



# HHS Public Access

Author manuscript

*Neurobiol Aging*. Author manuscript; available in PMC 2023 August 01.

Published in final edited form as:

*Neurobiol Aging*. 2022 August ; 116: 25–31. doi:10.1016/j.neurobiolaging.2022.04.007.

## Longitudinal associations of absolute versus relative moderate-to-vigorous physical activity with brain microstructural decline in aging

Qu Tian<sup>1,\*</sup>, Jennifer A. Schrack<sup>2</sup>, Bennett A. Landman<sup>3</sup>, Susan M. Resnick<sup>4</sup>, Luigi Ferrucci<sup>1</sup>

<sup>1</sup>Longitudinal Studies Section, National Institute on Aging, Baltimore, MD 21224

<sup>2</sup>Department of Epidemiology, Johns Hopkins University, Baltimore, MD 21205

<sup>3</sup>Electrical Engineering and Computer Science, Vanderbilt University, Nashville, TN 37235

<sup>4</sup>Laboratory of Behavioral Neuroscience, National Institute on Aging, Baltimore, MD 21224

### Abstract

Higher moderate-to-vigorous intensity (MVPA) may preserve brain structural integrity, but evidence is mostly cross-sectional and relies on absolute PA measures. We examined longitudinal associations of absolute MVPA using population-level activity count thresholds and relative MVPA using individual heart rate reserve (HRR) via Actiheart with subsequent changes in brain diffusion tensor imaging (DTI) over average 3.8 years in 248 initially cognitively normal individuals (56–91 years). DTI markers included areas important for memory (temporal areas), executive (prefrontal cortex, superior longitudinal fasciculus), and motor function (precentral gyrus, putamen, caudate, body of corpus callosum). Associations of MVPA with changes in DTI markers were examined using linear mixed-effects models, adjusted for demographics and apolipoprotein e4 carrier status. Each additional 22 minutes of relative MVPA per day was significantly associated with less decline in fractional anisotropy of uncinate fasciculus and cingulum-hippocampal part and with less increase in mean diffusivity of entorhinal cortex and parahippocampal gyrus. Absolute MVPA was not associated with DTI changes. More time spent in relative MVPA by HRR may prevent brain microstructural decline in selected temporal areas.

### Keywords

diffusion tensor imaging; longitudinal relationship; relative physical activity intensity; aging

\*Correspondence: Qu Tian, Ph.D., 251 Bayview Blvd., Suite 100, Baltimore, Maryland 21224.

**Publisher's Disclaimer:** This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

**Conflict of interest:** None declared.

Credit author statement:

**Qu Tian:** Conceptualization, Investigation, Methodology, Formal analysis, Software, Writing- Original draft preparation

**Jennifer A. Schrack:** Data curation, Writing- Reviewing and Editing

**Bennett A. Landman:** Data curation, Writing- Reviewing and Editing, Visualization

**Susan M. Resnick:** Supervision, Writing- Reviewing and Editing

**Luigi Ferrucci:** Conceptualization, Supervision, Writing- Reviewing and Editing

## 1. Introduction

While it has been well established that regular participation in physical activity (PA) is associated with preserved brain structure in old age (Domingos et al., 2021), the intensity level that is most beneficial to brain health is less conclusive (Domingos et al., 2021; Sexton et al., 2016). Recent studies have provided new evidence regarding the intensity level associated brain health. Several studies have suggested that engaging in PA, especially at moderate-to-vigorous intensity (MVPA), may produce more benefits for cognition and brain structure than light intensity PA among older adults (Burzynska et al., 2014; Burzynska et al., 2020; Erickson et al., 2019; Ikuta et al., 2019; Machida et al., 2021; Northey et al., 2020; Palta et al., 2021). However, not all studies have found consistent results. Other data shows time spent in MVPA is not associated with brain structure or function, such as total brain volume, hippocampal volume, or functional integrity of brain networks (Spartano et al., 2019; Varma et al., 2015; Voss et al., 2016). These discrepancies may be due to different thresholds used to define the intensity of movement. We have previously hypothesized that the intensity of exercise associated with preservation of aerobic capacity and cardiovascular health with aging is heterogeneous across individuals and here we extend the same hypothesis to the brain (Schrack et al., 2018). Our hypothesis is based on the idea that to perform the same quantity of activity, an older person may need to engage in greater effort with more exertion than a younger person due to different aerobic capacity and health conditions. One feasible approach to address such heterogeneity is to quantify relative intensity levels as the individual heart rate reserve expressed as the percent difference between maximal heart rate and resting heart rate (Ozemek et al., 2013; Schrack et al., 2018; Shephard, 2001). This method assesses an individual's relative intensity while accounting for aerobic capacity (Astrand et al., 1973; Karvonen et al., 1957; Tanaka et al., 2001).

While previous neuroimaging studies have shown that higher MVPA is associated with greater brain volumes in the dorsolateral prefrontal cortex and hippocampus and fewer lacunar (Domingos et al., 2021; Northey et al., 2020; Palta et al., 2021), data on microstructural integrity of the brain are limited, especially concerning longitudinal changes with aging (for review see (Sexton et al., 2016)). Studying microstructural integrity in aging is critical as some studies have shown age-related degeneration in microstructural integrity is associated with cognitive decline and predicts future risk of neurodegenerative disorders, such as Alzheimer's disease (AD) (Fellgiebel et al., 2006; Scola et al., 2010; Weston et al., 2015). With aging, DTI measures may be more sensitive to vascular-related brain changes than conventional volumetric measures (Hugenschmidt et al., 2008). Several previous studies examined the relationship between PA and brain microstructure via diffusion tensor imaging, but most were cross-sectional and did not examine individualized PA levels (Burzynska et al., 2014; Gons et al., 2013; Kim et al., 2020; Strommer et al., 2020; Tian et al., 2014; Tian et al., 2015). Specifically, among older adults, more PA participation has been associated with higher fractional anisotropy of the temporal areas (Burzynska et al., 2014; Tian et al., 2015), including uncinate fasciculus (Strommer et al., 2020) and the hippocampal part of the cingulum (Tian et al., 2015) and with lower mean diffusivity of the medial temporal lobe and the cingulate cortex (Tian et al., 2014). More PA participation has also been associated with higher fractional anisotropy of other white

matter tracts, including external capsule, anterior limb of the internal capsule, (Strommer et al., 2020), superior longitudinal fasciculus, inferior fronto-occipital fasciculus, (Tian et al., 2015), the genu (Strommer et al., 2020) and body of the corpus callosum (Kim et al., 2020), and with lower mean diffusivity, radial diffusivity, and axial diffusivity of widespread white matter tracts (Gons et al., 2013). To date, only one study examined the longitudinal change in white matter microstructural integrity and found that compared to inactive persons, those who were active had less increase in the mean diffusivity of the uncinate fasciculus. Notably, this study did not find cross-sectional associations (Maltais et al., 2020). Moreover, this study did not differentiate between absolute and relative intensities which may have underestimated the association between PA and microstructure (Mann et al., 2013; Shephard, 2001).

