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Probing Evidence of Cerebral White Matter Microstructural Disruptions in Ischemic Heart Disease Before and Following Cardiac Rehabilitation: A Diffusion Tensor MR Imaging Study.

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Probing Evidence of Cerebral White Matter Microstructural Disruptions in Ischemic Heart Disease Before and Following Cardiac Rehabilitation: A Diffusion Tensor MR Imaging Study

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Background: Ischemic heart disease (IHD) is linked to brain white matter (WM) breakdown but how age or disease effects WM integrity, and whether it is reversible using cardiac rehabilitation (CR), remains unclear.
Purpose: To assess the effects of brain aging, cardiovascular disease, and CR on WM microstructure in brains of IHD patients following a cardiac event.
Study Type: Retrospective.
Population: Thirty-five IHD patients (9 females; mean age = 59 ± 8 years), 21 age-matched healthy controls (10 females; mean age = 59 ± 8 years), and 25 younger controls (14 females; mean age = 26 ± 4 years).
Field Strength/Sequence: 3 T diffusion-weighted imaging with single-shot echo planar imaging acquired at 3 months and 9 months post-cardiac event.
Assessment: Tract-based spatial statistics (TBSS) and tractometry were used to compare fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) in cerebral WM between: 1) older and younger controls to distinguish age-related from disease-related WM changes; 2) IHD patients at baseline (pre-CR) and age-matched controls to investigate if cardiovascular disease exacerbates age-related WM changes; and 3) IHD patients pre-CR and post-CR to investigate the neuroplastic effect of CR on WM microstructure.
Statistical Tests: Two-sample unpaired *t*-test (age: older vs. younger controls; IHD: IHD pre-CR vs. age-matched controls). One-sample paired *t*-test (CR: IHD pre- vs. post-CR). Statistical threshold: $P < 0.05$ (FWE-corrected).
Results: TBSS and tractometry revealed widespread WM changes in older controls compared to younger controls while WM clusters of decreased FA in the fornix and increased MD in body of corpus callosum were observed in IHD patients pre-CR compared to age-matched controls. Robust WM improvements (increased FA, increased AD) were observed in IHD patients post-CR.
Data Conclusion: In IHD, both brain aging and cardiovascular disease may contribute to WM disruptions. IHD-related WM disruptions may be favorably modified by CR.
Level of Evidence: 3
Technical Efficacy: Stage 2

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Cognitive impairment secondary to cerebrovascular dysfunction in older adults can be accelerated in presence of ischemic heart disease (IHD) after a major cardiac event, such as myocardial infarction (MI).[1,2] Cognitive impairment in cardiovascular disease is associated with damage to the brain white matter (WM),[3,4] likely due to vascular-related cardiac injury inducing recurrent ischemic insults to the brain. Specifically, changes in cerebral WM structure have been implicated in other brain conditions highly susceptible to vascular abnormalities including brain aging,[5] heart failure,[6] stroke,[7] and dementia.[8] However, the fundamental biological mechanism driving WM damage in IHD and these brain conditions, and how these impact cognitive performance, is unclear. To facilitate understanding of potential biomechanisms, a comprehensive assessment of cardiovascular disease-related changes in aging brain WM structure is necessary to investigate cerebral WM disruptions in IHD following ischemic cardiac injury and potential downstream outcomes in memory and cognition.

To date, assessment of brain WM structure in IHD has been mostly limited to assessment of fixed macroscopic WM injuries (i.e., WM lesions) identified as hyperintensities on T_2-weighted MRI.[9] However, less is known about disruptions to the underlying WM microstructure of the brain in cardiovascular disease which may occur prior to the appearance of larger-scale WM lesions and may correlate better to cognitive function.[10] Diffusion tensor imaging (DTI) can provide indirect quantitative measurements of WM disintegration in vascular diseases by non-invasively characterizing the integrity of cerebral WM microstructure using DTI scalars of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD).[11] It has been shown that decrease in FA, increase in MD, and increase in RD can indicate breakdown of cerebral WM pathways in patients with vascular cognitive impairment[12] and dementia,[13] suggesting that DTI scalars may be useful biomarkers of WM disintegration in IHD patients at risk for cognitive decline.

