Low-Intensity Daily Walking Activity is Associated With Hippocampal Volume in Older Adults

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ABSTRACT: Hippocampal atrophy is associated with memory impairment and dementia and serves as a key biomarker in the preclinical stages of Alzheimer's disease. Physical activity, one of the most promising behavioral interventions to prevent or delay cognitive decline, has been shown to be associated with hippocampal volume; specifically increased aerobic activity and fitness may have a positive effect on the size of the hippocampus. The majority of older adults, however, are sedentary and have difficulty initiating and maintaining exercise programs. A modestly more active lifestyle may nonetheless be beneficial. This study explored whether greater objectively measured daily walking activity was associated with larger hippocampal volume. We additionally explored whether greater low-intensity walking activity, which may be related to leisure-time physical, functional, and social activities, was associated with larger hippocampal volume independent of exercise and higher-intensity walking activity. Segmentation of hippocampal volumes was performed using Functional Magnetic Resonance Imaging of the Brain's Software Library (FSL), and daily walking activity was assessed using a step activity monitor on 92, nondemented, older adult participants. After controlling for age, education, body mass index, cardiovascular disease risk factors, and the Mini Mental State Exam, we found that a greater amount, duration, and frequency of total daily walking activity were each associated with larger hippocampal volume among older women, but not among men. These relationships were specific to hippocampal volume, compared with the thalamus, used as a control brain region, and remained significant for low-intensity walking activity, independent of moderate- to vigorous-intensity activity and self-reported exercise. This is the first study, to our knowledge, to explore the relationship between objectively measured daily walking activity and hippocampal volume in an older adult population. Findings suggest the importance of examining whether increasing nonexercise, lifestyle physical activities may produce measurable cognitive benefits and affect hippocampal volume through molecular pathways unique to those related to moderate-intensity exercise. © 2014 Wiley Periodicals, Inc.

KEY WORDS: aging; physical activity; African Americans; cognition; brain

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INTRODUCTION

Given the disappointing results of numerous dietary and pharmaceutical studies and primary prevention trials to delay or halt Alzheimer's disease (AD) (Daviglus et al., 2010), focus has shifted toward more promising behavioral and activity-based approaches to prevent or delay cognitive decline. The relationship between increased physical activity and reduced risk of AD (Abbott et al., 2004; Podewils et al., 2005; Larson et al., 2006; Buchman et al., 2012) as well as increased physical activity and cognitive health (Yaffe et al., 2001; Weuve et al., 2004; Rockwood and Middleton, 2007; Angevaren et al., 2008; Lautenschlager et al., 2008) have been shown in a number of large, epidemiologic studies.

Animal models have provided much of the neurobiologic evidence linking physical activity to enhanced brain function, implicating the hippocampus as particularly structurally and functionally sensitive to exercise (Cotman and Berchtold, 2007), a subcategory of physical activity. In mice models, voluntary exercise increases cell proliferation in the adult hippocampus (van Praag et al., 1999a,b) and reduces age-dependent decline in hippocampal neurogenesis (Kronenberg et al., 2006); this relationship may be partially mediated through trophic factors, including insulin-like growth factor 1 and brain-derived neurotrophic factor (Vaynman et al., 2004; Ferris et al., 2007) and increased cerebral blood flow and angiogenesis (van Praag et al., 2005; Pereira et al., 2007). Mice with access to a running wheel have additionally shown better spatial learning and memory on water maze tests (van Praag et al., 1999b; Adlard et al., 2004).

Recent neurobiologic evidence in human models have began to link physical activity to key neurocognitive pathways vulnerable to dementia. Research has shown that exercise training may reduce brain atrophy in nondemented individuals (Colcombe et al., 2004, 2006; Erickson et al., 2010). Exercise and fitness may have a positive effect specifically on the size of the hippocampus (Erickson et al., 2009, 2010, 2011). Hippocampal atrophy is associated with memory impairment and dementia (Driscoll et al., 2003; Jack et al., 2009; Mueller et al., 2010) and may serve as a key biomarker in early and presymptomatic diagnosis of AD (Cummings, 2009; Jack et al., 2013). Thus, identifying modifiable factors that can have a positive effect on the hippocampus is critical for preventive and therapeutic strategies to preserve cognitive health and delay the onset of cognitive impairment (Fotuhi et al., 2012).

The majority of neurobiologic evidence showing the benefits of physical activity on cognition has indicated that exercise and improvements in cardiovascular fitness are associated with structural and functional benefits. Physical activity, however, includes a broad range of activities, in addition to exercise, which increases energy expenditure above a resting level (Howley, 2001; NHLBI, 2011). These activities can include nonexercise leisure-time and life-style activities (e.g., walking, gardening, etc.) and instrumental activities of daily living (e.g., shopping, housework, etc.), which are typically in the low-intensity range. Research using self-reported measures of walking activity indicates that these nonexercise physical activities may be associated with cognitive health benefits (Scarmeas et al., 2001; Yaffe et al., 2001). More recently, studies using objective measures of physical activity found that total physical activity and daytime movement, including both exercise and nonexercise physical activities, as well as total energy expenditure, were associated with better cognitive function, lower odds of cognitive impairment, and reduced risk of AD (Barnes et al., 2008; Buchman et al., 2008, 2012; Middleton et al., 2011).

Research into the cognitive benefits of low-intensity physical activity is extremely important considering that the majority of older adults are sedentary (Centers for Disease Control and Prevention, 2013; Harvey et al., 2013) and have difficulty initiating and adhering to exercise programs (Resnick and Spellbring, 2000; Schutzer and Graves, 2004). This is of particular concern for older adults of low socioeconomic status who have low baseline levels of physical activity and fewer physical activity-related facilities because of restrictive environmental and neighborhood characteristics (Day, 2006; Powell et al., 2006; United States Department of Health and Human Services, 2008; Parra-Medina et al., 2010). For older adults who may not participate in or have access to formal exercise programs, a more active lifestyle may be beneficial.

To our knowledge, no study has yet explored the relationship between objectively measured daily physical activity and brain structure, as well as the independent relationship between low-intensity physical activity and brain structure, in an older adult cohort. We, therefore, explored the cross-sectional associ-

ation between objectively measured daily walking activity and hippocampal volume in a nondemented, older, mostly sedentary cohort at elevated sociodemographic risk for cognitive and functional decline.

