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The effects of a six-month exercise intervention on white matter microstructure in older adults at risk for diabetes

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ABSTRACT

Older adults with prediabetes or obesity (i.e., those at risk for diabetes) exhibit impaired structural brain networks. Given findings that resistance training (RT) can combat brain impairments in many populations, this study aimed to test the effects of this type of exercise on white matter microstructure in older adults at risk for diabetes. Seventeen community-dwelling older adults (mean age 67.8 ± 5.7, 52.9 % female) with prediabetes or obesity were randomly allocated to thrice weekly RT or balance and tone training (BAT; control group) for six months. Diffusion weighted imaging via a 3T scanner was used to assess changes in white matter parameters –fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) – over time. Participants in the RT group showed no significant changes in FA but had increased MD and RD in various regions related to cognitive function including the cingulate gyrus. Participants in the control group had both increased and decreased FA depending on the specific white matter tracts; increased FA was seen in areas related to motor coordination such as the middle cerebellar peduncle. The control group also exhibited decreased MD and RD in areas responsible for motor function (e.g., left anterior limb of the internal capsule). We conclude that both resistance and balance exercises result in changes in white matter microstructure albeit in divergent tracts that may be linked to the specific exercises performed.

1. Introduction

Cognitive impairment is an increasing concern in our society given our rapidly expanding older adult population. From minor inconveniences (e.g., misplacing car keys) to major impacts on functional independence and quality of life (e.g., unable to independently care for oneself), declines in cognition have important implications for the daily lives of older adults. Cognitive function is supported by brain health, which refers to the effectiveness, efficiency, and integrity of brain structure and function required for an individual to perform desired activities [1]. It has been shown that brain health declines with age; for example, studies have found that total brain volume decreases by >0.5 % annually after the age of 60 [2]. Importantly, declines in brain health are both a biomarker and a predictor of dementia [3].

The rate and degree of age-related declines in brain health, however, are not universal. Certain clinical populations are more susceptible to declines in brain health, and consequently are at greater risk for dementia. One example is those with type 2 diabetes (T2D). Older adults who have T2D experience neurodegeneration and cognitive dysfunction beyond normative aging, thus increasing their risk of dementia [4,5]. Importantly, individuals who are at-risk for diabetes (e.g., those who have prediabetes or are overweight/obese) also show evidence of accelerated declines in brain health. In a recent systematic review, older adults with prediabetes were shown to have impaired structural connectivity compared to age-matched controls [6]. Moreover, Raji and colleagues [7] demonstrated that older adults who are obese have significant atrophy in key brain areas that support cognitive function, such as the frontal lobes, anterior cingulate gyrus, hippocampus, and thalamus, above and beyond fasting blood glucose levels or diabetes status, and controlling for age, gender, and race.

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Previous research has pointed specifically towards alterations in white matter (WM) microstructure in this population. For example, differences in microstructure along WM tracts, microscopic WM lesions, and disrupted WM neural network organization were all observed in the prediabetic stage [8,9]. Further, evidence from observational studies demonstrated significant associations between prediabetes and decreased WM volume and increased risk of WM hyperintensities [10]. Along the same lines, deficits in WM microstructure have been consistently exhibited in those who are overweight or obese. Indeed, BMI has been found to be negatively correlated with WM microstructure, including in young adults [11], adults [12], and in two large independent cohorts [13]. Collectively, these results provide evidence that those at-risk for diabetes have detectable declines in brain health. Given their current trajectory towards further cognitive impairment, those at-risk for diabetes represent an ideal population for targeted interventions to maintain or improve brain health.

Physical activity is a modifiable behaviour that can improve cognition and brain health and may also reduce dementia risk [14]. Indeed, there is robust cross-sectional and intervention evidence demonstrating the positive impact that exercise can have for cognitive function [15,16], brain function [17,18], and brain structure [19]. The majority of exercise interventions to-date have focused on aerobic training (e.g., [17,20,21]), which includes exercise aimed at increasing cardiovascular capacity, such as walking or running. However, resistance training (RT) – defined as exercises aimed at increasing muscle mass, has also been shown to benefit cognition and brain health. Older females who completed 52 weeks of twice-weekly progressive RT improved their executive functioning and had corresponding changes in functional brain activation [22,23]. Reductions in WM atrophy and WM lesions after an RT intervention were also reported [24]. Similarly, RT was shown to improve executive function, memory, and functional brain plasticity in older females with mild cognitive impairment (MCI) [25,26], and in older adults at-risk for diabetes [27-29]. However, RT in general has been much less widely studied, and more specifically, the effects of RT on WM microstructure in older adults at-risk for diabetes remain unknown. Because of the essential role that WM microstructure plays in cognitive, motor, and sensory functions [30], understanding how lifestyle modifications can impact WM microstructure specifically has important functional and clinical implications.

The aim of this study was to examine the effects of a six-month RT intervention in older adults at-risk for diabetes on WM microstructure, as measured using diffusion tensor imaging (DTI). DTI is a highly sensitive tool that allows in vivo assessment of the microstructure of WM tracts, which include but are not limited to: axon diameter, axon packing density, membrane permeability, myelination, and architectural paradigm [31]. We extracted three DTI parameters (fractional anisotropy, FA; mean diffusivity, MD; radial diffusivity, RD). Each of these provide information about the property of WM [32]. FA is a quantitative measure that describes the general status of the underlying neural tissue architecture and is measured on a scale from 0 (isotropic movement of water molecules) to 1 (anisotropic movement of water molecules). Changes in microstructural properties (e.g., cell damage, loss in cell density) result in changes in FA. Previous pathological studies show that reductions in FA are associated with neurodegenerative diseases, representing a loss of organized structure [33,34]. While FA is sensitive to general microstructural changes, it is not specific to the type of changes (i.e., whether changes are attributed to increases in axonal density, increases in myelin, etc.); therefore, MD and RD are often measured to better interpret FA changes [35]. MD is an indicator of overall cellular integrity [32]. When structurally organized tissue (i.e., WM tracts) undergo degeneration, MD increases and FA decreases [34]. RD, on the other hand, is associated with axonal density, axonal diameter, and myelin integrity [36,37]. Animal studies have found increased RD with demyelination of specific brain regions, representing a potential marker of myelin disintegration [38].