Several diffusion MRI analysis methods exist for assessing WM microstructural integrity in the human brain. Tract-based spatial statistics (TBSS) is a widely used approach that aligns multi-subject DTI scalar maps to a standard WM skeleton and then conducts voxel-wise statistical comparison of DTI indices in the WM skeleton between two groups of interest.[14] For example, a previous study by Chen et al[12] used TBSS to compare FA and MD values in cerebral WM tracts between patients with vascular cognitive impairment and cognitively normal controls, and found widespread decreases in FA and increases in MD throughout brain WM tracts linked to cognition (inferior fronto-occipital fasciculus, inferior/superior longitudinal fasciculi, uncinate fasciculus) in the cognitively impaired patient group.[12] WM microstructure can also be assessed using diffusion tractography—a diffusion MRI technique used to map out and visualize WM fiber pathways in the brain.[15] Novel advanced tractography-based WM fiber quantification approaches, such as tractometry, are proposed for analyzing DTI indices along individual WM bundles[16] and may shed further insight into WM alterations, associations to pathophysiology, and their relationship to cognitive impairment.

This study explored the sensitivity of tractometry in detecting subtle changes in DTI scalars (FA, MD, AD, RD) related to IHD. TBSS and tractometry analyses of DTI indices were used to assess the effects of brain aging, cardiovascular disease, and exercise-based cardiac rehabilitation (CR) on WM microstructure integrity in brains of IHD patients with observed brain atrophy, hypoperfusion, and low cognitive performance shortly after a cardiac event. Specifically, the aims of this study were to investigate whether cardiovascular disease exacerbates age-related WM changes in IHD patients and to assess whether brain WM microstructure improved in patients who completed a 6-month exercise-based CR program.

Materials and Methods

Participants

This study was approved by the Western University Health Sciences Research Ethics Board, and written informed consent was obtained from all subjects. Participants were from two previous studies[17,18] and consisted of 35 IHD patients (9 females; mean age = 59 ± 8 years), 21 age-matched healthy controls (10 females; mean age = 59 ± 8 years) with no cognitive impairment, and 25 younger healthy controls (14 females; mean age = 26 ± 4 years). IHD patients were recruited from the London Health Sciences Centre for Cardiac Rehabilitation and Secondary Prevention Program, and age-matched controls and younger controls were recruited from the local community. A subset of the IHD cohort ($N = 19$; 5 females; mean age = 61 ± 6 years) participated in a 6-month CR program consisting of low-to-moderate intensity aerobic exercise training. Inclusion and exclusion criteria for this study are summarized in the two previous studies.[17,18] Briefly, the IHD cohort consisted of patients clinically diagnosed with MI, angina, or coronary artery disease. IHD patients were treated using standard-of-care drug therapy (i.e., statin, beta blocker, antihypertensive, antiplatelet, antidepressant), percutaneous coronary intervention, or coronary artery bypass surgery. None of the IHD patients had major arrhythmias (i.e., atrial fibrillation). All participants did not have any prior neurological or neurodegenerative diseases. Global cognitive function was assessed in all participants using the Montreal Cognitive Assessment (MoCA)[19] and repeated in IHD patients after CR.

Data Acquisition

This retrospective study consisted of a 10-minute diffusion-weighted MRI scan of the whole-brain acquired on all subjects between July 2010 and December 2011 using a Siemens 3T Verio MRI scanner (Siemens Medical Systems, Erlangen, Germany) and a single-shot echo planar imaging (EPI) sequence with the following acquisition protocol: 64 diffusion-encoding directions; b-values = 0 and 1000 s/mm^2; 2 mm^3 isotropic voxels. The details of the experimental design and brain MRI imaging protocol are described in the two

previous studies.[17,18] Briefly, diffusion-weighted imaging (DWI) scans were acquired in IHD patients at baseline (3 months after cardiac event) and following the 6-month exercise-based CR program (9 months after cardiac event), and once in age-matched and younger healthy controls.