MATERIALS AND METHODS

Participants

Participants were from the Brain Health Study (BHS), a sub-study within the larger Baltimore Experience Corps Trial (BECT), a sex-stratified, randomized, controlled effectiveness trial to evaluate the health benefits for older adults participating in Experience Corps Baltimore, a high-intensity volunteer service program, vs. a control group offered other low-service volunteer opportunities. Details on sex-stratification, randomization, study design, sampling methodology, and recruitment have been described previously (Fried et al., 2004, 2013). Enrollment criteria included the following: age ≥ 60 yrs; ≥ 24 on the Mini-Mental State Exam (MMSE) (Folstein et al., 1975); and ability to read at a minimum sixth grade level (Wilkinson, 1993). BHS enrollment criteria have been described previously (Agbedia et al., 2011; Chuang et al., 2013; Carlson et al., in press) and included right-hand dominance, free of a pacemaker or other ferrous metals in the body, and no history of brain cancer or brain aneurism/stroke in the past year.

Of the 123 participants enrolled in the BHS, 10 participants did not complete the magnetic resonance imaging (MRI) evaluation because of excessive head movement or claustrophobia and 21 did not complete or provide usable data for the objective walking activity assessment (see later for exclusion criteria). The final usable sample included 92 participants. The baseline evaluation occurred prior to randomization to BECT intervention or control groups. Participants in the final study sample did not vary significantly ($P < 0.05$) from the remaining BECT participants on any sociodemographic or health characteristic at baseline other than sex. The study protocol was approved by the Johns Hopkins School of Medicine Institutional Review Board, and each participant provided written informed consent.

Walking Activity Measure

Walking activity was measured using a step activity monitor (SAM; Orthocare Innovations, Mt. Terrace, WA), an accelerometer that is worn on the dominant ankle and measures step activity in daily life over continuous periods of time. The device measures the number of steps at 1-min intervals using acceleration, position, and timing information, and can therefore characterize the amount, duration, and frequency of daily walking activity. The SAM has been validated across a range of community-dwelling older adult populations with varying levels of function using self-report and objective measures (e.g.,

hand-tallied step counts and accelerometers) (Resnick et al., 2001; Cavanaugh et al., 2007; Storti et al., 2008). The SAM is particularly sensitive in measuring activity at decreased gait speeds (Storti et al., 2008) and is well tolerated by older adults because it is placed on the ankle vs. the hip (Algase et al., 2003).

Participants were instructed to wear the SAM for 3–7 days while keeping a wear time/activity diary at ~1-hr intervals. Participants were instructed to remove the SAM only when bathing, showering, or swimming, and replace the device immediately after. The majority of participants wore the SAM during the late summer and fall, which reduced the influence of seasonal effects. Additionally, the majority of participants were not employed at baseline (79%), which reduced the influence of weekday/weekend effects. The data cleaning protocol included exclusion of days that represented noncompliance based on SAM inactivity and by participants' self-reported noncompliance in their activity diaries. Detailed cleaning protocol for a larger sample, of which participants in this study are a subsample, has been described previously (Varma et al., 2014).

In order to characterize the proportion of participants meeting physical activity guidelines, we used the 10,000 steps/day threshold developed in previous studies as a reasonable equivalent of U.S. physical activity guidelines (Tudor-Locke and Bassett, 2004; Tudor-Locke et al., 2008; Table 1). We classified participants who met the 10,000 steps/day threshold across all days surveyed as active. Based on previous studies translating physical activity recommendations (30 min of moderate-intensity activity/day that can be split into three 10-min bouts) into a pedometer-based step goal (3 bouts/day of 1,000 steps in 10 min Tudor-Locke et al., 2005; Marshall et al., 2009), we additionally classified participants who met the 3 bouts/day threshold across all days surveyed as active.

Intensity ranges (effort associated with walking) included low-intensity (>0 steps/min and <100 steps/min) and moderate- to vigorous-intensity (≥100 steps/min) based on studies translating laboratory measurements of oxygen consumption while walking into pedometer-based metrics (Tudor-Locke et al., 2005; Marshall et al., 2009). Metrics representing components of activity, including amount, duration, and frequency (Howley, 2001; Kesaniemi et al., 2001) within intensity ranges are summarized in Table 1.

Activity amount was defined as the number of steps/day, and included total steps/day segmented into steps/day at low-intensity and at moderate- to vigorous-intensity. Activity duration was defined as the number of minutes/day of any activity and included total minutes/day segmented into minutes/day at low-intensity and at moderate- to vigorous-intensity. Activity frequency was defined as the number of bouts/day of continuous 10-min activity and calculated by adding the number of times participants completed 10 min of activity. We included total bouts/day as well as bouts/day at low-intensity and at moderate- to vigorous-intensity. All metrics were averaged across all valid days surveyed.

TABLE 1.

Baseline Characteristics of Brain Health Study Subjects (N = 92)

Characteristic	N (%) or mean ± SD
Age (years)	67.3 ± 6.1
Sex (women)	64 (69.6)
Race (African American)	82 (89.1)
Education (≤high school)	34 (37.0)
Income (<$15,000)	27 (29.4)
MMSE	28.4 (1.5)
Chronic disease	
Obesity (BMI ≥ 30)	52 (56.5)
Hypertension	66 (72.5)
Diabetes	29 (31.9)
Brain volume[a]	
Hippocampus (cm^3)	6.9 ± 0.8
Thalamus (cm^3)	15.1 ± 1.0
% Meeting physical activity guidelines	
10,000 steps/day[b]	
Active (≥10,000 steps/day)	11 (12.0)
30 min of moderate-intensity activity[c]	
Active (≥30 min/day)	0 (0.0)
Daily walking activity metrics	
Amount	
Steps/day (total)	7,969.4 ± 3,516.2
Steps/day at low-intensity[d]	7,212.1 ± 2,814.3
Steps/day at moderate to vigorous intensity[e]	757.3 ± 1,045.1
Duration	
Minutes of activity (total)	337.8 ± 94.8
Minutes of activity at low-intensity[d]	330.9 ± 91.4
Minutes of activity at moderate to vigorous intensity[e]	6.9 ± 9.6
Frequency	
Bouts of 10 min activity (total)	11.9 ± 6.9
Bouts of 10 min activity at low-intensity[d]	10.5 ± 6.0
Bouts of 10 min activity at moderate- to vigorous-intensity[e]	0.1 ± 0.4
Exercise	
Total caloric expenditure/week[f]	1,209.3 ± 1,616.8

[a]Adjusted for intercranial volume (ICV).
[b]10,000 steps/day is considered an estimate of daily recommended walking activity.
[c]30 minutes/day of moderate-intensity activity (≥100 steps/min) is considered an estimate of daily recommended walking activity.
[d]Low intensity is defined as walking activity at <100 steps/min.
[e]Moderate to vigorous intensity is defined as walking activity at ≥100 steps/min.
[f]Assessed using the self-report of exercise-related physical activities from the Community Health Activities Model Program for Seniors (CHAMPS) questionnaire.
SD, standard deviation; MMSE, Mini Mental State Exam.