DTI was selected as an outcome measure for this study because of the known declines in DTI metrics in this population. A recent meta-analysis found that in those with T2D, 10 white matter regions exhibited reduced FA compared to controls, including: genu of the corpus callosum, the body of corpus callosum, bilateral anterior corona radiata, bilateral superior corona radiata, bilateral cingulum, and bilateral superior fronto-occipital fasciculus [39]. Similar results have been found in those with prediabetes, where FA was shown to be reduced in right corpus callosum body, right superior longitudinal fasciculus, and left superior longitudinal fasciculus, compared to healthy controls [9]. Thus, there is evidence that targeted regions in the brain are susceptible to changes in DTI metrics as a result of diabetic status. Further, there is preliminary evidence that DTI metrics may be sensitive to changes resulting from an exercise intervention [21,40-42], although the work to date has focused almost exclusively on the effects of aerobic exercise and within healthy older adult populations. Further, the results from aerobic exercise interventions on DTI metrics have reported inconsistent results with insignificant or small effect sizes. Thus, examining changes in DTI metrics resulting from RT in an at-risk population represents a novel addition to the literature and has the potential to inform a new intervention strategy that may alter white matter in the brain.

We hypothesized that six months of RT would result in increased microstructural integrity of WM tracts in older adults at-risk for diabetes. Further, these would be most strengthened in areas responsible for cognitive function, including executive function and memory (e.g., fornix, cingulum) as these functions have been shown to positively respond to RT interventions [22,23,25-27,29] and appear to be negatively impacted to a greater extent in this population, as discussed above. Given that increases in FA and decreases in MD and RD are associated with better white matter integrity, we hypothesized that RT would result in increased FA and decreased MD and RD after six months. This pilot study represents the first to examine the effects of RT on microstructure in older adults at-risk for diabetes; yet such findings would have the potential to provide a feasible and accessible intervention to improve brain health in this at-risk population.

2. Methods

2.1. Study design

This is a secondary analysis from a randomized controlled trial (RCT) examining the feasibility of a six-month RT intervention in older adults at-risk for diabetes. Details of the RCT protocol have been reported elsewhere [27-29]. Briefly, we conducted a single-blinded, six-month intervention with two arms: 1) RT (experimental arm), and 2) balance and tone exercises (BAT; control arm). Magnetic resonance imaging (MRI) was performed at baseline and trial completion. Written informed consent was obtained from all participants, and ethics approval was obtained from the Health Sciences Research Ethics Board at Western University. The trial was registered at clinicaltrials.gov (ID: NCT03254381).

2.2. Participants

The full list of inclusion and exclusion criteria for the RCT is reported elsewhere [28]. Briefly, we included participants who were community-dwelling older adults aged 60–80 years old and who were at-risk for diabetes (body mass index of $\geq$ 25 and/or fasting blood glucose level of 6.1 to $<$ 7.0 mmol/L) [43]. Participants were excluded if they had a medical condition for which exercise was contraindicated, regularly participated in exercise over the past six months, had been diagnosed with a neurodegenerative disease or psychiatric condition, or were unable to participate in MRI (e.g., claustrophobic, metal implants). Randomization of participants into the two arms was completed using an online randomization site (randomization.com) by the Principal Investigator who held the sequence remotely.

2.3. Exercise intervention

Participants in both groups attended their respective exercise classes thrice weekly on non-consecutive days for 26 weeks. All classes were held at Western University and led by research assistants (RAs) who were undergraduate students in the School of Kinesiology at Western University. The classes were 60 min in duration, which included a 10-minute warm-up and a 10-minute cool-down. Participants exercised in small groups of two to four people. Attendance was recorded at each class to measure adherence and program fidelity was assessed by an independent assessor who attended classes randomly each month.

The protocol for the RT group is outlined by Liu-Ambrose and colleagues [23]. Briefly, the RT group underwent progressive RT using the 7RM method, where the participants were required to complete two sets of six to eight repetitions of each exercise. The exercises included were: leg press, lat pulldown, leg curl, chest press, bicep curl, tricep curl, and seated row. In addition, participants performed mini-squats, mini--lunges, and walking lunges with body weight. Once exercises were performed with proper form and without discomfort, the intensity was increased. The warm-up and cool-downs consisted of independently walking on a treadmill or a light pace on an elliptical machine. Participants in the BAT group were required to perform light-intensity upper and lower limb gentle movements. Warm-up and cool-down sessions consisted of stretching as a group. The BAT group served to control for the potential benefits of socialization and committing to a new exercise program [23].

