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ABSTRACT

Background: White matter (WM) integrity declines with normal aging. Physical activity may attenuate age-related WM integrity changes and improve cognitive function. This study examined brain WM integrity in Masters athletes who have engaged in life-long aerobic exercise training. We tested the hypothesis that life-long aerobic training is associated with improved brain WM integrity in older adults.

Methods: Ten Masters athletes (3 females, age = 72.2 ± 5.3 years, endurance training >15 years) and 10 sedentary older adults similar in age and educational level (2 females, age = 74.5 ± 4.3 years) participated. MRI fluid-attenuated-inversion-recovery (FLAIR) images were acquired to assess white matter hyperintensities (WMH) volume. Diffusion tensor imaging (DTI) was performed to evaluate the WM microstructural integrity with a DTI-derived metric, fractional anisotropy (FA) and mean diffusivity (MD).

Results: After normalization to whole-brain volume, Masters athletes showed an 83% reduction in deep WMH volume relative to their sedentary counterparts (0.05 ± 0.05% vs. 0.29 ± 0.29%, $p < 0.05$). In addition, we found an inverse relationship between aerobic fitness (VO_{2max}) and deep WMH volume ($r = -0.78$, $p < 0.001$). Using TBSS, Masters athletes showed higher FA values in the right superior corona radiata (SCR), both sides of superior longitudinal fasciculus (SLF), right inferior fronto-occipital fasciculus (IFO), and left inferior longitudinal fasciculus (ILF). In addition, Masters athletes also showed lower MD values in the left posterior thalamic radiation (PTR) and left cingulum hippocampus.

Conclusions: These findings suggest that life-long exercise is associated with reduced WMH and may preserve WM fiber microstructural integrity related to motor control and coordination in older adults.

Introduction

The hallmark of brain aging includes declines in several aspects of cognitive function such as processing speed, working memory, inhibitory function, and long-term memory (Park and Reuter-Lorenz, 2009). Concurrently, structural as well as physiologic changes also occur in the brain with advancing age (Raz et al., 2005). Brain aging is likely to be determined by both genetic and environmental factors (Seshadri et al., 2007). Increasing evidence demonstrates that physical activity is a modifiable factor important not only for cardiovascular fitness, but also for brain health (Hillman et al., 2008). Specifically, previous studies have shown that aerobic exercise training from several months to a year increased regional brain volume in older adults (Colcombe et al., 2006) and that the magnitude of brain volume change was associated with physical fitness level (Erickson et al., 2011). In addition, functional magnetic resonance imaging (fMRI) studies suggest that physical activity modulates brain activation during executive or memory tasks (Smith et al., 2011) and increases functional connectivity (Voss et al., 2010) as well as processing speed (Rosano et al., 2010) in older adults.

"Masters athletes" (http://www.usatf.org/groups/Masters/) comprise a unique group of older adults who have participated in life-long, high volume and high intensity exercise training and competed in sports at the elite level. Previous studies have shown marked cardiovascular benefits accredited to life-long aerobic training (Okazaki et al., 2005). In addition, preliminary results have shown that life-long exercise is beneficial for executive function and may attenuate age-related brain volume loss in the regions related to visuospatial function, motor control, and working memory (Tseng et al., in press). The purpose of this study was to test the hypothesis that life-long exercise training in Masters athletes is associated with improved WM integrity when compared to sedentary but otherwise healthy older adults.

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White matter hyperintensities (WMH), or leukoaraiosis, most likely represents cerebral microangiopathies and/or white matter (WM) fiber dysmyelination (Debette and Markus, 2010). WMH are commonly revealed by fluid-attenuated-inversion-recovery (FLAIR) magnetic resonance (MR) images. The presence and extent of WMH have been linked to the increased risks for stroke, cognitive impairment and/or dementia in older adults (Debette et al., 2010). Diffusion tensor imaging (DTI) is one of the MRI modalities which measures water diffusion in multiple directions to probe the structural and functional properties of biological tissues. Two frequently used DTI metrics are tissue fractional anisotropy (FA) and mean diffusivity (MD), which can serve as a non-invasive measures of WM microstructural integrity (Huang et al., 2012). Tract-based-spatial-statistics (TBSS) is a voxelwise analysis method which has advantages of alleviating errors caused by partial volume effects when conducting voxel level comparisons (Smith et al., 2006). Both FLAIR imaging (Grueter and Schulz, 2012) and DTI (Kennedy and Raz, 2009) have been used in study of age-related decline in brain WM integrity and neurodegenerative diseases. Age-related increases in WMH (Grueter and Schulz, 2012) and decreases in FA (Kennedy and Raz, 2009) have been well documented. Although a few studies have suggested a positive relationship between physical activity (as estimated by self-reported questionnaires) and brain white matter integrity (Gow et al., 2012; Ho et al., 2011; Rosano et al., 2010), to our knowledge, no study has been conducted to reveal the effects of life-long exercise training on WM integrity in older adults. In the present study, we hypothesized that higher aerobic fitness in older adults attributing to long term (>15 years) endurance training is associated with better white matter integrity as measured by WMH volume, FA and MD.