In the present study, we aimed to extend prior literature by examining the longitudinal change in microstructural integrity of both gray matter and white matter and investigating its relationship with both absolute and relative MVPA in a sample of initially cognitively normal and well-functioning community-dwelling adults aged 55 or older. We hypothesized that higher MVPA would be associated with less decline in microstructural integrity with aging, indicated by less increase in mean diffusivity and less decline in fractional anisotropy.

## 2. Methods

### 2.1 Study Population

Participants were drawn from the Baltimore Longitudinal Study of Aging (BLSA). BLSA is a prospective cohort study with continuous enrollment that began in 1958 (Ferrucci, 2008). BLSA participants are community-dwelling adults. At the enrollment, participants must be free of cognitive impairment, functional limitations, chronic diseases, and cancer within the past 10 years to be eligible for the study. Enrolled participants receive regularly scheduled comprehensive health, cognitive, and functional evaluations over a 3-day visit to the National Institute on Aging (NIA) Clinical Research Unit at Harbor Hospital in Baltimore, Maryland. Visits occur every 4 years for persons younger than 60, every 2 years for persons aged 60 to 79, and annually for persons aged 80 or older. In this study, data were collected between June 2008 and December 2017, and the first concurrent assessment of Actiheart and brain microstructural imaging markers of mean diffusivity and fractional anisotropy was considered “baseline”. We analyzed 248 participants aged 55 or older who were cognitively normal (i.e. free of cognitive impairment or dementia) and had gait speed  $\geq 1$  m/sec at baseline and had baseline data on Actiheart accelerometer and one or more measures of microstructural imaging markers by diffusion tensor imaging (DTI). Exclusion criteria at baseline included diagnoses of mild cognitive impairment (MCI) or dementia, slow gait speed ( $< 1$  m/sec), and age younger than 55 years old. Diagnoses of cognitive impairment and dementia follow standard BLSA procedures, described previously (Driscoll et al., 2009). MCI was determined using the Petersen criteria (Petersen et al., 1997) which is a standardized and commonly used test for MCI diagnosis. BLSA diagnoses of dementia and Alzheimer’s disease have continued to follow the Diagnostic and Statistical Manual, the third edition, revised (DSM-III-R) and the National Institute of Neurological and Communication Disorders and Stroke-Alzheimer’s Disease and Related Disorders

Association (NINCDS-ADRDA) criteria, respectively (American Psychiatric Association, 1987)(McKhann et al., 1984).

The BLSA protocol was approved by the Institutional Review Board of the National Institutes of Health. Participants provided written informed consent at each BLSA visit.

### 2.3 Physical activity via Actiheart accelerometer

Physical activity was measured using the Actiheart accelerometer, which assesses both heart rate and uniaxial activity counts in 1-minute epochs (Actiheart, CamNtech, Cambridge, United Kingdom). On the last day of their BLSA clinic visit, participants were fitted with an ActiHeart monitor and were instructed to wear the Actiheart accelerometer for 7 consecutive days at all times except when bathing or swimming. The ActiHeart monitor was positioned horizontally on the chest at the third intercostal space with two standard electrocardiogram electrodes. At the end of the 7 days, participants were instructed to return the Actiheart accelerometer via express mail. Data were then downloaded using commercial software (Actiheart, version 4.0.32) to obtain heart rate in beats per minute and PA in counts per minute. A minimum of three days of valid wear time was required for inclusion in this analysis.

Time spent in relative MVPA was determined using an individualized threshold of intensity based on heart rate reserve (Karvonen et al., 1957). Details of relative MVPA were previously published (Schrack et al., 2018). First, individual heart rate reserve was calculated using the “Karvonen formula,” which expresses heart rate reserve as the percent difference between an individual’s maximal heart rate and resting heart rate. After defining individual heart rate reserve, activities at the minute level were categorized into sedentary/sleep, light, moderate, or vigorous intensities as follows: when minute-level PA was at 20% heart rate reserve, it was considered as sedentary/sleep, 20–39% as light intensity, 40–59% as moderate intensity, and 60% as moderate to vigorous intensity.

Time spent in absolute levels of exertion was determined using population-based activity count thresholds; 10 activity count per minute as sedentary/sleep; 10–95 activity counts per minute as light intensity, 95–234 as moderate, and >234 as vigorous.

### 2.4 Imaging acquisition

Neuroimaging data were acquired on one of three comparable 3T Philips Achieva scanners at the Kennedy Krieger Institute (KKI) or the National Institute on Aging (NIA) in Baltimore, Maryland. Imaging evaluations for each participant included a T1-weighted magnetization-prepared rapid gradient-recalled echo (MPRAGE) scan, an interleaved proton density and T2-weighted dual-echo scan, a fluid-attenuated inversion recovery (FLAIR) scan, and two DTI scans. The MPRAGE protocol was as follows: number of slices = 170, voxel size = 1mm×1mm×1.2mm, reconstruction matrix = 256×256, flip angle = 8 degrees and TR/TE = 6.5ms/3.1ms. DTI acquisition protocol was identical for KKI scanners: number of gradients = 32, number of b0 images = 1, max b-factor = 700 s/mm<sup>2</sup>, TR/TE = 6801/75 msec, number of slices = 65, voxel size = 0.83 × 0.83 × 2.2 mm, reconstruction matrix = 256 × 256, acquisition matrix = 96 × 95, field of view = 212 × 212 mm, flip angle = 90°. DTI acquisition protocol for the NIA scanner was: number of gradients = 32, number

of b0 images = 1, max b-factor = 700 s/mm<sup>2</sup>, TR/TE = 7454/75 msec, number of slices = 70, voxel size = 0.81 × 0.81 × 2.2 mm, reconstruction matrix = 320 × 320, acquisition matrix = 116 × 115, field of view = 260 × 260 mm, flip angle = 90°. Each DTI acquisition included two b0 images, which were averaged in k-space. Two separate DTI acquisitions with NSA = 1 were obtained and then combined offline (as explained in Image processing below) for an effective NSA = 2 to improve signal-to-noise ratio (Lauzon et al., 2013).