Tract-Based Spatial Statistics Analysis

Preprocessing and tensor-fitting of each subject's DWI data were performed as previously described[20] to generate FA, MD, AD, and RD maps. To characterize the effects of brain aging, cardiovascular disease, and exercise-based CR on WM microstructural integrity in IHD, TBSS analysis was used to assess voxel-wise differences in DTI indices (FA, MD, AD, RD) between groups (age: older vs. younger controls; IHD: IHD pre-CR vs. age-matched older controls; and CR: IHD pre- vs. post-CR). All TBSS analysis steps were completed using functional MRI of the Brain Software Library (FSL).[21] First, each subject's DTI scalar maps were eroded by one voxel around the brain's edges to remove noise-related edge artifacts. The DTI scalar maps were then non-linearly aligned to the *FMRIB58_FA* Montreal Neurological Institute (MNI) 1-mm template. Using the aligned DTI scalar maps skeletonized with threshold of 0.2, FSL's *randomise* function was used to statistically assess voxel-wise differences in DTI scalars between groups using threshold-free cluster enhancement (TFCE) and 500 random permutations. To minimize partial-volume effects from non-WM signal (i.e., gray matter, cerebrospinal fluid), the group-wise statistical comparison of DTI indices was restricted to 40 a priori cerebral WM regions from the Johns Hopkins University (JHU) ICBM-80-DTI white-matter labels atlas.[22] All *P*-values were corrected for multiple-comparisons using family-wise error (FWE) and $P < 0.05$ (FWE-corrected) was considered statistically significant.

Diffusion Tractography and Tractometry Analysis

Diffusion tractography and tractometry were used to quantify specific changes in DTI indices (FA, MD, AD, RD) along a priori WM bundles between groups. Diffusion tractography and tractometry analysis were conducted using TractSeg,[23] a convolutional neural network-based tool for automatically segmenting and reconstructing WM fiber bundles in the human brain. Although TractSeg allows along-tract quantification of 50 WM bundles, the tractometry analysis was primarily focused on 8 WM bundles linked to impairment in higher-order cognitive functions (executive function, information processing speed, verbal memory) in IHD post-MI[1–3]: left/right cingulum (CG), left/right inferior fronto-occipital fasciculus (IFOF), left/right inferior longitudinal fasciculus (ILF), and left/right uncinate fasciculus (UF). In addition, tractometry was performed on 10 other WM bundles generally implicated in post-ischemic cerebrovascular injury and cognitive decline[24]: left/right arcuate fasciculus (AF), rostrum and splenium of the corpus callosum (CC), left/right superior longitudinal fasciculus (SLF) I, left/right SLF II, and left/right SLF III. Thus, a total of 18 WM bundles related to vascular cognitive impairment were analyzed by tractometry in this study.

For the diffusion tractography and tractometry analysis, the *FLIRT* tool in FSL was first used to rigidly align all subject's preprocessed DWI images, diffusion-encoding directions, and DTI scalar maps to a 1.25-mm MNI FA template in TractSeg using mutual information as cost function and six degrees of freedom. Diffusion tractography preprocessing steps were then completed on each subject's preprocessed DWI data using the constrained spherical deconvolution (CSD) algorithm in MRtrix3[25] as previously described[20] to generate CSD peaks images for tractography and tractometry analysis. Tractography and tractometry were performed on the CSD peaks images in TractSeg to automatically segment each subject's brain into the 18 WM bundles of interest. Each WM bundle was reconstructed using 5000 streamlines via automated probabilistic tractography. Specifically, 5000 streamlines were chosen for each WM bundle reconstruction to minimize reproducibility bias in WM tractography reconstruction and to reduce variations in tractometry-derived DTI scalar measurements. Tractometry was performed by evaluating DTI indices (FA, MD, AD, RD) at 100 equidistant points along each WM bundle.[26] Group-wise tractometry analysis was then performed to compare DTI indices in each WM bundle[27] between groups. All *P*-values were corrected for multiple-comparisons using FWE and $P < 0.05$ (FWE-corrected) was considered statistically significant.

Statistical Analysis

A χ^2 test of independence was performed to assess if there were any differences in sex distribution between older and younger controls. Group-wise TBSS and tractometry analyses were conducted using FSL and TractSeg, respectively. For the group-wise TBSS and tractometry analyses, a general linear model (GLM) with sex as a covariate of no interest was used to statistically assess differences in DTI metrics between groups. For the group-wise DTI comparisons between older and younger controls as well as between IHD patients pre-CR and age-matched controls, a two-sample unpaired *t*-test was used in the GLM. A one-sample paired *t*-test (repeated measures) design in the GLM was used to permit statistical comparison of within-group measures in IHD patients pre-CR and post-CR. Additionally, Pearson correlational analysis was used to assess regional associations between DTI tractometry measures in each WM bundle and MoCA scores across all IHD patients pre-CR and age-matched controls. For all statistical analyses, $P < 0.05$ (FWE-corrected) was considered statistically significant.