MR Image Acquisition and Preprocessing

High-resolution brain images were acquired on a 3.0 T Phillips scanner (Best, the Netherlands) using a 3D T1-weighted MPRAGE sequence (Magnetization Prepared Rapid Gradient

Echo Imaging) with the following parameters: repetition time- = 8.037 ms; echo time = 3.7 ms; flip angle = 8°; 200 contiguous 1-mm sagittal slices; field of view = 200 mm × 256 mm × 200 mm; matrix size = 256 mm × 256 mm; and voxel size =1 × 1 × 1 mm. The protocol has been described previously (Carlson et al., 2009; Chuang et al., 2013). Segmentation of hippocampal and thalamus volumes were performed using Functional MRI of the Brain's (FMRIB's) Integrated Registration and Segmentation Tool (FIRST) in FMRIB's Software Library (FSL) version 4.1 (Patenaude et al., 2011) and has been successfully used previously in older adult populations (e.g., Erickson et al., 2009, 2011) and validated against other automated methods and manual tracing (Seixas and de Souza, 2010; Eggert et al., 2012). FIRST is a model-based segmentation/registration tool using a Bayesian framework from shape and appearance models obtained from manually segmented images from the Center for Morphometric Analysis, Massachusetts General Hospital, Boston, MA. Briefly, images were first registered to Montreal Neurological Institute (MNI) 152 standard space using two-stage affine transformations based on 12 degrees of freedom. A subcortical mask was then applied to exclude voxels outside the subcortical regions. Then, the volumes were segmented with 30 modes of variation. Last, boundary correction was performed to classify the boundary voxels as belonging to the structure or not according to a statistical probability (z-score > 3.00; $P < 0.001$). Additional preprocessing steps included motion correction and nonuniform intensity normalization. All processed images were then visually inspected to identify any significant errors resulting from the segmentation process. No participants were excluded due to segmentation errors.

All brain volumes (hippocampus and thalamus) were adjusted for sex and height using a measure of intracranial volume (ICV) as a covariate in all analyses. ICV was calculated as the sum of gray, white, and cerebrospinal fluid using FMRIB's automated segmentation tool in FSL version 4.1 (Zhang et al., 2001; Smith et al., 2004) and used as a covariate in all analyses.

Covariates

In order to control for potential confounders of the relationship between daily walking activity and brain volume, all models included a number of covariates associated with both physical activity and hippocampal volume in prior studies. These included ICV, age, years of education, body mass index (BMI), cardiovascular disease (CVD) burden, exercise, and global cognitive function measured by the MMSE. All covariates were assessed at baseline. BMI was calculated using height and weight. CVD burden was calculated by summing participants' self-report of hypertension, diabetes, heart attack/myocardial infarction, intermittent claudication, congestive heart failure, and angina/chest pain due to heart disease. Self-reported exercise was assessed using the Community Health Activities Model Program for Seniors (CHAMPS) (Stewart et al., 2001) and included estimated caloric expenditure/week

for 12 exercise-related physical activities: jogging/running, walking fast for exercise, aerobic machines, water exercises, swimming moderately/fast, swimming gently, stretching/flexibility exercises, yoga/tai-chi, aerobics/aerobic dancing, moderate/heavy strength training, light strength training, and general conditioning. The MMSE, a global test of cognitive function useful in quantitatively estimating the severity of cognitive impairment (Folstein et al., 1975), was administered by a trained evaluator.

Statistical Analysis

The main objective of the analyses was to explore whether components of daily walking activity, including amount, duration, and frequency, were associated with hippocampal volume independent of covariates. Multiple linear regression using Stata version 12 (StataCorp., College Station, TX) was used to model the relationship between the dependent variable (brain volume) and explanatory variables (e.g., daily walking activity; Tables 2 and 3). The models were fit using the least squares approach to estimate model parameters. Standardized Beta (β) coefficients, standard errors (SE), and P-values of two-sided statistical tests are presented in Tables 2 and 3; F-statistics with degrees of freedom for the model and residuals, R^2 values (e.g., percent of variance of brain volume explained by daily walking activity), t-statistics, and P-values, in addition to coefficient values as a percentage of mean hippocampal volume, are reported in the Results section. Pearson's correlations between the explanatory variable of interest (daily walking activity) and confounders are also included in the Results section. To assess the regional specificity of daily walking activity, we explored the thalamus as a control region; this brain structure has been used previously to investigate regional specificity of physical activity (Erickson et al., 2011).

Model 1 explored the relationship between components of total daily walking activity and hippocampal volume as well as the control brain region. Model 2 explored whether objectively measured, low-intensity daily walking activity was associated with hippocampal volume independent of the relationship between exercise and hippocampal volume. Low-intensity walking activity, which may include nonexercise lifestyle activities (e.g., walking for pleasure) and instrumental activities of daily living (e.g., walking related to housework or shopping) (United States Department of Health and Human Services, 2008), and moderate- to vigorous-intensity walking activity were included as separate variables. Self-reported exercise and covariates included in Model 1 were additionally included in Model 2.

Analyses were stratified by sex *a priori*. The BHS was designed to allow for sex stratification in analyses of brain volume (Fried et al., 2013), given differences in brain morphology and differences in the association between exercise and neurocognition (Colcombe and Kramer, 2003; Coelho et al., 2012; Vaughan et al., 2012). Additionally, in exploratory analysis in the nonstratified models, we observed a significant sex by walking activity interaction (not shown). Estimated effect sizes of steps/day (amount) and minutes of activity (duration) were expressed in units of 1,000 steps/day and 10 min/day,

Multiple Linear Regression Models of Daily Walking Activity and Brain Volume Stratified by Sex: Model 1

	Hippocampal volume (cm3)				Thalamus volume (cm3)			
	Women		Men		Women		Men	
	β	SE	β	SE	β	SE	β	SE
Amount								
Total steps/day (per 1,000 steps increase)	0.10*	0.03	−0.08	0.05	0.02	0.05	−0.10	0.05
Age	−0.03**	0.01	0.00	0.04	−0.06*	0.02	−0.05	0.04
CVD[a]	−0.21**	0.09	−0.59**	0.24	−0.15	0.12	−0.55	0.26
Duration								
Total minutes/day (per 10 min increase)	0.02**	0.01	−0.05	0.02	0.00	0.01	−0.05	0.03
Age	−0.03**	0.01	0.01	0.04	−0.06*	0.02	−0.05	0.04
CVD[a]	−0.20**	0.09	−0.61**	0.23	−0.13	0.13	−0.55	0.26
Frequency								
Total bouts/day (per one 10-min bout)	0.04**	0.02	−0.04	0.02	0.01	0.02	−0.05	0.03
Age	−0.03**	0.01	0.00	0.04	−0.06*	0.02	−0.05	0.04
CVD[a]	−0.17	0.09	−0.59**	0.24	−0.14	0.12	−0.54	0.27

Note: All models included the following covariates: intercranial volume (ICV), age, years of education, body mass index (BMI), CVD, and the Mini Mental State Exam (MMSE).
[a]CVD calculated by summing participants self-report of vascular disease
*$P < 0.05$; **$P < 0.01$.
SE, standard error; CVD, cardiovascular disease burden.

respectively, based on previous studies as well as ease of interpretation (Sisson et al., 2010). The CHAMPS variable was log transformed because of its skewed distribution.