Materials and methods

Subjects

The Institutional Review Board of the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas approved this study. Informed consent was obtained from all study participants. Two groups of subjects were recruited: 1) Masters athletes (MA) — 12 Masters athletes with a history of endurance training >15 years, who were still engaged in endurance exercise at the time of this study. Masters athletes were regionally/nationally ranked runners and were recruited mainly from the running clubs or the records of competitive running events. 2) Sedentary elderly (SE) — 12 sedentary but otherwise healthy older adults similar in age, sex, and educational level to Masters athletes were recruited locally with newsletters or from senior centers. A sedentary lifestyle was defined as not engaging in moderate or high intensity aerobic exercise for more than 30 min, 3 times/week over the past two years. All subjects were free of major medical problems based on a detailed medical history and physical exams including 12-lead electrocardiogram (ECG) and echocardiogram. Subjects were excluded if they were smoking or used recreational drugs. They were also excluded if they had clinical evidence of cardiovascular (e.g., hypertension, diabetes mellitus, hyperlipidemia) or cerebrovascular diseases (e.g. history of stroke, transient ischemic attack or the presence of cortical infarction on MRI scans), dementia, major psychiatric and neurologic disorders. Of note, 2 Masters athletes and 2 sedentary elderly were unable to participate in MRI scans due to metal or other exclusion criteria.

Experimental protocol

All subjects underwent MRI and exercise testing on 2 separate visits. At least 48 h was given between 2 tests to eliminate potential effects of acute exercise on MRI study of brain structure. On testing days, subjects were asked to refrain from exercise, caffeine and alcohol at least 12 h prior to testing.

Magnetic resonance imaging

MRI scans were performed on a 3 T scanner (Philips Medical System, Best, The Netherlands) using a body coil for radiofrequency transmission and a 8-channel head coil with parallel imaging capability for signal reception. T1-weighted high-resolution ($1 \times 1 \times 1$ mm^3) images were acquired using a sagittal 3D magnetization-prepared-rapid-acquisition-of-gradient-echo (MPRAGE) sequence (Brant-Zawadzki et al., 1992) and brain tissue volumes were calculated with FreeSurfer (http://ftp.nmr.mgh.harvard.edu) (Dale et al., 1999). To assess WMH, we acquiredFLAIR images in the transverse plane: FOV = 230×230 mm^2, acquisition resolution = 0.65(anterior–posterior) × 0.87(right–left)mm^2, slices = 24, thickness = 5 mm, gap = 1 mm, TR/TI/TE = 11000 ms/2800 ms/150 ms, and duration = 3.6 min. DTI data were acquired using a single-shot-echo-planar-imaging (EPI) sequence with sensitivity encoding (SENSE) parallel imaging scheme (reduction factor = 2.2). The imaging matrix was 112×112 with FOV = 224×224 mm^2 (nominal resolution of 2 mm), which was zero filled to 256×256. Axial slices of 2 mm thickness (gap = 1 mm) were acquired parallel to the anterior–posterior commissure (AC–PC) line. A total of 60 slices covered the entire hemisphere and brainstem. TE/TR = 51 ms/11.9 s. The diffusion weighting was encoded along 30 independent orientations and the b value was 1000 s/mm^2. Automated image registration was performed on the raw diffusion weighted images to correct distortions caused by motion artifacts or eddy current (Woods et al., 1998). Six elements of 3×3 diffusion tensor were determined for each voxel by multivariate least-square fitting of diffusion weighted images. The tensor was diagonalized to obtain three eigenvalues (λ_{1-3}) and eigenvectors (ν_{1-3}). The tensor fitting and fractional anisotropy (FA) and mean diffusivity (MD) calculations were done using DtiStudio (Jiang et al., 2006).

Imaging data processing

White matter hyperintensities (WMH)

WMH regions were identified from FLAIR images using a semi-automatic method (Marquez de la Plata et al., 2007). Briefly, the FLAIR images were skull-stripped and the voxels with a signal intensity greater than 2 standard deviations above the average were delineated as possible lesions. This was followed by manual editing to remove spurious voxels due to fat signal, motion and edge effect, or coil sensitivity inhomogeneity (Marquez de la Plata et al., 2007). The differentiation between periventricular and deep WMH was performed by assessment of the lesion location and cluster continuation confirmed by superimposing FLAIR images on high-resolution T1 anatomical images (DeCarli et al., 2005a).