2.4. Behavioural measures

Executive function was assessed using paper-and-pen versions of three tests to tap into separate yet related components of executive function [44]: The Digit Span test (forward and backward) to assess working memory, the Trail Making test (Part A and B) to assess set-shifting, and the Stroop Colour Word test to assess response inhibition. For each test, we created a difference score between the two versions to examine executive function above and beyond basic cognitive processing (e.g., Trail Making Part B minus Trail Making Part A to examine the executive component of set-shifting controlling for motor response and processing time). Memory and learning were assessed using the Rey Auditory Verbal Learning test (RAVLT) [43] where our measure of interest was the number of words recalled after a 20-minute delay. Cognitive dysfunction was assessed using the Alzheimer's Disease Assessment Scale – Cognitive Version 11 (ADAS-Cog 11) [45], with higher score indicating greater cognitive dysfunction. Item and associative memory were assessed using a computerized memory task where participants were shown images of people and places and had to either memorize the individual items (e.g., people or places) or the items in conjunction (the people together in the context with the place; i.e., "face-place task"; associative memory) [29]. The measure of interest for this was dprime, a measure of signal detection that accounts for response bias, with higher numbers indicating greater memory performance. Physical measures included the Short Physical Performance Battery (SPPB) [46] which provides a total score out of 12 with higher scores indicating better balance and mobility and the Timed Up and Go test (TUG) [47] where participants stand from a seated position, walk 3 m, and return to their seat; a shorter time to complete the TUG indicates better mobility [47].

2.5. MRI data acquisition

All MRI data were collected on a Siemens Prisma 3T scanner located at the Centre for Functional and Metabolic Mapping (CFMM) at Western University. A single-shot T1-weighted sagittal MP2RAGE sequence ($1 \times 1 \times 1$ mm^3; GRAPPA 2; TR/TE 2300/2.98 ms) was acquired for each participant to check for any structural abnormalities (e.g., congenital abnormalities, vascular abnormalities, evidence of prior brain injury, etc.) that would preclude inclusion in the study. A thirty-direction diffusion-weighted sequence ($2 \times 2 \times 2$ mm^3; GRAPPA 2; 70 slices; TR/TE 9400/64 ms; Fat Sat weak; b0/b1 0/1000s/mm^2) was used to acquire DTI data for each participant at each time point (i.e., baseline and trial completion).

2.6. Diffusion image preprocessing

DTI analysis was performed using with FMRIB's Software Library (FSL V.6.0.10) for macOS. Following the standard FSL diffusion processing pipeline, we used the FMRIB's Diffusion Toolbox to pre-process each participant's diffusion images, individually (FDT, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT/) [48]. Non-brain tissues (e.g., skull, fat, etc.) were removed from the b0 image using FMRIB's Brain Extraction Tool (BET) [49]. The present study was unable to correct for susceptibility-induced distortions using FMRIB's TOPUP due to the failure of acquiring an opposing phase-encoding polarity diffusion-weighted image [48,50]. Correction for eddy current-induced distortions was performed using FMRIB's eddy_correct [51]. The diffusion tensor was fitted to the eddy corrected diffusion data using FMRIB's DTIFIT, using the default options, and FA, MD, and RD maps were computed.

2.7. Tract-Based spatial statistics (TBSS)

Following diffusion image preprocessing, we used FMRIB's Tract-Based Spatial Statistics (TBSS) to carry out voxel-wise statistical analysis [52]. Briefly, all participants' FA images were eroded slightly and the first and last slices were set to zero to remove potential outliers from the diffusion tensor fitting. Then, a nonlinear registration was run, aligning each participant's FA image to the $1 \times 1 \times 1$ mm FMRIB58_FA standard space image. As we chose to use the FMRIB58_FA standard space image as the target during the initial nonlinear registration step, no additional affine transformation was applied. The FMRIB58_FA mean, skeletonized FA image was used as the skeleton image using the default threshold of 0.2 to suppress areas of non-WM voxels. Finally, each participant's aligned FA data, for each time-point, was then projected on to the mean FA skeleton. We specifically note that the above TBSS run included all participants' FA images from both time-points. This procedure was repeated for each participant's MD and RD map using the registration and projection vectors obtained in the FA nonlinear registration.

2.8. Statistical analyses

2.8.1. Region-of-interest (ROI) analyses

The ICBM-DT-81 white-matter label atlas [53,54,55] was used to define tracts-of-interest for ROI (region-of-interest) analyses. The mean value for each subject and each time point was extracted for each tract and each DTI metric (FA, MD, and RD).

2.8.2. Statistical comparisons of ROI data

All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) Version 28.0 (IBM SPSS Statistics). As this is an exploratory sub-analysis that was not adequately powered to examine between group differences for our tertiary outcome measures from DTI, we focused on within group changes over time. Further, to fully capture results that can then be used to inform future full-scale RCTs, we did not correct for family-wise error rates or include covariates within this analysis. For each DTI metric, we tested for normality within each intervention group (i.e., RT, BAT), for each time point (i.e., baseline and trial completion), and for each of the 48 regions using the Shapiro-Wilk statistical test [56] and the normal Q-Q Plot. Significance for the Shapiro-Wilk test was assessed at $p > 0.05$, while significance for the Q-Q Plot was assessed by visually examining whether the majority of the data points followed the trend line. Any tract-of-interest that

exhibited normality was submitted to a paired-sample *t*-test, comparing the time points for a given intervention group (i.e., RT, BAT). For the paired-samples *t*-test, we set the statistical significance at $p \leq 0.05$. We excluded values in which one of the pairs was missing. In addition we report Cohen's d values for each significant *t*-test which we interpret using the standard guidelines where $d = 0.2$, $d = 0.5$, and $d = 0.8$ indicate a small, medium, and large effect size respectively.

