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White matter plasticity in healthy older adults: The effects of aerobic exercise

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ABSTRACT

White matter deterioration is associated with cognitive impairment in healthy aging and Alzheimer's disease. It is critical to identify interventions that can slow down white matter deterioration. So far, clinical trials have failed to demonstrate the benefits of aerobic exercise on the adult white matter using diffusion Magnetic Resonance Imaging. Here, we report the effects of a 6-month aerobic walking and dance interventions (clinical trial NCT01472744) on white matter integrity in healthy older adults (n = 180, 60–79 years) measured by changes in the ratio of calibrated T1- to T2-weighted images (T1w/T2w). Specifically, the aerobic walking and social dance interventions resulted in positive changes in the T1w/T2w signal in late-myelinating regions, as compared to widespread decreases in the T1w/T2w signal in the active control. Notably, in the aerobic walking group, positive change in the T1w/T2w signal correlated with improved episodic memory performance. Lastly, intervention-induced increases in cardiorespiratory fitness did not correlate with change in the T1w/T2w signal. Together, our findings suggest that white matter regions that are vulnerable to aging retain some degree of plasticity that can be induced by aerobic exercise training. In addition, we provided evidence that the T1w/T2w signal may be a useful and broadly accessible measure for studying short-term within-person plasticity and deterioration in the adult human white matter.

1. Introduction

Global incidence of dementia is projected to double every 20 years (Mayeux and Stern, 2012), thus developing effective strategies to reduce the risk of cognitive decline is critical. Cortical "disconnection" due to white matter degeneration is considered one of the primary mechanisms of cognitive decline in healthy aging (Bartzokis et al., 2004) and may precede gray matter pathology in Alzheimer's disease (Nasrabady et al., 2018). White matter integrity decreases in healthy aging and dementia, as demonstrated by studies using diffusion tensor imaging (DTI) (Madden et al., 2012). As within-person declines in white matter integrity can occur over a period as brief as 6 months in cognitively healthy older adults (Burzynska et al., 2017), it is critical to determine whether white matter deterioration is reversible or malleable.

It is commonly believed that white matter is not involved in adult neuroplasticity; however, studies in rodents have shown experience-dependent changes in oligodendrocyte differentiation (McKenzie et al., 2014; Simon et al., 2011), myelination (Chorghay et al., 2018; Kato et al., 2020), and axonal diameter (Bobinski et al., 2011), which correlated with improved motor and cognitive performance (Fields and Bukalo, 2020; Sampaio-Baptista et al., 2013). To date, there is little evidence of such plasticity in adult humans. Few DTI studies have reported increases in fractional anisotropy following motor training in healthy young adults (Lakhani et al., 2016) and cognitive training in older adults (de Lange et al., 2018; Lövdén et al., 2010). Several ran-

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domized controlled trials (RCT) in healthy older adults (Burzynska et al., 2017; Clark et al., 2019; Voss et al., 2012) or individuals with mild cognitive impairment or at risk of Alzheimer's Disease (Fissler et al., 2017; Tarumi et al., 2020; Venkatraman et al., 2020b), have reported no benefits of 6- to 24-month aerobic exercise interventions on white matter fractional anisotropy. This is surprising given the well documented positive effects of aerobic exercise interventions on cognitive function (Kramer and Colcombe, 2018), brain functional connectivity (Voss et al., 2016), and brain volumes (Erickson et al., 2011). As a result, white matter has rarely been considered as a target for interventions against Alzheimer's Disease and related dementias.

Fractional anisotropy is affected by multiple aspects of tissue microstructure (Jones and Cercignani, 2010). Therefore, it may not detect subtle changes in myelination or axonal health. There has been recent interest in using the ratio of the standardized T1 and T2-weighted images (T1w/T2w) as a measure of white matter integrity (Ganzetti et al., 2014). The phenomenon underlying the gray matter-white matter contrast in T1-w and T2-w images arise from the differences in the T1 and T2 relaxation properties of tissues (Sharma and Lagopoulos, 2010). In the white matter, the proton spins collide with macromolecules and myelin sheaths with hydrophobic properties, limiting water displacement, resulting in shorter T1 and T2 in white matter compared to the cell somas of the gray matter (Deoni, 2010). Since myelin increases signal in T1-w images but decreases signal in T2-w images it has been proposed that the division of the T1-w image by the T2-w image can provide an enhanced myelin contrast, especially in the cortex (Glasser and van Essen, 2011). However, although T1w/T2w has been shown to detect demyelination in multiple sclerosis (Cooper et al., 2019), recent studies reported correlations of the T1w/T2w signal with other elements of the white matter such as MRI estimates of axonal diameter (Arshad et al., 2017), axonal density (Fukutomi et al., 2018), and iron content (Shams et al., 2019). Accordingly, T1w/T2w detected differences in white matter integrity in cognitively healthy APOE-4 carriers (Operto et al., 2019) and in neurodegenerative disorders such as multiple systems atrophy (Sugiyama et al., 2020), which are of mixed etiology. Thus, even though the T1w/T2w may not be specific to any microstructural process, it is promising in providing complementary information to DTI or volumetric measures (Uddin et al., 2019). The availability of T1 and T2-w images in the existing datasets warrants investigations on cognitive relevance of the T1w/T2w and its ability to detect within-person changes in white matter.

In this study, we compared 6-month change in the T1w/T2w signal in participants randomized to one of three intervention groups: walking, dance, and active control. Our hypotheses were: 1) T1w/T2w signal would decline over 6 months in the control group, similar to earlier DTI findings (Burzynska et al., 2017), 2) Participants in the walking and dance conditions would show positive changes in the T1w/T2w signal compared to the control, 3) Changes in T1w/T2w signal would correlate with positive change in episodic memory, processing speed, executive function (cognitive abilities known to decline with age (Park et al., 2002)), 4) Changes in T1w/T2w would correlate with change in cardiorespiratory fitness (Kramer and Colcombe, 2018). Lastly, T1 and T2 relaxations are affected by white matter hypo- and hyperintensities, respectively, which are prevalent in older age (Birdsill et al., 2014). Hence, we explored the impact of T1-weighted white matter signal abnormalities on the intervention effects, as well as the effects of time and the intervention on T1-weighted signal abnormalities.

2. Materials and methods

2.1. Participants

Participants were 247 community-dwelling older adults (average age of 65 yrs., 68% women) enrolled in a 24-week randomized controlled exercise trial that examined the effects of aerobic exercise on cognitive performance and brain health. The trial is registered with United States National Institutes of Health ClinicalTrials.gov (ID: NCT01472744). Individuals were eligible to participate if they met the following inclusion criteria: (a) 60–80 years-old; (b) able to read and speak English; (c) scored <10 on the geriatric depression scale (GDS-15); (d) scored ≥ 75% right-handedness on the Edinburgh Handedness Questionnaire; (e) demonstrated normal or corrected-to-normal vision of at least 20/40 and no color blindness; (f) low-active, defined as engaging in less than two bouts of moderate-to-vigorous physical activity per week during the last 6 months, each bout lasting <30 min. In addition to this self-reported physical activity, the baseline accelerometer showed that only 0.5% ($n = 1$) of the current sample met the recommendation of at least 150 min of moderate-to-vigorous physical activity per week at baseline. Thus, our sample can be defined as low-fit and low-active, but otherwise healthy. (g) Local to the study location for the duration of the program; (h) willing to be randomized to one of four interventions; (i) not involved in another physical activity program; and (j) scored >21 on the Telephone Interview of Cognitive Status questionnaire and >23 on the Mini Mental State Exam (Fong et al., 2009). Eligibility also included meeting inclusion criteria for completing a magnetic resonance imaging (MRI) assessment, consisting of: (a) free from neurological disorders affecting the brain such as stroke, TBI, Alzheimer's disease, epilepsy; (b) no history of stroke, transient ischemic attach, head trauma or surgeries including the removal of brain tissue; and (c) no implanted devices or metallic bodies above the waist. Thus, our sample consisted of healthy, community-dwelling, typically low active older adults.

