HHS Public Access

Author manuscript

Neuroimage. Author manuscript; available in PMC 2022 January 10.

Published in final edited form as:

Neuroimage. 2021 January 15; 225: 117512. doi:10.1016/j.neuroimage.2020.117512.

Midlife aerobic exercise and brain structural integrity: Associations with age and cardiorespiratory fitness

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Abstract

Lower midlife physical activity is associated with higher risk of neurodegenerative disease in late life. However it remains unknown whether physical exercise and fitness are associated with brain structural integrity during midlife. The purpose of this study was to compare brain structures between middle-aged aerobically trained adults (MA), middle-aged sedentary (MS), and young sedentary (YS) adults. Thirty MA (54 ± 4 years), 30 MS (54 ± 4 years), and 30 YS (32 ± 6 years) participants (50% women) underwent measurements of brain volume cortical thickness, and white matter (WM) fiber integrity using MRI. MA participants had aerobic training for 24.8 ± 9.6

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Credit authorship contribution statement

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Declaration of Completing Interest

The authors have no actual or potential conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: 10.1016/j.neuroimage.2020.117512.

years and the highest cardiorespiratory fitness level (i.e., peak oxygen uptake: VO_{2peak}) among all groups. Global WM integrity, as assessed with fractional anisotropy (FA) from diffusion tensor imaging, was lower in the MS compared with the YS group. However, global FA in the MA group was significantly higher than that in the MS group (P <0.05) and at a similar level to the YS group. Furthermore, tract-based spatial statistical analysis demonstrated that FA in the anterior, superior, and limbic WM tracts (e.g., the genu of the corpus callosum, superior longitudinal fasciculus, uncinate fasciculus) was higher in the MA compared with MS groups, and positively associated with VO_{2peak}, independently from age and sex. From cortical thickness analysis MS and MA participants showed thinner prefrontal and parieto-temporal areas than the YS group. On the other hand, the MA group exhibited thicker precentral, postcentral, pericalcarine, and lateral occipital cortices than the MS and YS groups. But, the insula and right superior frontal gyrus showed thinner cortical thickness in the MA compared with the MS groups. Collectively, these findings suggest that midlife aerobic exercise is associated with higher WM integrity and greater primary motor and somatosensory cortical thickness.

Keywords

Midlife; Aerobic exercise; Brain volume; Cortical thickness; White matter integrity; Cardiorespiratory fitness

1. Introduction

Brain structural integrity starts declining during midlife, which increases the risk of age-related cognitive decline and neurodegenerative conditions such as Alzheimer's disease (AD) in later life (Park and Festini, 2017). Currently, we do not have effective treatments for AD (Cummings et al., 2019); thus, slowing age-related brain structural changes in earlier life may reduce the future risk. Gray matter atrophy and reduced white matter (WM) integrity represent the structural hall-marks of brain aging (Fjell et al., 2014, 2013; Westlye et al., 2010). By the fifth decade of life, mean cortical thickness decreases, with larger effects on the frontal and cingulate cortices (Shaw et al., 2016). Cortical infolding and subcortical structures also shrink during midlife while exhibiting substantial regional heterogeneity (Fjell et al., 2013). For example, hippocampal volume is relatively stable until ~60 years, whereas the other structures such as the thalamus may shrink linearly across the adult lifespan (Fjell et al., 2013). WM fiber integrity, as assessed by fractional anisotropy (FA) using diffusion tensor imaging (DTI), reaches a peak between the ages of 20–40 across brain regions (Lebel et al., 2012), then decreases with greater changes in the anterior and superior regions (Head et al., 2004; Sexton et al., 2014).

Growing evidence suggests that higher level of midlife physical activity is associated with lower risk of neurodegenerative disease in late life (Palta et al., 2019; Rovio et al., 2010; Zotcheva et al., 2018). In contrast, very little evidence currently exists as to whether physical exercise and fitness are associated with brain structural integrity during midlife. Based on a large number of studies conducted in older adults, we can speculate several regions of the brain which may benefit from physical exercise and fitness in midlife. For example, we previously reported that aerobically trained older adults (>70 years) had greater

sensorimotor and visual cortical volumes than sedentary age-matched adults (Tseng et al., 2013b). These individuals also exhibited higher FA in the superior WM tracts (e.g., superior longitudinal fasciculus, superior corona radiata) (Tseng et al., 2013a). In randomized controlled trials, 6 months of aerobic exercise training increased both gray and white matter volumes primarily located in the prefrontal and temporal cortices when compared with the stretching group in cognitively normal old adults (Colcombe et al., 2006). After 1 year of aerobic training, cardiorespiratory fitness gains were correlated with increased prefrontal WM fiber integrity in cognitively healthy older adults (Voss et al., 2013) and patients with amnestic mild cognitive impairment (MCI) (Tarumi et al., 2020).

Physical exercise may also influence hippocampal integrity. A recent meta-analysis (Firth et al., 2018) showed that the effect of aerobic exercise on the hippocampal volume is driven through preventing the age-related atrophy which, however, may not occur during middle age (Fjell et al., 2013). Nevertheless, the integrity of limbic WM tracts connecting to the hippocampus, such as the uncinate fasciculus, cingulum, and fornix, may be related to aerobic exercise and/or cardiorespiratory fitness during midlife, as shown by our previous study in older adults (Ding et al., 2018). Therefore, further understanding the relationship between aerobic exercise and brain structural integrity during midlife may provide mechanistic insights into late-life risk of neurodegenerative disease.

The purpose of this study was to compare brain volume, cortical thickness, and WM fiber integrity in middle-aged aerobically trained adults (MA) with middle-aged sedentary (MS) and young sedentary (YS) adults. Also, cognitive performance in the MA group was examined. Based on previous studies in older adults, we hypothesized that while MS group may present regional brain structural deteriorations when com- pared with the YS group, these deteriorations would be attenuated in MA participants. Moreover, higher cardiorespiratory fitness would be associated with greater regional cortical thickness and WM fiber integrity.

2. Material and methods

2.1. Participants

Data from 90 participants (50% women) consisting of three groups were included: 1) 30 MA, 2) 30 MS, and 3) 30 YS participants. The MS and YS participants were recruited for our previous studies that investigated the effect of normal aging on brain and vascular functions (Tarumi et al., 2014), and 30 MA participants were newly recruited for the present study. While all participants underwent the same data collection protocol, neuropsychological and self-reported physical and mental health assessments were conducted only in the MA sample. The proportions of men and women in the YS and MS groups were matched to the MA group because brain structure may be influenced by sex (Inano et al., 2011; Sowell et al., 2007). In this study, middle age was defined as 45–64 years based on a commonly accepted retirement age (i.e., 65 years old) (OECD, 2019), and young age was defined as <45 years.

