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Hippocampal Sub-Regional Shape and Physical Activity in Older Adults

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Abstract

Hippocampal atrophy is a hallmark of Alzheimer's disease pathology, and a target biomarker region for testing intervention efficacy. Over the last few decades, a growing body of evidence from animal and human models suggests that physical activity (PA) is associated with structural benefits to the hippocampus in older adults. Very few human studies, however have explored hippocampal sub-regional specificity of PA; this is significant considering that sub-regions of the hippocampus are associated with distinct cognitive tasks and are differentially affected by disease pathology. This study used objective and self-reported measures of daily walking activity and exercise, and surface-based regional shape analysis using high-field hippocampal sub-regional partitions to explore sub-region specific hippocampal associations in a sample of nondemented, community-dwelling older adults at elevated sociodemographic risk for cognitive decline. Vertex-wise surface areas, which may be more sensitive than global volume measures, were calculated using shape diffeomorphometry, and PA was assessed using step activity monitors and PA questionnaires. We found that daily walking activity in a participant's environment was associated in cross-section mainly with larger surface areas of the subiculum in women. Associations remained significant when controlling for self-reported exercise. Prior studies have found that PA related to exercise and aerobic fitness may be most closely associated with the anterior hippocampus, particularly the dentate gyrus of the hippocampus. These novel findings are the first, to our knowledge, in human models to suggest that PA related to navigation that may not reach the level of moderate-intensity exercise may be associated with specific sub-regions of the hippocampus. These findings underscore the importance of better understanding the independent and related biological mechanisms and pathways by which increasing exercise as well as non-exercise, lifestyle PA may influence structural brain health.

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Keywords

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INTRODUCTION

Over the last two decades, a growing body of evidence suggests that physical activity (PA), in particular exercise and increased aerobic fitness, may be beneficial to brain health (Hillman et al., 2008; Ahlskog et al., 2011; Brown et al., 2013; Carlson and Varma, 2015). Given the lack of successful pharmacologic interventions for Alzheimer's disease (AD) and other types of dementia (Daviglus et al., 2010; Blazer et al., 2015), an increasing number of recent clinical trials have explored the cognitive benefits of exercise-related interventions among older adults. While no major clinical trial has yet shown that exercise can reduce the incidence of AD, a number of trials have shown some success in targeting risk factors associated with AD (Lautenschlager et al., 2008; Williamson et al., 2009; Erickson et al., 2011), with some exceptions (e.g., Sink et al., 2015)). Additionally, non-exercise, lifestyle PA within complex environments may protect against cognitive decline and dementia, and may be more effective than single-modal activities (Carlson et al., 2008; Carlson et al., 2012; Voss et al., 2013).

Physical activity includes a broad range of activities that increase energy expenditure above a resting level (Howley, 2001; NHLBI, 2011), and can vary by intensity (i.e., low-intensity—vigorous-intensity) as well as context (i.e., varying environmental complexity). The type of PA may promote better brain health and cognition through different mechanisms; moderate-intensity exercise may lead to benefits through increased aerobic and cardiovascular fitness (Colcombe and Kramer, 2003; Erickson et al., 2011) while increased lower-intensity lifestyle activities may lead to benefits through pathways related to navigating socially and cognitively enriched environments (Carlson et al., 2012).

While PA, and exercise in particular, may positively impact a broad network of neural structures including the frontal lobes, anterior cingulate cortex, inferior-temporal lobe, and the parietal cortex (Hillman, Erickson et al. 2008, Thomas, Dennis et al. 2012), the majority of animal-based (Cotman and Berchtold, 2002; Cotman and Berchtold, 2007; Kempermann et al., 2010) and human-based evidence (Hillman et al., 2008; Bherer et al., 2013; Carlson and Varma, 2015) indicate that the hippocampus is particularly structurally and functionally sensitive to PA. Research using mice and other animal models has indicated that voluntary exercise is associated with increased neurogenesis (Kempermann et al., 2002; Pereira et al., 2007), angiogenesis, and blood flow (Bloor, 2005; Pereira et al., 2007), synaptic strength (Farmer et al., 2004; Cotman et al., 2007), and other neuronal benefits to the hippocampus. Evidence additionally indicates that PA within complex and enriched environments may add complementary benefits to the effects of PA on the hippocampus (van Praag et al., 2000). Neurobiological evidence in human models has generally followed animal evidence showing that exercise is associated with reduced hippocampal atrophy (Smith et al., 2014) increased hippocampal volume (Erickson et al., 2011) and increased hippocampal perfusion including blood volume and flow (Pereira et al., 2007; Maass et al., 2015). These findings are

promising particularly because hippocampal atrophy is an anatomical hallmark of the progression of AD, and serves as a key biomarker for the diagnosis of early and presymptomatic AD (Cummings, 2009; Jack et al., 2013) as well as a target for interventions (McEwen, 1997; Erickson et al., 2011; Carlson et al., 2015; Carlson et al., 2016).

While the hippocampus is a target biomarker region for understanding intervention effects and neuropathology, subregions within the hippocampus perform distinct cognitive and computational tasks and may be differentially affected by aging, AD, and PA interventions (Small et al., 2011). These structurally and functionally different sub-regions include the dentate gyrus (DG), cornu ammonis region 1 (CA1), CA region 2 (CA2), CA region 3 (CA3), and the subiculum. Evidence mainly from animal models indicates that voluntary exercise as well as environmental enrichment may lead to regionally specific increased cell proliferation and neurogenesis in the DG sub-region (van Praag et al., 1999; Faherty et al., 2003; Eadie et al., 2005; Sahay et al., 2011; Dery et al., 2013), the only subregion of the hippocampus where neurogenesis occurs. Some animal studies have also found evidence for synaptic remodeling in the CA3 and CA1 subregions, in addition to the DG subregion, after wheel running (Schaefer et al., 2010), and increased dendritic spine density in the CA1 subregion after environmental enrichment (Faherty et al., 2003) and voluntary running (Stranahan et al., 2007).