Detection of disrupted white matter clusters

Tract-based-spatial-statistics (TBSS) from FMRIB software library (http://www.fmrib.ox.ac.uk/fsl) was used for voxelwise comparison (Smith et al., 2006). This voxelwise method compared FA and MD values of each group at the core (skeleton) of WM to alleviate partial volume effects. Modifications were made to the standard TBSS processing pipeline to incorporate information of WM labeling from a previously established digital WM atlas (Mori et al., 2008). Specifically, the single subject template used for nonlinear registration process in the TBSS was identical to the template used for establishing the digital WM atlas JHU-ICBM-DTI-81 (Mori et al., 2008). Using this method, all FA and MD data were transformed into JHU-ICBM-DTI-81 space, and the atlas labeling was overlaid to the mean skeleton in the JHU-ICBM-DTI-81 space such that each skeleton voxel could be categorized into one of the 50 major tracts (Fan et al., 2010).

Randomize -c option in TBSS (ver 1.1) was used to reveal the clusters. The significant clusters with $p < 0.005$ (t-test, uncorrected) in the skeleton voxels of WM were identified for group comparisons. To avoid false positive results, only clusters with continuous voxels > 10

and mean FA > 0.25 were retained. After randomize processing in TBSS, the cluster filtering procedures described above were conducted with a home-made IDL program (ITT, Boulder, CO). Furthermore, small-volume false discovery rate (FDR) correction (Cullen et al., 2010; Saxena et al., 2012; Versace et al., 2008) was employed with R software package (R-2.13.1). Specifically, the small volumes were anatomically defined regional masks with the disrupted clusters detected above as the centers and containing skeleton voxels 100 times larger than the disrupted clusters.

Measurement of cardiopulmonary fitness level

Maximal oxygen uptake (VO_{2max}) was assessed using a modified Astrand–Saltin protocol (Balke et al., 1965) involving incremental exercise on a treadmill. Subjects walked, jogged or run at a constant speed, which was determined by an exercise physiologist based on the individual subjects' fitness level in order to achieve a peak work rate during maximal exercise testing (Okazaki et al., 2005). After data collection under resting conditions and 2 min of exercise at grade of 0%, the grade was increased incrementally by 2% every 2 min until exhaustion. Oxygen uptake (VO_2) during the second minute of each stage of exercise was measured by using the Douglas bag method (Hill et al., 1924) and breath-by-breath VO_2 was monitored continuously using an online computer system. Gas fractions were analyzed by mass spectrometry (Marquette MGA 1100) and ventilatory volume at rest and during exercise was measured with a Tissot spirometer (Wenzel et al., 1990). Electrocardiogram (ECG) and heart rate (HR) were monitored continuously by a registered nurse or a board-certified cardiologist. Fingertip capillary blood was obtained during approximately 1 min and 50 s to 1 min and 59 s of each stage of exercise for the measurement of lactate concentration (Yellow Springs Instruments (YSI) 23L, Yellow Springs, OH). Calibrations of all instruments and gas sampling were performed by highly-trained and -experienced technicians and exercise physiologists.

Maximal oxygen uptake (VO_{2max}) was defined as the highest oxygen uptake (VO_2) measured from at least a 40-second Douglas bag during the last stage of testing. The criteria to confirm that VO_{2max} was achieved included 1) an increase in VO_2 < 150 ml/min, despite increasing work rate of 2% grade (plateau); 2) a respiratory exchange (RER) ratio > 1.1; 3) HR within 5 beats/min of age-predicted maximal values (220 − age); and 4) blood lactate > 8.0 mmol/l. In all cases, at least three of these criteria were achieved, confirming the identification of VO_{2max} per the American College of Sports Medicine guidelines (ACSM, 2010). Of note, our previous studies have demonstrated that by using these methods, VO_{2max} can be measured reliably in sedentary elderly subjects (Fujimoto et al., 2010; Okazaki et al., 2005).

Statistical analysis

For the small sample size of this study, non-parametric statistical data analysis methods were used. Specifically, Spearman correlation was performed to determine the relationship between aerobic fitness and measurements of WM integrity. Mann–Whitney Rank Sum Test was conducted to detect differences in WMH volume and cardiopulmonary fitness between groups. Data analyses were performed using SigmaPlot 11.0 (SSTI, San Jose, CA).

Results

Subjects characteristics

Ten Masters athletes (3 females; median age 72 years, range = 61–80 years; median BMI 22.9, range = 17.9–28.4) and 10 sedentary older adults similar in age and educational level (2 females; median age 74 years, range = 66–82 years; median BMI 25.6, range = 20.6–30.8) participated. Subject characteristics are also presented in Table 1.

Table 1
Subject characteristics. Values are means ± SD.