2.8.3. Correlations between behavioural and DTI measures

To examine the relationship between changes in DTI measures and changes in behavioural measures, we report Pearson bi-variate correlations. The DTI measures included in the correlation analysis were those that were found to change significantly between baseline and trial completion in either of the two groups, and all participants were included in the correlations regardless of group allocation. Change was calculated as trial completion minus baseline values. Statistical significance was set at $p \leq 0.05$ for all correlations.

3. Results

3.1. Participant characteristics

Our secondary analysis included 17 participants, 11 of which were in the RT group and six of which were in the BAT group. Baseline characteristics of our sample are provided in Table 1 and study flow is presented in Fig. 1. Our sample was 67.8 years old on average (SD=5.7) and 52.9 % of the participants was female. At baseline, average BMI was 30.7 kg/m^2 and fasting blood glucose was 5.1 mmol/L.

Briefly, the intervention was found to be feasible from a recruitment, retention, and adherence standpoint [27]. Retention in the intervention was 100 % for participants in this sub-study (95.8 % for the study overall). Adherence to the exercise program for participants in this sub-study ranged from 45 to 74 classes out of 78 total, with a mean of 65.6 (84.1 %) (84.4 % for the study overall). Further, we reported preliminary evidence of the efficacy of the intervention on changing key cognitive outcome measures (task-switching, attention, and conflict resolution), as well as changes in activation consistent with increased efficiency as measured via functional magnetic resonance imaging (fMRI) during an associative memory task [29]. Other baseline characteristics and intervention changes are reported elsewhere [27,29]. Intervention changes for our key measures of interest within this sub-study are presented in Table 2.

3.2. Fractional anisotropy (FA)

DTI changes in the BAT group and the RT group are presented in Figs. 2 and Fig. 3 respectively. Changes in FA over the six-month intervention with p-value based on the paired-sample *t*-test and corresponding Cohen's d values are presented in Table 3. Participants in the BAT group exhibited a significant *increase* in FA at trial completion compared to baseline in the following regions: left uncinate fasciculus ($p = 0.019$), middle cerebellar peduncle ($p = 0.030$), pontine crossing tract ($p = 0.027$), and right superior front-occipital fasciculus ($p = 0.033$). At the same time, the BAT group showed a significant *decrease* in FA in the following regions: left posterior thalamic radiata (including optic radiation) ($p = 0.053$), fornix ($p = 0.051$), left posterior corona radiata left ($p = 0.010$), and right tapetum ($p = 0.041$). There were no significant changes over time in FA in the RT group.

Table 1
Participant baseline characteristics ($n = 17$).

Characteristics	BAT	RT	Total	*p*-value
Number of subjects, n (%)	6 (35.3 %)	11 (64.7 %)	17	
Age, years (mean ± SD)	67.3 ± 5.6	68.1 ± 6.1	67.8 ± 5.7	0.80
Sex, n females (%)	3 (50 %)	6 (54.6 %)	9 (52.9 %)	0.86
Education, n (%)				0.47
High school diploma	0 (0 %)	2 (18.2 %)	2 (11.8 %)	
Some college	1 (16.7 %)	2 (18.2 %)	3 (17.6 %)	
College/trade degree	0 (0 %)	2 (18.2 %)	2 (11.8 %)	
Bachelor's degree	2 (33.3 %)	3 (27.3 %)	5 (29.4 %)	
Graduate degree	3 (50 %)	2 (18.2 %)	5 (29.4 %)	
BMI (kg/m^2, mean ± SD)	31.8 ± 4.8	30.1 ± 2.5	30.7 ± 3.4	0.35
FBG (mmol, mean ± SD)	5.1 ± 0.8	5.1 ± 0.8	5.1 ± 0.8	0.86
FCI (mean ± SD)	2.5 ± 1.2	0.7 ± 0.8	1.4 ± 1.3	<0.01*

BAT, balance and tone; RT, resistance training; BMI, body mass index; FBG, fasting blood glucose; FCI, Functional Comorbidity Index.
* $p \leq 0.05$.

3.3. Mean diffusivity (MD)

Changes in MD over the six-month intervention are presented in Table 4. The BAT group showed a significant *decrease* in MD in the anterior limb of the left internal capsule ($p = 0.051$) and the left posterior limb of the internal capsule ($p = 0.047$). In contrast, the RT group demonstrated a significant *increase* in MD only in the left cingulum (cingulate gyrus) ($p = 0.021$) and a significant *decrease* in MD in the right anterior corona radiata ($p = 0.042$) and the left posterior corona radiata ($p = 0.038$).

3.4. Radial diffusivity (RD)

Changes in RD over the intervention are presented in Table 5. The BAT group elicited a significant *decrease* in RD in the left posterior limb of the internal capsule ($p = 0.045$) and the left superior front-occipital fasciculus ($p = 0.053$). Participants in the RT group had a significant *increase* in RD in the genu of the corpus callosum ($p = 0.038$) and the fornix ($p = 0.054$).

3.5. Correlations between behavioural and DTI measures

For FA, there was a positive correlation between changes in the fornix and changes in performance on the digit span after the six month intervention, r(17)=0.668, $p = 0.003$, where increased FA values were associated with declines in working memory. In contrast, the fornix was also positively correlated with changes in item memory, such that greater FA over time was associated with improved item memory, r(17)=0.704, $p = 0.002$. In terms of mobility, improved performance on the TUG over six months was associated with increased FA values in the pontine crossing tract, r(17)=−0.683, $p = 0.003$ and decreased FA values in the left posterior corona radiata, r(17)=0.496, $p = 0.043$.