For more information on participant recruitment and screening, see (Baniqued et al., 2018; Burzynska et al., 2017; Ehlers et al., 2017; Fanning et al., 2017; Voss et al., 2018). Participants underwent a series of MRI imaging, cognitive, and cardiorespiratory testing, before and after the 6-month intervention program.

The study was approved by and carried out in accordance with the recommendations of the Institutional Review Board at the University of Illinois at Urbana-Champaign with written informed consent from all participants. All participants provided written informed consent in accordance with the Declaration of Helsinki.

2.2. Intervention

After all baseline data were collected, participants were assigned to one of four interventions implemented over four waves from October 2011 to November 2014. Participants were randomized using a computer data management system and baseline-adaptive randomization scheme, taking into account equal distributions of age and gender (Begg and Iglewicz, 1980). Participants in all conditions attended three 1-h exercise sessions per week for 24 weeks (~6 months)(Burzynska et al., 2017; Ehlers et al., 2017). The four intervention groups were as follows: The **active control** involved exercises designed to improve flexibility, strength, and balance with the aid of yoga mats and blocks, chairs, and resistance bands, specifically designed for individuals 60 years of age and older. This intervention served as the active control group to account for the social engagement and novelty in the other interventions, with the difference that the active control was not aimed to increase cardiorespiratory fitness. The **walking** intervention was designed to increase cardiorespiratory fitness. Thus, it involved walking sessions at 50–60% of maximal heart rate, as ascertained from a maximal graded exercise test. Walking duration increased from 20 to 40 min during the first 6 weeks of the program. During the remaining 18 weeks, participants walked for 40 min at 60–75% of their maximal heart rate each session. Frequent assessment of heart rate, using either palpation or Polar Heart Rate Monitors, and rating of perceived exertion ensured that participants' exercise was performed at the prescribed intensity. Exercise logs were completed after each exercise session. The **walking + nutrition** group, in addition to the above walking intervention, received a nutritional supplement containing antioxidants, anti-inflammatories, vitamins, minerals, and beta alanine (Abbott Nutrition, Abbott Park, Illinois). Beta-alanine is thought to pro-

mote the effect of increased cardiorespiratory fitness by increasing lean muscle mass. However, the analyses of the primary outcomes indicated no differences in gain in cardiorespiratory fitness between the walking interventions (Baniqued et al., 2018; Ehlers et al., 2017; Voss et al., 2018) therefore, walking and walking + nutrition were combined for the present analyses. The **dance** intervention was designed to provide simultaneous cognitive and social enrichment combined with aerobic physical activity. The choreographed dance combinations became progressively more challenging over the course of the 6-months program. Group social dance styles were selected to minimize lead-follow roles. In each session, participants learned ~4 dances and recorded their heart rate and perceived exertion after each dance. Each participant learned and alternated between two roles for each dance, increasing the cognitive challenge.

2.3. Cardiovascular variables

Cardiorespiratory fitness was assessed before and after the intervention on a motor-driven treadmill by employing a modified Balke protocol (graded exercise test). The protocol involved walking at a self-selected pace with incremental grades of 2–3% every 2 min. We continuously collected measurements of oxygen uptake, heart rate and blood pressure. We measured oxygen uptake (VO_2) from expired air samples taken at 30-second intervals until a peak VO_2 (the highest VO_2) was attained; test termination was determined by symptom limitation, volitional exhaustion, and/or attainment of VO_2 peak as established by the American College of Sports Medicine guidelines (American College of Sports Medicine, 2013).

2.4. MRI acquisition

We acquired images on a 3T Siemens Trio Tim system with 45 mT/m gradients and 200 T/m/*sec* slew rates (Siemens, Erlangen, Germany). T1-weighted images were acquired using a 3D MPRAGE (TR = 1900 ms; TE = 2.32 ms; TI: 900 ms; matrix = 256 × 256; FOV = 230 mm; 192 slices; 0.9 × 0.9 × 0.9 mm^3 voxels size; GRAPPA acceleration factor 2). The non-diffusion weighted images from the diffusion-weighted acquisition were used as T2-weighted images (b-value = 0 s/mm^2, TR = 5500 ms; TE = 98 ms, matrix = 128 × 128; 1.7 × 1.7 × 3 mm^3 voxels size; GRAPPA acceleration factor 2) because the study protocol did not include a T2-W image scan besides FLAIR (which is suboptimal for the T1w/T2w calculation since it has a decreased gray-WM contrast due to the inversion pulse (Ganzetti et al., 2014)). Out of 213 participants who completed the intervention, 180 had good quality MRI data at pre- and post-intervention (see, Fig. A.1 for participant flow for the current analyses).

AMC and AZB checked for image quality (see, Fig. A.1 for details). Images were excluded from the analyses if they had motion or ghost artifacts that affected the gray-white matter boundary or image co-registration; 4 subjects were excluded due to brain anatomical concerns that affected image co-registration and could lead to partial volume effects (e.g., ventriculomegaly or asymmetrical ventricles); 8 subjects were excluded due to insufficient brain coverage of their T2-w images for intensity calibration with the MRTool. In addition, visual inspection of the T1-w and T2-w images revealed four participants with confluent white matter lesions beyond what is expected for typical aging, and thus were excluded from the analyses. 33 participants were excluded due to insufficient MRI quality (n = 11 active control, n = 11 dancing group, n = 10 the walking group), resulting in n = 43 for the active control, n = 51 for dance and n = 86 for the combined walking group. The full description of subject flow is detailed in Fig. A.1 and in our previous reports (Baniqued et al., 2018; Ehlers et al., 2017; Voss et al., 2018).

2.4.1. T1w/T2w calculation

We calculated T1w/T2w images with the MRTool registration-segmentation framework in SPM12 (Wellcome Trust center for Neuroimaging, London, UK; (Ganzetti et al., 2014). First, T2-W images in the individual space were co-registered to T1-W images through a 6 degrees of freedom rigid-body transformation. The effect of the transmit field intensity inhomogeneities (B1 field) differs between T1w and T2w images, and thus the division of the T1-w image by the T2-w image does not automatically cancel for the signal variations due to intensity non-uniformity (INU). Therefore, we corrected for INU using the INU correction algorithm from SPM12 before calculating the ratio. Additionally, because the T1-w and T2-w images have different intensity scales across individuals and scanners, we performed a calibration method to normalize the sensitivity profiles across subjects and scan sessions.