## 2.5 Diffusion tensor imaging processing

DTI processing follows the standard practice for tensor fitting and quality assessment and is explained in detail in earlier publications (Lauzon et al., 2013; Tian et al., 2016). Briefly, the individual diffusion-weighted volumes were affine co-registered to a minimally weighted (b0) target to compensate for eddy current effects and physiological motion. The gradient tables were corrected for the identified rotational component using finite strain (Alexander et al., 2001). To combine the two DTI sessions with different and unknown intensity normalization constants, each diffusion-weighted image was normalized by its own reference image before tensor fitting. To improve robustness, iteratively reweighted least squares fitting with outlier rejection using RESTORE (Chang et al., 2005) as implemented in CAMINO (Cook et al., 2006) was used to estimate tensors on a voxel-wise basis. QC was performed to remove scans with either excessive motion or images that had globally high diffusion measure bias after reviewing the distributions of QC summary statistics generated by our pipeline (Lauzon et al., 2013). Out of 1,404 sessions with two diffusion tensor imaging acquisitions, 20 sessions were identified as outliers during QC process, leaving 1,384 good quality DTI sessions for analysis (Williams et al., 2019).

## 2.6 Regions of interest

In this study, we focused on fractional anisotropy (FA) of white matter ROIs and mean diffusivity (MD) of gray matter ROIs. FA describes the degree of anisotropy of water molecules and can be used as an indirect measure of white matter integrity (Jones et al., 2013). Higher FA values may indicate higher integrity, and lower FA values may indicate lower integrity. MD describes the magnitude of water diffusion within tissues in all directions and can be used as an indirect measure of gray matter integrity (Jones et al., 2013). Lower MD values may indicate higher integrity, and higher MD values may indicate lower integrity. To segment gray matter regions, we used multi-atlas registration with the BrainCOLOR protocol using 35 manually labeled atlases from NeuroMorphometrics (Klein et al., 2010). The labels of ROIs obtained from the T1 image for each visit were affine registered to the diffusion image and used to extract region-specific average MD measures. To segment white matter, the Eve White Matter atlas (Lim et al., 2013) was combined with corresponding WM labels from the multi-atlas segmentation (Klein et al., 2010), and an FA mapped MRI. The WM labels were then intersected with WM segmentation and the resulting labels are iteratively grown to fill the remaining WM space from the multi-atlas labels. The WM labels of ROIs obtained from the T1 image for each visit were affine registered to the FA image and used to extract region-specific average FA measures.

Based on literature and anatomical locations, we selected bilateral ROIs important for memory (white matter: uncinate fasciculus, hippocampal part of the cingulum; gray matter:

hippocampus, parahippocampal gyrus, entorhinal cortex, executive function (white matter: superior longitudinal fasciculus; gray matter: prefrontal cortex including inferior, superior, middle, medial frontal, and orbitofrontal cortices), and motor function (white matter: the body of the corpus callosum; gray matter: precentral gyrus, putamen, caudate).

## 2.7 Statistical analysis

We examined the association of absolute or relative MVPA with changes in each neuroimaging marker of interest using linear mixed-effects models. Models were adjusted for baseline age, sex, race, years of education, body mass index, handedness, apolipoprotein e4 carrier status, and the scanner type. Random effects included interval and intercept. Measures of PA and DTI were computed as standardized Z scores.

Because individuals with fewer daily activities may have physical functional limitations, we adjusted for baseline gait speed as sensitivity analyses. As we examined multiple regions of interest (11 ROIs), we set significance at two-tailed  $p < 0.01$ .

## 3. Results

At baseline, the overall sample of 248 participants had a mean age of 71.3 years with a mean gait speed of 1.26 m/sec. Those with repeated measures of DTI had a mean age of 71.8 years with a mean gait speed of 1.25 m/sec at baseline ( $n=206$ ) (Table 1). Those with only one DTI assessment ( $n=42$ ) and those with repeated DTI did not differ in sample characteristics ( $n=206$ ). There were no significant differences in baseline FA or MD measures between those with repeated DTI and those with only one DTI assessment, or between scanner types (all  $p > 0.01$ ).

After adjustment, there were no significant cross-sectional associations between absolute or relative MVPA and any neuroimaging marker of interest (all  $p > 0.01$ ) (Table 2).

Longitudinally, each additional standard deviation time spent in relative MVPA per day (i.e. 22 minutes) was significantly associated with less decline in microstructural integrity of ROIs localized in the temporal area. Specifically, each additional 22 minutes of relative MVPA per day was associated with 0.0015 less annual decline in FA of the uncinate fasciculus, 0.0017 less annual decline in FA of the hippocampal part of the cingulum, 0.000003 less annual increase in MD of the parahippocampal gyrus, and 0.000008 less annual increase in MD of the entorhinal cortex (all  $p < 0.01$ ) (Table 2, Figure 1). These longitudinal associations remained similar with additional adjustment for baseline gait speed ( $\beta$  (SE),  $p$ -value for FA of the uncinate fasciculus=0.032 (0.012), 0.009;  $\beta$  (SE),  $p$ -value for FA of the hippocampal part of the cingulum=0.032 (0.013), 0.016;  $\beta$  (SE),  $p$ -value for MD of the parahippocampal gyrus=-0.021 (0.009), 0.017;  $\beta$  (SE),  $p$ -value for MD of the entorhinal cortex=-0.030 (0.012), 0.011). Time spent in relative MVPA was not associated with changes in other ROIs (all  $p > 0.01$ ) (Table 2). Time spent in absolute MVPA was not significantly associated with changes in any neuroimaging markers (all  $p < 0.01$ ) (Table 2).

## 4. Discussion

Our study established three important findings. We found that more time spent in relative MVPA based on individual heart reserve was associated with slower decline of brain microstructural integrity in aging, indicated by less decline in fractional anisotropy and less increase in mean diffusivity. More importantly, the relationship of relative MVPA with change in microstructural integrity is localized in temporal areas known to be important for memory, and not in other brain areas of interest. Interestingly, time spent in absolute MVPA was not associated with the change in microstructural integrity. We also found that in this sample of well-functioning adults aged 55 or older, there were no cross-sectional associations of microstructural integrity with neither relative nor absolute MVPA. Collectively, these results suggest that time spent in relative MVPA may be an important contributor to preserving brain microstructure in selected temporal areas.