For MD, we found that higher MD in the left posterior corona radiata was associated with better learning and memory performance, as assessed by the RAVLT, r(13)=0.663, $p = 0.013$; in contrast, lower MD in the left anterior limb of the internal capsule was significantly associated with better RAVLT performance, r(13)=−0.556, $p = 0.049$.

For RD, we found that increased RD in the genu of the corpus callosum and the fornix were associated with improved associative and item memory performance, respectively, as assessed by the face-place task, r(17)=0.532, $p = 0.028$ and r(17)=0.621, $p = 0.008$. Decreases in RD in the left posterior limb of the internal capsule were associated with better item memory performance, r(17)=−0.484, $p = 0.049$. Conversely, increased RD in the left superior fronto-occipital fasciculus was associated with better Trail Making performance, r(15)=−0.525, $p = 0.044$.

4. Discussion

In this secondary analysis of DTI data from a six-month exercise intervention in older adults at-risk for diabetes, we report that both types of exercise (RT and balance-and-toning) resulted in changes in key indices of WM microstructure. Within this exploratory analysis, several noteworthy patterns emerged that have implications for both physical and cognitive function in this at-risk population and provide evidence

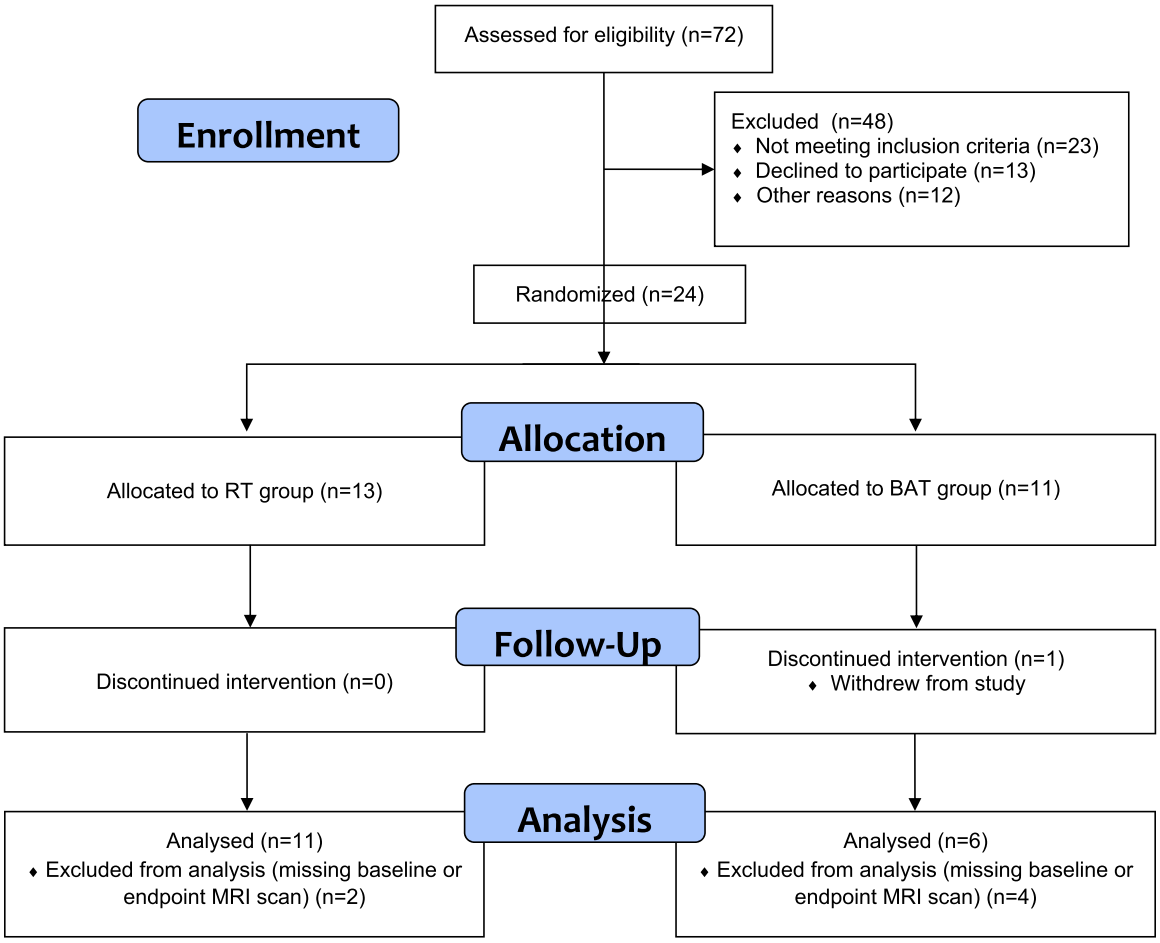

Fig. 1. Recruitment flow diagram. BAT, balance and tone; RT, resistance training.

Table 2
Change in behavioural measures ($n = 17$).

Measure[1]	BAT	RT
Digit Span (forward minus backward)	−1.8 (2.6)	0.8 (3.6)
Trail Making Test (Part B minus Part A)	6.3 (18.3)	−9.6 (17.0)
Stroop (Part C minus Part B)	−1.2 (10.9)	−7.7 (29.0)
RAVLT	6.5 (2.4)	1.7 (2.8)
ADAS-Cog	−1.6 (2.0)	−1.5 (2.6)
Item memory	0.0 (0.4)	0.3 (0.8)
Associative memory	−0.5 (3.0)	−0.1 (1.3)
SPPB	0.2 (1.6)	0.1 (1.7)
TUG	−0.1 (1.4)	0.1 (2.5)

[1] Δ Mean ± SD (trial completion minus baseline)

BAT, balance and tone; RT, resistance training; RAVLT, Rey Auditory Verbal Learning Test, ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go test.

towards the potential role that WM microstructure plays in the connection between participation in a regular exercise program and improved behavioural measures of physical and cognitive function.