The bias correction algorithm included the default SPM parameters for smoothing (60 mm) and regularization (10^{-4}). The regularization algorithm models the intensity variations between images, while the smoothing algorithm uses 60 mm of full-width half-maximum Gaussian smoothness of the intensity bias. The bias field smoothing parameter estimates the level of low-pass filtering (attenuation of high frequency data) applied to the estimated intensity non-uniformity field.

After the INU correction, the images were calibrated to standardize their intensity scales across sessions and participants (Ganzetti et al., 2014). We could not use the recommended external calibration (using the eye and temporal muscle) due to insufficient head coverage of the T2-w images. Instead, we used the internal calibration that rescales the images using the whole brain intensity distribution (Ganzetti et al., 2014; Glasser and van Essen, 2011). This calibration method chooses an internal hallmark inside the brain to standardize (i.e., normalize to a global mean) the intensity values. This is considered less optimal because it may attenuate differences in myelin levels between groups. To address this, we examined the variability in image histograms before and after calibration and across experimental groups, and we observed consistent intensity scales and ranges across groups after the calibration procedure. Fig. A.2 shows histograms of intensity values for T1w and T2w images before and after calibration for 5 random subjects from each intervention group.

Then, the T1w/T2w were calculated in individual space using the bias corrected and calibrated images. Then, images were brain extracted to remove non-brain tissue and transformed to Montreal Neurological Institute (MNI) space 1mm^3 in SPM (Ganzetti et al., 2014). The T1w/T2w signal shows values ranging from 0 to 2, with values closer to 0 representing CSF, values closer to 1 found in gray matter structures (e.g., caudate nucleus, thalamus), and higher values found in white matter regions (corpus callosum).

2.4.2. White matter signal abnormality volume estimation

Because FLAIR images (the gold-standard images to assess white matter hyperintensity volume) were not collected in this study, we used white matter hypointensities on T1-weighted images calculated in FreeSurfer v 5.3 (http://surfer.nmr.mgh.harvard.edu/) as a proxy for white matter signal abnormality, as described in our previous study (Tan et al., 2019). For details on the MRI preprocessing of the volumetric data see (Ehlers et al., 2017).

2.4.3. Skeletonization and region selection

We used Tract-Based Spatial Statistics (TBSS) in FSL (Smith et al., 2006) to restrict the analyses to the center of white matter tracks. This was to minimize the effects of possible partial volume due to individual and age differences in anatomy, to focus the analyses on the normal-appearing white matter, and to allow direct comparison with our earlier DTI findings from this sample (Burzynska et al., 2017). We used the non-FA TBSS pipeline for the T1w/T2w images to project them onto the group white matter skeleton with a threshold of fractional anisotropy > 0.2, as we described earlier (Burzynska et al., 2017). To confirm that the T1w/T2w voxels were correctly projected onto the white matter skeleton, we de-projected all skeletonized T1w/T2w images for visual inspection in subject's native space; the deprojection was accurate for

all participants and regions except for regions 3 and 4 of the corpus callosum in 5 participants, which were treated as missing values.

We extracted T1w/T2w regional values for statistical analyses. Total white matter was defined as all voxels on the white matter skeleton. We examined the five subsections of the corpus callosum (CC) (Hofer and Frahm, 2006) given the anterior-to-posterior gradient of CC's vulnerability to aging (Head et al., 2004). Region 1 (CC1) contains the most anterior fibers of the CC, which project to the prefrontal cortex. Region 2 (CC2) projects to the premotor and supplementary control areas. Region 3 (CC3), the posterior mid-body projects to the primary motor cortex. Region 4 (CC4) projects to the primary sensory cortex. The most posterior region (CC5), where callosal parietal, temporal and occipital fibers cross the CC is region 5 (Hofer and Frahm, 2006).

Other white matter regions included the association fibers connecting regions known to be affected by aging: the fornix (FX), the superior longitudinal fasciculus (SLF), the external capsule (EC), the cingulum (CING), and the uncinate fasciculus (UNC). In addition, we included two other major white matter landmarks: the forceps minor (fMIN) and forceps major (fMAJ), containing callosal fibers and thalamic projections to the frontal lobes and the occipital lobes, respectively. The corticospinal tract (CST) represented the major projection from the motor cortex to the lower motor neurons. To define fMIN, fMAJ, UNC, SLF and CST on the white matter skeleton, we used the tract probability maps from the Johns Hopkins University white matter tractography atlas (Hua et al., 2008); http://cmrm.med.jhmi.edu). We thresholded the tract probability maps at 10–15%, depending on a tract, with the aim to maximize the overlap with white matter skeleton but avoid including voxels from neighboring tracts (Fig. 1). For the FX and EC, we used the Johns Hopkins University white matter labels in FSL. Finally, since the prefrontal cortex is vulnerable to aging (Head et al., 2004) and its volume and function has been shown to benefit from greater cardiorespiratory fitness or aerobic exercise (Colcombe and Kramer, 2003; Voss et al., 2012), we defined prefrontal white matter using a cutoff of $y > 12$ in MNI space (Burzynska et al., 2013). To minimize the effects of the outliers but to avoid removing data points, we identified outliers as ⟨ 1st percentile or ⟩ 99th percentile of distribution (i.e., winsorized) by replacing them with the nearest value in the 1st or 99th percentile. This criterion was applied to mean T1w/T2w data for each region of interest. For each variable and intervention group, no more than 3% values were winsorized.

Finally, we inspected the normality of the T1w/T2w data and found a bimodal distribution in the following regions: fMAJ, UNC, EC and CST. This could have diluted the between-groups mean differences in these regions, leading to underestimation of the intervention effects and overestimation of the effects of time. We excluded these from the main analyses and included them in Table A.1.

2.5. Cognitive assessment

Cognitive assessment included the Virginia Cognitive Aging (VCAP) battery (Salthouse, 2009) and two additional experimental executive function tasks (task switching and spatial working memory (Baniqued et al., 2018). As the task switching and spatial working memory tasks load on the reasoning construct of the VCAP (Baniqued et al., 2018; Voss et al., 2018), we grouped them with the matrix reasoning, Shipley abstraction, letter sets, spatial relations, paper folding, and form boards to create an executive function composite (Baniqued et al., 2018; Voss et al., 2018). In addition, the VCAP assessed episodic memory (word recall, paired associates, logical memory tasks), perceptual speed (digit symbol substitution, letter comparison, pattern comparison), and vocabulary (Wechsler Adult Intelligence Vocabulary, picture vocabulary, and synonym/antonym). We used the vocabulary construct only for sample description, because there is no evidence linking physical activity interventions with gains in crystallized abilities.

We removed outliers (i.e., winsorized) from each cognitive task before calculation of the composite scores at one percent of their distributions, no more than 1% values were winsorized. Then, we expressed both pre and post-intervention individual values as standardized scores (z-scores) using the mean and standard deviation of the pre-intervention distribution. Finally, we calculated composite scores for both pre- and post-intervention as mean z-scores of tasks within each cognitive domain.