To ensure recruitment of aerobically trained adults, participants in the MA group had to meet all of the following criteria: 1) at least 10 years of aerobic training (e.g.,

running, cycling, swimming, or multi-modal training with moderate-to-vigorous intensity), 2) participation in at least 2 competing events per year, and 3) currently training for an event. Recruitment was conducted through a community-based advertisement using local newspapers and word-of-mouth at running clubs in the Dallas-Fort Worth metropolitan area. The criteria for MS and YS groups included no participation in a structured exercise or physical activity program for the past 2+ years and <90 minutes of moderate-to-vigorous physical activity (>4.0 METs) per week, as recorded individually by an Actical accelerometer (Actical, Philips Respironics, USA).

We rigorously screened each participant using 12-lead electrocardiogram, blood pressure, and echocardiogram to exclude potential cardiovascular disease which could confound the associations among brain structure, exercise training, and age. Carotid ultrasonography was performed to exclude individuals with atherosclerotic plaque or stenosis that occluded the common and/or internal carotid artery by >50% (Norris et al., 1991). Other exclusion criteria were uncontrolled hypertension or diabetes, body mass index >35 kg/m^2, current or history of smoking in the past 2 years, pregnancy, and the presence or history of clinical cerebrovascular, metabolic, neurodegenerative, psychiatric, or inflammatory diseases, brain trauma, hypothyroidism, active alcoholism or drug abuse. This study was approved by the Institutional Re- view Board of the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas, and was performed by the guidelines of the Declaration of Helsinki and Belmont Report. All participants gave informed written consent before participation.

2.2. Data acquisition and processing

Brain MRI and VO_2peak data were collected on separate days. Prior to measurements, each participant was asked to refrain from exercise and alcohol consumption for >24 hours and caffeine intake for >8 hours. All MRI data were collected by the same 3-Tesla scanner (Philips Medical System, Best, The Netherlands) using a body coil for radiofrequency transmission and 8-channel head coil with parallel imaging capability for signal reception. All participants underwent high-resolution T_1-weighted 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) imaging to assess brain volume and cortical thickness, and diffusion tensor imaging (DTI) to assess WM fiber integrity. Participant grouping and demographic information were blinded to investigators who conducted data analysis.

2.2.1. MPRAGE—The T_1-weighted 3D MPRAGE images were collected using the following parameters: field of view (FOV) = 256 × 256 mm, number of sagittal slices = 160 (no gap), voxel resolution = 1 × 1 × 1 mm^3, echo time (TE)/repetition time (TR) = 3.7/8.1 ms, flip angle = 12°, and sensitivity encoding (SENSE) factor = 2. Subsequently, 3D MPRAGE images were processed for brain segmentation by the FreeSurfer image analysis suite (version 6.0, http://surfer.nmr.mgh.harvard.edu/) (Fischl, 2012). Individual volume was visually inspected for segmentation errors. No manual correction was required. The *Desikan-Killiany* atlas was used to generate cortical thickness, volume, and area and subcortical volume of each brain region. The cortical data were analyzed with FreeSurfer's QDEC software (Query, Design, Estimate, Contrast, version 1.5). The QDEC was used to perform group averaging and inference on the morphometry data produced by the FreeSurfer

processing stream. Cortical maps were smoothed with a 10 mm fullwidth-at-half-maximum Gaussian kernel, and multiple comparisons were corrected with a Monte Carlo Simulation using a *P*-value set at <0.05. Statistical results were visualized by overlaying significant cortical regions onto the FreeSurfer semi-inflated cortical surfaces. These procedures for morphometric data analysis have shown good test-retest reliability (Han et al., 2006). Brain volumes were normalized as percent intracranial volume. The AD-signature regional thickness was calculated from the following 8 regions: middle temporal gyrus, temporal pole, inferior temporal gyrus, supramarginal gyrus, superior parietal lobule, precuneus, middle frontal gyrus, and superior frontal gyrus (Dickerson et al., 2009).

2.2.2. DTI—DTI data were collected using the following parameters: FOV = 224 × 224 mm^2, imaging matrix = 112 × 112, 65 axial slices covering the entire hemisphere, cerebellum, and brainstem (no gap), voxel resolution = 2 × 2 × 2.2 mm^3, TE/TR = 51/5630 ms, single-shot echo-planar-imaging sequence with a SENSE factor = 2.2, and 30 independent orientations with b-value = 1000 s/mm^2. Automated image registration was performed on the raw diffusion images to correct distortions caused by motion artifacts or eddy currents. DTI scanning was performed twice in each participant.

The FMRIB Software Library (FSL version 5.0, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL) was used to process DTI data. First, 2 sets of DTI data were merged in temporal order, corrected for eddy currents and head motion, and averaged within each participant to increase the signal-to-noise ratio. Individual brain masks were created by the Brain Extraction Tool to remove non-brain tissue, and diffusion metrics were calculated by the DTIFit (Popescu et al., 2012). Radial diffusivity (RD) was defined by ($\lambda 2 + \lambda 3$)/2. Individual fractional anisotropy (FA), axial diffusivity (AxD), and RD images were visually inspected before further processing.

Tract-based spatial statistics (TBSS) was used to perform voxelwise and region-of-interest statistical analyses (Smith et al., 2006). First, individual FA images were non-linearly registered into the *JHU-ICBM-FA-1mm* template (Mori et al., 2008), and the group-averaged FA image was created. Subsequently, FA value greater than 0.20 was used as a threshold to minimize partial volume effects from gray matter and cerebrospinal fluid, and a mean FA skeleton which represents the center of tracts common to all participants was created. Finally, individual RD and AxD images were transformed into the mean FA skeleton space for statistical analysis.

For global WM integrity analysis, the average values of FA, AxD, and RD were individually extracted from the *mean FA skeleton mask*. For regional analysis, voxelwise statistics were performed by general linear model with the “randomize ” program in FSL. Multiple comparisons were corrected by threshold-free cluster enhancement with 5,000 permutations (Winkler et al., 2014), and the corrected statistical maps were thresholded by *P*<0.05. Subsequently, the *JHU-ICBM-labels-1mm* atlas was used to identify the fiber tract and size of significant WM skeleton voxels.

Briefly, FA is the most widely used DTI metric that can assess the overall microstructural integrity of WM axonal fiber tracts (Alexander et al., 2007). For example, FA has been

shown to decrease with aging and is even lower in patients with MCI and AD (Damoiseaux et al., 2009). On the other hand, AxD and RD may suggest potential neurobiological mechanisms of altered FA (Winklewski et al., 2018). Specifically, lower AxD and higher RD have been shown to correlate with axonal degeneration and demyelination respectively (Song et al., 2003).