Within our RT group, we found no significant changes in FA for any tracts, and increased MD and RD over time in tracts related to cognitive function, including the cingulum cingulate gyrus, the corpus callosum, and the fornix [57-59]. These results were unexpected, as we hypothesized that FA would increase and MD and RD would decrease within this group, aligning with the assumption that higher FA and lower MD/RD reflect greater myelination [60]. These seemingly paradoxical results, however, correspond to findings in other exercise intervention studies in older adults [61-63]. For example, in the FINGER trial [35], a two-year multi-domain intervention, the authors found reductions in FA in both the intervention and control groups, as well as increases in MD and RD in both groups; this was despite a significant improvement in executive function and cognition observed in the intervention group. The authors speculated that such results may be due to axonal swelling and astrocytic hypertrophy that accompanies vascular risk factors leading to increased FA and decreased RD, rather than changes in myelination itself. Thus, they propose that their intervention may have targeted vascular risk factors resulting in a decrease in FA and increase in RD that reflect typical age-related values, mitigating inflated values due to inflammation. Given that our sample was similar to the FINGER trial in terms of risk factors and the known benefits of RT for reducing vascular risk factors [64], this explanation aligns with our results as well. Interestingly, a recent systematic review [65] of DTI in obesity found mixed evidence, where obese individuals had both higher and lower FA and MD compared to non-obese controls depending on the study. The authors cite that both a loss of myelination and neuroinflammation are contributing yet opposing factors in measures of DTI for this population – and that both negatively impact cognitive performance. Future research to elucidate the impact of obesity and other comorbidities on measures of DTI is warranted.

Another possible explanation for our results in the RT group is that the exercise intervention preserved WM microstructure. Importantly, for the aging brain, six months is a relatively long period of time where we would normally expect to see changes in several key metrics. For example, brain volume declines with age [66], with some areas being impacted more than others [67]. Evidence from DTI studies also supports this, where longitudinal changes have been found, with the most

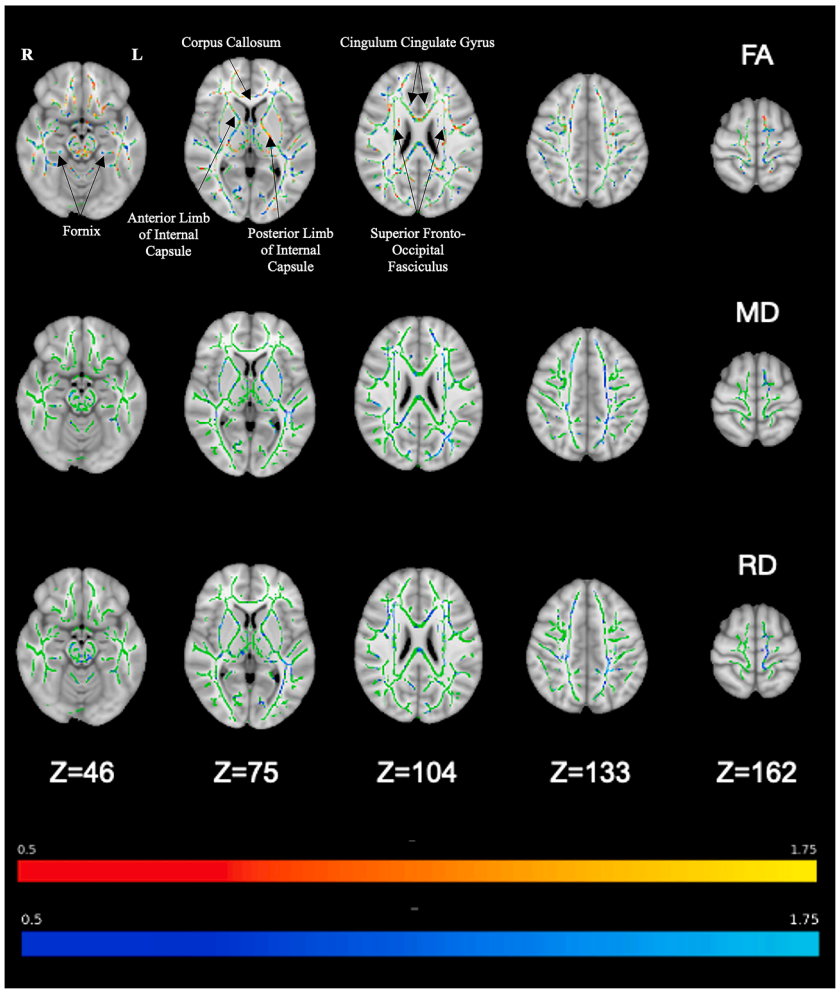

Fig. 2. Balance and tone (BAT) group: regions of significant changes in diffusivity parameters during the 6-month trial are projected on the skeleton (green) of WM ($p < 0.05$, not corrected for family-wise error). Increasing and decreasing fractional anisotropy (FA), shown in red-yellow and blue-turquoise, respectively. Decreasing mean diffusivity (MD), and radial diffusivity (RD) shown in blue-turquoise.

robust result being a decline in FA with age [68,69]. In one study comparing healthy older adults and those with MCI, declines in FA were reported in both groups, with greater declines in the MCI group after one year [70]. The areas that showed the largest decline included the corpus callosum, superior longitudinal fasciculus, uncinate fasciculus, inferior fronto-occipital fasiculus, and cingulate bundle. Thus, it is possible that while RT may not lead to increased FA, it may contribute to the prevention of age-related decreases. Future research should aim to elucidate these findings.