2.6. Statistical analyses

We used linear mixed-effects models with parameter estimates fitted using the R lme4 package (Bates et al., 2015) to compare change in T1w/T2w between the three groups (walking, dance, and active control). Models included fixed effects of time, group, and the time-by-group interaction as well as random intercepts. The group factor was coded using Helmert contrasts. This allowed us to compare the active control against the average of all the walking and dance groups. Then, to contrast the effects of walking vs active control and dance vs. active control we fitted additional linear mixed-effect models using a contrast matrix with dummy codes for the three groups, such that the active control was the reference. We standardized all quantitative variables, but not factors, to create partially standardized regression coefficients. The standardization of our variables rendered regression coefficients (β) that are loosely interpreted like correlation coefficients in terms of effect size (Ferguson, 2009). We tested the assumptions of the linear mixed-effects models by visually inspecting the normality of residuals, as well as the distribution of the residuals vs. fitted values.

For correlational analyses, 6-month change scores in the variables of interest were calculated as the post-intervention z-score minus pre-intervention z-score (note that we used the pre mean and standard deviation to transform both pre and post data). We used partial Pearson's correlations in R ppcor to study the associations between change in T1w/T2w and cognition (controlling for age, sex and education), and between change in T1w/T2w and cardiorespiratory fitness (controlling for age and sex) within each intervention group. Because these correlational analyses were exploratory, we corrected for multiple comparisons using the false discovery rate method as implemented by p.adjust (p.value, method="fdr") in R. Statistical significance was accepted at $p<0.05$ for two-tailed tests.

We created figures using the ggplot function in the ggplot2 package (Wickham, 2009) and the multiplot function within the coefplot package (Lander, 2016). All statistical analyses were completed using R version 4.0.1.

3. Results

One-way ANOVA showed no baseline differences in age, gender, education, resting blood pressure, cardiorespiratory fitness, regional T1w/T2w values and white matter hypointensity volume between the active control, walking, and dance groups (Table 1), indicating successful randomization. In addition, mean adherence rates were 80% for the active control, 78% for the dancing group and 77% for the walking group, $F = 0.88$, Df = 2, $p = 0.41$.

3.1. Intervention effects

We first compared the active control condition to the average effect of the walking and dance conditions. We found significant time-by-group interactions in total white matter, the genu and splenium of the corpus callosum, the forceps minor, the cingulum, and the superior longitudinal fasciculus (Table 2).

Next, we compared the effects of walking versus active control and the effects of dance versus active control. For the walking versus active control contrast, we found time-by-group interactions in total white matter, the genu and splenium of the corpus callosum, the forceps minor, and cingulum. For the dance versus active control contrast, we found time-by-group interactions in total white matter and the genu of the corpus callosum. Using Helmert contrasts, we found no difference in the

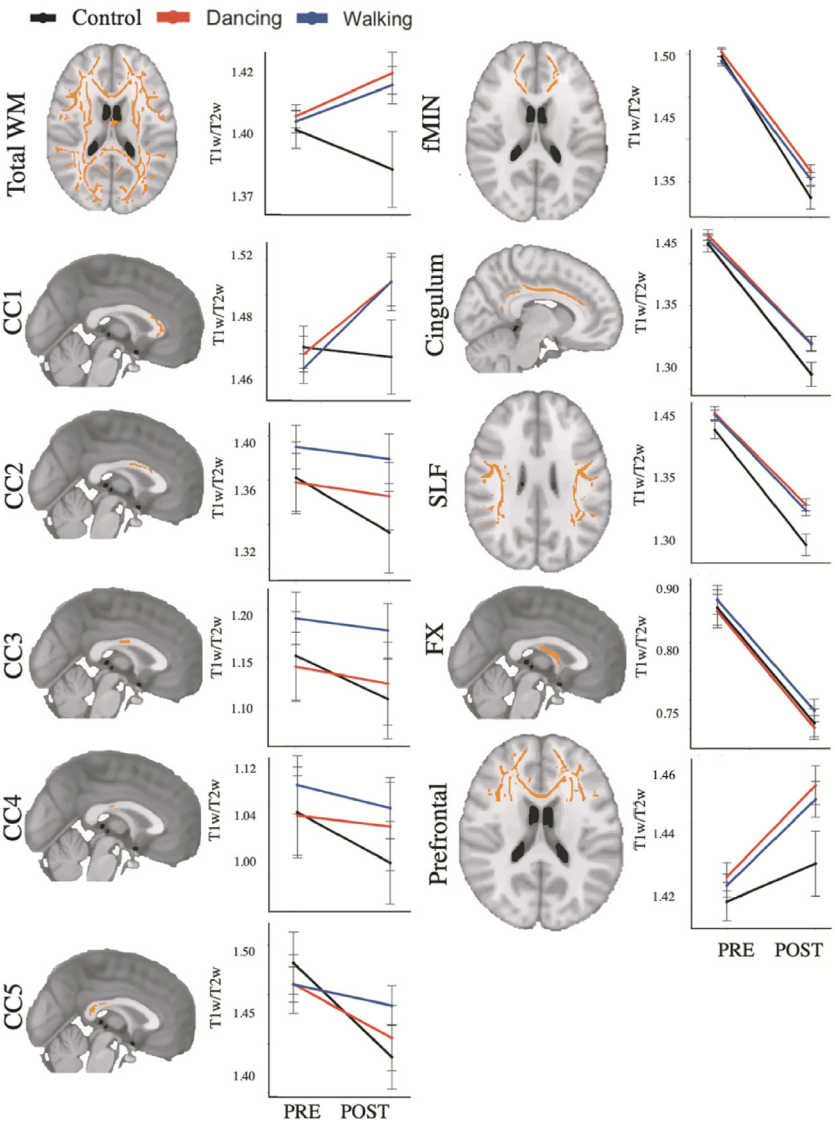

Fig. 1. 6-month change in T1w/T2w signal in the Active Control, Walking and Dance groups. The points represent the group means at both preintervention (PRE) and postintervention (POST) for each intervention group, and error bars represent 95% confidence intervals. WM = white matter; CC = corpus callosum; fMIN = forceps minor; SLF = superior longitudinal fasciculus; FX = fornix.

time-by-group interactions between the dance versus walking groups, see Table A.2. In addition, we found that both the walking and dance interventions resulted in an increase in white matter T1w/T2w signal or a reduced rate of decline relative to the active control condition, as shown in Fig. 1. Additional analyses demonstrated that controlling for total white matter signal abnormality volume did not impact the time-by-group interaction effect (Table A.3). In addition, there was no overall effect of time on white matter signal abnormality volume (i.e., no significant 6-month change). We also did not find time-by-group interaction effect for white matter signal abnormality volume as the dependent variable (Table A.4).

Additionally, we replicated results from Burzynska et al. (2017) using DTI-FA, showing significant time-by-group interactions in the fornix and forceps minor for the dance vs. control contrast (Table A.4). Lastly, we repeated the linear-mixed effects models using the raw T1w/T2w to demonstrate that removing outliers (i.e., winsorizing) did not have a significant impact on the main results (Table A.5.).

In sum, our results show positive intervention-related changes in the T1w/T2w signal when compared to the active control (Fig. 1), with more regions affected in the walking group than in the dance group.