Very few human studies have explored the relationship between PA and the hippocampus with sub-regional specificity. Some studies using specialized techniques to segment the hippocampus into sub-regions have found that aerobic exercise may primarily affect the anterior hippocampus, including the DG, CA1, and subiculum, with weaker effects on the posterior hippocampus (Erickson et al., 2011; Maass et al., 2015; Thomas et al., 2015). Additionally, cerebral perfusion associated with increased aerobic activity may affect all subregions (Maass et al., 2015) or may be specific to the DG subregion (Pereira et al., 2007). Understanding the region-specific associations with specific types of PA is critical to a better conceptual understanding of the biologic mechanisms and associated time course by which increased PA may positively impact brain health. Furthermore, understanding these specific associations will enable clinical trials of PA to better select target regions to explore intervention effects.

This study used objective and self-reported measures of daily walking activity and exercise, and surface-based regional shape analysis using high-field hippocampal subregional partitions to explore subregion specific hippocampal associations with PA in a nondemented, community-dwelling older adult sample at elevated sociodemographic risk for cognitive decline.

METHODS

Study Sample

Participants were from the Brain Health Study (BHS), a substudy within the Baltimore Experience Corps Trial (BECT), a sex-stratified, randomized, controlled effectiveness trial to explore the health benefits of volunteer service. Details on sex-stratification, randomization, descriptions of intervention and control conditions, recruitment and other

study design details have been described previously (Fried et al., 2013). Enrollment criteria for the larger BECT included 1) age ≥ 60 year; 2) a score of ≥ 24 on the Mini-Mental State Exam (MMSE) (Folstein et al., 1975); and an ability to read at a minimum sixth-grade level based on the Wide Range Achievement Test [WRAT-4; (Wilkinson, 1993)]. Additional enrollment criteria for the BHS has been described previously (Carlson et al., 2015), and included (1) right hand dominance; (2) free of a pacemaker or other ferrous metals in the body; and (3) no history of brain cancer or brain aneurism/stroke in the past year.

A total of 123 participants were enrolled in the BHS at baseline. For this study, 12 participants were excluded because they did not complete magnetic resonance imaging (MRI) protocol due to excessive head movement or claustrophobia. An additional 21 did not complete or did not provide usable PA data based on exclusion criteria (described later) resulting in a final sample of 90 participants. All measurements in this baseline, cross-sectional study occurred prior to intervention or control placement. Participants in the final study sample did not vary significantly ($P < 0.05$) from those in the remaining BECT sample on any socio-demographic characteristic other than sex; the BHS over-sampled men by design in order to allow for sex-stratified comparisons (Kuo et al., 2015). 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

The majority of evidence for the relationship between PA and cognition has focused on exercise measured by self-reported as well objective measures of fitness (e.g., VO₂ max, FEV) [e.g., (Colcombe and Kramer, 2003; Angevaren et al., 2008; Erickson et al., 2011)]. Recently, body-worn accelerometers have become a popular method to objectively measure total PA (Bassett et al., 2014; Troiano et al., 2014). Objective total PA measures incorporate a variety of activities including exercise (e.g., aerobic exercise) and non-exercise activities, including lifestyle activities (e.g., walking for pleasure) and instrumental activities of daily life (e.g., housework). Broadly, these measures indicate the amount of total movement—specific to body placement—within an individual's environment.

In this study, total PA was measured using an ankle worn accelerometer, developed to specifically measure total walking activity. The step activity monitor (SAM; Orthocare Innovations, Mt. Terrace, WA) is a pager-sized microprocessor-linked accelerometer that measures number of steps in one-minute intervals using acceleration, position, and timing information. The SAM has been validated across a range of community dwelling older adult samples with varying functional limitations using self-reported and objective measures (e.g., hand-tallied step counts and other accelerometers) (Resnick et al., 2001; Cavanaugh et al., 2007; Storti et al., 2008). The SAM is particularly sensitive to activity at decreased gait speeds (Storti et al., 2008), and is well tolerated by older adults (Algase et al., 2003).

Detailed wear and cleaning protocols have been described previously (Varma et al., 2014). Briefly, participants were instructed to wear the SAM for 3–7 days while keeping a wear-time diary used to determine compliance. Participants were instructed to remove the SAM only when bathing, showering, or swimming. Data cleaning protocol was designed based on a study population that was sedentary at baseline with a high number of chronic conditions,

and included the exclusion of days that represented noncompliance based on both a data driven compliance algorithm that defined wear and nonwear time during waking hours as well as participants' self-report of noncompliance in their diaries. Participants provided an average of 3 days of data (SD: 1.47; range: 1–9).

We defined total walking activity as the number of steps/day completed by participants. We additionally segmented total steps/day into steps at low-intensity (>0 steps/min and <100 steps/min) and at moderate- to vigorous-intensity (≥ 100 steps/min). Intensity ranges, or effort associated with walking, were based on studies translating laboratory measurements of oxygen consumption while walking into pedometer-based metrics (Tudor-Locke et al., 2005; Marshall et al., 2009).

Exercise Measure

Exercise was assessed using the Community Health Activity Model Program for Seniors (CHAMPS), a well-validated questionnaire developed to sensitively measure variability in PA among older adults (Stewart et al., 2001). The CHAMPS questionnaire was administered to all participants during their baseline assessment. Participants were asked whether they participated in a range of PA in the past 4 weeks; for activities that participants engaged in, frequency and total hours of participation were assessed. On the basis of a formula utilizing activity-specific metabolic equivalent (MET) values developed by the American College of Sports Medicine (Stewart et al., 2001), we calculated total caloric expenditure/week for each activity. To calculate a measure for exercise, we summed total caloric expenditure/week for all exercise-related PA (e.g., jogging or running; walking leisurely or fast for exercise/pleasure; riding a bicycle or stationary cycle). All measures were administered by a trained evaluator.

MRI Acquisition and Hippocampus Segmentation

The participants underwent MRI scans using a 3.0 T Phillips scanner (Best, the Netherlands). The imaging protocol was: high-resolution T1-weighted 3D-volume Magnetization Prepared Rapid Gradient Echo Imaging (sagittal acquisition; repetition time = 8.037 ms; echo time = 3.7 ms; flip angle = 8° ; field of view = $200\text{ mm} \times 256\text{ mm} \times 200\text{ mm}$; matrix size = $256\text{ mm} \times 256\text{ mm}$; and voxel size = $1\text{ mm} \times 1\text{ mm} \times 1\text{ mm}$).

