



## Research report

## Objective measures of physical activity, white matter integrity and cognitive status in adults over age 80



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## HIGHLIGHTS

- We examined physical activity components in relation to white matter integrity.
- More steps and longer duration were associated with greater white matter integrity.
- Associations were localized in frontal and temporal areas.
- Associations were independent of cardiometabolic conditions and physical limitation.

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## ABSTRACT

The neuroprotective effects of physical activity (PA) are consistently shown in older adults, but the neural substrates, particularly in white matter (WM), are understudied, especially in very old adults with the fastest growth rate and the highest risk of dementia. This study quantified the association between PA and WM integrity in adults over 80. The moderating effects of cardiometabolic conditions, physical functional limitations and WM hyperintensities were also examined, as they can affect PA and brain integrity. Fractional anisotropy (FA) from normal-appearing WM via diffusion tensor imaging and WM hyperintensities were obtained in 90 participants (mean age = 87.4, 51.1% female, 55.6% white) with concurrent objective measures of steps, active energy expenditure (AEE in kcal), duration (min), and intensity (metabolic equivalents, METs) via SenseWear Armband. Clinical adjudication of cognitive status, prevalence of stroke and diabetes, systolic blood pressure, and gait speed were assessed at time of neuroimaging. Participants were on average sedentary (mean  $\pm$  SD/day: 1766  $\pm$  1345 steps, 202  $\pm$  311 kcal, 211  $\pm$  39 min, 1.8  $\pm$  1.1 METs). Higher steps, AEE and duration, but not intensity, were significantly associated with higher FA. Associations were localized in frontal and temporal areas. Moderating effects of cardiometabolic conditions, physical functional limitations, and WM hyperintensities were not significant. Neither FA nor PA was related to cognitive status. Older adults with a sedentary lifestyle and a wide range of cardiometabolic conditions and physical functional limitations, displayed higher WM integrity in relation to higher PA. Studies of very old adults to quantify the role of PA in reducing dementia burden via WM integrity are warranted.

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## 1. Introduction

Loss of white matter (WM) integrity in frontal and medial temporal brain areas is related to difficulties in working memory and impaired processing speed [1,2]. Although working memory and processing speed decline more rapidly with older age, these cognitive domains have also been shown to improve in response to greater amounts of physical activity (PA) (for review, see [3]). However, associations between PA and white matter (WM) integrity and cognitive function have not been studied among octogenarians. With soaring incidence rates of dementia among adults aged 80 and older [4] and the sheer increase in the growth rate of this segment of the population [5], it is essential to rapidly identify strategies to promote cognition and WM integrity for these adults. Characterizing the relationship between objective measures of PA and WM integrity and cognition for these adults can also improve the design of targeted PA guidelines and prescriptions. With more than half adults aged 85 and over being able to walk [6], PA interventions appear feasible [7,8]. However, PA trials targeting very old adults to improve cognition appear premature at this time; most evidence to date is for younger and healthier old adults, with little information on the relative impact of other common health-related conditions on these associations.

Positive associations of higher PA with greater WM volume and fewer WM lesions have been reported in adults in their 60s and 70s [9–12]. A small intervention study shows exercise training increases WM volume [13]. Higher PA has also been associated with greater WM integrity using diffusion tensor imaging (DTI) in two descriptive studies [10,14] and in one fitness intervention trial aiming to increase walking [15] in adults younger than 80. Although very promising, these studies provide limited information on the potential PA beneficial effects for adults 80 and older, not only because of the few adults 80 and older examined, but also because the roles of cardiometabolic conditions, dementia, or physical functional limitations was not examined. This is critically important because chronic disease conditions and physical function limitations compromise the ability of older adults to safely engage in PA and may also affect WM integrity.