In contrast, within the BAT group we found that FA both increased and decreased depending on the specific WM tract. Many of the regions that exhibited an increase in FA in the BAT group are involved in motor coordination and spatial awareness, including the middle cerebellar peduncle, the pontine crossing tract, and the right superior fronto-occipital fasciculus [71,72]. This also corresponds to the results for the BAT group with respect to MD and RD, where they exhibited decreased values in tracts related to motor and somatosensory function (e.g., left anterior and posterior limbs of the internal capsule) [73] and visual processing and spatial awareness (e.g., left superior fronto-occipital fasciculus) [74]. These results align closely with the training provided in the BAT group, which includes exercises that focus on balance and coordination. Hence, our results endorse the notion that exercise training focused on these movements and skills can strengthen connections in tracts that support somatosensory function and spatial awareness. This has important implications for targeting populations in which balance and coordination is a concern, including older adults at-risk for falls, Parkinson's patients, and those who have experienced a stroke.

While the focus of this secondary analysis was on DTI measures, our correlational analysis provides insight into the potential functional consequences of these changes. Notably, we found strong alignment between changes in specific DTI tracts and corresponding behavioural changes; for example, increased FA in the fornix, which is a major output tract of the hippocampus and is implicated in the acquisition and consolidation of new episodic memories [57] was positively associated with improved item memory performance in our participants. Similarly, increased FA in the left posterior corona radiata, which is related to motor pathways [75], was significantly correlated with improved TUG performance, a motor task. These results suggest that exercise can positively impact WM microstructure related to both cognitive and motor function, further providing evidence for the widespread impacts of exercise on the brain. Additionally, this research shows that different modalities of exercise can have different yet converging benefits for brain health.

We acknowledge the strengths and limitations of this study. This is among the first studies to examine the effects of RT on DTI measures of WM microstructure, especially in a population of older adults at-risk for diabetes and consequently cognitive decline. Further, our exercise intervention itself included a robust program of thrice-weekly supervised training for six months with an active control group to examine the

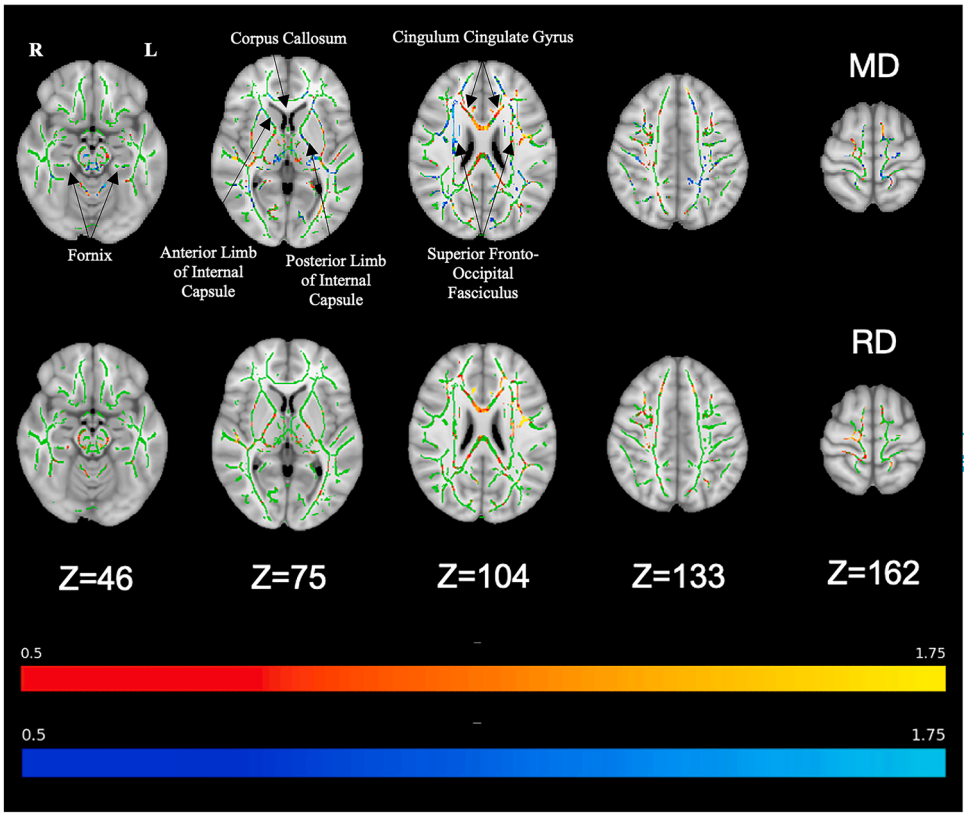

Fig. 3. Resistance training (RT) group: regions of significant changes in diffusivity parameters during the 6 month trial are projected on the skeleton (green) of WM ($p < 0.05$, not corrected for family-wise error). Increasing and decreasing mean diffusivity (MD) shown in red-yellow and blue-turquoise, respectively. Increasing radial diffusivity (RD) shown in red-yellow.

Table 3
Change in fractional anisotropy of brain regions in the Balance and tone (BAT) group.

