Journal of Alzheimer's Disease 61 (2018) 729–739
DOI 10.3233/JAD-170415
IOS Press

Cardiorespiratory Fitness and White Matter Neuronal Fiber Integrity in Mild Cognitive Impairment

Kan Ding[a,1], Takashi Tarumi[a,e,1], David C. Zhu[g], Benjamin Y. Tseng[b,e], Binu P. Thomas[c], Marcel Turner[e], Justin Repshas[e], Diana R. Kerwin[f], Kyle B. Womack[a,d], Hanzhang Lu[c], C. Munro Cullum[a,d] and Rong Zhang[a,b,e,*]

[a]*Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, TX, USA*
[b]*Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA*
[c]*Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, TX, USA*
[d]*Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA*
[e]*Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas, Dallas, TX, USA*
[f]*Texas Alzheimer's and Memory Disorders, Texas Health Presbyterian Hospital Dallas, Dallas, TX, USA*
[g]*Departments of Radiology and Psychology, and Cognitive Imaging Research Center, Michigan State University, East Lansing, MI, USA*

Handling Associate Editor: Jack de la Torre

Accepted 26 September 2017

Abstract.
Background: Mounting evidence showed the self-reported levels of physical activity are positively associated with white matter (WM) integrity and cognitive performance in normal adults and patients with mild cognitive impairment (MCI). However, the objective measure of cardiorespiratory fitness (CRF) was not used in these studies.
Objective: To determine the associations of CRF measured by maximal oxygen uptake (VO_2max) with WM fiber integrity and neurocognitive performance in older adults with MCI.
Methods: Eighty-one participants (age = 65 ± 7 years, 43 women), including 26 cognitively normal older adults and 55 amnestic MCI patients, underwent VO_2max test to measure CRF, diffusion tensor imaging (DTI) to assess WM fiber integrity, and neurocognitive assessment focused on memory and executive function. DTI data were analyzed by the tract-based spatial statistics and region-of-interest approach.
Results: Cognitively normal older adults and MCI patients were not different in global WM fiber integrity and VO_2max. VO_2max was associated positively with DTI metrics of fractional anisotropy in ∼54% WM fiber tracts, and negatively with mean and radial diffusivities in ∼46% and ∼56% of the WM fiber tracts. The associations of VO_2max with DTI metrics remained statistically significant after adjustment of age, sex, body mass index, WM lesion burden, and MCI status. The DTI metrics obtained from the area that correlated to VO_2max were associated with executive function performance in MCI patients.

[1]These authors contributed equally to this work.

[*]Correspondence to: Rong Zhang, PhD, 7232 Greenville Avenue, Dallas, TX 75231, USA. Tel.: +1 214 345 8843; Fax: +1 214 345 4618; E-mail: RongZhang@TexasHealth.org.

ISSN 1387-2877/18/$35.00

Conclusions: Higher levels of CRF are associated with better WM fiber integrity, which in turn is correlated with better executive function performance in MCI patients.

Keywords: Cardiorespiratory fitness, executive function, mild cognitive impairment, white matter

INTRODUCTION

Alzheimer's disease (AD) currently lacks effective treatment; therefore, identification of modifiable risk factors is critical for AD prevention [1]. Amnestic mild cognitive impairment (MCI) is considered as an intermediate phase between age-related cognitive decline and AD, and may represent a critical time window for implementing prevention strategies to attenuate or delay cognitive decline [2].

White matter (WM) fiber integrity, as assessed by MRI diffusion tensor imaging (DTI), is correlated with cognitive performance [3] and is sensitive to WM fiber damage [4]. DTI studies in AD have observed WM fiber damage in widespread brain regions, most notably in the frontal and temporal lobes, the posterior cingulum, the corpus callosum (CC), the superior longitudinal fasciculus (SLF), and the uncinate fasciculus (UF) related to the memory and executive function [5, 6]. Similar observations are reported in MCI patients; however, findings in MCI are inconsistent, most likely due to the heterogeneity of MCI population [5].

Mounting evidence indicates that 1) individual levels of physical activity or cardiorespiratory fitness (CRF) are associated positively with WM integrity and cognitive performance in normal older adults and patients with MCI [7–10]; 2) regular exercise may improve cognitive performance [11, 12]. However, these studies are relied mainly on the self-reported physical activity questionnaires that may not reflect objective measurements of CRF.

The purpose of this study was to examine the relationships between objective measure of CRF, WM fiber integrity, and cognitive performance in MCI patients. Maximal oxygen uptake (VO_2max), the "gold-standard" measurement of CRF [13], was used to quantify the level of physical fitness [14], and DTI metrics was used to assess white matter integrity. We hypothesized that there are positively correlations between VO_2max, WM fiber integrity, and cognitive performance in MCI patients.

MATERIALS AND METHODS

Participants

Fifty-five participants with amnestic MCI and 26 cognitively normal older adults who were similar in age and sex were recruited through community-based advertisement and the University of Texas Southwestern Medical Center Alzheimer's Disease Center. The diagnosis of amnestic MCI was based on Petersen criteria [2], as modified by the Alzheimer's Disease Neuroimaging Initiative project (http://adni-info.org). Specifically, we used a global Clinical Dementia Rating scale of 0.5 with a score of 0.5 in the memory category, objective memory loss as indicated by education-adjusted scores on the Logical Memory subtest of the Wechsler Memory Scale-Revised immediate and delayed recalls, and a Mini-Mental State Examination (MMSE) score between 24 and 30 [15]. Further clinical evaluation of MCI was performed based on the recommendations from the Alzheimer's Disease Cooperative Study Diagnostic Criteria (http://adni-info.org).