The bilateral hippocampi were obtained using a fully automated segmentation pipeline (Tang et al., 2013, 2015) which is based upon a multi-atlas approach. This pipeline has been proven to be capable of delivering automated results with a segmentation accuracy of 92% for the hippocampus in each hemisphere for this BHS dataset. Details on selecting the multiple atlases, manually delineating the atlases' hippocampal labels, and validating the segmentation performance for these data can be found in a forthcoming study (Tang et al., 2016). Briefly, we used 16 atlases (a subset of the BHS sample) with the left and right hippocampus manually delineated. The accuracy of this hierarchical pipeline in segmenting the bilateral hippocampi was evaluated using a leave-one-out strategy; one atlas image was treated as the to-be-segmented image and the remainder served as the atlas set to segment that excluded image.

Shape Processing

In recent years, advancements in neuroimaging and associated analytic techniques have allowed researchers to develop novel ways of characterizing hippocampal morphometry that may be more sensitive to age-related effects than traditional global volume measures (Voineskos et al., 2015). Changes in the shape and surface area of the hippocampus may be particularly important in understanding disease progression in Alzheimer's (Carmichael et al., 2012; Tondelli et al., 2012), and provide a more nuanced and multi-dimensional (via vertices) representation of hippocampal subregions rather than a single number volumetric measure (Voineskos et al., 2015).

In this study, the hippocampal shapes for both hemispheres were represented by 2D triangulated surfaces contouring the boundary of the 3D structural segmentations. To generate these surfaces, we employed an approach that has been validated on a variety of MRI datasets [e.g., (Miller et al., 2015; Tang et al., 2015a,b)]. Details of this approach have been detailed previously (Tang et al., 2014). After generation of the surfaces, to quantify the vertex-wise surface areas of each participant's shape, the focus of our correlation analyses, we relied on diffeomorphometry wherein a diffeomorphism is used to quantify the localized shape morphometrics. The participant-specific diffeomorphisms, each connecting a common template shape to an individual participant shape, were created using Large Deformation Diffeomorphic Metric Mapping for surfaces (Vaillant and Glaunes, 2005). The "common" or average template surfaces of the bilateral hippocampi were generated from the collection of surfaces from the total sample ($n = 90$) of this study using a Bayesian estimation algorithm [detailed in (Ma et al., 2010)] to ensure "sample-averaging".

A scalar field was then calculated from each participant-specific diffeomorphism; the log-determinant of the Jacobian of the diffeomorphism, which is indexed by the vertices of the common template surface. In this way, the vertex-wise surface morphometrics of all participants are indexed in a common space, allowing for inter-participant analyses. Mathematically, the log-determinant of the diffeomorphism's Jacobian quantifies the factor by which the diffeomorphism expands or shrinks the localized surface area in the participant relative to the common template surface in a logarithmic scale. In other words, a positive value corresponds to a localized surface area expansion relative to the common template while a negative value corresponds to a localized surface area contraction. This scalar field (surface area expansion or contraction) is referred to as the deformation marker; this study focused on the correlation of this marker with PA.

Template Surface Partition

To identify the region-specific associations, we partitioned our bilateral hippocampal template surface into four anatomical sub-regions (CA1, CA2, CA3 combined with the dentate gyrus, and the subiculum) using the approach detailed in (Tang et al., 2014). Briefly, this partition procedure was accomplished by manually partitioning the hippocampal surfaces of a high-field MR scan (obtained from a 7 Tesla scanner with an image voxel resolution of 0.8 mm) and transferring the boundary definitions of those sub-regions to our template surfaces using the LDDMM transfer technique.

Covariates

To control for potential confounders, we included covariates associated with both PA and brain volume, including intracranial volume (ICV), age, years of education, body mass index (BMI), cardiovascular disease burden (CVD), and global cognitive function. ICV was calculated as the sum of grey matter, white matter, and cerebrospinal fluid using FreeSurfer software and protocol (Chuang et al., 2013; Carlson et al., 2015); 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; and global cognitive function was assessed using the MMSE. All covariates were administered by trained evaluators and were calculated at baseline.

Analysis

The values of the shape deformation marker at each voxel of the bilateral hippocampi were examined for correlations with PA measures (including objective walking activity and self-reported exercise), with the correlation strength quantified by the Pearson correlation coefficient (PCC). The statistical significance of the correlation is measured by a *P* value obtained from nonparametric permutation tests (40,000 permutations were employed in this study). Because correlations were performed at each vertex, we corrected for multiple comparisons by using two standard approaches; controlling the family-wise error rate (FWER) (Nichols and Hayasaka, 2003) and the false discovery rate (FDR) at a level of 0.05 (Benjamini and Hochberg, 1995).

For our primary analyses, we explored shape correlation separately for total walking activity (steps/day) and total caloric expenditure/week in exercise-related PA. For our secondary and more exploratory analysis, we explored whether nonexercise walking activity may be correlated with shape of the hippocampi. To target this activity, we excluded moderate- to vigorous-intensity walking activity and explored shape correlations specific to low-intensity walking activity while covarying for self-reported exercise. This methodology was similar to that used previously to explore associations between hippocampal volume and nonexercise walking (Varma et al., 2014).

In all correlational analyses, we included all covariates described previously. Additionally, in keeping with our previous study (Varma et al., 2014), we performed all analyses separately for women and men; the BHS was designed specifically to explore sex differences (Fried et al., 2013).

RESULTS

Table 1 presents baseline demographic, health and PA characteristics of the sex-stratified study sample. Study participants averaged 67.3 years, 70.0% were women, 89.0% were African-American, 38.2% had a high school level of education or lower, and on average had an MMSE score of 28.4. Women and men did not vary significantly ($P = 0.05$) on any sociodemographic characteristic at baseline.