2.2.3. Cardiorespiratory fitness—VO_{2peak}, the gold standard measure of cardiorespiratory fitness, was collected using a modified Astrand-Saltin protocol on a treadmill (Astrand and Saltin, 1961). The treadmill grade was increased by 2% every 2 minutes until exhaustion while participants walked, jogged, or ran at a fixed speed. The speed was individually selected based on the participant's fitness level which was assessed via a submaximal exercise test conducted prior to VO_{2peak} testing. VO_2 was measured during the 2^{nd} minute of each stage using the Douglas bag method (Douglas, 1911). Gas fractions were analyzed by mass spectrometry (Marquette MGA 1100), and ventilatory volume was measured by a Tissot spirometer. Mass spectrometry and gas sampling system were calibrated before each testing to ensure measurement accuracy and reliability. Exercise blood pressure, 12-lead electrocardiogram, and heart rate were continuously monitored by a registered nurse or a board-certified cardiologist for participants' safety.

VO_{2peak} was defined as the highest VO_2 measured from a >30-second Douglas bag during the last stage of testing. The criteria to confirm that VO_{2peak} was achieved included an increase in VO_2 <150 ml despite in- creasing work rate of 2% grade, a respiratory exchange ratio ≥1.1, and heart rate within 5 beats/min of age-predicted maximal values (i.e., 220- age). In all cases, at least two of these criteria were achieved, confirming the identification of VO_{2peak} based on the American College of Sports Medicine guidelines (American College of Sports Medicine, 2013). In cases where we could not collect > 30 seconds of the final stage bag or a participant did not meet at least two of these criteria, the test was repeated on another day. At our institute, VO_{2peak} has reliably been measured in sedentary and endurance-trained participants using this method (Fujimoto et al., 2010).

2.2.4. Neuropsychological and self-reported physical and mental health assessments—Neuropsychological assessment was conducted by a trained research team member using the National Institutes of Health Toolbox Cognition Battery (NIHTB-CB) in the MA group in order to explore relation- ships with neuroimaging findings. The NIHTB-CB is a computerized, 30- minute cognitive screening tool which consists of the flanker inhibitory control and attention test, dimensional change card sorting test, picture sequence memory test, picture vocabulary test, oral reading recognition test, pattern comparison processing speed test, and list sorting working memory test (Weintraub et al., 2014). Global cognitive performance was assessed by the total composite score, which is calculated from all tests above and represents a summary score of the NIHTB-CB. After adjustment for age, gender, education, and race/ethnicity (Casaletto et al., 2015), the NIHTB-CB generates adjusted T-scores [i.e., mean = 50, standard deviation (SD) = 10] where higher scores represent better neuropsychological performance. NIHTB-CB composite scores have shown good reliability and validity in healthy adults aged 20–85 years (Heaton et al., 2014).

The Patient-Reported Outcome Measurement Information System (PROMIS) computer-adaptive tests were used to assess self-reported physical and mental health in the MA group in order to examine aspects of sleep disturbance, sleep-related impairment, fatigue, pain interference, depression, anxiety and anger (Cella et al., 2007). These measures are scored on a corrected T-score metric (i.e., mean = 50, SD = 10) where higher scores represent worse physical or mental health.

2.3. Statistical analysis

The YS, MS, and MA groups were compared using chi-square tests for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. In case of a significant F-test, we used the posthoc pairwise Bonferroni test. The NIHTB-CB total composite score was compared with the population mean (i.e., t-score of 50) using a one-sample T-test. Pearson product-moment correlations and multiple linear regression analyses were used to examine the associations among age, brain structural measures, and VO_{2peak}. The QDEC was used to analyze regional cortical structures and TBSS for regional WM fiber integrity among groups and to examine the association with VO_2peak after adjustment for age and sex. QDEC and TBSS were also used to analyze the correlation between the NIHTB-CB total composite score and brain structural measures. Data are reported as mean ± SD for continuous data, frequency (%) for categorical data, and range (i.e., minimum-to-maximum values) for the NIHTB-CB and PROMIS scores. Effect size for group differences for global WM integrity was calculated by Cohen's *d*. Statistical significance was set *a priori* at $P<0.05$ for two-sided tests. Statistical analyses were performed using SPSS 25 (IBM Inc; Chicago, IL).

3. Results

3.1. Participant characteristics

A total of 30 MA participants (15 women, 46 to 61 years old with a mean of 54) who met the inclusion criteria were recruited (Table 1). The MA participants reported aerobic training for 24.8 ± 9.6 years while competing in endurance events such as marathon, triathlon, and ironman races. The primary component of their training programs was running (93%) but also combined with cycling (87%), swimming (60%), resistance exercise (62%), and other physical activities. On average, they were exercising 7.5 ± 2.5 sessions for 10.2 ± 4.6 hours per week. The MA group's NIHTB-CB total composite score was higher than the population normative score adjusted for age, sex, education, and race/ethnicity ($P = 0.004$) (Casaletto et al., 2015) and PROMIS scores were within the normal range.

Table 2 shows group demographic characteristics. VO_{2peak} was highest in the MA among all groups; age-related reduction was also observed between the YS and MS groups. Educational level was similar across all groups whereas body mass and BMI were smaller in the MA compared with MS groups.

3.2. WM fiber integrity

Global WM integrity assessed with FA from DTI exhibited significant group differences [$F(2, 87) = 9.305$, $P<0.001$] (Fig. 1 A). Specifically, FA of the global WM skeleton was

lower in the MS compared with YS groups ($P<0.001$, $d = 1.079$). However, the FA in MA group was significantly higher than that in the MS group ($P = 0.042$, $d = 0.601$) and at a similar level to the YS group ($P = 0.232$, $d = 0.521$). Moreover, when plotted with age, the global FA was lower in sedentary participants (YS and MS combined) whereas it remained at a higher level in the MA participants (Fig. 1 B). The global AxD was higher in the MA compared with MS and YS groups, whereas RD was higher in both of the middle-aged groups (Fig. S1).

Regional analysis using TBSS confirmed the results of global analysis (Fig. S2 and Table S1). Compared with YS group, MS participants showed lower FA across the association, commissural, projection, and brainstem fibers. Conversely, the MA group showed higher FA in many WM tracts than the MS group, including the genu of corpus callosum, anterior and superior corona radiata, anterior limb of internal capsule, superior longitudinal and fronto-occipital fasciculi, uncinate fasciculus, cingulum, and fornix. Compared with YS group, MA participants also showed higher FA in the anterior corona radiata, anterior limb of internal capsule, and superior longitudinal fasciculus.

The correlation analysis further demonstrated positive associations of VO_{2peak} with FA and AxD in the WM tracts that largely overlapped with significant regions shown by group-level analysis (Fig. 2 and Table 3). Specifically, greater VO_{2peak} was correlated with higher FA in the genu of corpus callosum, anterior and superior corona radiata, superior longitudinal and fronto-occipital fasciculi, uncinate fasciculus, and cingulum. On the other hand, greater VO_{2peak} was correlated with higher RD in the brainstem and lower RD in the external capsule. In the MA group, there was no WM tract showing significant correlation between the NIHTB-CB total composite score and FA.