Inclusion criteria were men and women aged 55–80 years who were diagnosed with amnestic MCI or judged to be cognitively normal. Medical conditions with potential impact on cardiorespiratory function and white matter integrity were excluded from this study. Exclusion criteria included major neurologic, vascular, or psychiatric disorders, uncontrolled hypertension, clinically diagnosed or self-reported diabetes mellitus, sleep apnea, body mass index (BMI) $\geq$35 kg/m^2, current or a history of smoking. Individuals with a pacemaker or any metals in their body were excluded as were subjects with a physically active lifestyle (defined as participation in moderate intensity aerobic exercise training over the past two years for 3 times per week with each session lasting >30 min). Screening procedures included a detailed medical history and medication questionnaire, a comprehensive physical examination, 12-lead electrocardiogram (ECG), echocardiography, carotid artery ultrasound to exclude severe stenosis (>50%), and 24-h ambulatory blood pressure monitoring. Group

Table 1
Demographics and neuropsychological performance in cognitively normal adults and MCI patients

	Normal	MCI	*p*-value
n (%women)	26 (50)	55 (55)	0.30
Age (y)	66 ± 7	65 ± 6	0.35
Education (y)	16 ± 2	16 ± 2	0.67
Height (cm)	171 ± 8	168 ± 9	0.19
Body mass (kg)	79 ± 15	78 ± 16	0.84
Body mass index (kg/m^2)	27 ± 4	27 ± 4	0.56
Whole brain volume (l)	1.57 ± 0.17	1.52 ± 0.16	0.23
24-h Ambulatory BP Monitoring Parameters			
Heart rate (bpm)	73 ± 9	71 ± 11	0.41
Systolic BP (mmHg)	131 ± 11	130 ± 12	0.62
Diastolic BP (mmHg)	76 ± 9	73 ± 8	0.19
Pulse pressure (mmHg)	55 ± 7	56 ± 10	0.56
Mean arterial pressure (mmHg)	94 ± 9	92 ± 9	0.28
Cardiorespiratory Fitness Parameters			
VO_2max (ml/kg/min)	24.1 ± 5.5	23.6 ± 5.6	0.73
Heart rate at VO_2max (bpm)	163 ± 11	160 ± 16	0.53
RER at VO2max (ratio)	1.17 ± 0.09	1.18 ± 0.11	0.72
Lactate at VO_2max (mmol/l)	7.2 ± 2.5	7.6 ± 2.3	0.38
Global White Matter Integrity			
Fractional anisotropy	0.42 ± 0.01	0.41 ± 0.02	0.58
Mean diffusivity ($\times 10^{-3}$ mm^2/sec)	0.73 ± 0.03	0.73 ± 0.02	0.58
Radial diffusivity ($\times 10^{-3}$ mm^2/sec)	0.55 ± 0.03	0.55 ± 0.02	0.54
Axial diffusivity ($\times 10^{-3}$ mm^2/sec)	1.10 ± 0.04	1.10 ± 0.04	0.86
White matter hypointensity volume (%ICV)	1.41 ± 1.6	1.89 ± 1.6	0.10
Neuropsychological Testing Measures			
Global Function			
Mini-Mental State Exam	29 ± 1	29 ± 1	0.70
Montreal Cognitive Assessment	27 ± 2	25 ± 3	**<0.01**
Executive Function			
Trail Making Test B	64 ± 18	77 ± 28	**0.03**
Trail Making Test B-A	36 ± 19	50 ± 23	**0.01**
Digit Span Backward	7 ± 2	6 ± 2	0.11
Wisconsin Card Sorting Test	52 ± 14	57 ± 20	0.24
Letter Fluency	39 ± 8	39 ± 10	0.86
Episodic Memory			
CVLT Long Delay Free Recall	12 ± 3	10 ± 3	**0.001**
CVLT Total Score	52 ± 10	47 ± 9	**0.02**

Values are mean ± standard deviation. $p < 0.05$ are bolded. BP, blood pressure; ICV, intracranial volume; CVLT, California Verbal Learning Test; RER, respiratory exchange ratio. Neuropsychological testing measures were presented as raw score except for Wisconsin Card Sorting test and CVLT total score which were T-score.

demographics and clinical features are presented in Table 1.

All subjects signed the informed consent approved by the Institutional Review Boards of University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital of Dallas. All the collected data were de-identified prior to further analysis and blinded for outcome measures.

Magnetic resonance imaging (MRI)

All MRI data were acquired by a 3-Telsa scanner (Philips Medical System, Best, The Netherlands) using a body coil for radiofrequency transmission and an 8-channel head coil with parallel imaging capability for signal reception.

DTI was acquired by a single-shot echo-planar-imaging (EPI) sequence with a sensitivity encoding (SENSE) parallel imaging scheme (reduction factor = 2.2). The imaging matrix was 112 × 112 with field of view (FOV) = 224 × 224 mm^2 (nominal resolution of 2 mm), which was filled to 256 × 256. Axial slices of 2.2 mm thickness (no gap) were acquired parallel to the anterior-posterior commissure line. A total of 65 slices covered the entire hemisphere and brainstem. Echo Time (TE)/Repetition Time (TR) was 51/5630 ms. Diffusion weighting was encoded along 30 independent orientations with the b-value

of 1000 s/mm^2. The scan duration was 4.3 min. Automated image registration was performed on the raw diffusion images to correct distortions caused by motion artifacts or eddy currents. DTI data was acquired twice in each subject to improve signal-to noise ratio (SNR) by averaging the scans.

FMRIB Software Library (FSL, https://surfer.nmr.mgh.harvard.edu/fswiki) was used to preprocess the DTI data and run voxelwise statistics. First, data from both DTI scans were merged in temporal order, corrected for eddy currents and head motion, and averaged over scans to increase signal-to-noise ratio. Next, a brain mask was created using the Brain Extraction Tool (BET) from FSL to delete non-brain tissue and the diffusion tensor was calculated by the DTIFIT [16]. Individual images with fractional anisotropy (FA), mean (MD), radial (RD), and axial (AxD) diffusivities were visually inspected and analyzed by voxelwise and regional-of-interest (ROI) statistics.

Tract-based spatial statistics (TBSS) was used to perform voxelwise statistic [17]. First, individual FA images were eroded slightly to remove outliers and registered non-linearly into the *JHU-ICBM-FA* template as a common space in order to correspond the results from voxelwise and ROI analyses [18]. Next, the group mean FA image was created and thinned to generate a mean FA skeleton which represents the centers of all tracts common to all subjects within the group. We then set a threshold for voxels with FA value greater than 0.20 to minimize partial volume effects from gray matter and cerebrospinal fluid. Finally, individual MD, RD, and AxD images were transformed into this skeleton space, by applying the parameters from the normalization of the FA image to the template space. The resulting MD, RD, AxD, and FA skeleton maps were then fed into voxelwise and ROI-based group statistics. ROI analysis limited to the TBSS skeleton was performed using the deep WM atlas (*ICBM-DTI-81 White-Matter Atlas*) [18].