	MA (n = 10)	SE (n = 10)
Male/female	7/3	8/2
$Age_{(years)}$	72.4 ± 5.6	74.6 ± 4.3
$Education_{(years)}$	16.2 ± 2.2	15.8 ± 2.3
$Height_{(cm)}$	173.4 ± 10.1	171.7 ± 7.4
$Weight_{(kg)}$	70.52 ± 15.48	76.15 ± 11.09
BMI	23.2 ± 3.1	25.7 ± 3.0
Resting $HR_{(bpm)}$	53.9 ± 5.9*	65.3 ± 6.5
$MAP_{(mm\ Hg)}$	89.1 ± 10.7	89.5 ± 9.3
$SBP_{(mm\ Hg)}$	126.6 ± 11.4	125.5 ± 19.0
$DBP_{(mm\ Hg)}$	70.4 ± 11.7	71.5 ± 5.9
$VO_{2max\ (ml/kg/min)}$	41.0 ± 5.8	22.9 ± 3.3*

MA	Masters athletes
SE	sedentary elderly
BMI	body mass index
HR	heart rate
MAP	mean arterial pressure
SBP	systolic blood pressure
DBP	diastolic blood pressure
VO_{2max}	maximal oxygen uptake

* Significant difference between groups p < 0.01.

White matter hyperintensities

No significant differences were found in GM, WM, CSF, WBV, ICV, total WMH, and periventricular WMH volumes between the groups (Table 2). No sex differences within and between groups were observed for these measures when they were normalized to WBV or ICV (data not shown). Notably, Masters athletes showed 83% reduction in deep WMH volume (p = 0.002) when compared to the sedentary elderly (Table 2, Fig. 1). In addition, Masters athletes also showed 44% reduction in total WMH volume relative to the sedentary elderly although this difference was not statistically significant most likely due to the small sample size of this study (statistical power = 0.20 for this index) (Table 2).

White matter microstructural integrity

Relative to the sedentary elderly, Masters athletes showed higher FA values ($P_{FDR\text{-}corrected}$ < 0.05) in right superior corona radiata (SCR), right and left superior longitudinal fasciculi (SLF), right inferior fronto-occipital fasciculus (IFO), and left inferior longitudinal fasciculus (ILF) as illustrated in Table 2 and Fig. 2. In addition, Masters athletes also showed lower MD values ($P_{FDR\text{-}corrected}$ < 0.001) in the left posterior thalamic radiation (PTR) and left cingulum hippocampus as illustrated in Table 2.

Cardiopulmonary fitness

As expected, Masters athletes showed significantly higher VO_{2max} (p < 0.01) and lower resting heart rate (p < 0.01) (Table 1). Using Spearman correlation, an inverse relationship between aerobic fitness (VO_{2max}) and normalized deep WMH volume was found (r = −0.78, p < 0.001) (Fig. 3). Furthermore, a strong positive relationship between VO_{2max} and FA was observed in the left SLF (r = 0.725, p < 0.001), and left ILF (r = 0.760, p < 0.001) (Fig. 4) in addition to the moderate positive relationship found in the right SCR (r = 0.524, p < 0.05), left SCR (r = 0.492, p < 0.05), right SLF (r = 0.554, p < 0.05), and right IFO (r = 0.591, p < 0.001).

Discussion

White matter hyperintensity and physical activity

The current understanding is that age-related WMH is prevalent (Grueter and Schulz, 2012), and progresses approximately linearly

Table 2
Brain volumetric and voxel-wise measurement. Values are means ± SD.

Brain volumetric measurements		MA (n = 10)	SE (n = 10)
$GM_{(cm^3)}$		559 ± 27	565 ± 39
$WM_{(cm^3)}$		522 ± 41	506 ± 57
$WBV_{(cm^3)}$		1080 ± 62	1071 ± 60
$CSF_{(cm^3)}$		320 ± 44	321 ± 40
$ICV_{(cm^3)}$		1630 ± 130	1661 ± 168
Deep WMH volume[a]		0.05 ± 0.05*	0.29 ± 0.29
Periventricular WMH volume[a]		0.41 ± 0.62	0.53 ± 0.42
Total WMH volume[a]		0.46 ± 0.66	0.82 ± 0.68
	MNI coordinates (X, Y, Z)		
Regional FA			
Right SCR	68, 122, 91	0.592 ± 0.035**	0.523 ± 0.039
Right SLF	43, 91, 105	0.401 ± 0.039**	0.328 ± 0.028
Left SLF	125, 70, 114	0.401 ± 0.076**	0.266 ± 0.089
Right IFO	59, 60, 99	0.494 ± 0.053**	0.388 ± 0.062
Left ILF	113, 57, 95	0.553 ± 0.069**	0.428 ± 0.085
Regional MD			
Left PTR	120, 56, 78	0.0020 ± 0.0002***	0.0025 ± 0.0002
Left CH	113, 99, 54	0.0017 ± 0.0002***	0.0021 ± 0.0001