3.3. Brain volume and cortical thickness

Whole brain and cerebral WM volumes were similar across all groups (Table S2). Conversely, mean cortical thickness and AD-signature regional thickness were thinner in both middle-aged groups than in the YS group. In subcortical regions, the accumbens nucleus and putamen showed smaller volumes in middle-aged groups than in the YS group. The hippocampal volume was similar across all groups. The rightward symmetry was observed for amygdala, caudate, hippocampus, and pallidum volumes and the leftward symmetry for thalamus.

Fig. 3 and Table 4 show the results of regional cortical thickness analysis. Compared with YS group, both of the middle-aged groups showed thinner superior frontal gyrus, pars opercularis, isthmus cingulate gyrus, superior parietal lobule, lingual gyrus, and fusiform gyrus. On the other hand, MA group showed thicker left precentral gyrus, right postcentral gyrus, and bilateral pericalcarine cortices than the MS group. Furthermore, compared with YS group, MA group had thicker lateral occipital sulcus, left pericalcarine cortex, and right postcentral gyrus. The insular cortex and right superior frontal gyrus were thinner in the MA compared with MS groups. After adjustment for age and sex, cortical thickness was not correlated with VO_{2peak} or global neuropsychological test performance. In the MA group, no significant correlations were observed between the NIHTB-CB total composite score and cortical thickness in any region.

Fig. S3 and Table S3 present the results from regional cortical volume analysis which generally showed similar patterns to the cortical thickness analysis, although fewer clusters with significant group differences were observed. Across all participants, higher VO_{2peak} was associated with greater postcentral gyrus volume after adjustment for age and sex. The analysis of regional cortical area did not result in significant clusters.

4. Discussion

The main findings from this study are as follows. First, FA for the global WM was higher in MA compared with MS group, and was similar between the MA and YS groups. Furthermore, MA participants had higher FA in the anterior, superior, and limbic WM tracts than the MS group, including the genu of corpus callosum, superior longitudinal fasciculus, and uncinate fasciculus. Consistent with group-level analysis, greater VO_{2peak} was associated with higher FA and AxD across all participants, independently from age and sex. Second, the primary motor (M1) and somatosensory (S1) cortices and the visual cortical areas showed greater thickness in the MA group than in the MS and YS groups, despite similar, potentially age-related cortical thinning in other areas in the MA group. We observed thinner insular and right superior frontal cortices in the MA compared with MS groups. Collectively, these findings suggest that midlife aerobic exercise may attenuate age-related WM deterioration and increase M1, S1, and visual cortical thickness. Below we discuss the novel aspects, potential mechanisms, and clinical implications of our findings.

4.1. WM fiber integrity

Structural integrity of the global WM measured by FA using DTI has been shown to peak at the age of 30–40 while exhibiting substantial regional variability (Lebel et al., 2012; Westlye et al., 2010). Consistently, the present study found that FA of the global WM skeleton was significantly lower in the MS compared with YS groups. To the contrary, we observed that FA for global WM was significantly higher in MA com- pared with MS groups, and was similar between the MA and YS groups. Therefore, these findings extend our prior knowledge in older adults (Tseng et al., 2013a) that midlife aerobic exercise may prevent or, at least in part, slow the age-related reduction of global WM integrity.

Tract-based spatial statistical analysis further confirmed the results of global WM analysis, as shown by higher FA in the MA compared with MS groups across the WM. In particular, MA participants had higher FA in the WM tracts vulnerable to age and neurodegenerative disease (Huang et al., 2012), including the uncinate fasciculus, cingulum, and fornix. From a clinical perspective, patients with amnestic MCI, a prodromal stage of AD dementia, have been shown to have lower FA in these limbic tracts (Remy et al., 2015). In the current study, our middle-aged participants (~55 years old) are younger than most MCI or AD patients (generally >70 years old), but it can, at least, be speculated that higher integrity of the WM tracts in earlier life may provide neuroprotection or resilience against the future risk of neurodegenerative disease which could manifest after decades (Fratiglioni et al., 2020).

In older adults, positive associations between higher cardiorespiratory fitness and WM integrity have been reported by several studies (Hayes et al., 2015; Johnson et al., 2012; Tarumi et al., 2020; Tian et al., 2014; Tseng et al., 2013a; Voss et al., 2013). For example,

in our cross-sectional sample of older adults (~65 years old) including cognitively healthy adults and MCI patients, positive associations between VO_{2peak} and FA across the WM were observed (Ding et al., 2018). In randomized controlled trials, change in VO_{2peak} after a 1-year aerobic exercise training was associated with improved WM integrity in the prefrontal area in both cognitively healthy old adults (Voss et al., 2013) and amnestic MCI patients (Tarumi et al., 2020). Therefore, our results add to the current literature by demonstrating that higher levels of cardiorespiratory fitness at younger ages are also associated with improved WM integrity.

Regarding the neurobiological mechanism of altered FA, higher AxD in the global and regional WM tracts may reflect attenuation of axonal damages in MA participants, as suggested by animal model studies (Song et al., 2003). On the other hand, a positive correlation between RD and VO_{2peak} in the brainstem was an unexpected finding because RD in the cerebral WM has generally been shown to increase with aging (Westlye et al., 2010) or neurodegenerative disease (Huang et al., 2012). Thus, future studies need to confirm this finding as to whether midlife aerobic exercise may alter RD in the brainstem.

4.2. Brain volume and cortical thickness

In the current study, whole brain and cerebral WM volumes were similar across all groups. In subcortical regions, the accumbens and putamen areas showed potential age-related atrophy. Furthermore, exercise status was not related to whole brain or subcortical gray matter volumes. The hippocampal volume was similar across all groups in contrast to previous observations in older adults which showed that physical fitness level is positively associated with hippocampal volume (Erickson et al., 2009; Szabo et al., 2011). Based on the literature, these observations may be explained by heterogeneous patterns of regional brain atrophy with normal aging and their responses to exercise status. For example, the hippocampal volume has been shown to remain relatively stable during middle age but decreases after ~60 years old in healthy adults (Fjell et al., 2013) while its age-related atrophy may be prevented by aerobic exercise training in older adults (Firth et al., 2018). Likewise, whole brain volume may not be sensitive to age because the cerebral WM volume remains stable or can even increase until middle age (Westlye et al., 2010). The putamen atrophy in our middle-aged adults is also consistent with the literature, which suggests that it may be relatively sensitive to age among the subcortical structures (Raz et al., 2010). Aside from the age-related differences, we observed a general trend of rightward symmetry in regional brain volumes such as the amyglada and hippocampus, which is consistent with the results of a meta-analysis and systematic review (Pedraza et al., 2004).