Our study advanced prior research in several aspects. We examined both relative and absolute MVPA, extended the longitudinal assessment of microstructural integrity in both gray matter and white matter, and focused on early microstructural changes in a sample of initially cognitively normal and well-functioning adults aged 55 or older.

Our longitudinal findings in temporal areas are consistent with previous cross-sectional DTI studies reporting the relationship between PA and uncinate fasciculus (Maltais et al., 2020; Tian et al., 2014). The use of relative MVPA allowed us to identify additional brain areas that were longitudinally associated with PA, including the hippocampal part of the cingulum, parahippocampal gyrus, and entorhinal cortex. While exercise is a subcategory of physical activity, our findings are in line with the beneficial effects of exercise on brain structure and function in temporal areas as well as memory shown in several intervention studies (Erickson et al., 2011; Nagamatsu et al., 2013; Smith et al., 2013). It has been hypothesized that exercise-induced angiogenesis, blood rheological changes, and neurogenesis may be particularly beneficial in these watershed brain areas, and this hypothesis has been supported by both animal and human exercise intervention studies (Duzel et al., 2016; Gauthier et al., 2015). We also examined other gray matter and white matter areas of interest important for executive function and motor function, but we did not find an association with relative MVPA. Our findings seem to be in line with previous report that the relationship between PA and cognition is specific to memory function (Rathore & Lom, 2017).

The different results obtained when using an individualized, relative measure versus a direct, absolute measure of MVPA may have important clinical implications. The relative measure of MVPA based on cardiac reserve quantifies the effort required for accomplishing a certain level of PA at the individual level and, therefore, our findings suggest that it is the level of personalized effort that is important for brain integrity protection. Our findings are in line with one recent study reporting the relative proportion of time spent in MVPA compared to sedentary behaviors and light intensity PA is associated with greater hippocampal volume (Machida et al., 2021). The traditional approach using the absolute threshold may have underestimated MVPA in older age because light activities in younger age may require moderate to vigorous effort in older age. The relative threshold using individual heart rate reserve accounts for individual differences in aerobic capacity and functional abilities.

Previous findings have suggested that intensity levels by an individualized physiological threshold may best characterize activities with aging to avoid systematic biases (Schrack et al., 2018). Future studies examining the relationship of PA with brain health should consider individualized thresholds to quantify intensity levels.

Consistent with recent results, we did not observe cross-sectional associations of DTI markers with MVPA using either absolute or relative thresholds (Maltais et al., 2020). Although some previous DTI studies reported significant cross-sectional associations with PA (Gons et al., 2013; Tian et al., 2015), we noted that our sample characteristics may be different. Because we focused on a sample of initially cognitively normal and well-functioning adults aged 55 or older, the sample at baseline may be more homogeneous and the cross-sectional association may not be detected. Our null cross-sectional findings also highlight the importance to investigate within-individual longitudinal changes to detect the development and changes in microstructural degeneration.

This study has limitations. First, the BLSA population is healthier than the general population which may affect the generalizability of the findings. Second, the sample size is modest with a relatively wide age range between 56 and 91. Future studies of larger samples in older age are needed to confirm our findings. Third, findings from this observational study do not establish causation. This study has several strengths. First, the study population is well-characterized community-dwelling adults aged 55 or older. The rigorous adjudication of cognitive impairment and dementia and assessment of 6-meter gait speed allow us to identify initially cognitively unimpaired and well-functioning participants. Second, the inclusion of MVPA using the relative threshold of individual heart rate reserve advances prior knowledge on PA intensities with brain health in older age. Third, the examination of multiple areas of interest allows us to determine regional specificity. We note that this study focused on a *priori* defined regions of interest involved in different cognitive domains, rather than an empirically based discovery study. Future studies of whole brain voxel-based analyses are needed to confirm our findings. We also note that as DTI assesses different aspects of diffusion, FA and MD are indirect measures of microstructural integrity.

## 5. Conclusions

In conclusion, more time spent in MVPA at 60% or above of individual heart rate reserve is associated with less microstructural decline, especially in selected temporal areas. MVPA using the absolute threshold of activity counts does not predict microstructural changes. Future intervention studies aimed at preserving brain health should consider individualized thresholds to define intensity levels of physical activity among older persons.

### Funding:

This work was supported entirely by the Intramural Research Program of the National Institute on Aging. JAS was supported by grant U01AG057545.