T1-weighted high-resolution image was acquired by 3D magnetization-prepared-rapid-acquisition-of-gradient-echo (MPRAGE) sequence using the following parameters [19]: TE/TR = 3.7/8.1 ms, flip angle = 12°, FOV = 256 × 256 mm, number of slices = 160 (no gap), resolution = 1 × 1 × 1 mm^3, SENSE factor = 2, and scan duration = 4 min. Brain tissue volumes were calculated by the FreeSurfer (http://ftp.nmr.mgh.harvard.edu). WM lesion volume was estimated by the volume of hypointensity signals and normalized to intracranial volume [20]. The reproducibility of DTI and brain tissue volume measurements with T1-weighted image have been documented in previous studies [21].

Maximal oxygen uptake (VO_2max)

VO_2max was measured on a treadmill using a modified Astrand-Saltin protocol [22]. The treadmill grade was increased by 2% every 2 min until exhaustion while subjects walked, jogged, or ran at a fixed speed. The speeds were selected based on the individual subject's cardiorespiratory fitness level, which was assessed via a submaximal exercise test conducted prior to VO_2max testing [8]. VO_2 was measured during the second minute of each stage using the Douglas bag method, and breath-by-breath VO_2 was also monitored continuously using an online computer system. Gas fractions were analyzed by mass spectrometry (Marquette MGA 1100) and ventilatory volume was measured by a Tissot spirometer. Exercise blood pressure, 12-lead ECG, and heart rate (HR) were monitored continuously by a registered nurse or a board-certified cardiologist. Lactate concentration at maximal exercise intensity was measured by finger stick (Yellow Springs Instruments (YSI) 23L, Yellow Spring, OH). Mass spectrometry and gas sampling system were calibrated before each test to ensure measurement accuracy and reliability.

VO_2max was defined as the highest VO_2 measured from $a > 30$-s Douglas bag during the last stage of testing. The criteria to confirm that VO_2max was achieved included an increase in VO_2 <150 ml despite increasing work rate of 2% grade, a respiratory exchange ratio ≥ 1.1, and HR within 5 beats/min of age-predicted maximal values. In all cases, at least two of these criteria were achieved, confirming the identification of VO_2max based on the American College of Sports Medicine guidelines [23]. In cases in which a subject did not meet at least two of these criteria, they were brought in to repeat testing a minimum of one week after the original test. Of note, our previous studies have demonstrated that by using these methods, VO_2max can be measured reliably in sedentary elderly subjects [8, 14, 24].

Neuropsychological test

Neuropsychological assessment focused on executive function and episodic memory was administered and scored by a trained psychometrician. Executive function was assessed using scores from the Trail Making Test (Part B total time and total time of Trails A subtracted from Trail B- TMT B-A), Digit

Span Backward (total correct), Letter Fluency (FAS total), and the Wisconsin Card Sorting Test (WCST) (total perseverative responses). Episodic memory was assessed with long delayed free recall and total learning scores from the California Verbal Learning Test and delayed recall from the Wechsler Memory Scale-III Visual Reproduction subtest. Global cognitive function was assessed with the MMSE and the Montreal Cognitive Assessment.

Statistical analysis

Cognitively normal older adults and MCI subjects were compared by independent *t*-test. TBSS was used to perform voxelwise correlation analysis of VO_2max and DTI metrics in all subjects. In TBSS, multiple comparisons were corrected by threshold-free cluster enhancement with 5,000 permutations [25]. The corrected statistical maps were threshold by $p < 0.05$. Subsequently, individual mean values of DTI metrics were extracted from the significant voxels identified by TBSS and analyzed by multiple linear regression. In multiple linear regression analysis, we examined whether VO_2max explains the variability of FA, MD, and RD after adjusting for age, sex, BMI, WM lesion burden, and MCI status. To explore the association between neuropsychological measures and FA, MD, and RD, we used partial correlation, including age, sex, and education as covariates. Because neuropsychological performance was different between the groups, we conducted this analysis separately in normal subjects and MCI patients. Data normality was checked by the Shapiro-Wilk test and the visual inspection of histogram and Q-Q plots. All data are reported as mean ± standard deviation. Statistical significance was set *a priori* at $p < 0.05$. Statistical analyses were performed using SPSS 20 (IBM Inc.; Chicago, IL).

RESULT

Subject demographics

Cognitively normal older adults and MCI patients were similar in age and educational level (Table 1). MCI subjects showed lower performance on Montreal Cognitive Assessment, memory, and executive function tests including CLVT delayed recall and TMT part B relative to normal older adults ($p < 0.05$); however, the scores on MMSE, WCST's perseverative response, letter fluency, and backward digit span were not different. Global WM integrity, as measured by DTI metrics extracted from the whole brain TBSS WM skeletons and lesion volume, whole brain volume, and VO_2max were not different between normal older adults and MCI patients ($p > 0.05$) (Table 1).

VO_2max and DTI metrics

TBSS showed that VO_2max is associated positively with FA in ∼54% tracts, negatively with MD, RD, and AxD in ∼46%, ∼56%, and ∼5% of the WM fiber tracts (Fig. 1A, Table 2). Anatomically, these voxels were located in the CC, UF, SLF subcomponent I (SLF I), and cingulum (Table 2). Figure 1B shows the scatter plots of VO_2max with FA, MD, RD, and AxD extracted from the significant WM skeletons.

Results from multiple linear regression analysis are summarized in Table 3. After adjustment for age, sex, BMI, and WM lesion volume, VO_2max explained an additional 9% variance of FA, 3% variance of MD, and 4% variance of RD. Of note, MCI status also showed statistically significant influences on MD and RD after accounting for the covariates.

DTI metrics and neuropsychological performance

Table 4 summaries the results of partial correlation between cognitive performance and DTI metrics that were extracted from the areas correlated with VO_2max. In all subjects, FA positively, and MD and RD were negatively correlated with the performance on several aspects of executive function as assessed by TMT part B, TMT part B-A, letter fluency, and backward digit span (partial correlation coefficients ranged between 0.30 to 0.40; $p < 0.05$). Of note, these correlations were observed primarily in patients with MCI.

DISCUSSION

The main findings from this study are that 1) VO_2max, an objective assessment of CRF, is positively correlated with WM fiber integrity in older adults who have normal cognitive function or MCI; and 2) WM fiber integrity is also positively correlated with executive function, especially in MCI patients. These findings suggest that maintenance or improvement of CRF in older age may delay or slow cognitive decline even in those who have high risk of AD.