In contrast to the whole brain or subcortical gray matter volumes, mean cortical thickness and AD-signature regional thickness were significantly thinner in middle-aged participants than in the young adults. Moreover, regional cortical analysis exhibited an anterior-to-posterior atrophy gradient. In particular, we observed large clusters potentially suggestive of age-related cortical thinning (i.e., YS vs. MS and MA groups) in the superior frontal gyrus, pars opercularis, isthmus cingulate gyrus, superior parietal lobule, lingual gyrus, and fusiform gyrus. Overall, these regions with potential age-related atrophy are consistent with recent longitudinal findings from middle-aged adults (Shaw et al., 2016) and may

also suggest that age- and exercise-related differences in brain anatomy may not overlap (Fletcher et al., 2016). Methodologically, our results also suggest that cortical thickness analysis (Fig. 3) is more sensitive than the volume analysis (Fig. S3) in detecting age-related atrophy, as reported from other studies (Liem et al., 2015). In addition, our observation of no group differences in the cortical surface area suggests that the area analysis may be less sensitive than the thickness analysis, as shown by a previous study that the age-cortical thickness correlations were stronger than the age-cortical area correlations (Hogstrom et al., 2013).

Our findings that MA participants had thicker M1, S1, and visual cortical areas than the MS and YS groups are in line with our previous findings from older endurance athletes (>70 years old) who showed greater volumes in the secondary sensorimotor cortex (superior parietal lobule) and the secondary visual cortex (inferior occipital gyrus) (Tseng et al., 2013b). Therefore, our results from the current and previous studies may support the dogma of “use it or lose it, ” which indicates that regular physical exercise induces adaptations in particular brain regions (Gaser and Schlaug, 2003; Maguire et al., 2003). Accordingly, the thicker M1 was an expected finding because this region controls voluntary movement of skeletal muscles and joints during exercise (Todorov, 2000). The adjacent S1 is connected to M1 via corticocortical projections, and plays an important role in motor learning (Pavlides et al., 1993). The visual cortical areas are involved in visuospatial processing of environmental stimuli during running, cycling, and other modes of aerobic exercise (Sirevaag et al., 1988).

In the current study, MA group showed thinner cortical thickness at the insula and right superior frontal gyrus than the MS group. As we did not expect these findings based on the current literature, it is difficult to speculate the potential mechanisms by which aerobic exercise would reduce these regional cortical thicknesses during midlife. These brain regions are involved in autonomic control, stress responses, negative emotions and feelings (Ding et al., 2020; Ochsner et al., 2004), and it is well known that regular aerobic exercise is associated with changes in autonomic neural activity (Hautala et al., 2009), stress reduction (Salmon, 2001), lower risks of anxiety and depression (Martinsen, 2008). While regular exercise has positive effects on autonomic activity, stress reduction, emotion and feeling, it is still challenging to link these positive effects to the thinner insula and right superior frontal gyrus in these MA participants.

4.3. Neuropsychological function and clinical perspective

In MA participants, the total cognitive composite scores from the NIHTG-CB were slightly but statistically higher than the population average, although the scores were not correlated with brain structural measures. The lack of correlation between cognitive and brain structural measures may be related to the small sample size and relatively homogeneous characteristics of MA participants, which limited data dispersion, thereby limiting potential associations if any exist. It is also possible that the relation between cognitive and brain structural measures may not be reflected properly by the simple linear correlation assessment used in the present study, and/or that the NIHTB-CB measures, as brief cognitive screening tasks, may lack sensitivity to the neuroimaging metrics examined.

From a clinical perspective, higher levels of cognitive performance and WM integrity in the MA participants could potentially contribute to greater 'resistance' to and 'resilience' against the future risks of neurodegenerative disease and dementia (Arenaza-Urquijo and Vemuri, 2018; Fratiglioni et al., 2020). Midlife aerobic exercise may improve cardiovascular health and reduce cardiovascular risk factors (e.g., hypertension, obesity) which are associated with higher rates of cognitive impairment and dementia in later life (Horder et al., 2018). Longitudinal DTI studies have also demonstrated that lower FA in the normal-appearing WM is associated with the higher risk of developing WM hyperintensities (de Groot et al., 2013; Maillard et al., 2014). Stronger connectivity of the limbic WM tracts may also increase resilience to cope with neurodegenerative pathologies, such as hippocampal and medial temporal atrophy in later life (Scahill et al., 2002; Smith, 2002).

Given the limited understanding of neuroprotective mechanism by which midlife physical activity is associated with the lower risk of neurodegenerative disease in later life (Rovio et al., 2005; Rovio et al., 2010), our findings provide additional evidence that regular aerobic exercise during middle age is associated with higher brain structural integrity, particularly the attenuation of age-related WM fiber deteriorations.

4.4. Limitations and strengths

There are several limitations to this study. First, causal associations among age, midlife exercise, and brain structures cannot be inferred from this cross-sectional design which needs to be confirmed by randomized controlled studies, although conducting randomized longitudinal exercise studies over a prolonged time (>10 years) would be daunting if not impossible. Thus, we cannot exclude the possibility that other pre- exercise training differences between the groups (e.g., general health, motor skills, socioeconomic status) may affect outcome measures. Second, this study had relatively small sample sizes which limited statistical power of detecting significant correlations and regression within each group or across all groups. Additionally, the effects of different modalities of exercise training (e.g., swimmers vs. runners vs. cyclists) were difficult to compare due to the limited sample sizes and the combined exercise modalities performed by many of the MA participants. Third, although diffusion-weighted MRI is currently the only method capable of assessing WM fibers *in vivo*, FA calculated from DTI has inherent limitations to assess WM integrity. In particular, FA in the WM fibers is not only influenced by structural damage or degeneration, but also by the anatomical (e.g., crossing fibers), structural (e.g., packing density and diameter), and functional (e.g., membrane permeability) properties of axons (Jones et al., 2013). Therefore, our results need to be interpreted carefully and confirmed by other imaging modalities, such as the High Angular Resolution Diffusion Imaging which can partly resolve issues of intravoxel fiber orientations (Tuch et al., 2002). Fourth, the lack of genetic data may be an important limitation. As such, apolipoprotein E4, the established risk factor for AD dementia, has been shown to modulate the effects of physical activity or exercise on brain function (Schuit et al., 2001). Moreover, genome-wide association studies showed that train- ability of VO_{2peak} in response to aerobic exercise training is determined by multiple genes of small effects (Bouchard et al., 2011). Thus, the association between brain structure and VO_{2peak} could be confounded by genetic factors. Fifth, our MA participants may be unique in other lifestyle factors than exercise training such as diet

and other health practices. Lastly, the NIHTB-CB and PROMIS scores are relatively brief screening tools and were available only in the MA group, which made us unable to compare their scores with the MS and YS groups.

Despite these limitations, this study has several important strengths. First, this study focused on middle age that is a unique component of the lifespan and has received relatively little attention in the past (Park and Festini, 2017). Therefore, this study provides one of the first pieces of evidence on the association between midlife aerobic exercise and brain structural integrity. Second, our MA participants were trained well, as they have been exercising for ~25 years and had ~90%ile of VO_{2peak} according to the American College of Sports Medicine guideline (American College of Sports Medicine, 2013). Thus, our results should reflect at least some impact of aerobic exercise on their brain structures when compared with the sedentary groups. Third, brain volume, cortical thickness, and WM integrity analyses within a single study provided a comprehensive dataset to investigate the association between regular aerobic exercise and brain structures during midlife. Finally, VO_{2peak} provided the objective, gold-standard index of cardiorespiratory fitness and the complementary results of group-level analysis.