3.2. 6-month longitudinal decline in T1w/T2w

We observed a consistent pattern of decline in the T1w/T2w signal over a period of 6 months in the active control group for all white matter regions, except the genu of the corpus callosum and prefrontal white matter. The largest effect sizes were observed in forceps minor and cingulum, where we also observed significant time-by-group interactions. Fig. 1, shows the means for the T1w/T2w at preintervention and postintervention for each group, while Fig. 2 shows the standardized β-coefficients for all white matter regions for the effect of time in the active control group. Finally, exploratory correlations between changes in T1w/T2w and chronological age group revealed significant associations in the genu, anterior body of the corpus callosum, and the splenium in the active control group (Fig. 3).

3.3. Change in T1w/T2w signal and cognition

We correlated the 6-month change in T1w/T2w in the five regions that showed time-by-group interactions in the walking group with change in memory, perceptual speed, and executive function. All anal-

Table 1
Baseline characteristics of the sample.

Variables	Control $n = 43$	Dance $n = 51$	Walking $n = 86$	p value
General characteristics				
Age	66.3 ± 4.5	65.8 ± 4.6	64.8 ± 4.2	0.143
Women, n (%)	26 (65.0)	37 (75.5)	54 (67.5)	0.508
Education, yrs	16.3 ± 3.0	15.3 ± 3.3	15.9 ± 2.6	0.321
MMSE	28.5 ± 1.4	28.4 ± 1.5	28.5 ± 1.4	0.879
BMI	30.4 ± 6.1	30.5 ± 5.9	30.4 ± 4.9	0.993
Systolic BP	132.2 ± 14.9	132.6 ± 12.6	131.9 ± 14.2	0.963
Diastolic BP	79.6 ± 7.9	82.7 ± 17.7	78.5 ± 7.5	0.137
CRF	19.0 ± 4.5	19.5 ± 4.1	20.0 ± 4.5	0.456
Cognition				
Word recall	43.9 ± 8.9	44.6 ± 8.4	43.7 ± 9.0	0.842
Paired associate	0.33±0.2	0.30±0.2	0.36±0.2	0.500
Logical memory	43.6 ± 9.1	45.1 ± 8.2	44.4 ± 8.1	0.684
Digit symbol	62.0 ± 13.0	66.3 ± 15.0	65.8 ± 12.7	0.238
Letter comparison	9.1 ± 1.8	9.6 ± 1.6	9.5 ± 1.7	0.373
Pattern comparison	14.2 ± 2.1	14.8 ± 2.4	15.1 ± 2.6	0.189
Matrix reasoning	8.6 ± 2.9	8.5 ± 3.1	7.6 ± 2.8	0.079
Shipley abstraction	12.5 ± 3.5	12.9 ± 3.5	11.6 ± 3.5	0.097
Letter set	11.3 ± 2.4	11.2 ± 2.7	10.7 ± 2.7	0.373
Spatial relations	8.3 ± 5.1	7.7 ± 5.0	7.9 ± 3.9	0.820
Paper folding	5.1 ± 2.6	5.5 ± 2.6	5.1 ± 2.4	0.532
Formboard	5.6 ± 3.8	5.8 ± 3.5	5.3 ± 3.5	0.810
SPWM	0.79±0.1	0.80±0.1	0.81±0.1	0.677
Task switching RT	296.8 ± 151.0	318.5 ± 183.2	320.5 ± 152.5	0.727
T1w/T2w levels				
Total	1.39±0.1	1.40±0.1	1.39±0.1	0.818
CC1	1.47±0.1	1.48±0.1	1.46±0.1	0.664
CC2	1.36±0.2	1.35±0.2	1.38±0.2	0.572
CC3	1.15±0.3	1.14±0.3	1.19±0.2	0.513
CC4	1.06±0.3	1.06±0.3	1.09±0.3	0.784
CC5	1.48±0.2	1.46±0.2	1.46±0.2	0.812
prefrontal	1.42±0.1	1.43±0.1	1.43±0.1	0.545
fMIN	1.49±0.1	1.49±0.1	1.48±0.1	0.466
Cingulum	1.46±0.1	1.47±0.1	1.47±0.1	0.698
SLF	1.43±0.1	1.45±0.1	1.45±0.1	0.186
FX	0.90±0.1	0.89±0.1	0.91±0.1	0.863
T1 WM hypointensity (mm^3) log	7.54±0.64	7.49±0.66	7.50±0.59	0.915

MMSE= Mini-mental state examination, BMI= body mass index, BP=blood pressure, CRF=cardiorespiratory fitness, SPWM= spatial working memory, RT = reaction time, CC = corpus callosum, fMIN= forceps minor, SLF = superior longitudinal fasciculus, FX = fornix; WM = white matter.

Table 2
Time-by-group interactions in white matter T1w/T2w.

	Walking + Dance vs. Control			Walking vs. Control			Dance vs. Control		
Region	β	SE	p	β	SE	P	β	SE	p
Total	0.26	0.11	**0.02**	0.25	0.11	**0.03**	0.27	0.13	**0.04**
CC1	0.24	0.09	**0.01**	0.22	0.10	**0.02**	0.22	0.11	**0.05**
CC2	0.09	0.06	0.12	0.09	0.06	0.13	0.09	0.06	0.19
CC3	0.05	0.05	0.26	0.06	0.05	0.26	0.05	0.06	0.38
CC4	0.06	0.04	0.13	0.05	0.04	0.25	0.07	0.05	0.25
CC5	0.14	0.06	**0.01**	0.18	0.06	**0.01**	0.10	0.07	0.12
Prefrontal	0.17	0.10	0.10	0.16	0.10	0.14	0.18	0.12	0.14
fMIN	0.14	0.07	**0.03**	0.15	0.07	**0.04**	0.14	0.07	0.20
CING	0.15	0.06	**0.02**	0.16	0.07	**0.02**	0.14	0.02	0.07
SLF	0.15	0.07	**0.05**	0.13	0.07	0.09	0.16	0.09	0.08
FX	0.01	0.05	0.86	0.01	0.05	0.70	−0.03	0.05	0.94

Bold highlights $p<0.05$. SE= standard errors, CC= corpus callosum, fMIN= forceps minor, CING= cingulum, SLF= superior longitudinal fasciculus, FX= fornix. β are standardized. White matter regions are explained and visualized in Fig. 1.

yses controlled for age, sex, and education. A positive change in the T1w/T2w correlated with a positive change in episodic memory in the genu of the corpus callosum and the cingulum (Table 3). None of these effects were significant in the active control and dance groups. Lastly, we found no associations between baseline T1w/T2w and baseline cognitive scores (Table A.6).

3.4. Change in T1w/T2w signal and cardiorespiratory fitness

We examined whether intervention-related changes in T1w/T2w were associated with increased cardiorespiratory fitness. Pearson partial correlations, controlling for age and sex, revealed no significant associations between change in T1w/T2w and cardiorespiratory fitness (Table 4).

Table 3
Partial correlation coefficients between change in T1w/T2w and change in cognitive scores.