Results

Study demographics including MoCA scores and other clinical assessments are summarized in Table 1. The χ^2 test of independence showed no significant differences in sex distribution between older and younger controls (χ^2 (1) = 0.32, $P = 0.57$). The MoCA assessment was completed in 33/35 IHD patients at baseline (pre-CR), 20/21 age-matched older controls, 21/25 younger controls, and 15/19 IHD patients post-CR.

Tract-Based Spatial Statistics Analysis

A summary of the TBSS findings between groups is provided in Fig. 1a–c.

OLDER VS. YOUNGER HEALTHY CONTROLS. TBSS analysis revealed widespread changes in DTI metrics, indicative of normal brain aging, throughout cerebral WM of older controls compared to younger controls. Specifically, older controls had decreased FA in WM clusters in the fornix, left anterior corona radiata, and right superior corona radiata

TABLE 1. Study Demographics and Clinical Characteristics

Variables	Younger Controls ($N = 25$)	Older Controls ($N = 21$)	IHD Patients Pre-CR ($N = 35$)	IHD Patients Post-CR ($N = 19$)
Age (years)	26 ± 4	59 ± 8[a]	59 ± 8	61 ± 6
Females (%)	56.0	47.6	25.7	26.3
Body mass index (kg/m^2)	24.5 ± 5.35	24.8 ± 3.30	30.1 ± 4.84[b]	30.0 ± 5.06
Fasting blood glucose (mmol/L)	4.70 ± 0.78	4.75 ± 0.88	5.37 ± 1.66	8.07 ± 11.6
Total cholesterol (mmol/L)	3.76 ± 0.72	4.18 ± 0.94	3.08 ± 0.79[b]	3.00 ± 0.99
High-sensitivity C-reactive protein (mg/L)	1.47 ± 1.74	1.00 ± 0.89	2.38 ± 3.16	1.13 ± 0.86
Rest supine systolic blood pressure (mmHg)	108.7 ± 11.4	120.7 ± 15.7[a]	125.9 ± 21.4	117.6 ± 14.0
Rest supine diastolic blood presume (mmHg)	63.6 ± 7.97	68.6 ± 7.79[a]	71.0 ± 12.6	67.7 ± 8.37
Cardiac output (L/min)	6.21 ± 1.48	6.54 ± 1.63	9.71 ± 15.3	7.52 ± 1.66
Resting heart rate (beats per min)	63.8 ± 9.48	58.6 ± 9.75	59.2 ± 6.79	61.0 ± 11.7
Left ventricular ejection fraction (%)	68.0 ± 5.42	67.2 ± 9.50	64.0 ± 7.46	63.9 ± 9.20
Intima media thickness, carotid (mm)	0.36 ± 0.07	0.53 ± 0.12[a]	0.64 ± 0.12[b]	Not completed
Compliance, carotid (mm/mmHg)	0.014 ± 0.005	0.009 ± 0.003[a]	0.008 ± 0.003	0.007 ± 0.003
MoCA	28.7 ± 1.95	28.3 ± 1.63	26.8 ± 2.10[b]	27.5 ± 2.00
VO_2max (mL/kg/min)	44.8 ± 9.72	37.1 ± 9.71[a]	27.7 ± 9.45[b]	29.3 ± 8.80

Modified from two previous studies,[17,18] where subject characteristics and clinical assessments for younger healthy controls and IHD patients post-CR have now been added. Clinical variables reported as mean ± SD are compared between younger and older controls, between IHD patients pre-CR and age-matched older controls, as well as between IHD patients pre-CR and post-CR.
[a]Statistical difference between younger and older healthy controls at $P < 0.05$.
[b]Statistical difference between IHD patients pre-CR and age-matched older controls at $P < 0.05$.

(0.37 ± 0.04 vs. 0.43 ± 0.05). The older controls showed widespread changes of increased MD throughout several WM regions linked to cognition, including the genu and body of CC, fornix, bilateral corona radiata, bilateral posterior thalamic radiation, bilateral external capsule, bilateral SLF, bilateral superior fronto-occipital fasciculi (SFOF), and right UF (0.73 ± 0.02 vs. 0.69 ± 0.03 μm^2/msec). There were diffuse patterns of increased AD in frontal lobe WM regions of older controls, including body of CC, fornix, left anterior corona radiata, right posterior corona radiata, left SFOF, and right UF (1.53 ± 0.12 vs. 1.39 ± 0.10 μm^2/msec). The older controls showed widespread changes of increased RD throughout several WM clusters spanning the genu of CC, fornix, bilateral anterior and superior corona radiata, bilateral posterior thalamic radiation, right external capsule, left CG, right SLF, and left SFOF (0.55 ± 0.03 vs. 0.51 ± 0.03 μm^2/msec). Of note, the older controls had overlapping WM clusters of decreased FA, increased MD, increased AD, and increased RD in the fornix and left anterior corona radiata. Likewise, overlapping WM clusters of decreased FA, increased MD, and increased RD were observed in the right superior corona radiata of older controls.