5. Conclusions

The present study demonstrated that WM integrity measured by DTI in the middle-aged adults who had aerobic training for >10 years was higher than that in sedentary adults of the same age group, and was at a similar level to young adults. Furthermore, we observed that those aerobically trained middle-aged adults had greater thickness in the primary motor (M1), the primary somatosensory (S1), and the visual cortical areas than in the sedentary groups of similar age and younger groups. These findings collectively suggest that midlife aerobic exercise may prevent or slow age-related WM deteriorations while increasing cortical thickness at the sensorimotor and visual areas.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Institutes of Health (K99HL133449 and R01HL102457) and the Japanese Society for the Promotion of Science (19K19970). We thank each of the study participants for their effort and time contributing to the study. Also, we thank the editor and reviewers for their time and effort for providing us constructive comments to improve the manuscript.

Data and code availability statement

All data used for this study are stored at the Institute for Exercise and Environmental Medicine. Data are accessible upon request as far as allowed by guidelines established with the ethics committee of the UT Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas. Requests should be addressed to T. Tarumi.

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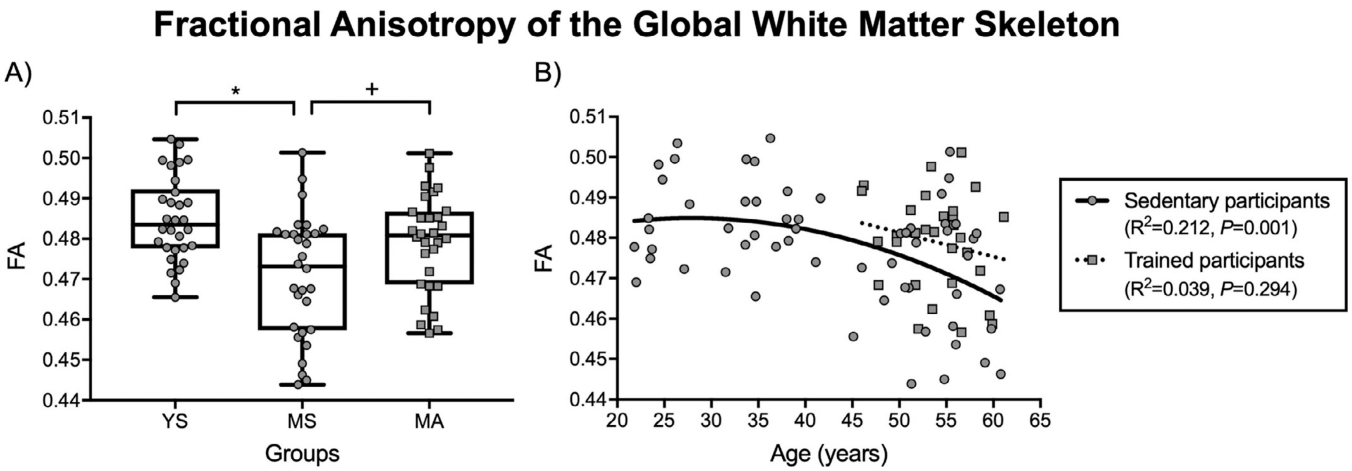

Fig. 1.

A) Global fractional anisotropy (FA) compared among the young sedentary (YS), middle-aged sedentary (MS), and middle-aged aerobically trained (MA) groups. *vs. YS group, +vs. MS group. *P*-value for analysis of variance was <0.001. (B) Associations between age and global FA within the sedentary participants (YS and MS groups combined) and the aerobically trained middle-aged participants (MA group). R^2 was calculated by regression model including a quadratic age term of age (i.e., age^2).

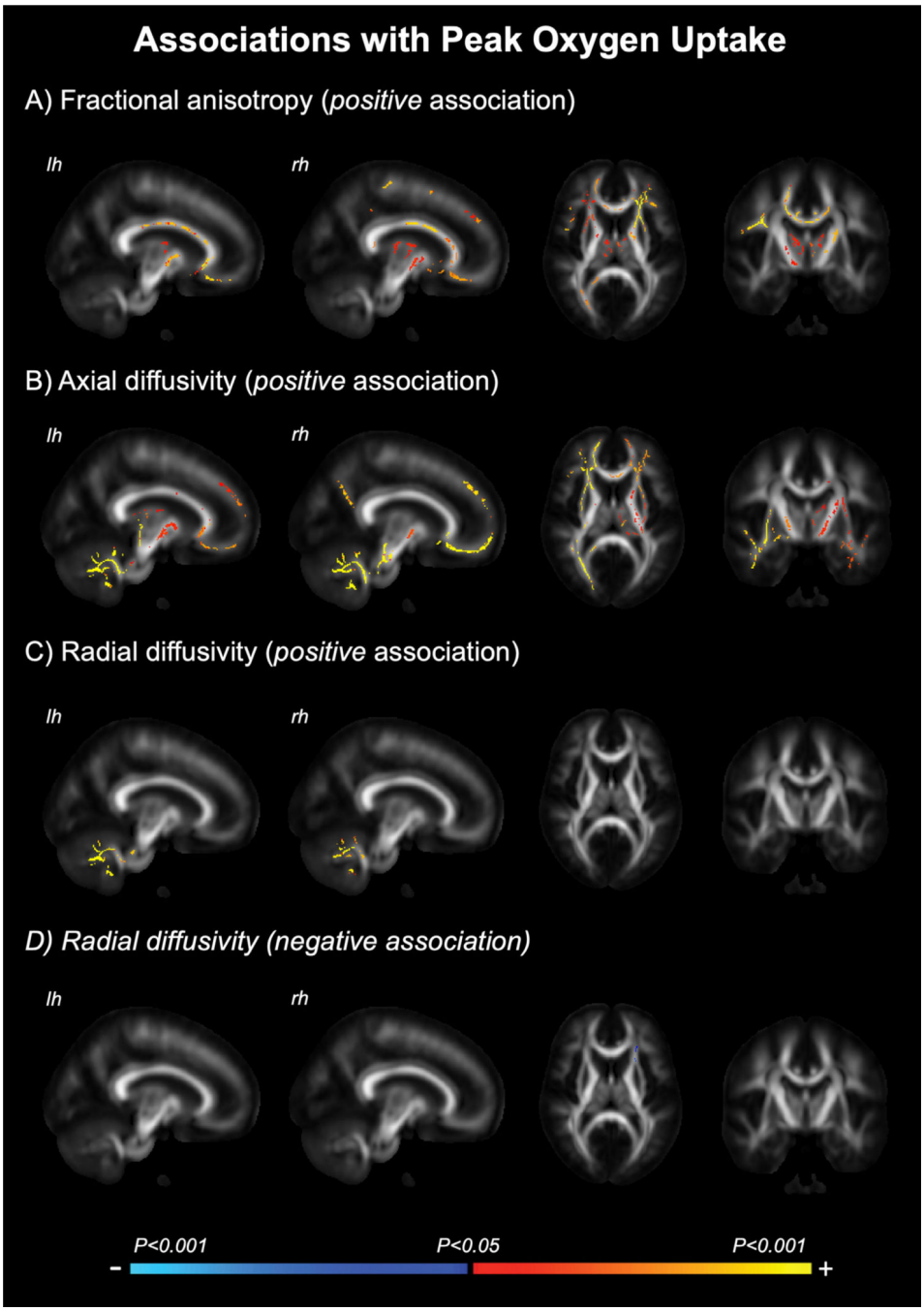

Fig. 2.