Another limitation of prior studies is the use of relatively crude measures of WM and of PA. The use of self-report PA measures cannot distinguish duration from intensity and cannot accurately assess low intensity or short duration of PA, commonly seen in this age group. Furthermore, self-report measures require recall accuracy which is challenging for older persons with declining memory functions. One recent study using accelerometry reported that light PA was associated with greater temporal WM integrity in adults in their mid-sixties [16]. Although objective, accelerometer only provides a crude measure of the activity counts. Similarly, by focusing on WM macrostructure, prior studies have mostly provided information on overall WM volume or radiologically overt lesions. Compared to crude measures of WM lesions and hyperintensities, DTI provides more accurate measures of brain parenchyma microstructure and it has been related to earlier stages of cognitive impairment [17]. Disruption of WM integrity is frequently observed as decreased fractional anisotropy (FA), commonly resulted from increased radial diffusivity (RD) or decreased axial diffusivity (AD). Increased RD may indicate demyelination, whereas decreased AD suggests axonal damage [18]. Therefore, the application of DTI can help uncover the mechanisms underlying the relationship between PA and WM integrity.

The objective of this study was to examine the cross-sectional association between objective multidimensional measures of PA and WM integrity measured as FA using DTI, and cognitive function, in a cohort of adults over 80 years old with extensive retrospective clinical and cognitive data over the prior 14 years. It was hypothesized that higher active energy expenditure (AEE), more

step counts, longer duration and higher intensity of PA would be associated with lower dementia prevalence and higher FA. We further hypothesized these associations would be stronger for frontal and medial temporal areas than other areas. A second objective was to examine the roles of cardiometabolic conditions, dementia, and physical functional limitations as potential modifiers of these associations.

## 2. Methods

### 2.1. Study population

Participants were recruited from the Health, Aging and Body Composition Study cohort, an ongoing longitudinal study that began in March 1997 to assess the relationship between changes in body composition and health outcomes in 3075 community-dwelling older adults (52% female, 42% black) aged 70–79 years [19]. Among 1527 participants entering the study at the Pittsburgh site, 819 were alive and seen in the clinic or had a home visit in 2006–2008. Of the 819, 315 received a brain Magnetic Resonance Imaging (MRI) scan at 3 Tesla [20] and 10 received a brain MRI at 1.5 Tesla because joint replacements or implants had not been cleared for safety at 3 Tesla as part of the Healthy Brain Project. Of the 819, 99 did not meet the eligibility for a brain MRI. 169 were ineligible for the Healthy Brain Project because they were walking with a cane and/or did not have mobility performance measures (this served as exclusion criteria as the original study was designed to investigate mobility). 145 were not interested in participating in the brain MRI or refused. 17 were not scanned either because of intervening illness, death before the scan, or because they changed their mind, although eligible. 64 were not included either because of hospitalization for major clinic events in the previous three months (fracture, psychiatric problem) or for other reasons (missing data).

In 2010–2012, 163 participants received a follow-up MRI with DTI and were offered the SWA assessment. Of the 163, 103 were eligible and interested in wearing a SenseWear Armband (SWA). 90 out of 103 had usable SWA data with at least 3-day on-body time [21] as well as DTI data and were included in this study (Supplementary Figure 1). All participants provided written informed consent. The University of Pittsburgh Institutional Review Board approved the protocol. The average interval between SWA and the follow-up MRI was 7.7 months (SD = 6.3). Age was obtained at time of the SWA measurement. Sex, race, and education were obtained at the Health, Aging and Body Composition Study entry examination.

Supplementary material related to this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bbr.2015.01.045>.