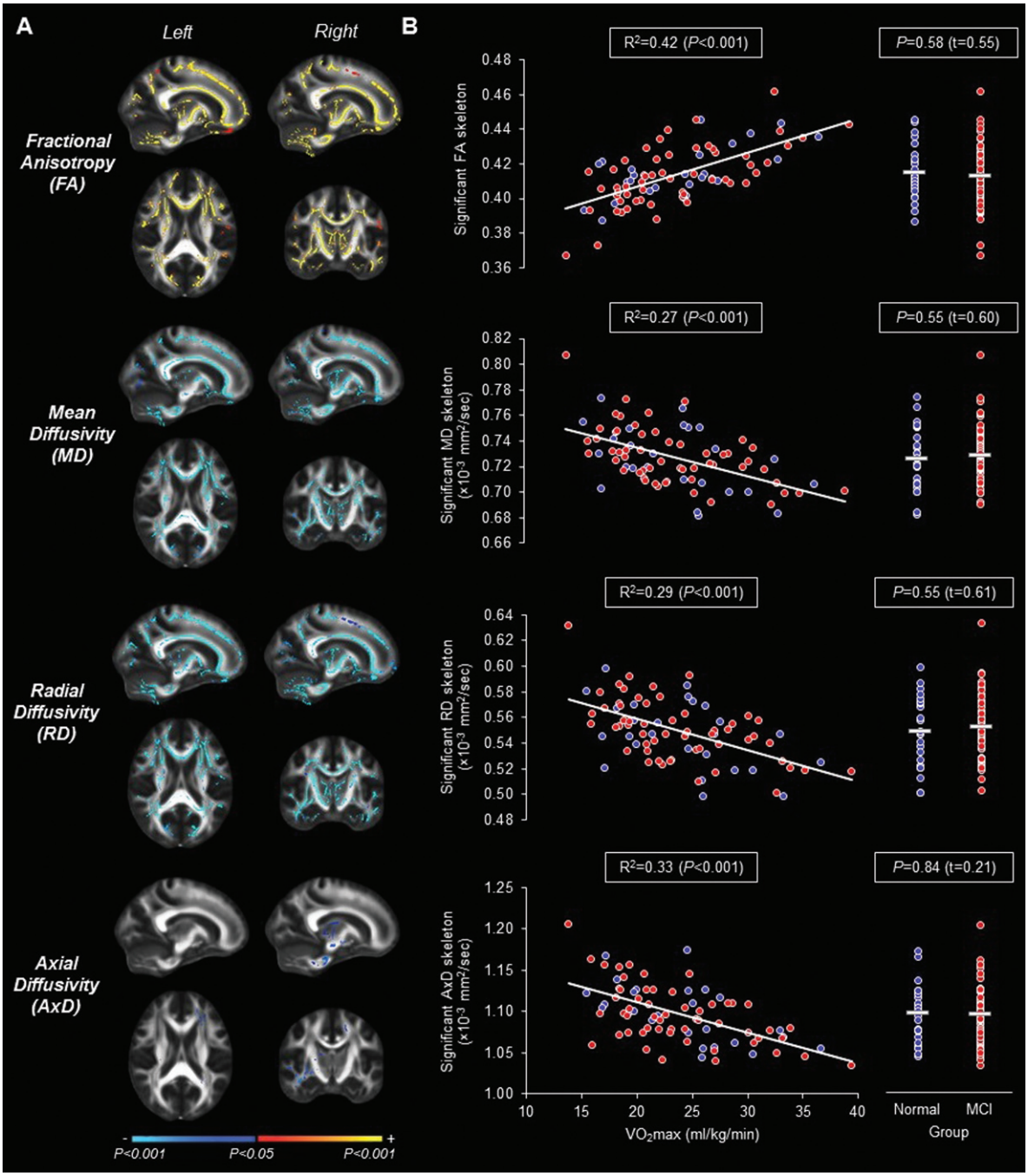

Fig. 1. Association between VO_2max and DTI metrics in cognitively normal adults and mild cognitive impairment (MCI) patients. A) Tract-based spatial statistic maps exhibiting the association between diffusion metrics and maximal oxygen uptake (VO_2max) in older adults with normal cognitive function or mild cognitive impairment. The color bar illustrates the directionality and *p*-value of the associations. B) Scatter plots show the correlations of diffusion metrics with VO_2max (blue: normal and red: MCI). Diffusion metrics were extracted from the significant WM skeletons shown by panel A. Horizontal lines represent mean values for each group.

Current literature suggests that increase in CRF may improve WM microstructural integrity in cognitively normal older adults [7, 8]. Our prior study in the Masters Athletes showed an 83% reduction in the volume of deep WM lesions and higher FA values in the right superior corona radiate, both sides of the SLF,

Table 2
Anatomical location and voxel count of subcortical white matter skeleton that associated with maximal oxygen uptake

White matter fibers	FA (%)	MD (%)	RD (%)	AxD (%)
Commissural Fibers				
Genu of corpus callosum	1, 773 (95)	1, 181 (63)	1, 751 (94)	0 (0)
Body of corpus callosum	2, 820 (85)	2, 190 (66)	2, 729 (83)	0 (0)
Splenium of corpus callosum	1, 116 (50)	1, 612 (72)	1, 461 (65)	2 (0)
Tapetum	81 (48)	148 (88)	140 (83)	11 (7)
Projection Fibers				
Anterior corona radiata	2, 484 (78)	2, 395 (75)	2, 807 (88)	364 (11)
Superior corona radiata	1, 550 (54)	1, 889 (66)	1, 953 (69)	195 (7)
Posterior corona radiata	677 (44)	921 (60)	953 (62)	0 (0)
Anterior limb of internal capsule	1, 084 (75)	590 (41)	960 (67)	0 (0)
Posterior limb of internal capsule	1, 424 (76)	1, 088 (58)	1, 415 (75)	245 (13)
Retrolenticular part of internal capsule	631 (42)	771 (52)	779 (52)	235 (16)
Posterior thalamic radiation	827 (45)	726 (39)	947 (51)	26 (1)
Cerebral peduncle	962 (89)	669 (62)	927 (86)	201 (19)
Association Fibers				
Superior longitudinal fasciculus	1, 497 (43)	1, 768 (51)	1, 949 (56)	88 (3)
Superior fronto-occipital fasciculus	178 (86)	84 (41)	182 (88)	0 (0)
Uncinate fasciculus	95 (92)	94 (91)	97 (94)	33 (32)
Sagittal stratum	580 (45)	643 (50)	706 (55)	239 (19)
External capsule	1, 769 (61)	1, 552 (54)	1, 830 (63)	167 (6)
Cingulum	514 (54)	543 (57)	729 (77)	0 (0)
Fornix	506 (55)	320 (35)	434 (47)	112 (12)
Tracts in the Brainstem				
Corticospinal tract	505 (68)	443 (60)	571 (77)	124 (17)
Superior cerebellar peduncle	321 (72)	271 (61)	312 (70)	0 (0)
Middle cerebellar peduncle	2, 137 (74)	2, 126 (73)	2, 365 (81)	331 (11)
Inferior cerebellar peduncle	351 (79)	135 (30)	300 (67)	0 (0)
Medial lemniscus	273 (87)	198 (63)	261 (83)	0 (0)