Participants were at high risk for cognitive and physical function decline due to high rates of chronic disease; a significantly greater percentage of women were obese compared to men (65.1% vs. 40.7%), and 75.8% and 29.0% of women reported hypertension and diabetes respectively. Sixty-four percent and 33% of men reported hypertension and diabetes respectively. On average, women completed a total of 7519.1 (SD: 2814.5) steps/day, with 6875.7 (SD: 2454.1) steps at low-intensity and 643.5 (SD: 802.0) steps at moderate- to vigorous-intensity. Women additionally expended 1595.2 (SD: 1593.8) calories/week in exercise related activity. Generally, women had marginally lower PA across all measures compared to men. On average, men completed a total of 8755.2 (SD: 3496.1) steps/day, with 7737.0 (SD: 2454.1) steps at low-intensity and 1018.2 (SD: 1472.8) steps at moderate- to vigorous-intensity. Men also expended 2124.1 (SD: 2365.7) calories/week in exercise related activity. Women in a larger sample (Varma et al., 2014), within which this BHS study is nested, had significantly ($P < 0.05$) lower PA than men. We additionally explored associations between total daily walking activity and self-reported exercise on the CHAMPS (Fig. 1). In women, walking activity was not correlated with exercise (Pearson's correlation: $r = 0.04$; $P = 0.78$; Spearman's correlation: $\rho = 0.07$; $P = 0.61$) while in men both metrics were correlated (Pearson's correlation: $r = 0.51$; $P = 0.01$; Spearman's correlation: $\rho = 0.33$; $P = 0.10$), suggesting that walking activity in women may reflect nonexercise activity.

The maps of correlation between PA and the vertex-wise diffeomorphometrics, or shape, for superior and inferior views of the bilateral hippocampi (left and right hippocampus) are included in Figure 2; correlations are displayed only in regions where shape vertices correlated statistically significantly with PA after performing multiple comparison correction by controlling the FWER at the level of 0.05. Panel (a) includes the significant results from the primary analyses: vertex-wise PCC values obtained when correlating total walking activity with shape diffeomorphometry in women for the left and right hippocampus. Panel (b) includes significant results from the exploratory analysis describing values from correlating low-intensity walking activity, when controlling for self-reported exercise, with shape diffeomorphometry in women for the left hippocampus (no significant results detected for the right hippocampus). Finally, Panel (c) provides a reference for the subdivisions of the template surface into four subregions: CA1, CA2, CA3 combined with the DG, and the subiculum for superior and inferior views of the left and right hippocampus. We included exploratory analyses only when significant associations were indicated in the primary analyses.

For women, significant positive correlations were found between total walking activity and hippocampal shape (Panel (a)) on selected vertices mainly belonging to the inferior rostral subiculum and secondarily to the superior rostral CA2 (immediately adjacent to the subiculum) of the left hippocampus (total surface area: 13.47 mm²) and the caudal subiculum (inferior) of the right hippocampus (total surface area: 15.38 mm²). No significant correlations were detected between self-reported exercise and bilateral hippocampal shape. Significant positive correlations were found between low-intensity walking activity, after partialing out the effect of self-reported exercise, and left-hippocampal shape (Panel (b)); significant vertices (total surface area: 39.96 mm²) included part of the inferior rostral subiculum and the superior part of the rostral CA1. For men, no

significant correlations after the FWER correction were found between PA, including total walking activity and self-reported exercise, and bilateral hippocampal shape.

While low-intensity walking activity was significantly correlated with moderate- to vigorous-intensity walking activity in men ($r = 0.79$; $P < 0.01$) and women ($r = 0.32$; $P = 0.01$), moderate- to vigorous-intensity walking activity was not significantly correlated with hippocampal shape in men or women.

DISCUSSION

In this study, we explored the associations between PA and shape of sub-regions of the bilateral hippocampi within a sample of community-dwelling older adults at sociodemographic risk for functional and cognitive declines. Using shape diffeomorphometry to explore sub-regional associations that are more specific than global volume associations used in the majority of prior studies, we found in women and not men that objectively measured walking activity was cross-sectionally associated mainly with larger surface areas of the subiculum in the hippocampus. These novel findings suggest that PA that does not reach the level of moderate-intensity exercise within an environment may be associated with specific subregions of the hippocampus which are not typically associated with exercise and aerobic fitness. This underscores the importance of better understanding the independent and related biological mechanisms and pathways by which increasing exercise as well as nonexercise PA in daily life may influence structural brain health.

Prior human studies, albeit limited, exploring the relationship between PA and subregional structural volumes of the hippocampus have focused on PA related to exercise and aerobic or cardiorespiratory fitness [e.g., (Erickson et al., 2009)]. These studies indicate that increased exercise may be associated with benefits to the anterior hippocampus, a region that includes the DG, CA1, and subiculum. Animal studies focusing on neurogenesis have mainly indicated that PA primarily affects the DG subregion (van Praag et al., 1999; Faherty et al., 2003; Eadie et al., 2005; Sahay et al., 2011; Dery et al., 2013). The effects of low-intensity daily PA that may be unrelated to exercise or aerobic fitness, on the hippocampus as well as its subregions, are only beginning to be explored using sensitive, real-world measurement techniques (Voss et al., 2014; Burzynska et al., 2015; Voss et al., 2015). Our novel, regionally specific shape findings can be interpreted through an understanding of both the function of the subiculum as well as the type of PA measure used in this study. The dorsal hippocampus, which includes the subiculum and CA1 subregions, are located at the end of the trisynaptic circuit ($DG \rightarrow CA3 \rightarrow CA1 \rightarrow \text{Subiculum}$); this region is the primary source of output projections from the hippocampus to other brain regions (de la Prida et al., 2006; O'Mara et al., 2009; Fanselow and Dong, 2010). There has been evidence indicating that projections from this region to other cortical regions, including the ventral tegmental area, play a critical role in locomotion (Swanson and Kalivas, 2000). Functionally, the subiculum provides a cognitive map for navigation and is involved primarily in the mediation of cognitive processing related to navigation and exploration, as well as learning and memory (Taube, 2007; Fanselow and Dong, 2010).