### 2.2. MRI acquisition

MRI scans were obtained at the MR Research Center of the University of Pittsburgh with a 3 Tesla Siemens TIM TRIO scanner equipped for echo-planar imaging using the protocol previously described [20]. DTI were acquired using single-shot spin-echo echo planar imaging sequence with the following parameters: TR = 5300 ms; TE = 88 ms; TI = 2500 ms; Flip angle = 90°; FOV = 256 mm × 256 mm; two diffusion values of  $b = 0$  and 1000 s/mm<sup>2</sup>; 12 diffusion directions; four repeats; 40 slices; matrix size = 128 × 128; voxel size = 2 mm × 2 mm; slice thickness = 3 mm; and GRAPPA = 2. Two series of sagittal scans (with and without the off-resonance saturation pulse with an offset frequency of 1.5 kHz) were obtained for the MT acquisition across 120 slices with matrix size = 256 × 192; TR = 35 ms; TE = 2.86 ms; TI = 300 ms; Flip angle = 15°; slice thickness: 1.5 mm; voxel size = 0.89 mm × 0.89 mm; and FOV = 230 mm × 230 mm.

Fluid-attenuated inversion recovery (FLAIR) images were acquired in the axial plane: TR=9160 ms; TE=89 ms; TI=2500 ms; FA=150°; FOV=256 mm × 212 mm; slice thickness=3 mm; matrix size=256 × 240; number of slices=48 slices; and voxel size=1 mm × 1 mm. A radiologist checked the MR images used in this study and excluded any participants with incidental findings.

### 2.3. Image processing and analysis

Magnetization-prepared rapid gradient echo images and fluid attenuated inversion recovery images were acquired to obtain volumes of WM and WM hyperintensities (WMHs), respectively. The DTI was preprocessed using the FMRIB's Diffusion Toolbox to correct eddy current-induced distortions [22]. The FA map was registered to the FMRIB58.FA template [22] using the FMRIB's non-linear image registration tool (FNIRT). Using the segmentation of WM and WMHs, the FA map was restricted to normal-appearing WM. Mean FA was calculated for normal-appearing WM. Using Automated Labeling Pathway [23–25], WM tracts were identified based on the Johns Hopkins University White Matter Atlas.

The FA from normal-appearing WM was the primary neuroimaging outcome in this study. The RD and AD maps from normal-appearing WM were also generated and the mean value of RD and AD were analyzed in the exploratory analysis. In order to explore the spatial distribution of WM integrity in relation to PA, specific WM tracts were also examined in the exploratory analysis. The FA in each WM tract was computed as a weighted average by WM volume. WM tracts included genu of corpus callosum, body of corpus callosum, splenium of corpus callosum, uncinate fasciculus, superior longitudinal fasciculus, anterior thalamic radiation, corticospinal tract, cingulate gyrus part of cingulum, hippocampal part of the cingulum, and inferior occipitofrontal fasciculus.

T2-weighted FLAIR images were acquired to obtain the WM hyperintensities (WMHs) volume. The WMH quantification was done using a fuzzy connected algorithm [24,25].

### 2.4. Physical activity measurement

Physical activity (PA) was measured by a SenseWear Armband (SWA, BodyMedia Inc., Pittsburgh, Pennsylvania). The SWA collects a variety of physiological data through portable multiple sensors (a three-axis accelerometer, heat flux sensor, skin temperature sensor, near-body ambient temperature sensor, and galvanic skin response sensor). It can detect various types of activities, using pattern detection algorithms based on physiological signals. The SWA measures energy expenditure and provides good accuracy and reliability at rest, during exercise at different intensities, and in a free-living surrounding [26–28]. The unique combination of multiple sensors and its high accuracy across the spectrum of the free-living activities, moderate price and ease of assessment in large-scale studies overcome limitations of other objective measures [29].

Participants were instructed to wear the SWA on the left upper arm for seven consecutive days and to remove it when bathing or engaging in water activity as the device is not waterproof. They were allowed to remove the armband for up to 1 h each day for a rest. After wearing the device for seven consecutive days, participants were instructed to return the SWA by mail. Data were downloaded to the SWA software (SenseWear Pro 7.0) and information on age, sex, body weight, height, handedness, and smoking status were entered into the software to calculate energy expenditure. Data with at least 3 days of on-body time were necessary for analyses [21]. The average percent of on-body time was 93.7% (SD=10.7). PA was defined as activities equal to or greater than 3 metabolic equivalents (METs). The AEE was estimated as energy expenditure during activities equal to or greater than 3 METs. In

this study, the multidimensional measures of PA included the daily average of AEE (kcal), step (counts), duration (minutes of PA) and intensity (METs). Daily averages were calculated by dividing total AEE, steps, minutes, and METs over the number of days that the armband was worn. The counts of steps were also converted to miles by multiplying the step counts and the average step length measured by the GaitMat II [30].