## References:

- Alexander DC, Pierpaoli C, Basser PJ, & Gee JC (2001). Spatial transformations of diffusion tensor magnetic resonance images. *IEEE Trans Med Imaging*, 20(11), 1131–1139. 10.1109/42.963816 [PubMed: 11700739]
- Alfaro-Almagro F, Jenkinson M, Bangerter NK, Andersson JLR, Griffanti L, Douaud G, Sotiropoulos SN, Jbabdi S, Hernandez-Fernandez M, Vallee E, Vidaurre D, Webster M, McCarthy P, Rorden C, Daducci A, Alexander DC, Zhang H, Dragonu I, Matthews PM, Miller KL, & Smith SM (2018). Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. *Neuroimage*, 166, 400–424. 10.1016/j.neuroimage.2017.10.034 [PubMed: 29079522]
- Astrand I, Astrand PO, Hallback I, & Kilbom A (1973). Reduction in maximal oxygen uptake with age. *J Appl Physiol*, 35(5), 649–654. 10.1152/jappl.1973.35.5.649 [PubMed: 4770349]
- Burzynska AZ, Chaddock-Heyman L, Voss MW, Wong CN, Gothe NP, Olson EA, Knecht A, Lewis A, Monti JM, Cooke GE, Wojcicki TR, Fanning J, Chung HD, Awick E, McAuley E, & Kramer AF (2014). Physical activity and cardiorespiratory fitness are beneficial for white matter in low-fit older adults. *PLoS One*, 9(9), e107413. 10.1371/journal.pone.0107413 [PubMed: 25229455]
- Burzynska AZ, Voss MW, Fanning J, Salerno EA, Gothe NP, McAuley E, & Kramer AF (2020). Sensor-measured sedentariness and physical activity are differentially related to fluid and crystallized abilities in aging. *Psychol Aging*, 35(8), 1154–1169. 10.1037/pag0000580 [PubMed: 32969693]
- Chang LC, Jones DK, & Pierpaoli C (2005). RESTORE: robust estimation of tensors by outlier rejection. *Magn Reson Med*, 53(5), 1088–1095. 10.1002/mrm.20426 [PubMed: 15844157]
- Cook P, Bai Y, Nedjati-Gilani S, Seunarine K, Hall M, Parker G, & Alexander D (2006). Camino: open-source diffusion-MRI reconstruction and processing. 2006. Seattle, WA, USA, 2759.
- Domingos C, Pego JM, & Santos NC (2021). Effects of physical activity on brain function and structure in older adults: A systematic review. *Behav Brain Res*, 402, 113061. 10.1016/j.bbr.2020.113061 [PubMed: 33359570]
- Driscoll I, Davatzikos C, An Y, Wu X, Shen D, Kraut M, & Resnick SM (2009). Longitudinal pattern of regional brain volume change differentiates normal aging from MCI. *Neurology*, 72(22), 1906–1913. 10.1212/WNL.0b013e3181a82634 [PubMed: 19487648]
- Duzel E, van Praag H, & Sendtner M (2016). Can physical exercise in old age improve memory and hippocampal function? *Brain*, 139(Pt 3), 662–673. 10.1093/brain/awv407 [PubMed: 26912638]
- Erickson KI, Hillman C, Stillman CM, Ballard RM, Bloodgood B, Conroy DE, Macko R, Marquez DX, Petruzzello SJ, Powell KE, & For Physical Activity Guidelines Advisory, C. (2019). Physical Activity, Cognition, and Brain Outcomes: A Review of the 2018 Physical Activity Guidelines. *Med Sci Sports Exerc*, 51(6), 1242–1251. 10.1249/MSS.0000000000001936 [PubMed: 31095081]
- 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(7), 3017–3022. 10.1073/pnas.1015950108 [PubMed: 21282661]
- Fellgiebel A, Dellani PR, Greverus D, Scheurich A, Stoeter P, & Muller MJ (2006). Predicting conversion to dementia in mild cognitive impairment by volumetric and diffusivity measurements of the hippocampus. *Psychiatry Res*, 146(3), 283–287. 10.1016/j.psychres.2006.01.006 [PubMed: 16530394]
- Ferrucci L (2008). The Baltimore Longitudinal Study of Aging (BLSA): a 50-year-long journey and plans for the future. *J Gerontol A Biol Sci Med Sci*, 63(12), 1416–1419. 10.1093/gerona/63.12.1416 [PubMed: 19126858]
- Gauthier CJ, Lefort M, Mekary S, Desjardins-Crepeau L, Skimminge A, Iversen P, Madjar C, Desjardins M, Lesage F, Garde E, Frouin F, Bherer L, & Hoge RD (2015). Hearts and minds: linking vascular rigidity and aerobic fitness with cognitive aging. *Neurobiol Aging*, 36(1), 304–314. 10.1016/j.neurobiolaging.2014.08.018 [PubMed: 25308963]
- Gons RA, Tuladhar AM, de Laat KF, van Norden AG, van Dijk EJ, Norris DG, Zwiers MP, & de Leeuw FE (2013). Physical activity is related to the structural integrity of cerebral white matter. *Neurology*, 81(11), 971–976. 10.1212/WNL.0b013e3182a43e33 [PubMed: 23921884]