Physical activity measures related to real-world navigation within open environments may be associated with the neurobiology of the subiculum (O'Mara, 2005). In this study, we used an accelerometer to objectively measure daily walking activity within a community-living cohort. While other studies exploring the brain structural benefits from PA have focused primarily on aerobic exercise and fitness, including aerobic capacity [e.g., (Erickson et al., 2009; Erickson et al., 2011)], the measure used in this study was designed to precisely quantify daily walking activity, which may be considered a measure of locomotion and navigation within an environment. Women in this cohort were generally sedentary (Varma et al., 2014) with very low levels of exercise. Additionally walking activity in women, compared to men, was not correlated with self-reported exercise. While there may be a sex difference in self-report bias (Prince et al., 2008), the lack of correlation suggests that walking activity among women in our sample may be related to nonexercise activity and unrelated to fitness. Furthermore our exploratory analyses (excluding moderate- to vigorous-intensity walking activity and covarying for exercise) that indicated consistent hippocampal subregional specificity in women, suggests that low-intensity walking activities that require locomotion and navigation, including lifestyle activities and independent activities of daily living, may be specifically associated with the subiculum subregion of the hippocampus. Prior work from our group indicates that PA of participants within this study sample occur in a variety of environments within and outside the home, and greater PA, even at lower-intensity ranges, is associated with environmental navigation and complexity (Carlson, 2011; Carlson et al., 2012, 2016). Future longitudinal investigation within lifestyle interventions, such as the Experience Corps program from which this sample was obtained, will inform understanding as to whether modest increases in PA may have subregion specific effects on the hippocampus, particularly in the subiculum.

Consistent with results from previous work (Varma et al., 2014), our significant findings were sex-specific; we found no significant shape correlations with any PA measures in men. Prior studies indicate a sex difference in biological responses to PA, including walking and exercise; the effect of PA on cognition may be more pronounced in women than men (Colcombe and Kramer, 2003; Day, 2008; Hamer and Chida, 2009; Brown et al., 2013). Sex hormones may partially explain this difference; older women may have lower levels of neuroprotective sex hormones (Pike et al., 2009) compared to men and may be more sensitive to differences in PA (Brown et al., 2013). Finally, women in many study samples have lower PA levels and are at a higher risk of developing cognitive impairment than men, which may influence associations (Brown et al., 2013). It is important to note that in our study sample, women generally had greater chronic disease burden and lower levels of walking activity and exercise compared to men.

While we generally found bilateral symmetry in effects across analyses, we found left hippocampus-specific correlations with low-intensity walking activity and no correlation with the right hippocampus in women. These lateralized results may have been driven partially by a conservative statistical approach to controlling the FWER. When we decreased the *P* value threshold, we found significant bilateral correlations.

This study has limitations. First, although the cross-sectional design of the study allows us to explore correlations; we cannot come to a causal conclusion about the effect of walking

activity on sub-regions of the hippocampus. While the inclusion of a global cognitive test (MMSE) as a covariate may partially account for reverse causation, we cannot discount this possibility. Second, while this study represented a unique, and understudied at-risk segment of the older adult population, the sex-stratified study sample was relatively small. The lack of significant findings in men in particular must be considered with caution. Finally, while our analytic models allowed us to speculate about the associations between nonexercise walking activity and brain structure, the SAM does not discriminate among types of activity.

Using novel shape diffeomorphometry based methods and sensitive measures of walking activity; this study is, to the best of our knowledge, one of the first to find sub-regional associations between PA and shape of the subiculum of the hippocampus. Considering that subicular atrophy is one of the earliest signs of AD pathogenesis in the hippocampus (Apostolova et al., 2006; Carlesimo et al., 2015), this study's findings encourage us to better understand the underlying biological mechanisms that may explain how the brain can benefit from even modest increases in daily activity.

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REFERENCES

- Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. 2011 Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. *Mayo Clin Proc* 86:876–884. [PubMed: 21878600]
- Algae DL, Beattie ER, Leitsch SA, Beel-Bates CA. 2003 Biomechanical activity devices to index wandering behavior in dementia. *Am J Alzheimers Dis Other Dement* 18:85–92. [PubMed: 12708223]
- 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* CD005381.
- Apostolova LG, Dutton RA, Dinov ID, Hayashi KM, Toga AW, Cummings JL, Thompson PM. 2006 Conversion of mild cognitive impairment to Alzheimer disease predicted by hippocampal atrophy maps. *Arch Neurol* 63:693–699. [PubMed: 16682538]
- Bassett DR, Troiano RP, McClain JJ, Wolff DL. 2014 Accelerometer-based physical activity: Total volume per day and standardized measures. *Med Sci Sports Exerc*.
- Benjamini Y, Hochberg Y. 1995 Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Stat Soc Ser B Methodol* 57:289–300.
- Bherer L, Erickson KI, Liu-Ambrose T. 2013 A review of the effects of physical activity and exercise on cognitive and brain functions in older adults. *J Aging Res* 2013:657508. [PubMed: 24102028]
- Blazer DG, Yaffe K, Liverman CT. 2015 Cognitive aging: Progress in understanding and opportunities for action. Washington, D.C.: Institute of Medicine.