### 2.5. Health-related conditions

Cognitive and physical function, and prevalence of diabetes and stroke were measured at regular intervals (years 1, 4, 6, 8, 9, 10, 11, 12, 13 of the Health, Aging and Body Composition Study) with clinical adjudication of cognitive status and extensive cognitive exam conducted at the time of MRI and SWA (years 14/15). Additionally, trajectories of systolic blood pressure, gait speed, and scores on the Modified Mini-Mental State Examination (3MSE), Center for Epidemiologic Studies Depression Scale (CES-D), and Digit Symbol Substitution Test (DSST) were also computed using all available data points and tested for their potential confounding effects on the associations between PA measures and FA.

Cardiometabolic conditions, cognitive status, physical functional limitations, and WMHs were selected as potential moderators due to their known associations to either PA or brain health. Prevalence of stroke and diabetes was measured using prevalent disease algorithms, according to self-reported diagnoses by physicians and record of medication use from study entry to the time of MRI in 2010–2012. Systolic blood pressure was obtained as the average from two measurements. Cognitive status was characterized as either cognitively normal or evidence of mild cognitive impairment (MCI) or dementia, ascertained by an adjudication committee using a previously published protocol [31] and extensive neuropsychological testing including Premorbid intelligence: the American Version of the National Reading Test and Raven's Colored Progressive Matrices; Memory: California Verbal Learning Test, and Rey-Osterrieth Figure; Language: Boston Naming Test and Verbal Fluency Test; Visuo-perceptual/visuo-constructional: Block design (from the Wechsler Adult Intelligence Scale-revised) and copy of a geometric figure; and Executive Function: Stroop test. The classification of MCI or dementia was based on the number of impaired tests from the neuropsychological battery, severity of the impairment, scores on the 3MSE, DSST, and CES-D, and the evaluation of the instrumental activities of daily living or the activities of daily living. Physical function was measured as gait speed at a usual pace over a 4-m-long walkway using the GaitMat II™ system (EQ Inc., Chalfont, Pennsylvania). Gait speed was computed as the distance between the first switch closure of the first and last steps divided by the time between the earliest closures of the first and last steps. For those who did not have the GaitMat measure, gait speed was computed in meters/second while walking at a usual pace over 3, 4 or 6 m [32]. Gait speed is a valid and reliable assessment of physical function among older adults in both clinical and aging research settings [33,34]. Slower gait speed is strongly associated with greater co-morbidity and higher mortality risk [35–37].

### 2.6. Statistical analysis

To examine whether multidimensional measures of PA reflect distinguishable components of PA, univariate associations between PA measures were examined using Pearson's correlation or Spearman rank order correlation coefficients as appropriate. Univariate associations of PA and FA with cognitive function measured by 3MSE and DSST were examined using Pearson's correlation coefficient. Univariate associations of PA and FA with cognitive status were examined using independent *t* test.

**Table 1**  
Characteristics of the analytic sample and the Healthy Brain Project (HBP) cohort with diffusion tensor imaging (DTI) but without usable SWA data.