GM	gray matter
WM	white matter
WBV	whole brain volume
CSF	cerebral spinal fluid
ICV	intracranial volume
WMH	white matter hyperintensities
MNI	Montreal Neurological Institute
FA	fractional anisotropy
MD	mean diffusivity
SCR	superior corona radiata
SLF	superior longitudinal fasciculus
IFO	inferior fronto-occipital fasciculus
ILF	inferior longitudinal fasciculus
PTR	posterior thalamic radiation
CH	cingulum hippocampus

* Significant difference between groups $p < 0.05$.
** Significant difference between groups $P_{FDR\text{-}corrected} < 0.05$.
*** Significant difference between groups $P_{FDR\text{-}corrected} < 0.0001$.
[a] Standardized to whole brain volume.

with age (DeCarli et al., 2005b). In a large cohort study, periventricular and deep WMH were detected in 80% and 92% of older adults age 60 and older, respectively; and it was reported that only 5% of elderly people were free of any WMH (de Leeuw et al., 2001). These findings are consistent with the present study where we found that 90% of the participants exhibited age-related WMH, suggesting that even in normal aging, WMH can occur in the absence of any major medical problems and/or vascular risk factors such as hypertension, diabetes or dyslipidemia.

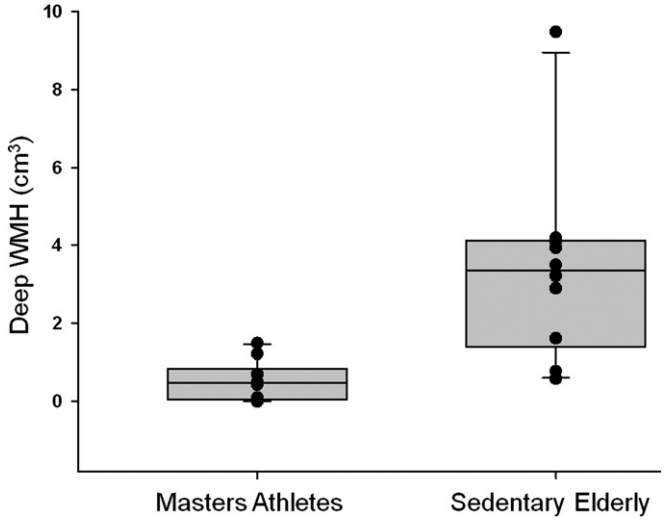

Fig. 1. Individual deep WMH volume indicates that sedentary older adults showed higher deep WMH volume ($p = 0.002$) than Masters athletes. A Mann–Whitney's U test was conducted after excluding one sedentary subject with unusually high deep WMH volume.

It is generally agreed that the presence of WMH is clinically significant due to their close associations with small vessel disease, cerebral amyloid angiopathy, and cerebral atherosclerosis (Greenberg, 2006). WMH has several profound pathological consequences such as increased stroke risk (Debette et al., 2010), cognitive decline (Debette and Markus, 2010), and motor deficits (Srikanth et al., 2009). As indicated in Table 2, Masters athletes showed nearly a 44% reduction of total WMH volume relative to the sedentary elderly although this trend did not reach statistical significance, likely due to a small sample size. On further examination, a substantial reduction (83%) in deep WMH volume was detected in Masters athletes, suggesting the potential salutary effect of life-long aerobic exercise on white matter integrity. Consistently, an inverse relationship between aerobic fitness (VO_{2max}) and deep WMH volume was found. These findings are in agreement with the results of a recent large cohort study that examined physical activity level and white matter lesion burden using in 691 older adults and reported that a physically active lifestyle may be associated with reduced white matter lesion burden (Gow et al., 2012). In addition, Ho and colleagues also reported that BMI, an index that can be profoundly influenced by physical activity, accounts for some variance in brain white structure (Ho et al., 2011).

The pathogenesis of WMH remains controversial (DeCarli et al., 2005a). A common ischemic etiology has been suggested regardless of the anatomical location of the lesions (DeCarli et al., 2005a). However, some have suggested a non-ischemic origin for WMH related to arterial stiffness (Poels et al., 2012) and increased pulse-pressure (Kim et al., 2011) which may have different impacts on periventricular and deep WMH. This may explain our observation of the close association between deep WMH and aerobic fitness, as regular exercise has been shown to reduce arterial stiffness and improve brain perfusion. Although the biological significance of deep WMH is not known, distinctions in pathogenesis suggest different WMH subtypes (Chimowitz et al., 1992). The finding of the present study suggests that aerobic exercise is associated with the alleviation of white matter damage via a mechanism(s) that is relatively specific to deep WMH.