	Episodic Memory			Perceptual Speed			Executive Function		
Region	Control	Walking	Dance	Control	Walking	Dance	Control	Walking	Dance
	$n = 43$	$n = 86$	$n = 51$	$n = 43$	$n = 86$	$n = 51$	$n = 43$	$n = 86$	$n = 51$
Total	0.04	**0.28**	−0.04	−0.27	−0.06	0.12	−0.34	0.01	−0.04
CC1	−0.12	**0.27**	−0.04	−0.21	0.10	0.09	0.10	0.10	0.10
CC5	−0.25	0.16	−0.20	−0.04	0.17	0.03	0.17	0.17	0.17
Fmin	0.01	0.21	0.06	−0.27	0.01	0.08	0.01	0.01	0.01
Cingulum	−0.09	0.21	0.01	−0.24	−0.07	0.10	−0.07	−0.07	−0.07

Bold highlights $p<0.05$. CC= corpus callosum, fMIN= forceps minor, CING= cingulum. Partial correlations between change in T1w/T2w and cognition within each intervention group, controlling for age, sex, and education. Significance corrected for false discovery rate.

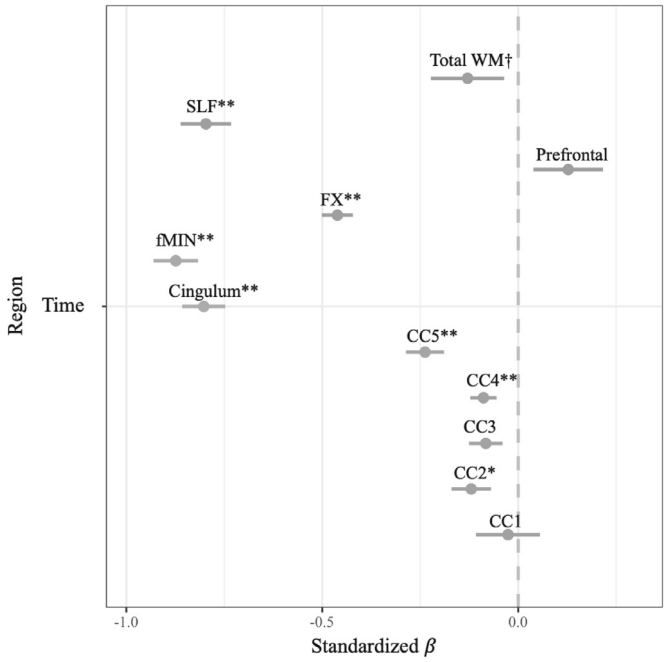

Fig. 2. Standardized β coefficients for the fixed effects of time in the active control. Asterisks indicate $\dagger p<0.10$, $^{*}p<0.05$, $^{**}p<0.01$. Error bars represent 95% confidence intervals. WM = white matter; CC = corpus callosum; fMIN = forceps minor; SLF = superior longitudinal fasciculus; FX = fornix.

Table 4
Partial correlation coefficients between change in T1w/T2w and change in cardiorespiratory fitness.

Region	All	Control	Walking	Dance
	$n = 180$	$n = 43$	$n = 86$	$n = 51$
Total	−0.05	−0.05	−0.02	−0.05
CC1	−0.08	−0.09	−0.08	−0.04
CC5	−0.10	−0.10	−0.03	−0.18
fMIN	−0.06	−0.08	−0.02	0.02
Cingulum	−0.06	−0.09	−0.01	−0.03

CC= corpus callosum, fMIN= forceps minor, CING= cingulum. Partial correlation coefficients between change in T1w/T2w and cardiorespiratory fitness within each intervention group, controlling for age and sex.

4. Discussion

Results from our RCT revealed positive changes in the standardized T1w/T2w in the aerobic exercise groups, providing preliminary evidence for experience-induced plasticity in the aging white matter. These changes were observed in several late-myelinating white matter regions in the walking and dance groups as compared to a decline in the active control group. In the active control group, the T1w/T2w signal showed widespread within-person decline, and this decline was pronounced with advancing age. Controlling for total white matter signal abnormality volume did not impact the intervention effect. Finally, the change in T1w/T2w in the walking group correlated with a positive change in episodic memory. However, change in T1w/T2w was not associated with cardiorespiratory fitness.

4.1. Aerobic exercise training increased T1w/T2w in the adult white matter

As predicted, aerobic walking training resulted in an increase in the white matter T1w/T2w signal, relative to an active control condition which included flexibility, strength, and balance exercises. Thus, our findings are in alignment with the previous cross-sectional and intervention studies showing a positive relationship between aerobic exercise, gray matter structure, and functional activity (Colcombe et al., 2006; Erickson et al., 2011; Voss et al., 2010). Together, these findings are the first from a RCT showing exercise-related plasticity on white matter (Burzynska et al., 2017; Clark et al., 2019; Voss et al., 2012).

Interestingly, although the effects of the aerobic walking on the T1w/T2w signal were significant for the mean of all white matter voxels, regional analyses suggested that results were specific to the late-myelinating regions containing association and commisural fibers: the genu and splenium of the corpus callosum, forceps minor, and the cingulum (Lebel et al., 2019). This is consistent with earlier correlational studies that found positive correlations between aerobic exercise and fractional anisotropy in the body and genu of the corpus callosum (Loprinzi et al., 2020), and in the cingulum bundle (Marks et al., 2011) in healthy older adults. Because white matter regions that myelinate later in development are thought to deteriorate earlier with age (Brickman et al., 2012), our findings suggest that regions vulnerable to aging retain some level of plasticity that can be induced by aerobic exercise.

However, we found no associations between increased cardiorespiratory fitness and change in T1w/T2w signal; this is in contrast to earlier clinical trials reporting such correlations with brain functional activity (Voss et al., 2018), gray matter volume (Kramer and Colcombe, 2018), and fractional anisotropy (Burzynska et al., 2014). A possible explanation is that cardiorespiratory fitness is a multi-component measure that comprises oxygen supply (e.g., cardiac output, erythrocyte mass, vascular resistance) and demand factors (e.g., muscle mitochondrial respiration rate) (Lundby et al., 2017). Thus, changes in the T1w/T2w signal may be associated with some of these physiological adaptations to exercise, which we did not measure. It is also possible that such associations are no longer present at 6 months of training since cardiorespiratory fitness improvements taper off at 3–12 months of training, after the initial rapid increase (Erickson et al., 2011; Lundby et al., 2017; Vidoni et al., 2015; Voss et al., 2018). To identify the physiological mechanisms linking aerobic exercise to increases of T1w/T2w signal, future studies should include measures of physiological and vascular