	Total (n = 90)	HBP cohort with DTI but without usable SWA (n = 62)	p-value
Demographics			
Age, years, mean ± SD	87.4 ± 2.3	88.0 ± 3.0	0.171
Sex, female, N (%)	46 (51.1)	43 (69.4)	0.025
Race, black, N (%)	40 (44.4)	26 (41.9)	0.759
Education > high school, N (%)	45 (50.0)	31 (50.0)	0.891
Physical activity, mean ± SD			
Active energy expenditure, kcal/day	202 ± 311	–	–
Step, counts/day	1766 ± 1345	–	–
Duration, min/day	211 ± 39	–	–
Intensity, METs/day	1.8 ± 1.1	–	–
Fractional anisotropy			
Normal-appearing white matter	0.365 ± 0.014	0.362 ± 0.014	0.111
Health-related conditions, mean ± SD or N (%)			
Gait velocity, m/s	0.8 ± 0.2	0.8 ± 0.2	0.809
Systolic blood pressure, mm Hg	127.7 ± 18.1	123.9 ± 14.1	0.183
Diabetes	20 (22.5)	12 (20.3)	0.758
Stroke	3 (3.3)	11 (17.7)	0.003
Mild cognitive impairment/dementia	51 (56.7)	36 (58.1)	0.864

p-values were computed from independent t-test or chi-square test as appropriate.

To understand the mechanisms of neuroprotective effects of PA in a greater specificity, univariate associations of PA measures with FA as well as RD and AD from normal-appearing WM were examined using Pearson's correlation coefficients. To examine the strength of the association between PA measures and FA from normal-appearing WM, regression models were used with each PA measure as the predictor and FA from normal-appearing WM as the outcome, adjusting for race, education, prevalence of stroke and diabetes, systolic blood pressure, cognitive status, gait speed and WMHs. Because age, sex, body weight, and height were used as input in calculating energy expenditure by the SWA algorithm, these factors were not included in the model to avoid possible over-adjustment. In additional sensitivity analyses, the average interval between the SWA and the MRI, on-body percentage of time worn, and the number of days worn, were adjusted in the model as covariates. Models were also adjusted for trajectories of systolic blood pressure, gait speed, 3MSE, DSST, and CES-D from the prior 14 years.

The moderating effects of cardiometabolic conditions, cognitive status, gait speed, and WMHs on the strength of associations between PA and FA from normal-appearing WM were tested using hierarchical multiple regression models: (1) the predictor of PA measures and the moderator (if continuous) were both mean-centered, (2) the interaction term between centered PA measures and the moderator was created, and (3) hierarchical multiple regression models were conducted by first entering the measure of PA and the moderator and then adding the interaction term. A significant model change after adding the interaction term and a significance level of the interaction term at  $p < 0.05$  indicated a significant moderating effect.

In additional exploratory analyses, the associations between PA measures and FA in individual tracts were tested using Pearson's correlation coefficient. The associations of step and duration of PA with FA in individual tracts were adjusted for age and sex using partial correlation coefficient. The tracts of interest included corpus callosum, uncinate fasciculus, superior longitudinal fasciculus, inferior occipito-frontal fasciculus, cingulum and anterior thalamic radiation. These tracts were chosen as a priori because of their known associations with physical activity and cardiorespiratory fitness [38–41].

### 3. Results

The 90 participants included in this study had a mean age of  $87.4 \pm 2.3$  years (range: 83–92 years) and were more likely to be

female (51.1%) and white (55.6%) (Table 1). Compared to this sample of 90 participants, those who had DTI data in 2010–2012 but did not have usable SWA data ( $N = 62$ ) were more likely to be female and had a higher prevalence of stroke (Table 1). The 90 participants took an average of  $1766 \pm 1345$  steps per day, indicating a sedentary lifestyle [42]. Higher AEE was correlated with more step counts ( $r = 0.565$ ,  $p < 0.001$ ), more minutes of PA ( $r = 0.960$ ,  $p < 0.001$ ), and higher METs ( $r = 0.881$ ,  $p < 0.001$ ). More steps were correlated with more minutes of PA ( $r = 0.598$ ,  $p < 0.001$ ) and higher METs ( $r = 0.647$ ,  $p < 0.001$ ). More minutes of PA were correlated with higher METs ( $r = 0.927$ ,  $p < 0.001$ ). More step counts were associated with higher DSST scores ( $r = 0.226$ ,  $p < 0.05$ ). Associations of AEE, minutes of PA, and METs with DSST were not significant ( $p > 0.05$ ). Associations of PA measures with 3MSE were not significant ( $p > 0.05$ ). The FA from total white matter was not associated with DSST ( $r = 0.093$ ,  $p > 0.05$ ) or 3MSE ( $r = -0.013$ ,  $p > 0.05$ ). There were no significant differences in PA or DTI measures between cognitively normal participants and those diagnosed with MCI or dementia ( $p > 0.05$ ).