The extent of WMH has been well documented in large population-based studies (de Leeuw et al., 2001; DeCarli et al., 2005b) as well as in controlled clinical observations (Yoshita et al., 2006). More specifically, de Leeuw and colleagues reported that the deep WMH volume ranges from 0.61 cm^3 to 3.25 cm^3 in subjects 60 and older (de Leeuw et al., 2001); while DeCarli et al. detected approximately 8.39 cm^3 of total WMH in people 70 and older (male = 6.33 cm^3, female = 10.35 cm^3) (DeCarli et al., 2005b). In the present study, we found 0.49 cm^3 of deep WMH and 4.56 cm^3 of total WMH in Masters athletes, suggesting that Masters athletes showed marked attenuation in WMH volume when compared to the general population. In addition, our sedentary elderly showed 3.15 cm^3 of deep WMH and 8.97 cm^3 of total WMH, within the normal range previously reported in people of the same age group. This discussion supports our speculation that the lack of significant differences in total WMH between Masters athletes and the sedentary elderly is likely due to the limitation of small sample size of this study.

To date, no study has yet demonstrated the effects of life-long aerobic training on brain white matter integrity although a few attempts have been made to demonstrate the relationship between physical activity and brain white matter integrity using self-reported questionnaires and MR measurements (Gow et al., 2012; Ho et al., 2011; Rosano et al., 2010). One particular study has reported that exercise is beneficial for brain health by demonstrating regional brain volume

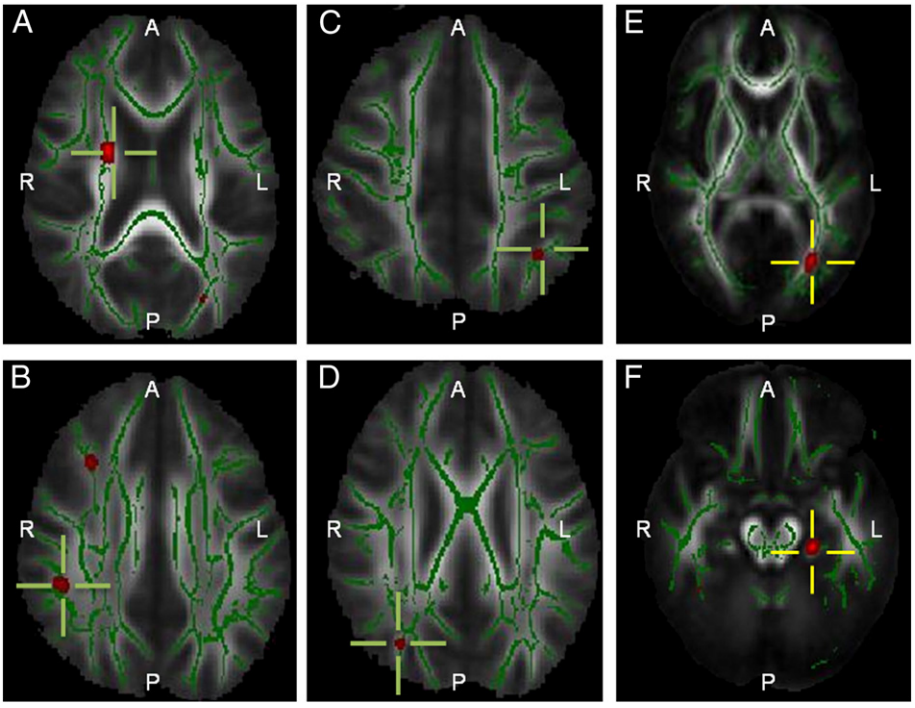

Fig. 2. Fractional anisotropy (FA, as shown in panels A–D) and mean diffusivity (MD, as shown in panels E and F) and white matter (WM) skeleton (green pixels) derived from all subjects are superimposed onto a standard single-subject template in the ICBM-DTI-81space. The red pixels demonstrate disruptions of WM fiber tracks in sedentary elderly when compared to Masters athletes as identified by TBSS in (A) right superior corona radiata; (B) right superior longitudinal fasciculus; (C) left superior longitudinal fasciculus; (D) right inferior fronto-occipital fasciculus; (E) left posterior thalamic radiation; and (F) left cingulum hippocampus. The yellow crosshair identifies the MNI coordinates of each cluster (reported in Table 2). A = anterior, P = posterior, L = left, R = right.

gains after several months to 1 year of moderate aerobic training in older adults (Colcombe et al., 2006; Erickson et al., 2011). In conjunction with the present study, this evidence supports the hypothesis that the age-related brain structural changes may be modulated by physical activity or exercise. On the contrary, a large 5-year follow-up cohort study assessed the relationship between physical activity and the progression of WMH among community dwellers and reported that physical activity was not associated with the rate of WMH progression (Podewils et al., 2007). However, as acknowledged by the authors of this study, the use of self-reported questionnaires to estimate weekly caloric expenditures and a qualitative method to assess WMH progression may have contributed to the negative findings.