RESULTS

Baseline Characteristics of Study Subjects

Table 1 presents baseline characteristics of the study sample. A large percentage of participants had low education (37.0% reporting high school or less education) and income (29.4% reporting household income less than $15,000). Participants were additionally at risk for cognitive and physical function decline due to high rates of chronic disease: 56.52% of participants were obese (BMI ≥ 30), 72.53% reported hypertension, and 31.87% reported diabetes. Women were more obese compared with men ($P < 0.05$) and did not vary significantly on any other sociodemographic or health characteristic.

According to the 10,000 steps/day walking activity guideline, 12.0% of participants were considered active. According to Department of Health and Human Services guidelines of 30 min of moderate-intensity activity/day, no participants met guidelines by completing three or more 10-min bouts/day of 1,000 steps/bout. Results did not vary significantly by sex.

Participants completed a total of 7,969.4 (SD: 3,516.2) steps/day and 337.9 (SD: 94.8) minutes of activity/day. The majority of activity was in the low-intensity range (7,212.1 (SD: 2,814.3); 90.5% of total steps/day and 330.9 min/day (SD: 91.4); 97.9% of total minutes of activity/day) with minimal activity in the moderate- to vigorous-intensity ranges (757.3 (SD: 1,045.1); 9.5% of total steps/day and 6.9 min/day (SD: 9.6); 2.1% of total daily minutes of activity) (Fig. 1). Participants averaged 11.9 (SD: 6.9) bouts/day of 10-min activity. On average, participants expended 1,209.2 (SD: 1,616.8) calories/week in exercise-related physical activity. Women had a marginally greater number of low-intensity minutes of activity/day and fewer exercise-related calories/week expended compared with men ($P < 0.10$).

The mean volume of participants' hippocampus was 6.9 cm^3 (SD: 0.8) and thalamus was 15.1 cm^3 (SD: 1.0). Women, on average, had significantly smaller hippocampal and thalamus volumes and ICV compared with men ($P < 0.05$).

Daily Walking Activity and Hippocampal Volume

Total steps/day, total minutes/day, and total bouts/day were significantly correlated with BMI ($r = −0.45$, $P < 0.01$; $r = −0.40$, $P < 0.01$; and $r = −0.45$, $P < 0.01$, respectively) and no other covariates in women. Daily walking activity

TABLE 3.

Multiple Linear Regression Models of Low-Intensity Daily Walking Activity and Hippocampal Volume Stratified by Sex: Model 2

| | Hippocampal Volume (cm3) | | | |
| | Women | | Men | |
	β	SE	β	SE
Amount				
Low-intensity steps/day[a] (per 1,000 steps increase)	0.10*	0.04	−0.16	0.10
Moderate- to vigorous-intensity steps/day[b] (per 1,000 steps increase)	0.04	0.10	0.09	0.25
Age	−0.03	0.01	−0.01	0.04
CVD[c]	−0.22**	0.09	−0.50**	0.22
Exercise[d]	0.08*	0.07	0.12	0.06
Duration				
Low-intensity min/day[a] (per 1,000 steps increase)	0.02**	0.01	−0.04	0.03
Moderate-intensity min/day[b] (per 1,000 steps increase)	0.06	0.11	−0.12	0.20
Age	−0.03**	0.01	−0.01	0.04
CVD[c]	−0.21**	0.09	−0.50**	0.23
Exercise[d]	0.08*	0.03	0.13	0.07
Frequency				
Low-intensity bouts/day[a] (per one 10-min bout)	0.04**	0.02	−0.04	0.04
Moderate- to vigorous-intensity bouts/day[b] (per one 10-min bout)	0.06	0.21	−0.38	0.79
Age	−0.03**	0.01	−0.01	0.04
CVD[c]	−0.18**	0.09	−0.49	0.23
Exercise[d]	0.08*	0.03	0.12	0.06

Note: All models included the following covariates: intercranial volume (ICV), age, years of education, body mass index (BMI), CVD, exercise, moderate- to vigorous-intensity walking activity, and the Mini Mental State Exam (MMSE).
[a]Low intensity is defined as walking activity at <100 steps/min.
[b]Moderate to vigorous intensity is defined as walking activity at ≥ 100 steps/min.
[c]CVD calculated by summing participants' self-report of vascular disease.
[d]Exercise calculated as estimated caloric expenditure/week of self-reported exercise-related physical activities using the Community Health Activities Model Program for Seniors (CHAMPS) questionnaire.
*$P < 0.01$; **$P < 0.05$.
SE, standard error; CVD, cardiovascular disease burden.
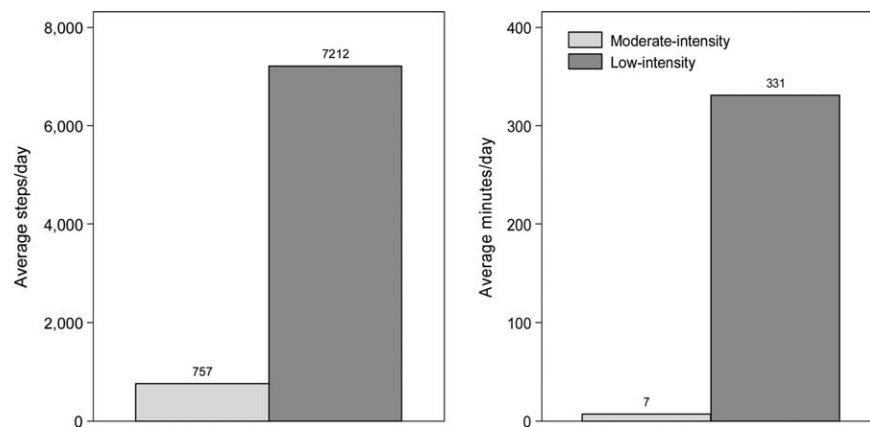