More steps taken, higher AEE, more minutes of PA, but not METs, were associated with higher FA from normal-appearing WM (Table 2). In additional analyses, more steps, but not other PA measures, were associated with lower RD from normal-appearing WM (Table 2). Associations between PA measures and AD were all not significant (Table 2).

The associations of steps, AAE and duration with FA remained similar after adjustment for race, education, systolic blood pressure, diabetes, stroke, cognitive status, and gait speed ( $\Delta\beta \leq 10\%$ , Table 3). Moderating effects of these health-related conditions and of WMHs on the associations between PA and FA were not statistically significant ( $p > 0.05$  for all interaction terms). Adjustment for the average interval of time between the SWA assessment and

**Table 2**  
Correlations of physical activity measures with fractional anisotropy, radial diffusivity, and axial diffusivity from normal-appearing white matter ( $n = 90$ ).

	Fractional anisotropy	Radial diffusivity	Axial diffusivity
Step (counts/day)	0.272 (0.009)	−0.222 (0.036)	−0.075 (0.482)
Active energy expenditure (kcal/day)	0.246 (0.020)	−0.204 (0.056)	−0.160 (0.135)
Duration (min/day)	0.222 (0.037)	−0.150 (0.162)	−0.085 (0.428)
Intensity (METs/day)	0.153 (0.150)	−0.098 (0.361)	−0.034 (0.750)

Values are presented as  $r$  (p-value). p-values were obtained using Pearson's correlation coefficient.

**Table 3**  
Regression models of associations between physical activity measures and fractional anisotropy from normal-appearing white matter significant at  $p < 0.50$ , standardized units ( $n = 90$ ).

	Model 1 Unadjusted	Model 2 (Race + Education)	Model 3 (Systolic blood pressure)	Model 4 (Diabetes)	Model 5 (Stroke)	Model 6 (Cognitive status)	Model 7 (Gait speed)
Standardized $\beta$ (95% CI), $p$ -value							
Step <sup>a</sup> (counts/day)	0.272 (0.067, 0.468) 0.009	0.259 (0.044, 0.466) 0.019	0.271 (0.064, 0.469) 0.010	0.273 (0.064, 0.473) 0.011	0.275 (0.069, 0.471) 0.009	0.274 (0.066, 0.472) 0.010	0.261 (0.018, 0.496) 0.035
Active energy expenditure (kcal/day)	0.246 (0.038, 0.442) 0.020	0.239 (0.026, 0.441) 0.028	0.245 (0.032, 0.447) 0.024	0.245 (0.034, 0.445) 0.023	0.242 (0.033, 0.440) 0.023	0.246 (0.037, 0.444) 0.021	0.223 (0.011, 0.425) 0.040
Duration <sup>a</sup> (min/day)	0.222 (0.014, 0.423) 0.037	0.208 (-0.004, 0.415) 0.054	0.219 (0.008, 0.425) 0.042	0.221 (0.009, 0.427) 0.041	0.217 (0.007, 0.420) 0.043	0.222 (0.012, 0.427) 0.038	0.199 (-0.012, 0.406) 0.065

<sup>a</sup> Adjustment for age and sex did not substantially change the associations of step and duration with fractional anisotropy from normal-appearing white matter (standardized  $\beta$  (95% CI),  $p$ -value: 0.250 (0.031, 0.468), 0.026; and 0.202 (-0.004, 0.407), 0.055, respectively).