White matter fiber microstructural integrity and physical activity

FA was calculated to characterize brain white matter microstructural integrity. Associations between FA and physical activity have been suggested in older adults (Johnson et al., 2012). Using TBSS, we found that Masters athletes showed higher FA values in the right SCR. Corona radiata is a white matter structure that continues ventrally as the internal capsule and dorsally as the centrum semiovale (Wakana et al., 2004). It contains both descending and ascending axons that carry nearly all of the neural traffic from and to the cerebral cortex. As part of the projection tract group of human brain white matter, the SCR is associated with motor function as demonstrated in both human

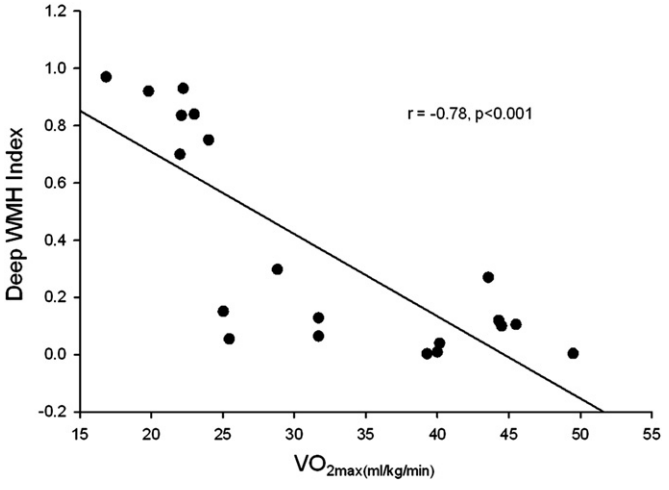

Fig. 3. Higher aerobic fitness (VO_{2max}) is associated with reduced deep WMH volume (indexed to whole-brain volume).

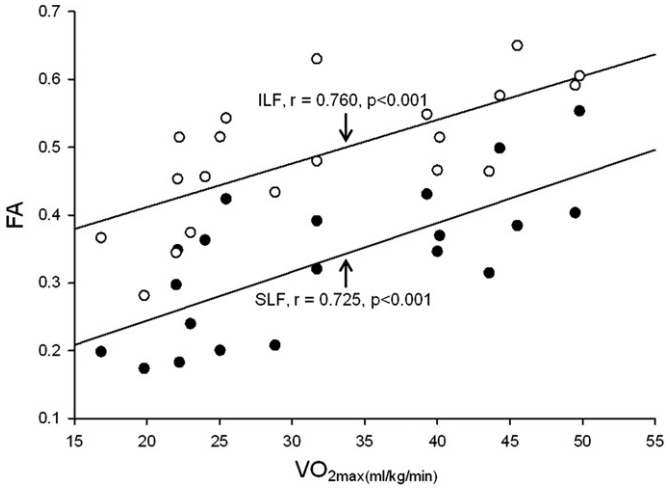

Fig. 4. Higher aerobic fitness (VO_{2max}) is associated with better white matter microstructural integrity (FA) in the left superior longitudinal fasciculus (SLF) and left inferior longitudinal fasciculus (ILF).

(Sasson et al., 2012) and non-human primate studies (Morecraft et al., 2002). Our data suggested structural differences of white matter in regions associated with motor function in Masters athletes.

Masters athletes also showed higher FA values in bilateral superior longitudinal fasciculus (SLF), right inferior fronto-occipital fasciculus (IFO), and left inferior longitudinal fasciculus (ILF). The SLF is a long fiber tract connecting the front and the back of the cerebrum (i.e. frontal, occipital, parietal, and temporal lobes). It travels from the frontal lobe and passes through the operculum and ends up at the posterior area of the lateral sulcus where numerous neurons radiate into the occipital lobe while many others turn downward and forward around the putamen and radiate to anterior temporal lobe (Wakana et al., 2004). The IFO connects the frontal and occipital lobes, running along the lateral border of the caudate nucleus, and the ILF connects the temporal and occipital lobes, running along the lateral walls of the inferior and posterior cornua of the lateral ventricle. In addition, we also found lower MD values in left posterior thalamic radiation (PTR) and left cingulum hippocampus (CH) in Masters athletes. The PTR fibers connect through the retrolenticular part of the posterior limb of the internal capsule, the pulvinar complex and lateral geniculate nucleus, and the posterior parietal and occipital lobes of the cerebral cortex. The cingulum bundle projects from the cingulate gyrus to the entorhinal cortex and allows both input and output to cingulate gyrus in the limbic system (Wakana et al., 2004). The findings of the present study suggest that life-long aerobic exercise may preserve brain network of front-and-back connections related to visuospatial function, motor control and coordination. This contention is supported by the positive relationship between VO_{2max} and FA in the left SLF and left ILF observed in the present study (Fig. 4). In addition, life-long aerobic exercise may preserve white matter integrity related to memory function as suggested by the lower MD in the CH.