IHD PATIENTS PRE-CR VS. AGE-MATCHED HEALTHY CONTROLS. A subtle effect of cardiovascular disease was observed in the fornix WM cluster (Fig. 1d). Specifically, in this fornix WM cluster, there was an 8.9% decrease in FA in older controls relative to younger controls (0.48 ± 0.06 vs. 0.53 ± 0.06) with an additional 9.8% reduction in FA in IHD patients pre-CR (0.43 ± 0.08 vs. 0.48 ± 0.06), and a 5.6% FA recovery (improved WM integrity) following CR (0.46 ± 0.08 vs. 0.43 ± 0.08) with no significant differences in FA observed between IHD patients post-CR and age-matched controls ($P = 0.30$). Compared to age-matched controls, IHD patients pre-CR had increased MD in a small WM cluster comprising the body of the CC, left superior corona radiata, and left SFOF. In this small WM cluster (Fig. 1e), there was a 2.2% increase in MD in older controls relative to younger controls (0.63 ± 0.02 vs. 0.62 ± 0.02 μm^2/msec) with a subtle effect of cardiovascular disease as suggested by an additional 3.2% increase in MD in IHD patients at baseline (0.65 ± 0.03 vs. 0.63 ± 0.02 μm^2/msec) and a minimal, non-significant 0.8% MD recovery following CR ($P = 0.97$). There were no significant differences in AD ($P = 0.16$) or RD