MRI, on-body percentage of time worn, or the number of days worn did not attenuate these associations ( $\Delta\beta < 10\%$  for all). Associations remained similar after adjustment for trajectories of systolic blood pressure, gait speed, and 3MSE, DSST, CES-D in the prior 14 years.

One way to interpret these associations is that for each standard deviation (SD) increase in step counts (1345, equivalent to 0.53 miles per day = 1766 step counts  $\times$  0.50 meter average step length  $\times$  0.0006 mile/meter), AEE (311 kcal), and duration of PA (39 min), there was an approximately 1% increase in FA from normal-appearing WM (SD of mean FA  $\times$  regression coefficient).

In further exploratory analyses of FA from individual tracts, more steps taken, higher AEE, and more minutes of PA were associated with higher FA in superior longitudinal fasciculus, inferior occipito-frontal fasciculus, and hippocampal part of the cingulum (Table 4). More steps taken were also associated with higher FA in body of corpus callosum, cingulate gyrus part of cingulum, and anterior thalamic radiation (Table 4). Higher AEE was also associated with higher FA in genu of corpus callosum (Table 4). The associations between steps and FA in superior longitudinal fasciculus and anterior thalamic radiation remained significant after Bonferroni adjustment ( $p \leq 0.006$ ). Results remained similar for the associations of step and duration of PA with FA after adjustment for age and sex (data not shown).

#### 4. Discussion

In this cohort of adults aged 80 years and older, more PA was associated with higher FA in normal-appearing WM, mostly localized in frontal and temporal areas. Walking as little as 1345 more steps per day (or 0.53 miles) was associated with an approximately 1% difference in FA, independent of cardiometabolic and cognitive conditions and physical functional limitations. Similar associations were found for higher levels of AEE (e.g. 311 kcal/day) and longer duration of PA (e.g. 39 min/day).

The FA from cerebral WM declines with advancing age. The annual decline rate of FA is approximately 0.5% in older adults [43]. If the observed positive associations between PA and WM integrity are replicated, this would be an indication that even small increases in PA (e.g. increase walking by 0.53 miles, or roughly six city blocks) could mitigate or even reverse age-related losses in WM integrity by two years. However, associations of PA or of FA with cognitive status were not significant, thus raising questions on the effectiveness of PA to promote cognition among adults older than 80.

This study extends previous investigations on the association between PA and WM integrity in relatively young older adults by applying objective measures of PA and high resolution imaging with DTI in a population older than 80 years, with extensive measures of health-related characteristics.

Participants in this study walked an average of  $1766 \pm 1345$  steps per day and were far off the recommended PA levels of walking at least 5486 steps per day (approximately 2.5 miles) [44], thus appeared to lead a sedentary lifestyle [42]. These participants were also living with chronic diseases and physical functional limitations. We expected that the neuroprotective effects of PA would have been reduced in the presence of these health-related conditions. Surprisingly, we found that there was a robust association between higher levels of PA and greater WM integrity, even after adjusting for health-related conditions.

The application of DTI in this study provided quantitative measures of microstructural integrity of WM tracts that appear "normal", that is free from hyperintensities. Our results suggest that the potential neuroprotective effects of PA may be due to preserved