Voxel counts were calculated based on Fig. 1A. The numbers in percentage represent the proportion of significant voxels relative to the whole white matter fiber tract. Each voxel is 1 mm^3. FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; AxD, axial diffusivity.

the right inferior fronto-occipital fasciculus, and the left inferior longitudinal fasciculus relative to sedentary older adults [8]. The Lothian Birth Cohort 1936, a longitudinal study of aging, also reported that higher level of self-reported physical activity was associated with higher FA in 12 major WM fiber tracts, normal-appearing WM volumes, less gray matter atrophy, and lower WM lesion load in adults in their 70 s [26]. Similar findings were also reported in older adults with cerebral small-vessel disease [7], seniors (older than 80 years) with multiple cardio-metabolic conditions and physical function limitations [27], and in cognitive healthy, middle-aged adults (between 40 and 65 years) with a positive family history for AD and positive apolipoprotein E4 (APOE4) [28].

The present study extended this line of literature by focusing on MCI patients who had a sedentary lifestyle, but otherwise healthy and without significant cardiovascular risk factors. While age, sex, and WM lesion burden are the major factors for the observed individual differences in WM fiber integrity, lower VO_2max contributed to an additional 9% reduction of FA and 4% elevation of RD in older adults including MCI patients. While FA provides an index of overall tissue microstructural integrity, alterations in RD, a measure of water molecule diffusion perpendicular to the WM fibers, are likely to reflect myelin integrity [29]. Thus, our data suggest that high level of CRF may delay or slow myelin deterioration and maintain WM integrity in older adults including MCI patients. Conversely, low level of CRF may accelerate WM damage and cognitive decline which should be monitored closely for further deterioration. Future clinical trials of increases in physical activity such as aerobic exercise training are needed to validate the benefit of high CRF in maintaining WM integrity.

Similar to the observations in AD, MCI is associated with reduced FA and increased MD in the temporal regions, the hippocampus, the posterior cingulum, the genu and the splenium of the CC when compared to cognitively normal controls [5, 6, 30]. The increased axial and mean diffusivity in mesial parietal/splenial white matter may be the early abnormalities to occur, but increased RD and decreased FA in the splenium of the CC is likely correlated

Table 3
Hierarchical multiple regression analysis of WM diffusion metrics

Model	Variable	β ± SE	(*p*-value)	ΔModel R^2	(*p*-value)
Dependent variable: Fractional anisotropy					
1	Age	–0.22 ± 0.10	**(0.03)**	0.43	(**<0.001**)
	Sex	–0.36 ± 0.09	(**<0.001**)		
	Body mass index	–0.18 ± 0.09	(0.06)		
	WM lesion volume	–0.37 ± 0.11	**(0.001)**		
2	MCI status	–0.14 ± 0.09	(0.13)	0.02	(0.13)
3	VO_2max	0.47 ± 0.12	(**<0.001**)	0.09	(**<0.001**)
Dependent variable: Mean diffusivity					
1	Age	0.36 ± 0.10	(**<0.001**)	0.50	(**<0.001**)
	Sex	0.23 ± 0.08	(**<0.01**)		
	Body mass index	0.03 ± 0.09	(0.75)		
	WM lesion volume	0.42 ± 0.10	(**<0.001**)		
2	MCI status	0.18 ± 0.08	**(0.03)**	0.03	**(0.03)**
3	VO_2max	–0.26 ± 0.12	**(0.03)**	0.03	**(0.03)**
Dependent variable: Radial diffusivity					
1	Age	0.37 ± 0.10	(**<0.001**)	0.48	(**<0.001**)
	Sex	0.23 ± 0.08	(**<0.01**)		
	Body mass index	0.06 ± 0.09	(0.51)		
	WM lesion volume	0.39 ± 0.10	(**<0.001**)		
2	MCI status	0.17 ± 0.08	**(0.04)**	0.03	**(0.04)**
3	VO_2max	–0.32 ± 0.12	(**<0.01**)	0.04	(**<0.01**)

WM diffusion metrics were extracted from the significant skeleton voxels shown by Fig. 1A. $p < 0.05$ are bolded. WM lesion volume was log-transformed before analysis. β, standardized beta coefficient; MCI, mild cognitive impairment; VO_2max, maximal oxygen uptake; WM, white matter.

Table 4
Partial correlations between white matter diffusion metrics and neuropsychological performance in all, normal, and MCI subjects

	Fractional Anisotropy			Mean Diffusivity			Radial Diffusivity		
	All	Normal	MCI	All	Normal	MCI	All	Normal	MCI
Trail Making Test B	–0.36	–0.19	–0.38	0.34	0.38	0.32	0.36	0.28	0.38
	(**<0.01**)	(0.40)	(**0.01**)	(**<0.01**)	(0.08)	(**0.03**)	(**<0.01**)	(0.21)	(**0.01**)
Trail Making Test B-A	–0.30	–0.16	–0.32	0.28	0.21	0.29	0.28	0.12	0.32
	(**0.01**)	(0.49)	(**0.03**)	(**0.02**)	(0.34)	(0.06)	(**0.02**)	(0.59)	(**0.04**)
Digit Span Backward	0.31	0.19	0.33	–0.29	0.05	–0.37	–0.31	–0.06	–0.36
	(**0.01**)	(0.40)	(**0.03**)	(**0.02**)	(0.82)	(**0.01**)	(**0.01**)	(0.77)	(**0.02**)
Wisconsin Card Sorting Test	0.21	0.06	0.28	–0.26	0.03	–0.41	–0.25	<0.01	–0.39
	(0.09)	(0.78)	(0.07)	(**0.03**)	(0.90)	(**<0.01**)	(**0.04**)	(0.98)	(**0.01**)
Letter Fluency	0.33	0.42	0.29	–0.33	–0.26	–0.33	–0.36	–0.29	–0.35
	(**<0.01**)	(0.05)	(0.06)	(**<0.01**)	(0.25)	(**0.03**)	(**<0.01**)	(0.19)	(**0.02**)
CVLT Long Delay Free Recall	0.16	0.26	0.08	–0.17	–0.22	–0.11	–0.16	–0.17	–0.13
	(0.19)	(0.25)	(0.60)	(0.17)	(0.32)	(0.49)	(0.19)	(0.46)	(0.42)
CVLT Total Score	0.09	0.32	–0.05	–0.09	–0.13	0.01	–0.12	–0.14	–0.05
	(0.45)	(0.14)	(0.77)	(0.44)	(0.55)	(0.93)	(0.34)	(0.54)	(0.77)