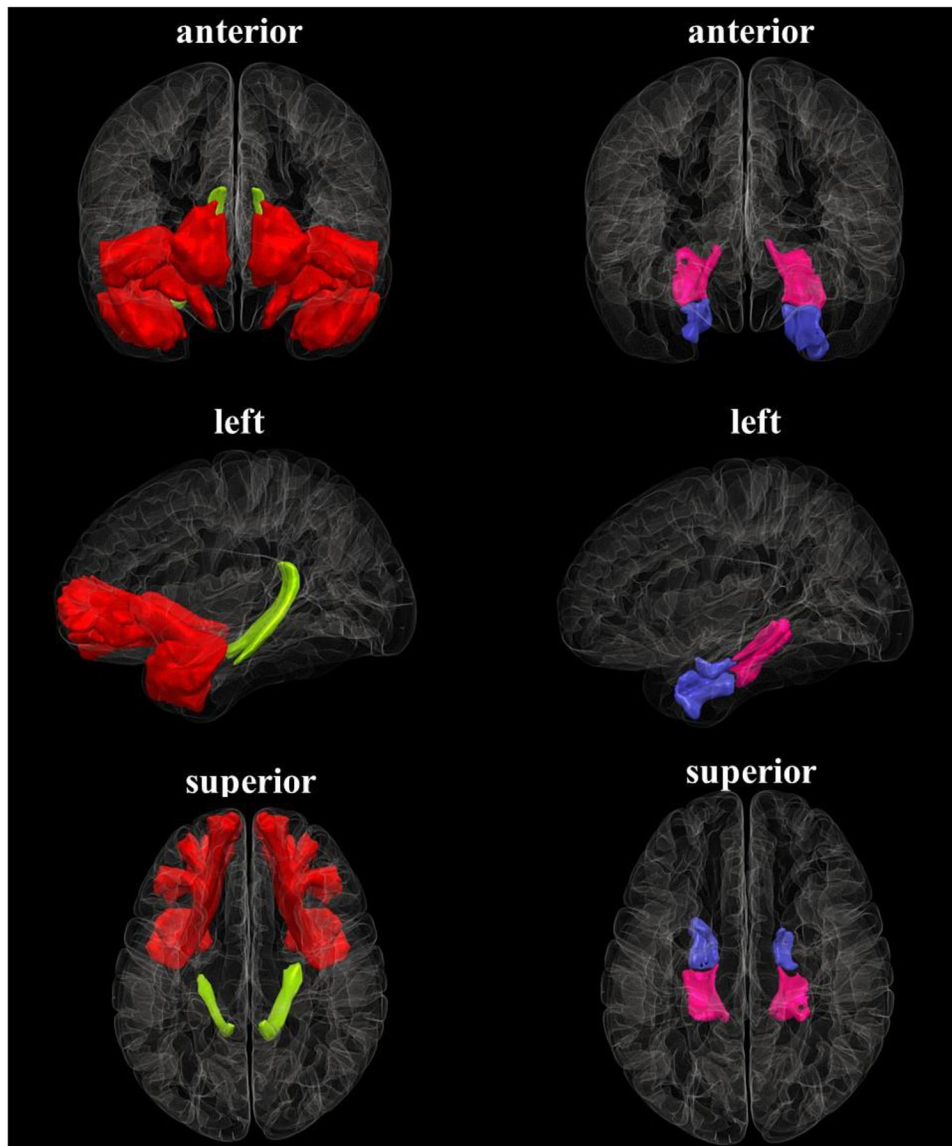
- Hugenschmidt CE, Peiffer AM, Kraft RA, Casanova R, Deibler AR, Burdette JH, Maldjian JA, & Laurienti PJ (2008). Relating imaging indices of white matter integrity and volume in healthy older adults. *Cereb Cortex*, 18(2), 433–442. 10.1093/cercor/bhm080 [PubMed: 17575289]
- Ikuta T, Frith E, Ponce P, & Loprinzi PD (2019). Association of physical activity on the functional connectivity of the hippocampal-orbitofrontal pathway. *Phys Sportsmed*, 47(3), 290–294. 10.1080/00913847.2018.1549461 [PubMed: 30449247]
- Jones DK, Knosche TR, & Turner R (2013). White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. *Neuroimage*, 73, 239–254. 10.1016/j.neuroimage.2012.06.081 [PubMed: 22846632]
- Karvonen MJ, Kentala E, & Mustala O (1957). The effects of training on heart rate; a longitudinal study. *Ann Med Exp Biol Fenn*, 35(3), 307–315. <https://www.ncbi.nlm.nih.gov/pubmed/13470504> [PubMed: 13470504]
- Kim BR, Kwon H, Chun MY, Park KD, Lim SM, Jeong JH, & Kim GH (2020). White Matter Integrity Is Associated With the Amount of Physical Activity in Older Adults With Super-aging. *Front Aging Neurosci*, 12, 549983. 10.3389/fnagi.2020.549983 [PubMed: 33192451]
- Klein A, Dal Canton T, Ghosh SS, Landman B, Lee J, & Worth A (2010). Open labels: online feedback for a public resource of manually labeled brain images. 16th Annual Meeting for the Organization of Human Brain Mapping,
- Lauzon CB, Asman AJ, Esparza ML, Burns SS, Fan Q, Gao Y, Anderson AW, Davis N, Cutting LE, & Landman BA (2013). Simultaneous analysis and quality assurance for diffusion tensor imaging. *PLoS One*, 8(4), e61737. 10.1371/journal.pone.0061737 [PubMed: 23637895]
- Lim IA, Faria AV, Li X, Hsu JT, Airan RD, Mori S, & van Zijl PC (2013). Human brain atlas for automated region of interest selection in quantitative susceptibility mapping: application to determine iron content in deep gray matter structures. *Neuroimage*, 82, 449–469. 10.1016/j.neuroimage.2013.05.127 [PubMed: 23769915]
- Machida M, Takamiya T, Amagasa S, Murayama H, Fujiwara T, Odagiri Y, Kikuchi H, Fukushima N, Kouno M, Saito Y, Yoshimine F, Inoue S, & Shobugawa Y (2021). Objectively measured intensity-specific physical activity and hippocampal volume among community-dwelling older adults. *J Epidemiol*. 10.2188/jea.JE20200534
- Maltais M, Rolland Y, Boisvert-Vigneault K, Perus L, Mangin JF, Grigis A, Chupin M, Bouyahia A, Gabelle A, Delrieux J, Vellas B, & de Souto Barreto P (2020). Prospective associations between physical activity levels and white matter integrity in older adults: results from the MAPT study. *Maturitas*, 137, 24–29. 10.1016/j.maturitas.2020.04.012 [PubMed: 32498933]
- Mann T, Lamberts RP, & Lambert MI (2013). Methods of prescribing relative exercise intensity: physiological and practical considerations. *Sports Med*, 43(7), 613–625. 10.1007/s40279-013-0045-x [PubMed: 23620244]
- Mazoyer B, Mellet E, Percey G, Zago L, Crivello F, Jobard G, Delcroix N, Vigneau M, Leroux G, Petit L, Joliot M, & Tzourio-Mazoyer N (2016). BIL&GIN: A neuroimaging, cognitive, behavioral, and genetic database for the study of human brain lateralization. *Neuroimage*, 124(Pt B), 1225–1231. 10.1016/j.neuroimage.2015.02.071 [PubMed: 25840118]
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, & Stadlan EM (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, 34(7), 939–944. 10.1212/wnl.34.7.939 [PubMed: 6610841]
- Nagamatsu LS, Chan A, Davis JC, Beattie BL, Graf P, Voss MW, Sharma D, & Liu-Ambrose T (2013). Physical activity improves verbal and spatial memory in older adults with probable mild cognitive impairment: a 6-month randomized controlled trial. *J Aging Res*, 2013, 861893. 10.1155/2013/861893 [PubMed: 23509628]
- Northey JM, Rattray B, Pumpa KL, Pryor DJ, Fraser MA, Shaw ME, Anstey KJ, & Cherbuin N (2020). Objectively measured physical activity is associated with dorsolateral prefrontal cortex volume in older adults. *Neuroimage*, 221, 117150. 10.1016/j.neuroimage.2020.117150 [PubMed: 32668298]
- Ozemek C, Cochran HL, Strath SJ, Byun W, & Kaminsky LA (2013). Estimating relative intensity using individualized accelerometer cutpoints: the importance of fitness level. *BMC Med Res Methodol*, 13, 53. 10.1186/1471-2288-13-53 [PubMed: 23547769]