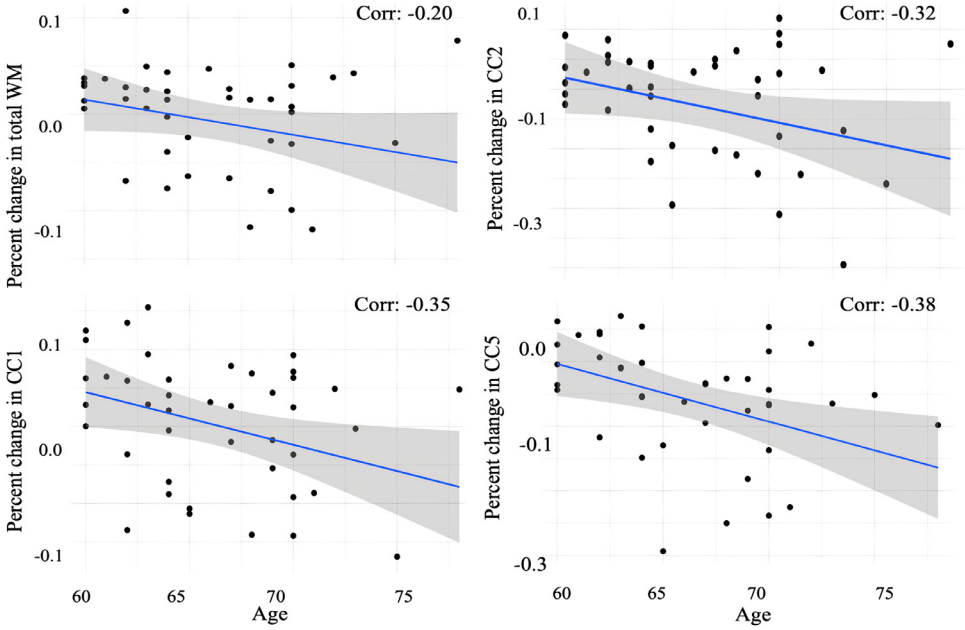

Fig. 3. Relationship between change in T1w/T2w and age. Scatterplots showing the relationship between the percent change in T1w/T2w and age in the active control group. The negative relationship indicates that greater age was associated with a more negative change in white matter T1w/T2w. White matter regions displayed are total white matter (WM), CC1 (genu), CC2 (anterior body), CC5 (splenium). Error shading indicates 95% confidence intervals.

adaptations associated with cardiorespiratory fitness, such as changes in neurotrophic factors, markers of vascular function and inflammation, as well as skeletal muscle metabolism (Tari et al., 2019).

4.2. Is walking more effective than dancing in increasing T1w/T2w?

Although we observed no significant differences in T1w/T2w signal change between the dance and walking conditions, the descriptive effect sizes observed hint at a possible advantage of walking. Possible explanations include the smaller sample size of the dancing ($n = 51$) compared to the walking group ($n = 86$) or the lower volume and intensity of the dance training compared to the aerobic walking. For example, the dance classes included a significant amount of low-intensity instructional time, which may explain lower gains in cardiorespiratory fitness in the dance group, as reported by Voss et al. (2018), where only the walking interventions led to gains in cardiorespiratory fitness relative to the active control.

Since the dance training required learning complex perceptual-motor sequences, we expected that this intervention would result in plasticity in additional white matter regions (e.g., the fornix) when compared to the walking training, as reported in (Burzynska et al., 2017) and Table A.4. It is possible that DTI is more sensitive to dance-induced changes in the fornix microstructure than the T1w/T2w signal, since about 40% of its fibers are unmyelinated (Peters et al., 2010). Together, our data suggest that dance and walking interventions may elicit spatially overlapping effects, possibly due to the shared aerobic exercise component.

4.3. White matter signal declined over time

T1w/T2w signal decreased over a 6-month period in the majority of white matter regions in the active control group, consistent with earlier findings of a widespread decline in fractional anisotropy that involved association, commisural, and limbic fibers (Bender et al., 2016; Burzynska et al., 2017; Sexton et al., 2014). However, we did not observe 6-month decline in T1w/T2w signal in the genu of the corpus callosum, a late-myelinating tract susceptible to age-related changes according to the development-to-degeneration or anterior-to-posterior gradient hypotheses of brain aging (Brickman et al., 2012; Head et al., 2004). Instead, we found significant 6-month changes in the more posterior sections of the corpus callosum: the body and the splenium. The discrepancy between T1w/T2w and DTI in detecting short-term changes may be related to different sensitivities of these methods. For example, fractional anisotropy is thought to be particularly sensitive to changes in regions with smaller diameter axons that are coherently oriented and densely packed (e.g., genu, fornix) (Burzynska et al., 2017, 2010). Conversely, the T1w/T2w signal may be better suited to detect longitudinal changes in regions with larger axonal diameter, such as the body and the splenium of the corpus callosum (Lamantia and Rakic, 1990), or in tracts containing more fiber crossings such as the cingulum bundle or the superior longitudinal fasciculi (Glenn et al., 2016). Lastly, we observed that the magnitude of decline of T1w/T2w signal within the corpus callosum was greater with advancing age in the active control group, consistent with earlier DTI findings (Fanning et al., 2017). However, the observation that the T1w/T2w changes with age is supported by studies using relaxometric measurements, where the amplitude of the T1 and T2 relaxation intensity values for the white matter changes as a function of age; with the highest peaks in the white matter observed after the age of 60 (Saito et al., 2009). This increase is thought to reflect brain demyelination, edema or inflammation (Deoni, 2010). Similarly, R1, a measure of longitudinal relaxation rate, shows consistent decline after the age of 70, possibly reflecting the rate of white matter degeneration and proliferation of glia (Yeatman et al., 2014). In sum, our results suggest that T1w/T2w signal can detect short-term age-related changes in the white matter.

4.4. Increases in white matter signal correlated with improved episodic memory

In the walking group, we found a positive association between changes in episodic memory and T1w/T2w in the total white matter, the genu of the corpus callosum and, at trend level, in the cingulum. The genu of the corpus callosum is known to be involved in interhemispheric integration and the recruitment of the ventrolateral prefrontal cortex in episodic memory processes in older adults (Bucur et al., 2008). Decreased fractional anisotropy in the dorsal cingulum has been linked to episodic memory impairment (Lockhart et al., 2012). Thus, our findings in humans complement studies in rodents showing activity-dependent myelin formation linked to improved memory performance (Fields and Bukalo, 2020). In particular, a recent study in mice demonstrated that new myelin formation is required for proper functioning of prefrontal regions and consolidation and retrieval of remote fear memories (Pan et al., 2020).

Our findings also agree with an earlier study that observed a correlation between increased gray matter volume in the prefrontal and cingulate cortices and improvement in episodic memory performance, independent of aerobic fitness measured with a lactate step test (Ruscheweyh et al., 2011). Overall, our results suggest that white matter plasticity measured as change in T1w/T2w signal is relevant for episodic memory processes, but this change in T1w/T2w was not associated with cardiorespiratory fitness gains.

Given the known effects of aerobic exercise on executive functions and processing speed (Colcombe and Kramer, 2003; Kramer and Colcombe, 2018), and the reliance of processing speed on white matter integrity (Chopra et al., 2018), we were surprised to find no associations between change in T1w/T2w and change in these two cognitive abilities. Future studies need to determine whether exercise-induced gains are specific to memory function, using a broader array of cognitive assessments as well as measures like brain-derived neurotrophic factor (Erickson et al., 2011).