Values are partial correlation coefficients and (*p*-values). $p < 0.05$ are bolded. Age, sex, and years of education were entered as covariates. DTI metrics were extracted from the significant white matter skeleton voxels that associated with VO_2max, as shown by Fig. 1A. CVLT, California Verbal Learning Test; MCI, mild cognitive impairment.

with dementia severity [31]. However, in the present study, we did not find group differences in both the global and voxelwise-based analysis of DTI metrics between MCI and healthy older adults. This discrepancy with previous studies is likely due to the selected cohort of early stage MCI subjects in the present study who were otherwise healthy and only had mild cognitive decline (mean MMSE score of 29, no group differences between normal older adults and MCI). However, we did find that even in this mild MCI cohort, MCI status contributed to an additional 3% elevation of MD and RD after adjustment for age, BMI, sex, and WM lesion burden in those WM tracts correlated with VO_2max (Table 3). These findings are consistent with the report that neurocognitive deficits at the early stage of AD are associated with WM fiber abnormalities [30, 32, 33].

In this study, we found strong associations between VO_2max and DTI metrics (FA, RD, and MD) in the genu of CC, UF, SLF I, and cingulum. The CC is the

major inter-hemispheric commissure that connects most of the neocortical areas. Fibers from the prefrontal and inferior frontal areas course through the rostrum and genus of the CC [34]. The UF connects the anterior temporal lobe with the medial and orbital prefrontal cortex [34]. The cingulum bundle stretches from the frontal lobe around the rostrum and the genu of the CC and lies in the WM of the parahippocampal gyrus [34]. SLF I links the superior parietal lobule and the superior frontal gyrus, and projects to the supplementary motor area, dorsal area 6, and area 9 [34]. Alterations to the integrity of these cortico-cortical association fiber tracts between the frontal lobes and other brain regions contribute to impaired executive performance observed in both rhesus monkeys and human subjects [3, 35, 36]. Our correlational analyses between DTI metrics and neuropsychological performance are consistent with these findings. We also observed that the correlation between the DTI metrics and executive function performance was stronger in MCI than cognitively normal older adults (Table 4). These findings suggest that the underlying AD process in MCI may result in aspects of executive performance becoming more susceptible to WM structural deteriorations [37].

The underlying mechanism(s) by which physical activity protects WM structural integrity leading to improvement in neurocognitive function are not well understood. A growing body of evidence suggests that attenuation of cardiovascular aging associated with increases in physical activity may be one mechanism. For example, increases in physical activity are associated with reduced carotid artery stiffness and improved brain perfusion and executive performance [38]. In addition, age-related elevation in central artery stiffness and pulse pressure has been shown to be associated positively with cerebral blood flow pulsatility and WM lesion volume which may be reversed with aerobic exercise training [39–42]. Further, Tarumi et al. have demonstrated that the decreases in FA and elevations in RD are associated with central arterial stiffening and reduced baroreflex sensitivity in many brain regions, suggesting a link between cardiovascular and brain health [43].

These potential underlying vascular mechanisms linking physical activity and WM integrity are consistent with extensive studies which indicate that the presence of cardiovascular disease risk factors is related to brain hypoperfusion which in turn may affect brain metabolic homeostasis and toxic protein clearance leading to neuronal damage, cognitive decline, and AD [44]. In this regard, neuroimaging studies have shown that brain hypoperfusion in the mediotemporal area, the posterior percuneus, and the associative fronto-temporal-parietal regions predict progressive cognitive decline in MCI [44–46]. In addition, both animal and human studies have shown that aerobic exercise stimulates the release of muscle-derived angiogenic growth factors such as vascular endothelial growth factor which may reach the brain via the circulation and increase brain capillary density via angiogenesis and lead to improvement in brain perfusion and function [47–49].

This study was strengthened by the measurement of VO_2max to investigate the associations between CRF and brain WM integrity in MCI patients. Further, the study population was screened rigorously to exclude neurological and psychiatric disorders, cardio- and cerebrovascular diseases, and other potential confounding variables which may influence the CRF-WM integrity relationship [50]. There are several limitations in the current study. First, this study is a cross-sectional study which limits the understanding of causality. Second, the present study was based on a relatively small sample size of sedentary older adults including MCI patients. Thus, the result may not be applicable to the general population. Finally, the data interpretation of WM integrity relied on the mechanisms and validity of DTI, an indirect assessment of WM microstructural integrity. In a setting of aging and associated brain atrophy, the influence of extracellular free water on the mapping of diffusion MRI should be considered in data interpretation [51, 52].

Conclusions

This study indicates that the level of VO_2max, an objective measure of cardiorespiratory fitness, is associated positively with WM fiber integrity measured with MRI diffusion tensor imaging, and several aspects of executive function performance in patients with amnestic MCI. These findings support the hypothesis that physical activity, which can improve physical fitness even in old age, may have protective effects on WM neuronal fiber integrity in older adults who have high risk for AD.

ACKNOWLEDGMENTS

The authors would like to thank study participants for their time and effort and the technical support by the staff at the Institute for Exercise and Environmental Medicine and the UTSW Medical Center

Alzheimer's Disease Center. This study was supported in part by the National Institute of Health (R01AG033106, R01HL102457, P30Ago12300, and K99HL133449), and the American Heart Association (14POST20140013).

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/17-0415r1).

REFERENCES

[1] Fyfe I (2015) Dementia: Researchers urge more dementia studies to focus on prevention rather than cure. *Nat Rev Neurol* **11**, 545.

[2] Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B (2001) Current concepts in mild cognitive impairment. *Arch Neurol* **58**, 1985-1992.

[3] Kantarci K, Senjem ML, Avula R, Zhang B, Samikoglu AR, Weigand SD, Przybelski SA, Edmonson HA, Vemuri P, Knopman DS, Boeve BF, Ivnik RJ, Smith GE, Petersen RC, Jack Jr CR (2011) Diffusion tensor imaging and cognitive function in older adults with no dementia. *Neurology* **77**, 26-34.

