2009) Conflict monitoring in early frontotemporal dementia. *Neurology* **73**, 349-355.
- [36] Kramer J, Domain Specific Tasks of Executive Function. <http://examiner.ucsf.edu/index.htm>. USCF
- [37] Ivanova I, Salmon DP, Gollan TH (2013) The multilingual naming test in Alzheimer's disease: Clues to the origin of naming impairments. *J Int Neuropsychol Soc* **19**, 272-283.
- [38] Tarlowe MH, Duffy A, Kannan KB, Itagaki K, Lavery RF, Livingston DH, Bankey P, Hauser CJ (2005) Prospective study of neutrophil chemokine responses in trauma patients at risk for pneumonia. *Am J Respir Crit Care Med* **171**, 753-759.
- [39] Roth DL, Dilworth-Anderson P, Huang J, Gross AL, Gitlin LN (2015) Positive aspects of family caregiving for dementia: Differential item functioning by race. *J Gerontol B Psychol Sci Soc Sci* **70**, 813-819.
- [40] Zarit SH, Reever KE, Bach-Peterson J (1980) Relatives of the impaired elderly: Correlates of feelings of burden. *Gerontologist* **20**, 649-655.
- [41] Radloff LS (1977) The CES-D scale: A self-report depression scale for research in the general population. *Appl Psychol Meas* **1**, 385-401.
- [42] Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, Cook JC, Murray J, Prince M, Levin E, Mann A, Knapp M (2005) Measurement of health-related quality of life for people with dementia: Development of a new instrument (DEMQOL) and an evaluation of current methodology. *Health Technol Assess* **9**, 1-93, iii-iv.
- [43] Moore M, Barker K (2017) The validity and reliability of the four square step test in different adult populations: A systematic review. *Syst Rev* **6**, 187.
- [44] Lamb SE, Keene DJ (2017) Measuring physical capacity and performance in older people. *Best Pract Res Clin Rheumatol* **31**, 243-254.
- [45] Laufer Y (2005) Effect of age on characteristics of forward and backward gait at preferred and accelerated walking speed. *J Gerontol A Biol Sci Med Sci* **60**, 627-632.
- [46] Caballer VB, Lison JF, Rosado-Calatayud P, Amer-Cuenca JJ, Segura-Orti E (2015) Factors associated with the 6-minute walk test in nursing home residents and community-dwelling older adults. *J Phys Ther Sci* **27**, 3571-3578.
- [47] Jones CJ, Rikli RE, Beam WC (1999) A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Exerc Sport* **70**, 113-119.
- [48] (2001) Dementia Questionnaire V2.0. Fred Hutchinson Cancer Research Center, Women's Health Initiative, [https://www.whi.org/researchers/data/Layouts/15/WopiFrame.aspx?sourcedoc=/researchers/data/whims%20documents/StudyForms/Dementia\\_Questionnaire\\_V2.0a.PDN.pdf&action=default](https://www.whi.org/researchers/data/Layouts/15/WopiFrame.aspx?sourcedoc=/researchers/data/whims%20documents/StudyForms/Dementia_Questionnaire_V2.0a.PDN.pdf&action=default)
- [49] Wharton W, Stein JH, Korcarz C, Sachs J, Olson SR, Zetterberg H, Dowling M, Ye S, Gleason CE, Underbakke G, Jacobson LE, Johnson SC, Sager MA, Asthana S, Carlsson CM (2012) The effects of ramipril in individuals at risk for Alzheimer's disease: Results of a pilot clinical trial. *J Alzheimers Dis* **32**, 147-156.
- [50] Okonkwo OC, Xu G, Oh JM, Dowling NM, Carlsson CM, Gallagher CL, Birdsill AC, Palotti M, Wharton W, Hermann BP, LaRue A, Bendlin BB, Rowley HA, Asthana S, Sager MA, Johnson SC (2014) Cerebral blood flow is diminished in asymptomatic middle-aged adults with maternal history of Alzheimer's disease. *Cereb Cortex* **24**, 978-988.
- [51] McKee KE, Hackney ME (2013) The effects of adapted tango on spatial cognition and disease severity in Parkinson's disease. *J Mot Behav* **45**, 519-529.
- [52] Murphy EC, Carson L, Neal W, Baylis C, Donley D, Yeater R (2009) Effects of an exercise intervention using Dance Dance Revolution on endothelial function and other risk factors in overweight children. *Int J Pediatr Obes* **4**, 205-214.
- [53] von Kanel R, Mills PJ, Mausbach BT, Dimsdale JE, Patterson TL, Ziegler MG, Ancoli-Israel S, Allison M, Chattillion EA, Grant I (2012) Effect of Alzheimer caregiving on circulating levels of C-reactive protein and other biomarkers relevant to cardiovascular disease risk: A longitudinal study. *Gerontology* **58**, 354-365.
- [54] Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* **53**, 695-699.
- [55] Rainville C, Amieva H, Lafont S, Dartigues JF, Orgogozo JM, Fabrigoule C (2002) Executive function deficits in



- patients with dementia of the Alzheimer's type: A study with a Tower of London task. *Arch Clin Neuropsychol* **17**, 513-530.
- [56] Golden C (1978) *The Stroop Color and Word Test: A manual for clinical and experimental uses*, Stoetling, Chicago.
- [57] Bowie CR, Harvey PD (2006) Administration and interpretation of the Trail Making Test. *Nat Protoc* **1**, 2277-2281.
- [58] Wechsler D (2008) *Wechsler Adult Intelligence Scale-Fourth Edition: Technical and interpretative manual*, Pearson Assessment, San Antonio, TX.
- [59] Buschke H (1973) Selective reminding for analysis of memory and learning. *J Verb Learn Verb Behav* **12**, 543-550.
- [60] Brooks LR (1967) The suppression of visualization by reading. *Q J Exp Psychol* **19**, 289-299.
- [61] Hackney ME, Hall CD, Echt KV, Wolf SL (2013) Dancing for balance: Feasibility and efficacy in oldest-old adults with visual impairment. *Nurs Res* **62**, 138-143.
- [62] Pearlin LI, Mullan JT, Semple SJ, Skaff MM (1990) Caregiving and the stress process: An overview of concepts and their measures. *Gerontologist* **30**, 583-594.
- [63] Murphy PJ, Williams RL (2013) Weight-loss study in African-American Women: Lessons learned from project take HEED and future, technologically enhanced directions. *Perm J* **17**, 55-59.
- [64] Vitaliano PP, Murphy M, Young HM, Echeverria D, Borson S (2011) Does caring for a spouse with dementia promote cognitive decline? A hypothesis and proposed mechanisms. *J Am Geriatr Soc* **59**, 900-908.
- [65] Caswell LW, Vitaliano PP, Croyle KL, Scanlan JM, Zhang J, Daruwala A (2003) Negative associations of chronic stress and cognitive performance in older adult spouse caregivers. *Exp Aging Res* **29**, 303-318.
- [66] Canonici AP, Andrade LP, Gobbi S, Santos-Galduroz RF, Gobbi LT, Stella F (2012) Functional dependence and caregiver burden in Alzheimer's disease: A controlled trial on the benefits of motor intervention. *Psychogeriatrics* **12**, 186-192.
- [67] Corbett A, Pickett J, Burns A, Corcoran J, Dunnett SB, Edison P, Hagan JJ, Holmes C, Jones E, Katona C, Kearns I, Kehoe P, Mudher A, Passmore A, Shepherd N, Walsh F, Ballard C (2012) Drug repositioning for Alzheimer's disease. *Nat Rev Drug Discov* **11**, 833-846.