Group	Brain Region	Δ Mean FA[1]	p-value[2]	Cohen's d
BAT	Left Uncinate Fasciculus	+ 0.00284 ± 0.00205	0.019	1.385
BAT	Middle Cerebellar Peduncle	+ 0.00184 ± 0.00151	0.030	1.221
BAT	Pontine Crossing Tract	+ 0.00657 ± 0.00518	0.027	1.268
BAT	Right Superior Fronto-Occipital Fasciculus	+ 0.00163 ± 0.00137	0.033	1.187
BAT	Left Posterior Thalamic Radiata	- 0.00185 ± 0.00179	0.053	1.031
BAT	Fornix	- 0.00332 ± 0.00318	0.051	1.045
BAT	Left Posterior Corona Radiata	- 0.00127 ± 0.00076	0.010	1.663
BAT	Right Tapetum	- 0.00057 ± 0.00051	0.041	1.121

[1] Δ Mean ± SD of fractional anisotropy (trial completion minus baseline).
[2] p-value based on the corresponding paired-sample *t*-test.

Table 4
Change in mean diffusivity of brain regions in the Balance and tone (BAT) and Resistance training (RT) groups.

Group	Brain Region	Δ Mean MD[1]	p-value[2]	Cohen's d
RT	Left Cingulum Cingulate Gyrus	+ 0.00001 ± 0.00001	0.021	0.828
RT	Right Anterior Corona Radiata	- 0.00001 ± 0.00001	0.042	0.701
RT	Left Posterior Corona Radiata	- 0.00002 ± 0.00003	0.038	0.720
BAT	Left Anterior Limb of Internal Capsule	- 0.00004 ± 0.00003	0.051	1.046
BAT	Left Posterior Limb of Internal Capsule	- 0.00006 ± 0.00005	0.047	1.069

[1] Δ Mean ± SD of mean diffusivity (trial completion minus baseline).
[2] p-value based on the corresponding paired-sample *t*-test.

effects of RT above and beyond other benefits that may come with an exercise intervention (e.g., socialization and other health-behaviour related changes). One limitation is that because this is an exploratory sub-analysis, we were not adequately powered to calculate between-group statistics and did not correct for family-wise error rates; we also note that due to MRI acquisition issues, the sample size for our control group was especially small. A related issue was our definition of "at-risk for diabetes" was based on weight and fasting glucose levels. While the gold standard for classification of prediabetes is HbA1C, our pilot study was limited to measures that could be obtained within the lab for this pilot study. The results we report are promising, yet future studies with larger sample sizes and better characterized clinical measures are required to make firm conclusions regarding the effects of different types of exercise on specific WM tracts in this population. That said, we highlight that the effect sizes reported are all in the medium to large range, thus providing us with confidence that our intervention resulted in substantial changes to our DTI metrics despite not having the power to statistically test between-group differences. Second, our assessment of WM microstructure was limited to three parameters – FA, MD, and RD. We recognize that other measures exist (e.g., axial diffusivity, AD; diffusion kurtosis imaging, DKI, etc.) which could provide further metrics of WM microstructure that may be more robust to crossing fibers [76]. Importantly, no single DTI measure should be used in isolation to

Table 5
Change in radial diffusivity of brain regions in the Balance and tone (BAT) and Resistance training (RT) groups.

Group	Brain Region	Δ Mean RD[1]	p-value[2]	Cohen's d
RT	Genu of Corpus Callosum	+ 0.00001 ± 0.00002	0.038	0.722
RT	Fornix	+ 0.00003 ± 0.00005	0.054	0.659
BAT	Left Posterior Limb of Internal Capsule	- 0.00005 ± 0.00004	0.045	1.084
BAT	Left Superior Fronto-Occipital Fasciculus	- 0.00001 ± 0.00001	0.053	1.032

[1] Δ Mean ± SD of radial diffusivity (trial completion minus baseline).
[2] p-value based on the corresponding paired-sample *t*-test.

describe WM microstructure; thus, the inclusion of three measures within our study along with the ability to place our results in context of the extant literature given the wide use of these parameters provides confidence in our results. Future studies may further quantify WM microstructure using additional measures. Finally, we acknowledge that there is still much work to be done in this field to identify the precise mechanisms for how exercise leads to changes in cognition and measures of brain function and structure.

In conclusion, we report that six-months of thrice-weekly exercise leads to changes in WM microstructure, as measured using DTI. Notably, both types of exercise used in our intervention (RT and balance-and-toning) resulted in changes in WM, albeit in divergent tracts that may be linked to the specific exercises performed. For example, RT may lead to changes resulting from decreased vascular risk factors and reduced inflammation whereas balance and tone training may strengthen regions integral for spatial awareness and coordination. This extends previous literature which has focused on examining DTI within the context of aerobic training in healthy older adult populations. Importantly, these results complement our previously published feasibility work [27] to demonstrate that an RT intervention is not only feasible in this population, but that inclusion of DTI in a future full-scale trial is warranted to examine these preliminary findings with the statistical rigour appropriate from a study with a larger sample size. Implementing strategies that preserve WM microstructure in older adults at-risk for diabetes should be prioritized to prevent the accelerated disruption of WM microstructure and cognition often seen in this population, which may ultimately reduce the risk of developing dementia.

CRediT authorship contribution statement

Ryu Lien: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Joyla A. Furlano:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Suzanne T. Witt:** Writing – review & editing, Visualization, Supervision, Software, Resources, Methodology, Investigation, Formal analysis. **Chengqian Xian:** Writing – review & editing, Validation, Supervision, Software, Resources, Formal analysis. **Lindsay S. Nagamatsu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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