[4] de Groot M, Verhaaren BF, de Boer R, Klein S, Hofman A, van der Lugt A, Ikram MA, Niessen WJ, Vernooij MW (2013) Changes in normal-appearing white matter precede development of white matter lesions. *Stroke* **44**, 1037-1042.

[5] Sexton CE, Kalu UG, Filippini N, Mackay CE, Ebmeier KP (2011) A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* **32**, 2322 e2325-2318.

[6] Yasmin H, Nakata Y, Aoki S, Abe O, Sato N, Nemoto K, Arima K, Furuta N, Uno M, Hirai S, Masutani Y, Ohtomo K (2008) Diffusion abnormalities of the uncinate fasciculus in Alzheimer's disease: Diffusion tensor tract-specific analysis using a new method to measure the core of the tract. *Neuroradiology* **50**, 293-299.

[7] Gons RA, Tuladhar AM, de Laat KF, van Norden AG, van Dijk EJ, Norris DG, Zwiers MP, de Leeuw FE (2013) Physical activity is related to the structural integrity of cerebral white matter. *Neurology* **81**, 971-976.

[8] Tseng BY, Gundapuneedi T, Khan MA, Diaz-Arrastia R, Levine BD, Lu H, Huang H, Zhang R (2013) White matter integrity in physically fit older adults. *Neuroimage* **82**, 510-516.

[9] Lee SH, Han JH, Jin YY, Lee IH, Hong HR, Kang HS (2016) Poor physical fitness is independently associated with mild cognitive impairment in elderly Koreans. *Biol Sport* **33**, 57-62.

[10] Sattler C, Erickson KI, Toro P, Schroder J (2011) Physical fitness as a protective factor for cognitive impairment in a prospective population-based study in Germany. *J Alzheimers Dis* **26**, 709-718.

[11] Colcombe S, Kramer AF (2003) Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychol Sci* **14**, 125-130.

[12] Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K, Browndyke JN, Sherwood A (2010) Aerobic exercise and neurocognitive performance: A meta-analytic review of randomized controlled trials. *Psychosom Med* **72**, 239-252.

[13] Ross R, Blair SN, Arena R, Church TS, Després JP, Franklin BA, Haskell WL, Kaminsky LA, Levine BD, Lavie CJ, Myers J, Niebauer J, Sallis R, Sawada SS, Sui X, Wisløff U, American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, Stroke Council (2016) Importance of assessing cardiorespiratory fitness in clinical practice: A case for fitness as a clinical vital sign: A scientific statement from the American Heart Association. *Circulation* **134**, e653-e699.

[14] Hawkins MN, Raven PB, Snell PG, Stray-Gundersen J, Levine BD (2007) Maximal oxygen uptake as a parametric measure of cardiorespiratory capacity. *Med Sci Sports Exerc* **39**, 103-107.

[15] Tarumi T, Harris TS, Hill C, German Z, Riley J, Turner M, Womack KB, Kerwin DR, Monson NL, Stowe AM, Mathews D, Cullum CM, Zhang R (2015) Amyloid burden and sleep blood pressure in amnestic mild cognitive impairment. *Neurology* **85**, 1922-1929.

[16] Popescu V, Battaglini M, Hoogstrate WS, Verfaillie SC, Sluimer IC, van Schijndel RA, van Dijk BW, Cover KS, Knol DL, Jenkinson M, Barkhof F, de Stefano N, Vrenken H, Group MS (2012) Optimizing parameter choice for FSL-Brain Extraction Tool (BET) on 3D T1 images in multiple sclerosis. *Neuroimage* **61**, 1484-1494.

[17] Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE (2006) Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *Neuroimage* **31**, 1487-1505.

[18] Mori S, Oishi K, Jiang H, Jiang L, Li X, Akhter K, Hua K, Faria AV, Mahmood A, Woods R, Toga AW, Pike GB, Neto PR, Evans A, Zhang J, Huang H, Miller MI, van Zijl P, Mazziotta J (2008) Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage* **40**, 570-582.

[19] Brant-Zawadzki M, Gillan GD, Nitz WR (1992) MP RAGE: A three-dimensional, T1-weighted, gradient-echo sequence–initial experience in the brain. *Radiology* **182**, 769-775.

[20] Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, Black SE, Brayne C, Breteler M, Chabriat H, Decarli C, de Leeuw FE, Doubal F, Duering M, Fox NC, Greenberg S, Hachinski V, Kilimann I, Mok V, Oostenbrugge R, Pantoni L, Speck O, Stephan BC, Teipel S, Viswanathan A, Werring D, Chen C, Smith C, van Buchem M, Norrving B, Gorelick PB, Dichgans M, nEuroimaging STfRVco (2013) Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* **12**, 822-838.

[21] Huang L, Wang X, Baliki MN, Wang L, Apkarian AV, Parrish TB (2012) Reproducibility of structural, resting-state BOLD and DTI data between identical scanners. *PLoS One* **7**, e47684.

[22] Balke B, Nagle FJ, Daniels J (1965) Altitude and maximum performance in work and sports activity. *JAMA* **194**, 646-649.

[23] American_College_of_Sports_Medicine (2013) *ACSM's guidelines for exercise testing and prescription*, Lippincott Williams & Wilkins.

[24] Fujimoto N, Prasad A, Hastings JL, Arbab-Zadeh A, Bhella PS, Shibata S, Palmer D, Levine BD (2010) Cardiovascular

effects of 1 year of progressive and vigorous exercise training in previously sedentary individuals older than 65 years of age. *Circulation* **122**, 1797-1805.

[25] Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE (2014) Permutation inference for the general linear model. *Neuroimage* **92**, 381-397.

[26] Gow AJ, Bastin ME, Munoz Maniega S, Valdes Hernandez MC, Morris Z, Murray C, Royle NA, Starr JM, Deary IJ, Wardlaw JM (2012) Neuroprotective lifestyles and the aging brain: Activity, atrophy, and white matter integrity. *Neurology* **79**, 1802-1808.

[27] Tian Q, Glynn NW, Erickson KI, Aizenstein HJ, Simonsick EM, Yaffe K, Harris TB, Kritchevsky SB, Boudreau RM, Newman AB, Lopez OL, Saxton J, Rosano C, Health ABCS (2015) Objective measures of physical activity, white matter integrity and cognitive status in adults over age 80. *Behav Brain Res* **284**, 51-57.