- Bloor CM. 2005 Angiogenesis during exercise and training. *Angiogenesis* 8:263–271. [PubMed: 16328159]
- Brown BM, Peiffer JJ, Martins RN. 2013 Multiple effects of physical activity on molecular and cognitive signs of brain aging: Can exercise slow neurodegeneration and delay Alzheimer's disease?" *Mol Psychiatry* 18:864–874. [PubMed: 23164816]
- Burzynska AZ, Wong CN, Voss MW, Cooke GE, Gothe NP, Fanning J, McAuley E, Kramer AF. 2015 Physical activity is linked to greater moment-to-moment variability in spontaneous brain activity in older adults. *PLoS One* 10:e0134819. [PubMed: 26244873]
- Carlesimo GA, Piras F, Orfei MD, Iorio M, Caltagirone C, Spalletta G. 2015 Atrophy of presubiculum and subiculum is the earliest hippocampal anatomical marker of Alzheimer's disease. *Neuroimaging* 1:24–32.
- Carlson MC. 2011 Introduction: A life course perspective on activity and neurocognitive health. *J Int Neuropsychol Soc* 17:970–974. [PubMed: 22040895]
- Carlson MC, Varma VR. 2015 Activity and neurocognitive health in older adults In: Waldstein SR, Elias MF. *Neuropsychology of Cardiovascular Disease*. New York, NY: Psychology Press pp 79–108.
- Carlson MC, Helms MJ, Steffens DC, Burke JR, Potter GG, Plassman BL. 2008 Midlife activity predicts risk of dementia in older male twin pairs. *Alzheimers Dement* 4:324–331. [PubMed: 18790459]
- Carlson MC, Parisi JM, Xia J, Xue QL, Rebok GW, Bandeen-Roche K, Fried LP. 2012 Lifestyle activities and memory: Variety may be the spice of life. The women's health and aging study II. *J Int Neuropsychol Soc* 18:286–294. [PubMed: 22172155]
- Carlson MC, Kuo JH, Chuang YF, Varma V, Harris G, Albert M, Erickson KI, Kramer AF, Parisi JM, Xue QL, Tan E, Tanner EK, Gross A, Seeman TE, Gruenewald T, McGill S, Rebok GW, Fried LP. 2015 Impact of the baltimore experience corps trial on cortical and hippocampal volumes. *Alzheimers Dement*.
- Carlson MC, Gross AL, Betz J, Xue Q, Varma VR, Chuang Y, Parisi JM, Seeman TE, Gruenewald T, Tanner EK, Tan E, McGill S, Fried LP, Rebok GW. 2016 Generalized Cognitive Benefits of a Community-based Volunteer Program: The Baltimore Experience Corps Randomized, Controlled Trial. Under Review.
- Carlson MC, Varma VR, Adam A, Crainiceanu C, Zipunnikov V. 2016 Linking Community Activity to Neurocognitive Health in Older Adults Using Wearable Technology. Under review.
- Carmichael O, Xie J, Fletcher E, Singh B, DeCarli C, Alzheimer's Disease Neuroimaging I. 2012 Localized hippocampus measures are associated with Alzheimer pathology and cognition independent of total hippocampal volume. *Neurobiol Aging* 33:1124 e1131–1141.
- 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. [PubMed: 17233695]
- 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* 35:13961403.
- Colcombe S, Kramer AF. 2003 Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychol Sci* 14: 125–130. [PubMed: 12661673]
- Cotman CW, Berchtold NC. 2002 Exercise: A behavioral intervention to enhance brain health and plasticity. *Trends Neurosci* 25: 295–301. [PubMed: 12086747]
- Cotman CW, Berchtold NC. 2007 Physical activity and the maintenance of cognition: Learning from animal models. *Alzheimers Dement* 3:S30–S37. [PubMed: 19595972]
- Cotman CW, Berchtold NC, Christie LA. 2007 Exercise builds brain health: Key roles of growth factor cascades and inflammation. *Trends Neurosci* 30:464–472. [PubMed: 17765329]
- Cummings JL. 2009 Defining and labeling disease-modifying treatments for Alzheimer's disease. *Alzheimers Dement* 5:406–418. [PubMed: 19751920]
- 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. [PubMed: 20547888]
- Day DS. 2008 Exercise physiologists talk about sex differences. *Med Sci Sports Exerc* 40:646–647. [PubMed: 18317382]
- de la Prida LM, Totterdell S, Gigg J, Miles R. 2006 The subiculum comes of age. *Hippocampus* 16:916–923. [PubMed: 17016818]
- Dery N, Pilgrim M, Gibala M, Gillen J, Wojtowicz JM, Macqueen G, Becker S. 2013 Adult hippocampal neurogenesis reduces memory interference in humans: Opposing effects of aerobic exercise and depression. *Front Neurosci* 7:66. [PubMed: 23641193]
- Eadie BD, Redila VA, Christie BR. 2005 Voluntary exercise alters the cytoarchitecture of the adult dentate gyrus by increasing cellular proliferation, dendritic complexity, and spine density. *J Comp Neurol* 486:39–47. [PubMed: 15834963]
- 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. [PubMed: 19123237]
- 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 USA* 108:3017–3022. [PubMed: 21282661]
- Faherty CJ, Kerley D, Smeyne RJ. 2003 A Golgi-Cox morphological analysis of neuronal changes induced by environmental enrichment. *Brain Res Dev Brain Res* 141:55–61. [PubMed: 12644248]
- Fanselow MS, Dong HW. 2010 Are the dorsal and ventral hippocampus functionally distinct structures?. *Neuron* 65:7–19. [PubMed: 20152109]
- Farmer J, Zhao X, van Praag H, Wodtke K, Gage FH, Christie BR. 2004 Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. *Neuroscience* 124:71–79. [PubMed: 14960340]
- 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. [PubMed: 1202204]
- Fried LP, Carlson MC, McGill S, Seeman T, Xue QL, Frick K, Tan E, Tanner EK, Barron J, Frangakis C, Piferi R, Martinez I, Gruenewald T, Martin BK, Berry-Vaughn L, Stewart J, Dickersin K, Willging PR, Rebok GW. 2013 Experience Corps: A dual trial to promote the health of older adults and children's academic success. *Contemp Clin Trials* 36:1–13. [PubMed: 23680986]
- Hamer M, Chida Y. 2009 Physical activity and risk of neurodegenerative disease: A systematic review of prospective evidence. *Psychol Med* 39:3–11. [PubMed: 18570697]
- Hillman CH, Erickson KI, Kramer AF. 2008 Be smart, exercise your heart: Exercise effects on brain and cognition. *Nat Rev Neurosci* 9: 58–65. [PubMed: 18094706]
- Howley ET. 2001 Type of activity: Resistance, aerobic and leisure versus occupational physical activity. *Med Sci Sports Exerc* 33:S364–S369; discussion S419–S320. [PubMed: 11427761]
- 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. [PubMed: 23332364]
- Kempermann G, Gast D, Gage FH. 2002 Neuroplasticity in old age: Sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. *Ann Neurol* 52:135–143. [PubMed: 12210782]
- Kempermann G, Fabel K, Ehninger D, Babu H, Leal-Galicia P, Garthe A, Wolf SA. 2010 Why and how physical activity promotes experience-induced brain plasticity. *Front Neurosci* 4:189. [PubMed: 21151782]
- 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. [PubMed: 18768414]
- Ma J, Miller MI, Younes L. 2010 A Bayesian generative model for surface template estimation. *Int J Biomed Imaging* 2010.