4.5. T1w/T2w as a measure of white matter plasticity

Because this is the first application using T1w/T2w to study white matter plasticity, our findings need to be interpreted with caution. Despite recent animal studies showing activity-dependent remodeling of myelin and axons as important mechanisms of neuroplasticity (Bobinski et al., 2011; Chen et al., 2019; Fields and Bukalo, 2020), it is still premature to relate changes in T1w/T2w to any particular microstructural mechanism. For example, T1w/T2w signal was initially used to map myelin content and showed a strong correlation with myeloarchitecture of the developing neocortex in humans and primates (Glasser and van Essen, 2011). Subsequently, T1w/T2w was shown to correlate with oligodendrocyte-specific gene expression in humans (Patel et al., 2020) and MRI-derived synthetic myelin volume fraction in human white matter (Saccenti et al., 2020). However, other studies have reported correlations of T1w/T2w signal with MRI estimates of axonal diameter (Arshad et al., 2017), axonal density (Fukutomi et al., 2018), iron content (Shams et al., 2019), as well as weak correlations between T1w/T2w and myelin water fraction in subcortical structures (Uddin et al., 2018). This is consistent with the fact that T1 and T2 relaxations are determined by biophysical properties that may be altered by several histological processes in the white matter tissue (Deoni, 2010), limiting T1w/T2w specificity. Also, T1 and T2 relaxations are not independent, namely, recovery of longitudinal T1 magnetization co-occurs with the loss of T2 transverse magnetization (Deoni, 2010). However, our results in combination with the high validity of the T1w/T2w signal after calibration (Arshad et al., 2017) suggest that the T1w/T2w offers a promising measure of white matter microstructure, independent of the tissue diffusivity properties. Therefore, although our results suggest that the T1w/T2w offers a promising measure of WM microstructure, further examination, using more accurate estimates of myelin and axonal density (Lee et al., 2020; MacKay and Laule, 2016), is required.

4.6. Limitations and future directions

We measured cardiorespiratory fitness as the main physiological variable to be manipulated by the aerobic exercise intervention. However, our results suggest that other measures need to be considered to understand white matter plasticity, such as neurotrophic factors as well as markers of inflammation and vascular function. Furthermore, we did not collect a measure of performance gain in the dance group, which limits our interpretation of the effects of dance training on the white matter. Another potential limitation is that the observed effect sizes can be seemingly small, but we believe these can be larger with longer longitudinal designs (>6 months) and more representative samples. For example, Erickson et al. (2011) reports medium to large effect sizes when studying exercise-induced changes in the hippocampus volume, with larger effect sizes observed in the anterior hippocampus. However, this change in hippocampal volume was studied in the context of a 12-month intervention and the effects were half at 6-months, comparable to those obtained in our study. In addition, our sample was composed of healthy older adults with few comorbidities, mostly normotensive (mean blood pressure of 132/69 mmHg), and highly educated (16 mean years of education) which could have diminished the intervention-induced effects observed. Lastly, although we used a false discovery rate correction for our exploratory analyses, our primary linear-mixed effect analyses were not corrected. Therefore, a replication of these findings is necessary. These intervention-induced plasticity effects need to be tested in larger and more diverse longitudinal and experimental studies. Thus, we provide effect size estimates to help guide sample size consideration in future clinical trials.

Given the prevalence of white matter hyperintensities in the aging population, and their predictive role in cognitive impairment and Alzheimer's Disease (Yoshita et al., 2006), we considered white matter signal abnormalities as both the target or confounding factor in the exercise intervention. In line with other studies measuring white matter hyperintensities, we found no effect of time or time-by-group interaction on white matter signal abnormality volume (Torres et al., 2015; Venkatraman et al., 2020a), consistent with the slow progression of white matter hyperintensities in healthy individuals with minimal cardiovascular risk (Ramirez et al., 2016). However, our findings need to be interpreted with caution, given that the gold-standard FLAIR images were not available in our study to estimate white matter hyperintensity volume. The volume of hypointense signal on T1-weighted images used in this study has been shown to misclassify signal or underestimate lesion volume, especially in subjects with low lesion burden (Olsson et al., 2013).

Furthermore, although Tract-Based Spatial Statistics searches for the highest local fractional anisotropy value, which should exclude voxels with typically low anisotropy within the white matter lesions, some voxels affected by white matter signal abnormality have been included in the analyses (Fig. A.3.). However, we expect that this effect would be localized to posterior periventricular regions and be present in a few participants, with little effect on T1w/T2w signal in the total white matter. This is supported by the fact that we found no impact of white matter signal abnormality volume on the intervention effect. Future studies should exclude voxels affected by hyperintensities using FLAIR images to determine whether the effects of exercise interventions differ between normal appearing white matter and white matter lesions. Nevertheless, our careful analysis of projection of voxels onto the skeleton across and within participants shows that Tract-Based Spatial Statistics successfully minimized partial volume effects with cerebrospinal fluid or gray matter, which are likely to occur in older samples with heterogenous brain anatomy due to age-related atrophy (Scahill et al., 2003).

Finally, because our T2-weighted images had limited brain coverage, we were not able to include other WM regions of the hippocampal formation that may be key for episodic memory processes (Burgess et al., 2002), fronto-temporal connections such as uncinate fasciculus, or lower sections of the corticospinal tract (i.e., cerebral peduncles). Future studies should include these white matter regions to further understand the effects of walking and dance training on the aging white matter and identify new associations between change in T1w/T2w signal with episodic memory, processing speed, and executive function. Another potential limitation is using $b = 0$ images from DTI acquisition as T2-w images for T1w/T2w calculation, as b0 images are subjected to echo planar imaging distortions, in addition to potential non-linear signal intensity variations due to the GRAPPA reconstruction. However, given that we used a small acceleration factor of 2, the typical posterior-to-anterior signal intensity variations due to GRAPPA were negligible in our images (Robson et al., 2008). However, because of these pulse sequence differences, the results from this study need to be replicated in other T1w/T2w studies using longer echo trains with lower flip angle pulses. In addition, future studies should consider evaluating the differences in performance of distinct processing workflows for the T1w/T2w signal (e.g., varying

INU algorithms, and the effects of possible regional differences in SNR), especially with the development of high-field MR scanners, where the INU correction becomes increasingly important (Uwano et al., 2014).

5. Conclusion

Our study provides evidence for white matter plasticity in older adults induced by aerobic walking and dance, measured as an increase in T1w/T2w signal. The findings suggest that the white matter in the adult brain retains plasticity in vulnerable regions and that these changes can be observed on a short-term scale. Further studies are needed to understand the exercise-induced adaptations that lead to increased T1w/T2w and that mediate effects on episodic memory function. Given that myelin-sensitive imaging MRI is often not collected within the large studies on aging (e.g. ADNI (Jack et al., 2008), UK Biobank (Alfaro-Almagro et al., 2018), ENIGMA (Thompson et al., 2014), HCP (Sotiropoulos et al., 2013)) or randomized controlled trials (e.g. IGNITE (Erickson et al., 2019)), our findings suggest that T1w/T2w may offer an alternative and accessible metric of white matter integrity. Our results encourage revisiting existing datasets to further explore the potential of T1w/T2w to detect white matter decline or plasticity.

Data statement

The data that support the findings of this study are openly available in Mendeley Data at DOI: http://dx.doi.org/10.17632/c7s4n48kd2.1

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Declaration of Competing Interest

The authors declare no competing financial interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.118305.

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