FIGURE 1.   Distribution of walking activity by intensity. Moderate- to vigorous-intensity walking activity contributed to only 9.5% of total steps/day and 2.1% of total minutes of activity/day. Note: low-intensity activity: <100 steps/min; moderate- to vigorous-intensity activity: $\geq$100 steps/min.
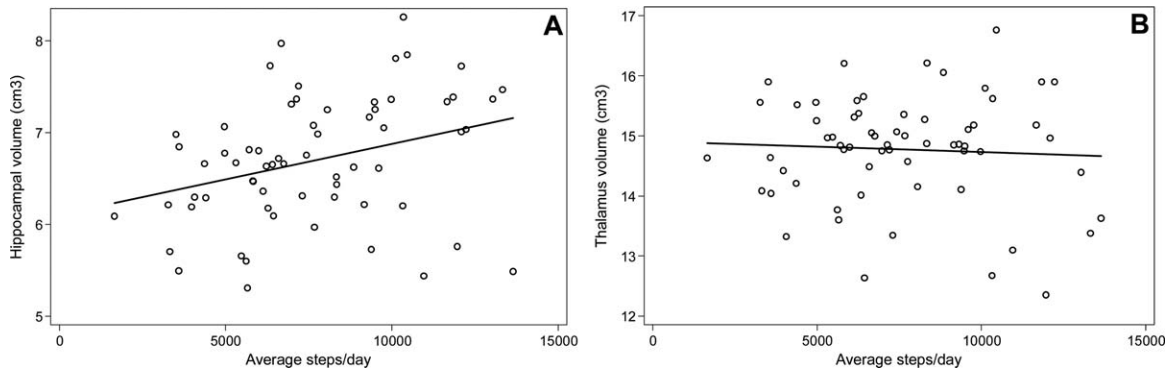
FIGURE 2. Relationship between daily walking activity and brain volume. A. Greater total daily walking activity was associated with larger hippocampal volume (adjusted for intracranial volume [ICV]) in women. Associations remained significant for low-intensity daily walking activity, and, after adding covariates exercise, moderate- to vigorous-intensity daily walking activity, age, years of education, body mass index (BMI), cardiovascular disease burden, and Mini Mental State Exam (MMSE). B. Total daily walking activity was not significantly associated with thalamus volume in women.

metrics were not significantly correlated with any other covariates in men. As expected, low-intensity steps/day, minutes/day, and bouts/day were each significantly correlated with moderate- to vigorous-intensity walking activity metrics in women (respectively, $r = 0.32$, $P = 0.01$; $r = 0.27$, $P = 0.03$; and bouts/day not significantly correlated) and men ($r = 0.80$, $P < 0.01$; $r = 0.52$, $P < 0.01$; and $r = 0.60$, $P < 0.01$, respectively).

Table 2 presents the sex-stratified associations between walking activity metrics and hippocampal volume. In Model 1, after adjusting for ICV, age, years of education, BMI, CVD burden, and MMSE, in women, an additional 1,000 steps/day was significantly associated with a 0.10 cm^3 larger hippocampal volume ($F(7, 54) = 5.63$; $R^2 = 0.42$; $t = 2.96$; $P < 0.01$; Fig. 2); an additional 10 min/day of total walking activity was significantly associated with a 0.02 cm^3 larger hippocampal volume ($F(7, 54) = 4.94$; $R^2 = 0.39$; $t = 2.35$; $P = 0.02$); and an additional 10-min bout of total walking activity was significantly associated with a 0.04 cm^3 larger hippocampal volume ($F(7, 54) = 5.11$; $R^2 = 0.40$; $t = 2.52$; $P = 0.02$). These associations were approximately 0.2%–1.4% of the mean hippocampal volume of the sample.

Table 3 presents the sex-stratified associations between low-intensity walking activity metrics and hippocampal volume independent of moderate- to vigorous-intensity walking activity and exercise. In women, an additional 1,000 steps/day in the low-intensity range was significantly associated with a 0.10 cm^3 larger hippocampal volume ($F(9, 52) = 6.04$; $R^2 = 0.51$; $t = 2.88$; $P < 0.01$); an additional 10 min/day of low-intensity walking activity was significantly associated with a 0.02 cm^3 larger hippocampal volume ($F(9, 52) = 5.57$; $R^2 = 0.49$; $t = 2.44$; $P = 0.02$); and an additional 10-min bout of low-intensity walking activity was significantly associated with a 0.04 cm^3 larger hippocampal volume ($F(9, 52) = 5.54$; $R^2 = 0.49$; $t = 2.50$; $P = 0.02$).

In men across all models, metrics of daily walking activity were not significantly associated with hippocampal volume or thalamus volume.

Covariates and Hippocampal Volume

We displayed covariates of interest (i.e., age, CVD burden, and exercise) in Tables 2 and 3. As expected, in women, older age was significantly associated with smaller brain regions (hippocampus and thalamus) across all models. CVD burden was associated with smaller hippocampal volume in Models 1 and 2 in women, and in men it was associated with smaller hippocampal volume in Models 1 and 2 (other than Model 2—Frequency). Greater exercise in women was significantly associated with larger hippocampal volume in Model 2.

We explored the relationship between daily walking activity and memory function measured by the Rey Auditory Verbal Learning Test and found no significant associations.

DISCUSSION

We observed that greater daily walking activity was cross-sectionally associated with larger hippocampal volumes among older women, but not among men, in a sample of nondemented, mostly sedentary older adults. As hypothesized, this relationship was specific to hippocampal volume, compared with the control brain region, thalamus volume, and remained significant for low-intensity walking activity, independent of moderate- to vigorous-intensity activity and self-reported exercise. Effect sizes in this sample ranged from 0.2% to 1.4% of average hippocampal volumes; considering annual hippocampal atrophy rates from 0.8% to 2.0% in healthy older adults (Du et al., 2006; Barnes et al., 2009; Fjell et al., 2009), these

findings underscore the importance of exploring whether modest increases in nonexercise, lifestyle activities in the low-intensity range may promote cognitive health related to memory and reduced risk of dementia.

These study results add to a growing body of evidence suggesting that in humans, physical activity may be linked to key brain regions vulnerable to dementia, including hippocampal volume. Prior evidence from human models shows that moderate-intensity exercise and aerobic fitness are associated with hippocampal volume (Erickson et al., 2009, 2010, 2011). Animal models have provided much of the mechanistic evidence supporting this relationship, suggesting that exercise may increase cerebral blood flow and angiogenesis, and may also promote neurogenesis through the upregulation of neurotrophic factors (Cotman and Berchtold, 2007; van Praag, 2008).

Recent research using objective physical activity monitors that can sensitively measure a broad range of physical activities in-community suggests that nonexercise physical activity may also be associated with cognitive health benefits (Buchman et al., 2012; Middleton et al., 2011). The results from this study extend this body of evidence to suggest that nonexercise walking activity within the low-intensity range may be associated with the same brain region most consistently shown to be affected by increased aerobic fitness and exercise. These findings lead us to ask whether increasing nonexercise, lifestyle physical activities may produce measurable cognitive benefits and affect hippocampal volume through biological pathways unique to those related to moderate-intensity exercise (Voss et al., 2014). Additionally, these findings suggest that it may be useful to explore the extent to which environmental enrichment and associated biological pathways may be critical to brain benefits independent of the intensity of physical activity within those contexts (van Praag et al., 2000).