A previous study using functional magnetic resonance imaging (fMRI) to investigate the effects of aerobic training on brain networks in older adults reported increased functional connectivity between frontal, posterior, and temporal lobes and that the improvement was associated with enhanced executive function (Voss et al., 2010). Similarly, a recent fMRI study (Rosano et al., 2010) examining the effect of a 1-year walking program on psychomotor processing speed in 30 older adults reported that those who were physically active showed better brain activations than their sedentary counterparts in the dorsolateral prefrontal cortex (Brodmann area 9), which is associated with motor planning, organization, and executive function. Furthermore, a one-year exercise intervention study reported the positive association between improved aerobic fitness and changes in WM integrity in the frontal and temporal lobes (Voss et al., in press). These observations highlighted the significance and potential role of exercise in brain aging not only at the structural, but also at the functional level.

Potential mechanisms of effects of exercise on brain health

Although it is undetermined via what mechanism(s) exercise protects the brain from its normal aging process, a growing body of evidence suggests that one of the factors may be brain derived neurotrophic factor (BDNF) (Pedersen, 2009; Seifert et al., 2010). These investigators report that during dynamic exercise BDNF is produced in the exercising muscle and in the brain tissue; and the BDNF emanating from the exercising muscle acts as a myokine, while the BDNF produced in the brain has paracrine or autocrine effects (Rasmussen et al., 2009).

The dogma of "use it or lose it" or activity-dependent neural plasticity is supported by studies in individuals who had an enlarged regional brain volume associated with either long-term, repeated stimuli or training in particular areas (Gaser and Schlaug, 2003). In addition, our pilot work suggests that life-long exercise may have protective effects on age-related brain volume loss in the regions related to motor control, visuospatial function, and working memory (Tseng et al., in press).

Johnson and colleagues studied 26 community dwellers between the age of 60 and 69 and reported a positive correlation between aerobic fitness and FA primarily in the corpus callosum (Johnson et al., 2012). Using a tractography method, they further reported that the portions of the corpus callosum associated with aerobic fitness involved those interconnecting frontal regions associated with high-level motor planning and concluded that physical activity may attenuate age-related myelin declines involved in motor planning. However, we were unable to confirm these observations in highly screened healthy control subjects and Masters athletes, suggesting that regional FA may be modulated by other factors besides physical activity.

Study limitations

This study was based on a small, but unique sample size. Thus, the results must be interpreted with caution. However, by utilizing the FLAIR and DTI techniques in carefully screened healthy subjects, we were able to detect differences in white matter integrity between Masters athletes and their sedentary counterparts. The findings of the present study are consistent with the emerging literature supporting the notion that exercise is beneficial to brain health.

Given the limitation of a cross-sectional study design, differences in the WM integrity observed in Masters athletes may not be solely attributed to exercise training. Many uncontrolled genetic and lifestyle factors may have an impact on our findings. Nonetheless, we implemented a stringent screening protocol to control for potential cardiovascular confounding factors and have matched sex, age and educational levels to the best of our ability to minimize the influence of potential confounding factors. Notably, our control group was healthier than average community dwellers of similar age regardless of the sedentary lifestyle. It is possible that the differences in WM integrity might be even greater had the comparisons been made between Masters athletes and a population-based sample of older adults.

We did not administer specific tests designed to measure motor function and thus cannot infer if the higher FA values observed in Masters athletes can be translated to superior motor control than their sedentary counterparts as it might be expected. In this regard, future studies using fMRI in combination with comprehensive cognitive function assessments in a larger sample size study may provide further insights.

Conclusion

This was the first MRI study of Masters athletes to reveal potential relationship between life-long aerobic exercise and brain white matter integrity. Our data suggest that life-long exercise may preserve age-related changes in brain WM integrity by demonstrating 1) lower deep WMH volume, and 2) higher white matter microstructural integrity as assessed by FA and MD in the regions related to motor and memory function as well as the front-and-back network connections in the brain in Masters athletes relative to sedentary older adults. These findings suggest the potential salutary effects of physical activity on brain health in older adults.

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Conflict of interest

The authors have no financial conflict of interest to disclose. A portion of this study was presented in the Alzheimer's Association International Conference in Vancouver, BC in July 2012. The content of this manuscript is solely the responsibility of the authors.

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