Results of tract-based spatial statistical analysis showing the age- and sex-adjusted associations of peak oxygen uptake in all participants. The colored white matter tracts show significant voxels. The color bar indicates the level of statistical significance. Table 3 presents the detailed information of significant voxels.

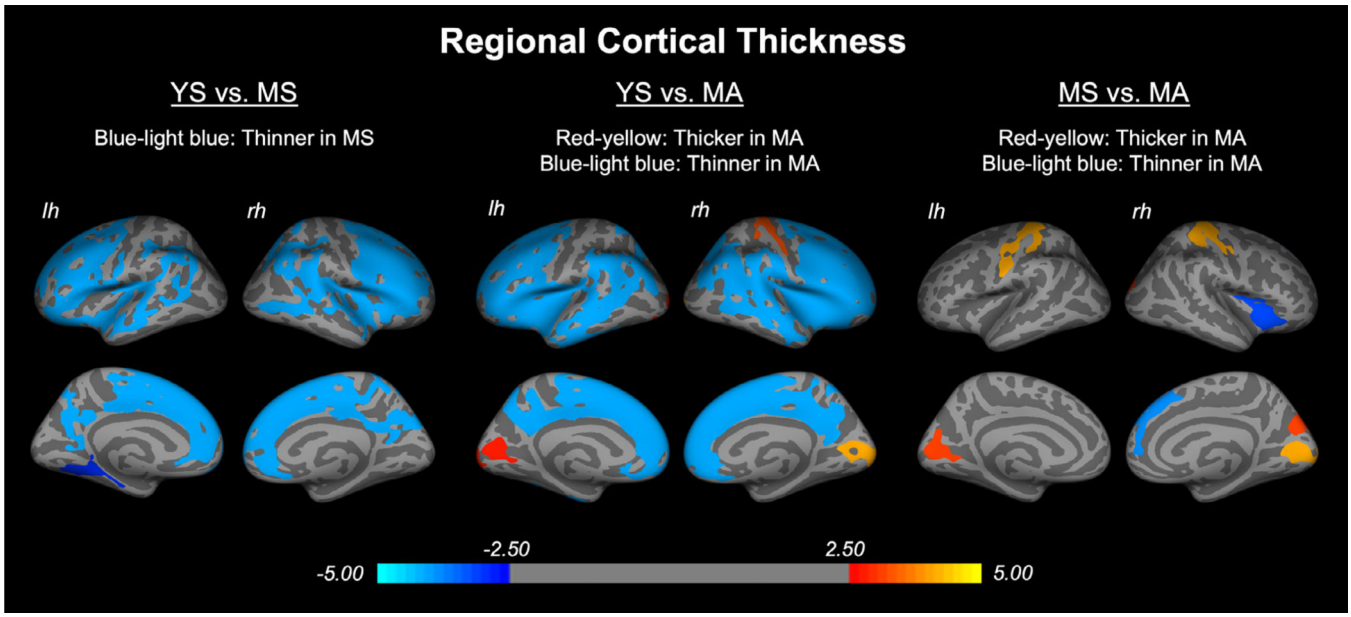

Fig. 3.

Results of regional cortical thickness analysis showing significant differences among the young sedentary (YS), middle-aged sedentary (MS), and middle-aged aerobically trained (MA) groups. The colored areas show significant clusters. The color bar indicates the level of statistical significance. The results were obtained using Monte Carlo simulation, with a threshold of $P<0.05$ to provide cluster-wise correction for multiple comparisons. The detailed information of each cluster is presented in Table 4.

Table 1

Exercise training history, neuropsychological testing scores, and physical and mental health measures in aerobically trained middle-aged adults.

	Mean ± SD	Range
Sample size (n)	30 (15 men, 15 women)	
Exercise training history		
Years of exercise training	24.8 ± 9.6	(10 to 40)
Number of exercise sessions per week	7.5 ± 2.5	(4 to 15)
Hours of exercise per week	10.2 ± 4.6	(5 to 23)
Modes of exercise perfomed (n): Running (28), Cycling (26), Swimming (18), Resistance exercise (18), Yoga (7), Hiking/Walking (3), Rowing (2), Boot camp (1), Cross-training (1), Stepmill (1), Barre class (1)		
NIH Toolbox Cognition Battery (NIHTB-CB) scores		
Total cognition composite	54.3 ± 7.3	(38 to 70)
Dimensional change card sort test	58.6 ± 11.1	(38 to 78)
Flanker inhibitory control and attention test	45.0 ± 8.6	(26 to 64)
List sorting working memory test	51.3 ± 8.7	(26 to 63)
Oral reading recognition test	57.0 ± 9.0	(36 to 79)
Pattern comparison processing speed test	44.7 ± 11.1	(25 to 66)
Picture sequence memory test	53.8 ± 7.8	(36 to 70)
Picture vocabulary test	53.8 ± 7.8	(36 to 70)
Patient-Reported Outcomes Measurement Information System (PROMIS) scores		
Anger	48.5 ± 4.9	(37.1 to 58.9)
Anxiety	50.6 ± 5.3	(43 to 67)
Depression	46.5 ± 5.0	(34.2 to 62.2)
Fatigue	47.5 ± 5.3	(34.4 to 55.6)
Sleep-related impairment	49.1 ± 8.4	(30.5 to 63.2)
Sleep disturbance	46.8 ± 9.2	(30.1 to 68.4)

Data are presented in mean ± standard deviation (SD). Range shows the minimal to maximal values. The NIHTB-CB and PROMIS scores are presented as normalized T-scores (mean of 50, SD = 10) adjusted for age, sex, education, and race/ethnicity.

Table 2

Group comparison of participant characteristics.