**Table 4**  
Correlations between physical activity measures and fractional anisotropy in individual tracts (n = 90).

	Genu of corpus callosum	Body of corpus callosum	Splenium of corpus callosum	Uncinate fasciculus	Superior longitudinal fasciculus	Inferior occipito-frontal fasciculus	Cingulate gyrus part of cingulum	Hippocampal part of cingulum	Anterior thalamic radiation
Step (counts/day)	0.179 (0.091)	0.243 (0.021)	0.142 (0.181)	0.199 (0.060)	0.285 (0.006)*	0.239 (0.024)	0.220 (0.037)	0.243 (0.021)	0.289 (0.006)*
Active energy expenditure (kcal/day)	0.228 (0.031)	0.128 (0.234)	0.105 (0.327)	0.115 (0.283)	0.282 (0.007)	0.226 (0.033)	0.181 (0.089)	0.269 (0.011)	0.195 (0.067)
Duration (min/day)	0.152 (0.155)	0.069 (0.522)	0.128 (0.231)	0.144 (0.179)	0.254 (0.016)	0.218 (0.040)	0.155 (0.147)	0.269 (0.011)	0.207 (0.051)
Intensity (METs/day)	0.143 (0.180)	0.017 (0.875)	0.008 (0.942)	0.112 (0.294)	0.195 (0.066)	0.154 (0.148)	0.060 (0.572)	0.203 (0.055)	0.150 (0.159)

Values are presented as  $r$  ( $p$ -value).  $p$ -values were obtained using Pearson's correlation coefficient.  
\*  $p$ -values were significant at  $p \leq 0.006$  with Bonferroni correction.

myelination or reduced myelin abnormalities, as indicated by decreased RD with higher amounts of PA.

Our results of the spatial distribution of WM integrity in relationship to PA can increase our understanding of the neural substrates underlying the beneficial effects of PA for this age group. The associations of steps and FA appeared stronger in the superior longitudinal fasciculus and anterior thalamic radiation. These tracts are related to information processing speed [45] and are involved in learning and episodic memory, respectively [46]. Although we did not find an effect of PA on cognition, it cannot be excluded that the neuroprotective effects of PA could be potentiated with concurrent cognitive activity interventions specifically targeting these two domains.

The application of the SenseWear Armband provided objective, accurate, and multifaceted measures of PA in older adults, and contributed to increase the internal validity of these measurements [26]. Effect sizes were remarkably similar across the three PA measures of AEE, steps, duration. This is not entirely surprising because of the highly significant correlations between the PA measures obtained by the SWA. Objective measures of PA are especially important when studying vulnerable populations of older adults, who are more likely to engage in low intensity activities, rather than moderate or vigorous ones, due to common physical functional limitations and generally less favorable health-related conditions.

The lack of significant association between PA intensity and any neuroimaging outcomes deserves attention. Intensity may not be as important as duration for WM health in very old age. It is also possible that the effect of PA intensity on WM integrity cannot be detected due to a truncated range of intensity levels for our participants. Future studies in older adults with a wider range of PA intensity can answer these questions, although advancing age itself may be the limiting factor for engaging in moderate-to-high intensity activity.

Several limitations of this study require us to interpret the results with caution. First, we may not have had sufficient statistical power to detect the potential moderating effects of health-related conditions or a positive association between PA intensity and WM integrity. Future studies should include large samples of adults older than 80. Second, the direction of the effects is uncertain due to the cross-sectional nature of the study design. Third, participants in our study tend to be healthier than the general population due to their voluntary participation and eligibility for MRI. Although the adjustment for the time interval between SWA and MRI measurements did not change the results, the time interval of 7.7 months may have introduced confounding effects, such as lifestyle and health status changes during this time interval. In additional exploratory analyses, we chose to analyze the relationship between each PA measure and FA in each tract. This approach required the correction for multiple comparisons. With Bonferroni correction for multiple comparisons, the associations of steps with FA in superior longitudinal fasciculus and anterior thalamic radiation were considered to be significant.

Notwithstanding these limitations, findings from this study may be useful in formulating PA recommendations for improving WM integrity in sedentary octogenarians living in the community. Future studies are needed to identify the dose of PA with the components of intensity, duration, or both, necessary to preserve WM integrity through older age and explore pathways to potentiate the effect of PA on cognition.

#### Conflict of interest

The authors have no conflicts of interest to declare. And the authors have no disclosure to make.

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