- Maass A, Duzel S, Goerke M, Becke A, Sobieray U, Neumann K, Lovden M, Lindenberg U, Backman L, Braun-Dullaeus R, Ahrens D, Heinze HJ, Muller NG, Duzel E. 2015 Vascular hippocampal plasticity after aerobic exercise in older adults. *Mol Psychiatry* 20:585–593. [PubMed: 25311366]
- 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. [PubMed: 19362695]
- McEwen BS. 1997 Possible mechanisms for atrophy of the human hippocampus. *Mol Psychiatry* 2:255–262. [PubMed: 9152991]
- Miller MI, Younes L, Ratnanather JT, Brown T, Trinh H, Lee DS, Tward D, Mahon PB, Mori S, Albert M, Team BR. 2015 Amygdalar atrophy in symptomatic Alzheimer's disease based on diffeomorphometry: The BIOCARD cohort. *Neurobiol Aging* 36 (Suppl 1):S3–S10. [PubMed: 25444602]
- NHLBI. 2011 What is physical activity? Explore physical activity and your heart retrieved 3/19/13, 2012. Available at: <http://www.nhlbi.nih.gov/health/health-topics/topics/phys/>.
- Nichols T, Hayasaka S. 2003 Controlling the familywise error rate in functional neuroimaging: A comparative review. *Stat Methods Med Res* 12:419–446. [PubMed: 14599004]
- O'Mara S 2005 The subiculum: What it does, what it might do, and what neuroanatomy has yet to tell us. *J Anat* 207:271–282. [PubMed: 16185252]
- O'Mara SM Sanchez-Vives MV, Brotons-Mas JR, O'Hare E. 2009 Roles for the subiculum in spatial information processing, memory, motivation and the temporal control of behaviour. *Prog Neuropsychopharmacol Biol Psychiatry* 33:782–790.
- Pereira AC, Heddlestone 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 USA* 104:5638–5643. [PubMed: 17374720]
- Pike CJ, Carroll JC, Rosario ER, Barron AM. 2009 Protective actions of sex steroid hormones in Alzheimer's disease. *Front Neuroendocrinol* 30:239–258. [PubMed: 19427328]
- Prince SA, Adamo KB, Hamel ME, Hardt J, Connor Gorber S, Tremblay M. 2008 A comparison of direct versus self-report measures for assessing physical activity in adults: A systematic review. *Int J Behav Nutr Phys Act* 5:56. [PubMed: 18990237]
- 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. [PubMed: 11881269]
- Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, Burghardt NS, Fenton AA, Dranovsky A, Hen R. 2011 Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature* 472:466–470. [PubMed: 21460835]
- Schaefer AT, Grafen K, Teuchert-Noodt G, Winter Y. 2010 Synaptic remodeling in the dentate gyrus, CA3, CA1, subiculum, and entorhinal cortex of mice: Effects of deprived rearing and voluntary running. *Neural Plast* 2010:870573. [PubMed: 20508828]
- Sink KM, Espeland MA, Castro CM, Church T, Cohen R, Dodson JA, Guralnik J, Hendrie HC, Jennings J, Katula J, Lopez OL, McDermott MM, Pahor M, Reid KF, Rushing J, Verghese J, Rapp S, Williamson JD, Investigators LS. 2015 Effect of a 24-month physical activity intervention vs health education on cognitive outcomes in sedentary older adults: The LIFE randomized trial. *JAMA* 314:781–790. [PubMed: 26305648]
- Small SA, Schobel SA, Buxton RB, Witter MP, Barnes CA. 2011 A pathophysiological framework of hippocampal dysfunction in ageing and disease. *Nat Rev Neurosci* 12:585–601. [PubMed: 21897434]
- Smith JC, Nielson KA, Woodard JL, Seidenberg M, Durgerian S, Hazlett KE, Figueroa CM, Kandah CC, Kay CD, Matthews MA, Rao SM. 2014 Physical activity reduces hippocampal atrophy in elders at genetic risk for Alzheimer's disease. *Front Aging Neurosci* 6:61. [PubMed: 24795624]
- 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. [PubMed: 11445760]

- 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. [PubMed: 18091020]
- Stranahan AM, Khalil D, Gould E. 2007 Running induces widespread structural alterations in the hippocampus and entorhinal cortex. *Hippocampus* 17:1017–1022. [PubMed: 17636549]
- Swanson CJ, Kalivas PW. 2000 Regulation of locomotor activity by metabotropic glutamate receptors in the nucleus accumbens and ventral tegmental area. *J Pharmacol Exp Ther* 292:406–414. [PubMed: 10604977]
- Tang X, Oishi K, Faria AV, Hillis AE, Albert MS, Mori S, Miller MI. 2013 Bayesian parameter estimation and segmentation in the multi-atlas random orbit model. *PLoS One* 8:e65591. [PubMed: 23824159]
- Tang X, Holland D, Dale AM, Younes L, Miller MI, Alzheimer's Disease Neuroimaging I. 2014 Shape abnormalities of subcortical and ventricular structures in mild cognitive impairment and Alzheimer's disease: Detecting, quantifying, and predicting. *Hum Brain Mapp* 35:3701–3725. [PubMed: 24443091]
- Tang X, Crocetti D, Kuttan K, Ceritoglu C, Albert MS, Mori S, Mostofsky SH, Miller MI. 2015 Segmentation of brain magnetic resonance images based on multi-atlas likelihood fusion: Testing using data with a broad range of anatomical and photometric profiles. *Front Neurosci* 9:61. [PubMed: 25784852]
- Tang X, Holland D, Dale AM, Miller MI. 2015 APOE affects the volume and shape of the amygdala and the hippocampus in mild cognitive impairment and Alzheimer's disease: Age matters. *J Alzheimers Dis* 47:645–660. [PubMed: 26401700]
- Tang X, Holland D, Dale AM, Younes L, Miller MI. 2015 Baseline shape diffeomorphometry patterns of subcortical and ventricular structures in predicting conversion of mild cognitive impairment to Alzheimer's disease. *J Alzheimers Dis* 44:599–611. [PubMed: 25318546]
- Tang X, Varma VR, Miller MI, Carlson MC. 2016 Education is associated with sub-regions of the hippocampus and the amygdala most vulnerable to neuropathologies of Alzheimer's disease. Under Review.
- Taube JS. 2007 The head direction signal: Origins and sensory-motor integration. *Annu Rev Neurosci* 30:181–207. [PubMed: 17341158]
- Thomas AG, Dennis A, Bandettini PA, Johansen-Berg H. 2012 The effects of aerobic activity on brain structure. *Front Psychol* 3:86. [PubMed: 22470361]
- Thomas AG, Dennis A, Rawlings NB, Stagg CJ, Matthews L, Morris M, Kolind SH, Foxley S, Jenkinson M, Nichols TE, Dawes H, Bandettini PA, Johansen-Berg H. 2015 Multi-modal characterization of rapid anterior hippocampal volume increase associated with aerobic exercise. *Neuroimage*.
- Tondelli M, Wilcock GK, Nichelli P, De Jager CA, Jenkinson M, Zamboni G. 2012 Structural MRI changes detectable up to ten years before clinical Alzheimer's disease. *Neurobiol Aging* 33:825 e825–836.
- Troiano RP, McClain JJ, Brychta RJ, Chen KY. 2014 Evolution of accelerometer methods for physical activity research. *Br J Sports Med* 48:1019–1023. [PubMed: 24782483]
- 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. [PubMed: 16485518]
- Vaillant M, Glaunes J. 2005 Surface matching via currents. *Inf Process Med Imaging* 19:381–392. [PubMed: 17354711]
- van Praag H, Kempermann G, Gage FH. 1999 Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci* 2:266–270. [PubMed: 10195220]
- van Praag H, Kempermann G, Gage FH. 2000 Neural consequences of environmental enrichment. *Nat Rev Neurosci* 1:191–198. [PubMed: 11257907]
- Varma VR, Chuang Y, Harris GC, Tan EJ, Carlson MC. 2014 Low-intensity daily walking activity is associated with hippocampal volume in older adults. *Hippocampus*.