Objective metrics of daily walking activity, including amount, duration, and frequency, may be important to accurately measure walking activity within a community setting, particularly among mostly sedentary older adults at elevated risk for cognitive and functional decline. Older adults within this cohort were mostly nonactive by traditional standards for exercise; very few met estimated physical activity guidelines, and the majority of daily walking activity was within the low-intensity range. Low-intensity walking activity in this study sample may be related to lifestyle physical activities as well as functional activities (e.g., walking to catch a bus, shopping, housekeeping, and caretaking of grandchildren). By adjusting for moderate- to vigorous-intensity walking activity and exercise—as well as age, education, CVD burden, BMI, and MMSE—all of which have been shown to be associated with hippocampal volume in older adults (e.g., Jack et al., 1998; Erickson et al., 2009, 2011; Szabo et al., 2011; Gattringer et al., 2012; Noble et al., 2012), these findings indicate that low-intensity daily walking activity is associated with hippocampal volume independent of these covariates. Hippocampal atrophy is one of the strongest predictors of progression to AD (Henneman et al., 2009). The results of this study suggest the importance of better understanding the brain health benefits of interventions that may increase low-intensity walking

activity, particularly for older adults who may be at high risk for functional decline and disability and may not be able to participate in moderate-intensity exercise.

In this study, we found a clear sex difference in the relationship between daily walking activity and hippocampal volume. These findings are consistent with a meta-analysis showing that physical activity may be more cognitively beneficial for women (Colcombe and Kramer, 2003) as well as the results of a number of randomized-clinical trials of exercise (van Uffelen et al., 2008; Baker et al., 2010; Vaughan et al., 2012). Additionally, compared with men in this study, women were more obese, and expended fewer calories/week in exercise-related activities. These risk factors may place women at elevated risk for physical and mobility difficulties, and therefore, hippocampal volumes in older women may be more sensitive to modest increases in low-intensity walking activity.

This study has limitations. Although the cognitive screening criteria used in the trial (MMSE ≥ 24) as well as the inclusion of a cognitive covariate in all analytic models may account for the possibility of reverse causation, the cross-sectional design of the study precludes causal inferences. Future longitudinal analyses within a randomized clinical trial design such as the BECT will enable us to explore whether intervention-related increases in nonexercise-related physical activity may result in increased hippocampal volume. In addition, although we excluded moderate- to vigorous-intensity from the low-intensity walking activity metrics, and controlled for self-reported exercise, the SAM does not differentiate among types of activities. In future analyses, we hope to utilize daily activity diaries to better understand how various types of daily walking activities may be associated with cognitive health. Finally, the study sample represented an understudied and at-risk segment of the older adult population, whereas a trial of high-intensity volunteer service may select for more health conscious members of the community. Therefore, generalization of findings to a larger population must be done so carefully.

To the best of our knowledge, this is the first study to explore the relationship between objectively measured total daily walking activity and hippocampal volume within a non-demented, community-dwelling cohort. The significant relationship between low-intensity daily walking activity and hippocampal volume, independent of moderate- to vigorous-intensity walking activity and self-reported exercise, indicates the importance of understanding the longitudinal benefits of modest increases in daily walking activity.

REFERENCES

Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H. 2004. Walking and dementia in physically capable elderly men. JAMA 292:1447–1453.

Adlard PA, Perreau VM, Engesser-Cesar C, Cotman CW. 2004. The timecourse of induction of brain-derived neurotrophic factor mRNA and protein in the rat hippocampus following voluntary exercise. Neurosci Lett 363:43–48.

Agbedia O, Varma V, Seplaki C, Seeman T, Fried L, Li L, Harris GC, Rebok GW, Xue QL, Tan EJ, Tanner E, Parisi JM, McGill S, Carlson MC. 2011. Blunted diurnal decline of cortisol among older adults with low socioeconomic status. Ann N Y Acad Sci 1231:56–64.

Algase DL, Beattie ER, Leitsch SA, Beel-Bates CA. 2003. Biomechanical activity devices to index wandering behavior in dementia. Am J Alzheimers Dis Other Demen 18:85–92.

Angevaren M, Aufdemkampe G, Verhaar HJ, 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:CD005381.

Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, Plymate SR, Fishel MA, Watson GS, Cholerton BA, Duncan GE, Mehta PD, Craft S. 2010. Effects of aerobic exercise on mild cognitive impairment: A controlled trial. Arch Neurol 67:71–79.

Barnes DE, Blackwell T, Stone KL, Goldman SE, Hillier T, Yaffe K. 2008. Cognition in older women: The importance of daytime movement. J Am Geriatr Soc 56:1658–1664.

Barnes J, Bartlett JW, van de Pol LA, Loy CT, Scahill RI, Frost C, Thompson P, Fox NC. 2009. A meta-analysis of hippocampal atrophy rates in Alzheimer's disease. Neurobiol Aging 30:1711–1723.

Buchman AS, Wilson RS, Bennett DA. 2008. Total daily activity is associated with cognition in older persons. Am J Geriatr Psychiatry 16:697–701.

Buchman AS, Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA. 2012. Total daily physical activity and the risk of AD and cognitive decline in older adults. Neurology 78:1323–1329.

Carlson MC, Erickson KI, Kramer AF, Voss MW, Bolea N, Mielke M, McGill S, Rebok GW, Seeman T, Fried LP. 2009. Evidence for neurocognitive plasticity in at-risk older adults: The experience corps program. J Gerontol A Biol Sci Med Sci 64:1275–1282.

Carlson MC, Kuo JH, Chuang YF, Varma VR, Harris GC, Albert MA, Erickson KI, Kramer AF, Parisi JM, Xue QL, Tan EJ, Tanner EK, Gross A, Seeman TW, Gruenwald TL, McGill S, Rebok GW, Fried LP. 2014. Impact of a multi-modal intervention on brain volume: the Baltimore Experience Corps trial brain health study. Alzheimer's & Dementia (in press).

Cavanaugh JT, Coleman KL, Gaines JM, Laing L, Morey MC. 2007. Using step activity monitoring to characterize ambulatory activity in community-dwelling older adults. J Am Geriatr Soc 55:120–124.

Centers for Disease Control and Prevention. 2013. One in Five Adults Meet Physical Activity Guidelines. Last updated May 2, 2013. Last accessed January 31, 2013. Available at: http://www.cdc.gov/media/releases/2013/p0502-physical-activity.html

Chuang YF, Eldreth D, Erickson KI, Varma V, Harris G, Fried LP, Rebok GW, Tanner EK, Carlson MC. 2013. Cardiovascular risks and brain function: A functional magnetic resonance imaging study of executive function in older adults. Neurobiol Aging 35:1396–1403.

