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White matter integrity in physically fit older adults☆

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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