- Varma VR, Tan EJ, Wang T, Xue QL, Fried LP, Seplaki CL, King AC, Seeman TE, Rebok GW, Carlson MC. 2014 Low-intensity walking activity is associated with better health. *J Appl Gerontol* 33:870–887. [PubMed: 24652915]
- Varma VR, Tan EJ, Gross AL, Harris G, Romani W, Fried LP, Rebok GW, Carlson MC. 2015 Effect of community volunteering on physical activity: A randomized controlled trial. *Am J Prev Med*.
- Voineskos AN, Winterburn JL, Felsky D, Pipitone J, Rajji TK, Mulsant BH, Chakravarty MM. 2015 Hippocampal (subfield) volume and shape in relation to cognitive performance across the adult lifespan. *Hum Brain Mapp* 36:3020–3037. [PubMed: 25959503]
- Voss MW, Vivar C, Kramer AF, van Praag H. 2013 Bridging animal and human models of exercise-induced brain plasticity. *Trends Cogn Sci* 17:525–544. [PubMed: 24029446]
- Voss M, Carr L, 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 Activity* (in press).
- Voss MW, Weng TB, Burzynska AZ, Wong CN, Cooke GE, Clark R, Fanning J, Awick E, Gothe NP, Olson EA, McAuley E, Kramer AF. 2015 Fitness, but not physical activity, is related to functional integrity of brain networks associated with aging. *Neuroimage*.
- Wilkinson G 1993 WRAT3: Wide Range Achievement Test 3. Wilmington, D, Wide Range Inc.
- Williamson JD, Espeland M, Kritchevsky SB, Newman AB, King AC, Pahor M, Guralnik JM, Pruitt LA, Miller ME. 2009 Changes in cognitive function in a randomized trial of physical activity: Results of the lifestyle interventions and independence for elders pilot study. *J Gerontol a Biol Sci Med Sci* 64:688–694. [PubMed: 19244157]

FIGURE 1.

In women, average total steps/day was not significantly correlated with self-reported exercise (Pearson's correlation: $r = 0.04$; $P = 0.78$; Spearman's correlation: $\rho = 0.07$; $P = 0.61$); in men average total steps/day was correlated with self-reported exercise (Pearson's correlation: $r = 0.51$; $P = 0.01$; Spearman's correlation: $\rho = 0.33$; $P = 0.10$).

FIGURE 2.

All panels indicate superior and inferior views of the bilateral hippocampi (left and right hippocampi) where correlations are statistically significant. Panel (a) indicates bi-lateral spatial maps of correlation between hippocampal shape diffeomorphometry and total walking activity in women. Panel (b) indicates bi-lateral spatial maps of correlation between hippocampal shape diffeomorphometry and low-intensity walking activity after co-varying for self-reported exercise in women. Panel (c) is a reference column indicating bi-lateral subdivisions of the template surfaces into four compatible subregions: CA1, CA2, CA3 combined with the dentate gyrus, and the subiculum. Correlations in women with self-report exercise did not reach statistical significance thresholds and therefore were not included; correlations between all physical activity measures and hippocampal shape diffeomorphometry in men did not reach statistical significance thresholds and therefore were not included. Note: The color bar denotes the Pearson product-moment correlation coefficient (PCC) values, which were plotted only for vertices whose correlations were statistically significant after a multiple comparison correction.

TABLE 1.

Baseline Characteristics of the Brain Health Substudy Sample (N = 90)

	N (%) or Mean $\pm$ SD	
Demographic		
Age (years)	67.3 $\pm$ 6.0	
Sex (women)	63 (70.0)	
Race (African American)	80 (89.0)	
Education (high school)	34 (38.2)	
MMSE	28.4 (1.5)	
	Women	Men
Chronic Disease		
Obesity (BMI $\geq$ 30)	41 (65.1)	11 (40.7) ^a
Hypertension	47 (75.8)	17 (64.0)
Diabetes	18 (29.0)	9 (33.3)
Physical activity		
Objective walking activity		
Steps/day (total)	7519.1 $\pm$ 2814.5	8755.2 $\pm$ 3496.1
Steps/day at low-intensity ^b	6875.7 $\pm$ 2454.1	7737.0 $\pm$ 2454.1
Steps/day at moderate- to vigorous-intensity ^c	643.5 $\pm$ 802.0	1018.2 $\pm$ 1472.8
Self-reported exercise		
Total caloric expenditure/week ^d	1595.2 $\pm$ 1593.8	2124.1 $\pm$ 2365.7

SD = standard deviation; MMSE = Mini Mental State Exam.

^a $P < 0.05$, t test/chi2 for differences by sex; women and men did not vary significantly on any demographic characteristic.^b Low-intensity defined as walking activity at <100 steps/min.^c Moderate- to vigorous-intensity is defined as walking activity at ≥ 100 steps/min.^d Assessed using the self-reported exercise-related physical activities from the Community Health Activities Model Program for Seniors (CHAMPS) questionnaire.