Coelho FM, Pereira DS, Lustosa LP, Silva JP, Dias JM, Dias RC, Queiroz BZ, Teixeira AL, Teixeira MM, Pereira LS. 2012. Physical therapy intervention (PTI) increases plasma brain-derived neurotrophic factor (BDNF) levels in non-frail and pre-frail elderly women. Arch Gerontol Geriatr 54:415–420.

Colcombe S, Kramer AF. 2003. Fitness effects on the cognitive function of older adults: A meta-analytic study. Psychol Sci 14:125–130.

Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, Webb A, Jerome GJ, Marquez DX, Elavsky S. 2004. Cardiovascular fitness, cortical plasticity, and aging. Proc Natl Acad Sci U S A 101:3316–3321.

Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, Elavsky S, Marquez DX, Hu L, Kramer AF. 2006. Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci 61:1166–1170.

Cotman CW, Berchtold NC. 2007. Physical activity and the maintenance of cognition: Learning from animal models. Alzheimers Dement 3:S30–S37.

Cummings JL. 2009. Defining and labeling disease-modifying treatments for Alzheimer's disease. Alzheimers Dement 5:406–418.

Daviglus ML, Bell CC, Berrettini W, Bowen PE, Connolly ES Jr, Cox NJ, Dunbar-Jacob JM, Granieri EC, Hunt G, McGarry K, Patel D, Potosky AL, Sanders-Bush E, Silberberg D, Trevisan M. 2010. National Institutes of Health State-of-the-Science Conference statement: Preventing Alzheimer disease and cognitive decline. Ann Intern Med 153:176–181.

Day K. 2006. Active living and social justice: Planning for physical activity in low-income, Black, and Latino communities. J Am Plann Assoc 72:88–99.

Driscoll I, Hamilton DA, Petropoulos H, Yeo RA, Brooks WM, Baumgartner RN, Sutherland RJ. 2003. The aging hippocampus: Cognitive, biochemical and structural findings. Cereb Cortex 13:1344–1351.

Du AT, Schuff N, Chao LL, Kornak J, Jagust WJ, Kramer JH, Reed BR, Miller BL, Norman D, Chui HC, Weiner MW. 2006. Age effects on atrophy rates of entorhinal cortex and hippocampus. Neurobiol Aging 27:733–740.

Eggert LD, Sommer J, Jansen A, Kircher T, Konrad C. 2012. Accuracy and reliability of automated gray matter segmentation pathways on real and simulated structural magnetic resonance images of the human brain. PLoS One 7:e45081.

Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, Morris KS, White SM, Wojcicki TR, McAuley E, Kramer AF. 2009. Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus 19:1030–1039.

Erickson KI, Raji CA, Lopez OL, Becker JT, Rosano C, Newman AB, Gach HM, Thompson PM, Ho AJ, Kuller LH. 2010. Physical activity predicts gray matter volume in late adulthood: The Cardiovascular Health Study. Neurology 75:1415–1422.

Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, Wojcicki TR, Mailey E, Vieira VJ, Martin SA, Pence BD, Woods JA, McAuley E, Kramer AF. 2011. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A 108:3017–3022.

Ferris LT, Williams JS, Shen CL. 2007. The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. Med Sci Sports Exerc 39:728–734.

Fjell AM, Walhovd KB, Fennema-Notestine C, McEvoy LK, Hagler DJ, Holland D, Brewer JB, Dale AM. 2009. One-year brain atrophy evident in healthy aging. J Neurosci 29:15223–15231.

Folstein MF, Folstein SE, McHugh PR. 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198.

Fried LP, Carlson MC, Freedman M, Frick KD, Glass TA, Hill J, McGill S, Rebok GW, Seeman T, Tielsch J, Wasik BA, Zeger S. 2004. A social model for health promotion for an aging population: Initial evidence on the Experience Corps model. J Urban Health 81:64–78.

Fotuhi M, Do D, Jack C. 2012. Modifiable factors that alter the size of the hippocampus with ageing. Nat Rev Neurol 8:189–202.

Fried LP, Carlson MC, McGill S, Seeman T, Xue QL, Frick K, et al. 2013. Experience Corps: A dual trial to promote the health of older adults and children's academic success. Contemp Clin Trials 36:1–13.

Gattringer T, Enzinger C, Ropele S, Gorani F, Petrovic KE, Schmidt R, Fazekas F. 2012. Vascular risk factors, white matter hyperintensities and hippocampal volume in normal elderly individuals. Dement Geriatr Cogn Disord 33:29–34.

Harvey JA, Chastin SF, Skelton DA. 2013. Prevalence of sedentary behavior in older adults: A systematic review. Int J Environ Res Public Health 10:6645–6661.

Henneman WJ, Sluimer JD, Barnes J, van der Flier WM, Sluimer IC, Fox NC, Scheltens P, Vrenken H, Barkhof F. 2009. Hippocampal

atrophy rates in Alzheimer disease: Added value over whole brain volume measures. Neurology 72:999–1007.

Howley ET. 2001. Type of activity: Resistance, aerobic and leisure versus occupational physical activity. Med Sci Sports Exerc 33:S364–S369; discussion S419–S420.

Jack CR Jr, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, et al. 1998. Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. Neurology 51:993–999.

Jack CR Jr, Lowe VJ, Weigand SD, Wiste HJ, Senjem ML, Knopman DS, et al. 2009. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: Implications for sequence of pathological events in Alzheimer's disease. Brain 132: 1355–1365.

Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ. 2013. Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. Lancet Neurol 12: 207–216.

Kesaniemi YK, Danforth E Jr, Jensen MD, Kopelman PG, Lefebvre P, Reeder BA. 2001. Dose-response issues concerning physical activity and health: An evidence-based symposium. Med Sci Sports Exerc 33:S351–S358.

Kronenberg G, Bick-Sander A, Bunk E, Wolf C, Ehninger D, Kempermann G. 2006. Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus. Neurobiol Aging 27:1505–1513.

Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, Kukull W. 2006. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med 144:73–81.

Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, Greenop KR, Almeida OP. 2008. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: A randomized trial. JAMA 300:1027–1037.

Marshall SJ, Levy SS, Tudor-Locke CE, Kolkhorst FW, Wooten KM, Ji M, Macera CA, Ainsworth BE. 2009. Translating physical activity recommendations into a pedometer-based step goal: 3000 steps in 30 minutes. Am J Prev Med 36:410–415.

Middleton LE, Manini TM, Simonsick EM, Harris TB, Barnes DE, Tylavsky F, Brach JS, Everhart JE, Yaffe K. 2011. Activity energy expenditure and incident cognitive impairment in older adults. Arch Intern Med 171:1251–1257.