[28] Boots EA, Schultz SA, Oh JM, Larson J, Edwards D, Cook D, Koscik RL, Dowling MN, Gallagher CL, Carlsson CM, Rowley HA, Bendlin BB, LaRue A, Asthana S, Hermann BP, Sager MA, Johnson SC, Okonkwo OC (2015) Cardiorespiratory fitness is associated with brain structure, cognition, and mood in a middle-aged cohort at risk for Alzheimer's disease. *Brain Imaging Behav* **9**, 639-649.

[29] Klawiter EC, Schmidt RE, Trinkaus K, Liang HF, Budde MD, Naismith RT, Song SK, Cross AH, Benzinger TL (2011) Radial diffusivity predicts demyelination in ex vivo multiple sclerosis spinal cords. *Neuroimage* **55**, 1454-1460.

[30] Bozzali M, Giulietti G, Basile B, Serra L, Spano B, Perri R, Giubilei F, Marra C, Caltagirone C, Cercignani M (2012) Damage to the cingulum contributes to Alzheimer's disease pathophysiology by deafferentation mechanism. *Hum Brain Mapp* **33**, 1295-1308.

[31] Acosta-Cabronero J, Alley S, Williams GB, Pengas G, Nestor PJ (2012) Diffusion tensor metrics as biomarkers in Alzheimer's disease. *PLoS One* **7**, e49072.

[32] Kavcic V, Ni H, Zhu T, Zhong J, Duffy CJ (2008) White matter integrity linked to functional impairments in aging and early Alzheimer's disease. *Alzheimers Dement* **4**, 381-389.

[33] Radanovic M, Pereira FR, Stella F, Aprahamian I, Ferreira LK, Forlenza OV, Busatto GF (2013) White matter abnormalities associated with Alzheimer's disease and mild cognitive impairment: A critical review of MRI studies. *Expert Rev Neurother* **13**, 483-493.

[34] Schmahmann JD, Pandya, Deepak N (2006) *Fiber Pathways of the Brain*, Oxford University Press.

[35] Schermuly I, Fellgiebel A, Wagner S, Yakushev I, Stoeter P, Schmitt R, Knickenberg RJ, Bleichner F, Beutel ME (2010) Association between cingulum bundle structure and cognitive performance: An observational study in major depression. *Eur Psychiatry* **25**, 355-360.

[36] Makris N, Papadimitriou GM, van der Kouwe A, Kennedy DN, Hodge SM, Dale AM, Benner T, Wald LL, Wu O, Tuch DS, Caviness VS, Moore TL, Killiany RJ, Moss MB, Rosene DL (2007) Frontal connections and cognitive changes in normal aging rhesus monkeys: A DTI study. *Neurobiol Aging* **28**, 1556-1567.

[37] Tosto G, Zimmerman ME, Carmichael OT, Brickman AM, Alzheimer's Disease Neuroimaging I (2014) Predicting aggressive decline in mild cognitive impairment: The importance of white matter hyperintensities. *JAMA Neurol* **71**, 872-877.

[38] Tarumi T, Gonzales MM, Fallow B, Nualnim N, Pyron M, Tanaka H, Haley AP (2013) Central artery stiffness, neuropsychological function, and cerebral perfusion in sedentary and endurance-trained middle-aged adults. *J Hypertens* **31**, 2400-2409.

[39] Tarumi T, Ayaz Khan M, Liu J, Tseng BY, Parker R, Riley J, Tinajero C, Zhang R (2014) Cerebral hemodynamics in normal aging: Central artery stiffness, wave reflection, and pressure pulsatility. *J Cereb Blood Flow Metab* **34**, 971-978.

[40] Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ (2011) Arterial stiffness, pressure and flow pulsatility and brain structure and function: The Age, Gene/Environment Susceptibility–Reykjavik study. *Brain* **134**, 3398-3407.

[41] Aribisala BS, Morris Z, Eadie E, Thomas A, Gow A, Valdes Hernandez MC, Royle NA, Bastin ME, Starr J, Deary IJ, Wardlaw JM (2014) Blood pressure, internal carotid artery flow parameters, and age-related white matter hyperintensities. *Hypertension* **63**, 1011-1018.

[42] Katulska K, Wykretowicz M, Minczykowski A, Krauze T, Milewska A, Piskorski J, Marciniak R, Stajgis M, Wysocki H, Guzik P, Wykretowicz A (2014) Aortic excess pressure and arterial stiffness in subjects with subclinical white matter lesions. *Int J Cardiol* **172**, 269-270.

[43] Tarumi T, de Jong DL, Zhu DC, Tseng BY, Liu J, Hill C, Riley J, Womack KB, Kerwin DR, Lu H, Munro Cullum C, Zhang R (2015) Central artery stiffness, baroreflex sensitivity, and brain white matter neuronal fiber integrity in older adults. *Neuroimage* **110**, 162-170.

[44] de la Torre JC (2012) Cerebral hemodynamics and vascular risk factors: Setting the stage for Alzheimer's disease. *J Alzheimers Dis* **32**, 553-567.

[45] Chetelat G, Desgranges B, de la Sayette V, Viader F, Eustache F, Baron JC (2003) Mild cognitive impairment: Can FDG-PET predict who is to rapidly convert to Alzheimer's disease? *Neurology* **60**, 1374-1377.

[46] Hansson O, Buchhave P, Zetterberg H, Blennow K, Minthon L, Warkentin S (2009) Combined rCBF and CSF biomarkers predict progression from mild cognitive impairment to Alzheimer's disease. *Neurobiol Aging* **30**, 165-173.

[47] Ambrose C (2015) Muscle weakness during aging: A deficiency state involving declining angiogenesis. *Ageing Res Rev* **23**, 139-153.

[48] Ambrose CT (2016) The role of capillaries in the lesser ailments of old age and in Alzheimer's disease and vascular dementia: The potential of pro-therapeutic angiogenesis. *J Alzheimers Dis* **54**, 31-43.

[49] Ambrose CT (2017) Pro-angiogenesis therapy and aging: A mini-review. *Gerontology* **63**, 393-400.

[50] Tarumi T, Zhang R (2015) The role of exercise-induced cardiovascular adaptation in brain health. *Exerc Sport Sci Rev* **43**, 181-189.

[51] Pasternak O, Sochen N, Gur Y, Intrator N, Assaf Y (2009) Free water elimination and mapping from diffusion MRI. *Magn Reson Med* **62**, 717-730.

[52] Berlot R, Metzler-Baddeley C, Jones DK, O'Sullivan MJ (2014) CSF contamination contributes to apparent microstructural alterations in mild cognitive impairment. *Neuroimage* **92**, 27-35.