- Palta P, Sharrett AR, Gabriel KP, Gottesman RF, Folsom AR, Power MC, Evenson KR, Jack CR Jr., Knopman DS, Mosley TH, & Heiss G (2021). Prospective Analysis of Leisure-Time Physical Activity in Midlife and Beyond and Brain Damage on MRI in Older Adults. *Neurology*, 96(7), e964–e974. 10.1212/WNL.0000000000011375 [PubMed: 33408144]
- Petersen RC, Smith GE, Waring SC, Ivnik RJ, Kokmen E, & Tangelos EG (1997). Aging, memory, and mild cognitive impairment. *Int Psychogeriatr*, 9 Suppl 1, 65–69. 10.1017/s1041610297004717
- Rathore A, & Lom B (2017). The effects of chronic and acute physical activity on working memory performance in healthy participants: a systematic review with meta-analysis of randomized controlled trials. *Syst Rev*, 6(1), 124. 10.1186/s13643-017-0514-7 [PubMed: 28666470]
- Rheault F, Houde JC, Goyette N, Morency F, & Descoteaux M (2016). MI-Brain, a software to handle tractograms and perform interactive virtual dissection.
- Schrack JA, Leroux A, Fleg JL, Zipunnikov V, Simonsick EM, Studenski SA, Crainiceanu C, & Ferrucci L (2018). Using Heart Rate and Accelerometry to Define Quantity and Intensity of Physical Activity in Older Adults. *J Gerontol A Biol Sci Med Sci*, 73(5), 668–675. 10.1093/gerona/gly029 [PubMed: 29509832]
- Scola E, Bozzali M, Agosta F, Magnani G, Franceschi M, Sormani MP, Cercignani M, Pagani E, Falautano M, Filippi M, & Falini A (2010). A diffusion tensor MRI study of patients with MCI and AD with a 2-year clinical follow-up. *J Neurol Neurosurg Psychiatry*, 81(7), 798–805. 10.1136/jnnp.2009.189639 [PubMed: 20392973]
- Sexton CE, Betts JF, Demnitz N, Dawes H, Ebmeier KP, & Johansen-Berg H (2016). A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the ageing brain. *Neuroimage*, 131, 81–90. 10.1016/j.neuroimage.2015.09.071 [PubMed: 26477656]
- Shephard RJ (2001). Absolute versus relative intensity of physical activity in a dose-response context. *Med Sci Sports Exerc*, 33(6 Suppl), S400–418; discussion S419–420. 10.1097/00005768-200106001-00008 [PubMed: 11427764]
- Smith JC, Nielson KA, Antuono P, Lyons JA, Hanson RJ, Butts AM, Hantke NC, & Verber MD (2013). Semantic memory functional MRI and cognitive function after exercise intervention in mild cognitive impairment. *J Alzheimers Dis*, 37(1), 197–215. 10.3233/JAD-130467 [PubMed: 23803298]
- Spartano NL, Davis-Plourde KL, Himali JJ, Andersson C, Pase MP, Maillard P, DeCarli C, Murabito JM, Beiser AS, Vasan RS, & Seshadri S (2019). Association of Accelerometer-Measured Light-Intensity Physical Activity With Brain Volume: The Framingham Heart Study. *JAMA Netw Open*, 2(4), e192745. 10.1001/jamanetworkopen.2019.2745 [PubMed: 31002329]
- Strommer JM, Davis SW, Henson RN, Tyler LK, Cam CAN, & Campbell KL (2020). Physical ctivity Predicts Population-Level Age-Related Differences in Frontal White Matter. *J Gerontol A Biol Sci Med Sci*, 75(2), 236–243. 10.1093/gerona/gly220 [PubMed: 30285083]
- Tanaka H, Monahan KD, & Seals DR (2001). Age-predicted maximal heart rate revisited. *J Am Coll Cardiol*, 37(1), 153–156. 10.1016/s0735-1097(00)01054-8 [PubMed: 11153730]
- Tian Q, Erickson KI, Simonsick EM, Aizenstein HJ, Glynn NW, Boudreau RM, Newman AB, Kritchevsky SB, Yaffe K, Harris TB, & Rosano C (2014). Physical activity predicts microstructural integrity in memory-related networks in very old adults. *J Gerontol A Biol Sci Med Sci*, 69(10), 1284–1290. 10.1093/gerona/glt287 [PubMed: 24474004]
- Tian Q, Ferrucci L, Resnick SM, Simonsick EM, Shardell MD, Landman BA, Venkatraman VK, Gonzalez CE, & Studenski SA (2016). The effect of age and microstructural white matter integrity on lap time variation and fast-paced walking speed. *Brain Imaging Behav*, 10(3), 697–706. 10.1007/s11682-015-9449-6 [PubMed: 26399234]
- Tian Q, Glynn NW, Erickson KI, Aizenstein HJ, Simonsick EM, Yaffe K, Harris TB, Kritchevsky SB, Boudreau RM, Newman AB, Lopez OL, Saxton J, Rosano C, & Health ABCS (2015). Objective measures of physical activity, white matter integrity and cognitive status in adults over age 80. *Behav Brain Res*, 284, 51–57. 10.1016/j.bbr.2015.01.045 [PubMed: 25655514]
- Varma VR, Chuang YF, Harris GC, Tan EJ, & Carlson MC (2015). Low-intensity daily walking activity is associated with hippocampal volume in older adults. *Hippocampus*, 25(5), 605–615. 10.1002/hipo.22397 [PubMed: 25483019]

- Voss MW, Weng TB, Burzynska AZ, Wong CN, Cooke GE, Clark R, Fanning J, Awick E, Gothe NP, Olson EA, McAuley E, & Kramer AF (2016). Fitness, but not physical activity, is related to functional integrity of brain networks associated with aging. *Neuroimage*, 131, 113–125. 10.1016/j.neuroimage.2015.10.044 [PubMed: 26493108]
- Weston PS, Simpson IJ, Ryan NS, Ourselin S, & Fox NC (2015). Diffusion imaging changes in grey matter in Alzheimer's disease: a potential marker of early neurodegeneration. *Alzheimers Res Ther*, 7(1), 47. 10.1186/s13195-015-0132-3 [PubMed: 26136857]
- Williams OA, An Y, Beason-Held L, Huo Y, Ferrucci L, Landman BA, & Resnick SM (2019). Vascular burden and APOE epsilon4 are associated with white matter microstructural decline in cognitively normal older adults. *Neuroimage*, 188, 572–583. 10.1016/j.neuroimage.2018.12.009 [PubMed: 30557663]

### Highlights

- Relative moderate-to-vigorous physical activity prevents microstructural decline.
- This longitudinal association is localized to selected temporal areas.
- Absolute moderate-to-vigorous activity is not associated with microstructure.



**Figure 1. Brain areas associated with relative moderate-to-vigorous physical activity.** uncinata fasciculus (from a RecobundlesX template) (red); tail of the cingulum, leading to the hippocampal region (from a RecobundlesX template) (lemon green); 1016 ctx-lh-parahippocampal (wmparc, freesurfer) (magenta); 1006 ctx-lh-entorhinal (wmparc, freesurfer) (violet) The regions of interest and cortical surfaces were extracted from a population average template (mni152nlin2009c) using Freesurfer (ctx-lh-parahippocampal and ctx-lh-entorhinal, 1016/2016 and 1006/2006 respectively). The bundles of interest are from a population average template (<https://zenodo.org/record/5165374#.YjyHUdDMKUK>). Manual segmentations of streamlines from 20 BIL&GIN (Mazoyer et al., 2016) and 20 UKBioBank (Alfaro-Almagro et al., 2018) were co-registered, cleaned and merged to create a representation of their spatial extend. Visualization is done in the MI-Brain software (Rheault et al., 2016).