Mueller SG, Schuff N, Yaffe K, Madison C, Miller B, Weiner MW. 2010. Hippocampal atrophy patterns in mild cognitive impairment and Alzheimer's disease. Hum Brain Mapp 31:1339–1347.

NHLBI. 2011. What is Physical Activity?—Explore Physical Activity and Your Heart. Last updated Sep 26, 2011. Last accessed March 19, 2013. Available at: http://www.nhlbi.nih.gov/health/health-topics/topics/phys/

Noble KG, Grieve SM, Korgaonkar MS, Engelhardt LE, Griffith EY, Williams LM, Brickman AM. 2012. Hippocampal volume varies with educational attainment across the life-span. Front Hum Neurosci 6:307.

Parra-Medina D, Wilcox S, Wilson DK, Addy CL, Felton G, Poston MB. 2010. Heart Healthy and Ethnically Relevant (HHER) lifestyle trial for improving diet and physical activity in underserved African American women. Contemp Clin Trials 31:92–104.

Patenaude B, Smith SM, Kennedy DN, Jenkinson M. 2011. A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage 56:907–922.

Pereira AC, Heddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, Sloan R, Gage FH, Brown TR, Small SA. 2007. An in vivo correlated of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci U S A 104:5638–5643.

Podewils LJ, Guallar E, Kuller LH, Fried LP, Lopez OL, Carlson M, Lyketsos CG. 2005. Physical activity, APOE genotype, and dementia risk: Findings from the Cardiovascular Health Cognition Study. Am J Epidemiol 161:639–651.

Powell LM, Slater S, Chaloupka FJ, Harper D. 2006. Availability of physical activity-related facilities and neighborhood demographic and socioeconomic characteristics: A national study. Am J Public Health 96:1676–1680.

Resnick B, Spellbring A. 2000. The factors that influence exercise behavior in older adults. J Gerontol Nurs 26:34–42.

Resnick B, Nahm ES, Orwig D, Zimmerman SS, Magaziner J. 2001. Measurement of activity in older adults: Reliability and validity of the Step Activity Monitor. J Nurs Meas 9:275–290.

Rockwood K, Middleton L. 2007. Physical activity and the maintenance of cognitive function. Alzheimers Dement 3:S38–S44.

Scarmeas N, Levy G, Tang MX, Manly J, Stern Y. 2001. Influence of leisure activity on the incidence of Alzheimer's disease. Neurology 57:2236–2242.

Schutzer KA, Graves BS. 2004. Barriers and motivations to exercise in older adults. Prev Med 39:1056–1061.

Seixas F, de Souza A. 2010. Anatomical brain MRI segmentation methods: Volumetric assessment of the hippocampus. Paper presented at the 17th International Conference on Systems, Signals and Image Processing.

Sisson SB, Camhi SM, Church TS, Tudor-Locke C, Johnson WD, Katzmarzyk PT. 2010. Accelerometer-determined steps/day and metabolic syndrome. Am J Prev Med 38:575–582.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, Bannister PR, Luca MDe, Drobnjak I, Flitney DE, Niazy R, Saunders J, Vickers J, Zhang Y, Stefano NDe, Brady JM, Matthews PM. 2004. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage 23: 208–219.

Stewart AL, Mills KM, King AC, Haskell WL, Gillis D, Ritter PL. 2001. CHAMPS physical activity questionnaire for older adults: Outcomes for interventions. Med Sci Sports Exerc 33:1126–1141.

Storti KL, Pettee KK, Brach JS, Talkowski JB, Richardson CR, Kriska AM. 2008. Gait speed and step-count monitor accuracy in community-dwelling older adults. Med Sci Sports Exerc 40:59–64.

Szabo AN, McAuley E, Erickson KI, Voss M, Prakash RS, Mailey EL, Wojcicki TR, White SM, Gothe N, Olson EA, Kramer AF. 2011. Cardiorespiratory fitness, hippocampal volume, and frequency of forgetting in older adults. Neuropsychology 25:545–553.

Tudor-Locke C, Bassett DR Jr. 2004. How many steps/day are enough? Preliminary pedometer indices for public health. Sports Med 34:1–8.

Tudor-Locke C, Sisson SB, Collova T, Lee SM, Swan PD. 2005. Pedometer-determined step count guidelines for classifying walking intensity in a young ostensibly healthy population. Can J Appl Physiol 30:666–676.

Tudor-Locke C, Hatano Y, Pangrazi RP, Kang M. 2008. Revisiting "how many steps are enough?" Med Sci Sports Exerc 40:S537–S543.

United States Department of Health and Human Services. 2008. Physical Activity Guidelines Advisory Committee Report. Washington, DC: United States Department of Health and Human Services.

van Praag H. 2008. Neurogenesis and exercise: Past and future directions. Neuromol Med 10:128–140.

van Praag H, Kempermann G, Gage FH. 1999a. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci 2:266–270.

van Praag H, Christie BR, Sejnowski TJ, Gage FH. 1999b. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci U S A 96:13427–13431.

van Praag H, Kempermann G, Gage FH. 2000. Neural consequences of environmental enrichment. Nat Rev Neurosci 1:191–198.

van Praag H, Shubert T, Zhao C, Gage FH. 2005. Exercise enhances learning and hippocampal neurogenesis in aged mice. J Neurosci 25:8680–8685.

van Uffelen JG, Chinapaw MJ, 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 42:344–351.

Varma VR, Tan EJ, Wang T, Xue QL, Fried LP, King AC, Seplaki CL, Seeman TE, Rebok GW, Carlson MC. 2014. Low-intensity walking activity is associated with better health. J Appl Gerontol 33:870–887

Vaughan S, Morris N, Shum D, O'Dwyer S, Polit D. 2012. Study protocol: A randomised controlled trial of the effects of a multi-modal exercise program on cognition and physical functioning in older women. BMC Geriatr 12:60.

Vaynman S, Ying Z, Gomez-Pinilla F. 2004. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. Eur J Neurosci 20:2580–2590.

Voss MW, Carr LJ, Clark R, Weng T. 2014.Revenge of the "sit" II: Does lifestyle impact neuronal and cognitive health through distinct mechanisms associated with sedentary behavior and physical activity? Mental Health Phys Act 7:9–24.

Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F. 2004. Physical activity, including walking, and cognitive function in older women. JAMA 292:1454–1461.

Wilkinson GS. 1993.WRAT3: Wide Range Achievement Test 3. Wilmington, DE: Wide Range Inc.

Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K. 2001. A prospective study of physical activity and cognitive decline in elderly women: Women who walk. Arch Intern Med 161:1703–1708.

Zhang Y, Brady M, Smith S. 2001. Segmentation of brain MR images through a hidden Markov random field model and the expectation maximization algorithm. IEEE Trans Med Imag 20:45–57.