	YS Mean ± SD	MS Mean ± SD	MA Mean ± SD	*P* -value(ANOVA)
n (%women)	30 (50)	30 (50)	30 (50)	1.000
Age (years)	32 ± 6	54 ± 4 *	54 ± 4 *	< 0.001
Education (years)	16.0 ± 2.2	16.2 ± 2.0	15.9 ± 2.0	0.880
Height (cm)	170 ± 10	170 ± 13	173 ± 8	0.532
Body mass (kg)	72 ± 14	81 ± 17	72 ± 12 +	0.024
Body mass index (kg/m^2)	25 ± 4	28 ± 5 *	24 ± 3 +	< 0.001
VO_{2peak} (ml/kg/min)	34.4 ± 7.0	27.1 ± 4.6 *	42.5 ± 5.2 *,+	< 0.001

Data are presented in mean ± standard deviation (SD).

* vs. YS group,

+ vs. MS group. *P*-values are calculated by chi-square test or one-way analysis of variance. ANOVA = analysis of variance, MA = middle-aged aerobically trained adults, MS = middle-aged sedentary adults, VO_{2peak} = peak oxygen uptake, YS = young sedentary adults

Neuroimage. Author manuscript; available in PMC 2022 January 10.

Table 3

Anatomical location and count of significant white matter skeleton voxels that were significantly associated with peak oxygen uptake in Fig. 2.

White matter fibers	A) FA Count (%)	B) AxD Count (%)	C) RD Count (%)	D) RD Count (%)
Global white matter	18203 (18.3)	31874 (32.0)	7218 (7.2)	414 (0.4)
Commissural fibers				
Genu of corpus callosum	784 (48.6)	552 (34.2)	0 (0)	0 (0)
Body of corpus callosum	1475 (47.3)	176 (5.6)	0 (0)	0 (0)
Splenium of corpus callosum	344 (15.3)	208 (9.2)	0 (0)	0 (0)
Tapetum	0 (0)	60 (29.4)	0 (0)	0 (0)
Projection fibers				
Anterior corona radiata	1949 (64.5)	1897 (62.8)	0 (0)	92 (3)
Superior corona radiata	681 (25.5)	274 (10.3)	0 (0)	0 (0)
Posterior corona radiata	325 (21.6)	331 (22.0)	0 (0)	0 (0)
Anterior limb of internal capsule	726 (49.4)	576 (39.2)	0 (0)	12 (0.8)
Posterior limb of internal capsule	434 (22.0)	635 (32.1)	0 (0)	0 (0)
Retrolenticular part of internal capsule	72 (4.8)	646 (42.8)	0 (0)	0 (0)
Posterior thalamic radiation	346 (20.1)	599 (34.7)	0 (0)	0 (0)
Cerebral peduncle	27 (4.1)	314 (47.4)	0 (0)	0 (0)
Association fibers				
Superior longitudinal fasciculus	1119 (31.9)	415 (11.8)	0 (0)	0 (0)
Superior fronto-occipital fasciculus	156 (79.6)	129 (65.8)	0 (0)	0 (0)
Uncinate fasciculus	36 (40.4)	64 (71.9)	0 (0)	0 (0)
Sagittal stratum	102 (8.0)	559 (43.9)	0 (0)	0 (0)
External capsule	1098 (38.2)	1644 (57.2)	0 (0)	235 (8.2)
Cingulum	315 (32.9)	116 (12.1)	0 (0)	0 (0)
Fornix	0 (0)	228 (24.7)	0 (0)	0 (0)
Brainstemfibers				
Middle cerebellar peduncle	0 (0)	1843 (95.9)	1504 (78.3)	0 (0)
Superior cerebellar peduncle	0 (0)	247 (65.3)	63 (16.7)	0 (0)
Inferior cerebellar peduncle	0 (0)	303 (91.5)	140 (42.3)	0 (0)
Pontine crossing tract	0 (0)	293 (89.3)	161 (49.1)	0 (0)

White matter fibers	A) FA Count (%)	B) AxD Count (%)	C) RD Count (%)	D) RD Count (%)
Medial lemniscus	0 (0)	257 (88.9)	196 (67.8)	0 (0)
Corticospinal tract	0 (0)	180 (63.6)	1 (0.4)	0 (0)

Columns A-C show the results of positive associations whereas column D shows the results of a negative association with peak oxygen uptake. % represents the percent of significant voxels relative to the whole white matter tract. FA = fractional anisotropy, AxD = axial diffusivity, RD = radial diffusivity

Table 4

Cortical regions where significant group differences in thickness were observed in Fig. 3.

Hemisphere	Cortical regions	Max	VtxMax	Cluster size (mm^2)	TalX	TalY	TalZ	CWP
			YS vs. MS groups					
Thinner in MS group								
lh	Superior frontal	−8.24	152627	27088	−12.6	28.7	45.0	< 0.001
lh	Isthmus cingulate	−2.69	31565	1501	−9.6	−46.1	29.3	< 0.001
lh	Lingual	−4.22	10138	1171	−27.4	−53.2	−2.5	0.003
lh	Superior parietal	−4.70	66929	784	−23.2	−51.4	61.3	0.037
rh	Superior frontal	−6.51	13593	32582	7.1	21.3	53.9	< 0.001
rh	Fusiform	−3.56	114383	847	37.0	−52.9	−12.1	0.024
			YS vs. MA groups					
Thinner in MA group								
lh	Superior frontal	−10.42	117197	37792	−13.0	27.8	25.2	< 0.001
rh	Pars opercularis	−11.05	72987	39838	43.7	10.0	5.3	< 0.001
Thicker in MA group								
lh	Lateral occipital	2.76	122796	1100	−14.3	−94.9	−6.3	0.004
lh	Pericalcarine	5.47	87468	1069	−7.5	−79.2	15.0	0.005
rh	Lateral occipital	4.40	13245	1936	16.6	−95.5	−2.8	< 0.001
rh	Postcentral	8.50	4009	1246	23.0	−27.7	54.8	0.001
			MS vs. MA groups					
Thicker in MA group								
lh	Precentral	5.44	48470	2348	−34.0	−19.3	37.5	< 0.001
lh	Pericalcarine	4.84	87476	1250	−9.6	−81.0	14.7	0.002
rh	Postcentral	6.38	42408	1885	23.7	−27.3	53.5	< 0.001
rh	Pericalcarine	5.84	6081	1570	13.8	−82.1	5.5	< 0.001
rh	Cuneus	3.56	130082	1176	7.9	−77.9	35.4	0.002
Thinner in MA group								
lh	Insula	−5.10	1190	888	−29.8	20.0	1.2	0.018
rh	Superior frontal	−4.52	454	1477	8.1	32.3	34.2	< 0.001
rh	Insula	−4.48	20380	1216	32.1	15.9	2.0	0.001

The table lists clusters along with the maximum value found in the cluster (Max), the vertex at which this maximum value was found (VtxMax), the surface area of the cluster (Size), the Talaiarach coordinates of the maximum, and the clusterwise *P*-value (CWP). The Max values indicate the maximum -log10(*P*-value) in the cluster, where *P* is the significance. lh = left hemisphere, MA = middle-aged aerobically trained, MS = middle-aged sedentary, rh = right hemisphere, YS = young sedentary.