**Table 1.**

Baseline participants' characteristics

	Overall sample (n=248)		Those with repeated DTI (n=206)	
	Mean $\pm$ SD or N (%)	range	Mean $\pm$ SD or N (%)	range
Age, years	71.3 $\pm$ 8.4	56 – 91	71.8 $\pm$ 8.4	56 – 91
Women	126 (51)	-	104 (50)	-
Black	54 (22)	-	43 (21)	-
Education, years	17.7 $\pm$ 2.7	7 – 25	17.8 $\pm$ 2.7	7 – 25
Body mass index, kg/m <sup>2</sup>	26.8 $\pm$ 4.4	17.7 – 39.2	26.5 $\pm$ 4.1	17.8 – 38.3
Mini mental state exam	28.6 $\pm$ 1.3 (n=222)	24 – 30	28.6 $\pm$ 1.3 (n=187)	24 – 30
Right-handedness	206 (83)	-	185 (90)	-
Apolipoprotein e4 carriers	65 (26)	-	46 (22)	-
Gait speed, m/sec	1.26 $\pm$ 0.17	1.00 – 1.83	1.25 $\pm$ 0.17	1.00 – 1.83
Relative MVPA, min/day	15 $\pm$ 22	0 – 143	16 $\pm$ 22	0 – 143
Absolute MVPA, counts/day	32 $\pm$ 23	0 – 268	32 $\pm$ 23	1 – 105
Number of monitor wear days	5.2 $\pm$ 1.1	3 – 7	5.3 $\pm$ 1.1	3 – 7
Follow-up interval, years	3.8 $\pm$ 2.4	0 – 9	4.7 $\pm$ 1.8	1 – 9
Number of visits per person	2.8 $\pm$ 1.3	1 – 7	3.2 $\pm$ 1.1	2 – 7
<b>Neuroimaging markers</b>				
FA of uncinate fasciculus	0.352 $\pm$ 0.042	0.238–0.447	0.352 $\pm$ 0.041	0.238–0.444
FA of hippocampal part of cingulum	0.388 $\pm$ 0.050	0.267–0.514	0.386 $\pm$ 0.051	0.267–0.514
FA of superior longitudinal fasciculus	0.444 $\pm$ 0.030	0.360–0.536	0.444 $\pm$ 0.030	0.360–0.536
FA of body of the corpus callosum	0.517 $\pm$ 0.042	0.359–0.605	0.517 $\pm$ 0.040	0.400–0.602
MD of hippocampus	0.0013 $\pm$ 0.0002	0.0010–0.0019	0.0013 $\pm$ 0.0002	0.0010–0.0019
MD of parahippocampal gyrus	0.0013 $\pm$ 0.0001	0.0010–0.0018	0.0013 $\pm$ 0.0001	0.0010–0.0018
MD of entorhinal cortex	0.0014 $\pm$ 0.0003	0.0009–0.0023	0.0014–0.0003	0.0010–0.0023
MD of prefrontal cortex	0.0012 $\pm$ 0.0001	0.0010–0.0016	0.0012 $\pm$ 0.0001	0.0010–0.0016
MD of precentral gyrus	0.0011 $\pm$ 0.0001	0.0009–0.0015	0.0011 $\pm$ 0.0001	0.0009–0.0015
MD of putamen	0.0008 $\pm$ 0.0001	0.0007–0.0013	0.0008 $\pm$ 0.0001	0.0007–0.0013
MD of caudate	0.0009 $\pm$ 0.0001	0.0006–0.0013	0.0009 $\pm$ 0.0001	0.0006–0.0013

**Note:** MVPA= moderate-to-vigorous physical activity. FA=fractional anisotropy. MD=mean diffusivity.

**Table 2.**

Associations of moderate-to-vigorous physical activity (MVPA) with microstructural neuroimaging markers of interest (n=248)

	Independent variable: relative MVPA		Independent variable: absolute MVPA	
	Cross-sectional $\beta$ (SE), p-value	Longitudinal $\beta$ (SE), p-value	Cross-sectional $\beta$ (SE), p-value	Longitudinal $\beta$ (SE), p-value
<b>ROIs important for memory</b>				
FA in uncinate fasciculus	-0.072 (0.057) 0.21	<b>0.035 (0.012)</b> <b>0.005</b>	0.034 (0.060) 0.57	-0.007 (0.014) 0.62
FA in hippocampal part of the cingulum	-0.107 (0.052) 0.04	<b>0.034 (0.013)</b> <b>0.01</b>	0.057 (0.055) 0.30	0.006 (0.014) 0.66
MD in hippocampus	-0.005 (0.043) 0.92	-0.011 (0.007) 0.09	-0.095 (0.044) 0.03	0.0003 (0.007) 0.97
MD in parahippocampal gyrus	-0.028 (0.051) 0.58	<b>-0.021 (0.009)</b> <b>0.01</b>	-0.095 (0.053) 0.07	-0.007 (0.010) 0.50
MD in entorhinal cortex	-0.005 (0.053) 0.93	<b>-0.030 (0.012)</b> <b>0.01</b>	-0.015 (0.056) 0.78	0.013 (0.013) 0.31
<b>ROIs important for executive function</b>				
FA in superior longitudinal fasciculus	-0.017 (0.064) 0.79	0.003 (0.009) 0.76	0.027 (0.067) 0.68	-0.011 (0.010) 0.25
MD in prefrontal cortex	-0.046 (0.046) 0.31	0.001 (0.009) 0.95	-0.077 (0.048) 0.11	0.018 (0.010) 0.06
<b>ROIs important for motor function</b>				
FA in body of the corpus callosum	-0.044 (0.057) 0.44	0.015 (0.010) 0.14	0.135 (0.060) 0.02	-0.001 (0.012) 0.96
MD in precentral gyrus	-0.020 (0.049) 0.68	-0.018 (0.013) 0.17	-0.092 (0.051) 0.07	0.031 (0.014) 0.03
MD in putamen	-0.016 (0.053) 0.77	-0.007 (0.006) 0.28	-0.048 (0.056) 0.39	0.005 (0.007) 0.42
MD in caudate	-0.010 (0.055) 0.86	-0.017 (0.009) 0.06	0.001 (0.058) 0.98	-0.004 (0.010) 0.66

**Note.** Measures of PA and DTI were computed as standardized Z scores. ROIs=regions of interest. FA=fractional anisotropy. MD=mean diffusivity. The prefrontal cortex includes inferior, superior, middle, medial frontal, and orbitofrontal cortices. Higher values of FA and lower values of MD indicate higher microstructural integrity. Lower values of FA and higher values of MD indicate lower microstructural integrity. Bold number reflects associations at two-tailed p 0.01.