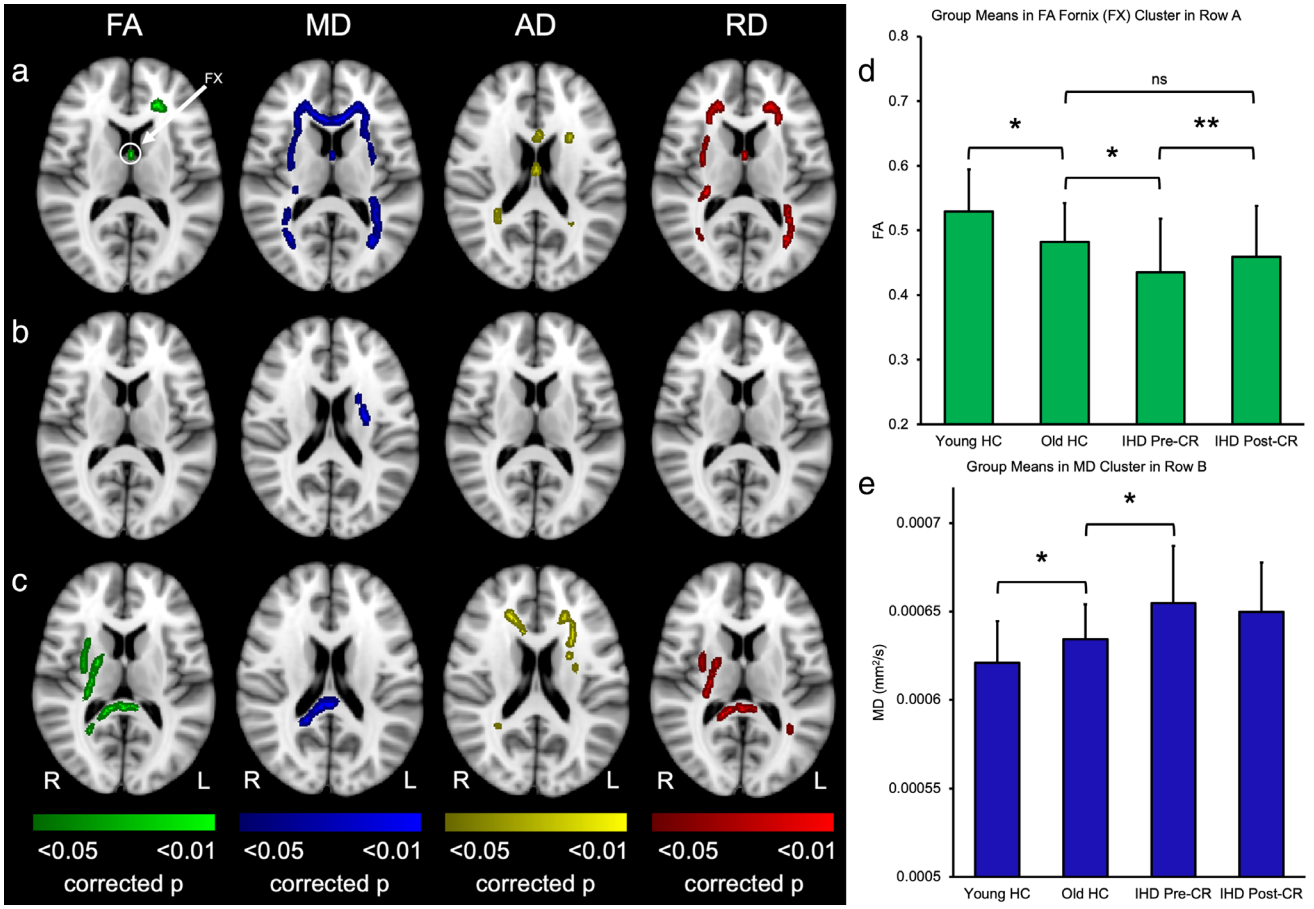

FIGURE 1: Tract-based spatial statistics images (colored regions) showing: (a) decreased FA (green), increased MD (blue), increased AD (yellow), and increased RD (red) in cerebral white matter (WM) of older healthy controls (HC) compared to younger controls; (b) increased MD (blue) in WM of IHD patients at baseline compared to age-matched controls; and (c) signs of WM recovery (relative to baseline) as evidenced by increased FA (green), decreased MD (blue), increased AD (yellow), and decreased RD (red) in IHD patients following 6 months of cardiac rehabilitation (CR). Bar graphs of: (d) decreased FA in fornix WM cluster (from row a) and; (e) increased MD in WM cluster (from row b) of IHD patients pre-CR relative to age-matched controls show evidence of a subtle IHD effect on aging cerebral WM microstructure with WM recovery (increased FA, decreased MD) observed in IHD patients following CR.

($P = 0.08$) in any of the WM regions between IHD patients pre-CR and their healthy age-matched counterparts.

IHD PATIENTS POST-CR VS. PRE-CR. Using known positive effects of exercise-based CR[17,18] to test DTI sensitivity, potential favorable effects of exercise training on cerebral WM microstructure were observed in IHD patients post-CR. This was indicated by widespread increases in FA (improved WM integrity) throughout several WM tracts linked to cognitive functions including the splenium of CC, fornix, right medial lemniscus, right anterior and posterior limb of internal capsule, bilateral superior corona radiata, left posterior corona radiata, and right external capsule (0.63 ± 0.07 vs. 0.60 ± 0.06). IHD patients post-CR had decreased MD in splenium of CC (0.65 ± 0.04 vs. 0.68 ± 0.03 μm^2/msec), diffuse patterns of increased AD in genu of CC, fornix, bilateral anterior corona radiata, left superior corona radiata, and left external capsule (1.04 ± 0.07 vs. 1.02 ± 0.08 μm^2/msec) and widespread decreases in RD throughout multiple WM clusters including the splenium of CC, fornix, right posterior limb of internal capsule, left posterior thalamic radiation, right external capsule, left CG, and left UF (0.34 ± 0.05 vs. 0.37 ± 0.05 μm^2/msec).

Diffusion Tractography and Tractometry Analysis

WM bundle tractometry plots showing along-tract differences in FA and MD between groups are provided in Figs. 2–5. Tractometry plots for AD and RD can be found in Figs. S1–-S4 in the Supplemental Material.

OLDER VS. YOUNGER HEALTHY CONTROLS. Tractometry revealed localized changes in DTI metrics along cognition-associated WM bundles, indicative of normal brain aging, in older controls compared to younger controls. Specifically, the older controls had decreased FA in the left ILF and left UF (Fig. 2b), increased MD in the left UF (Fig. 4b), right CG, right IFOF, right ILF (Fig. 5b), left AF, and left SLF III, as well as increased RD in the left UF, right CG, bilateral IFOF, and bilateral ILF (see Figs. S3 and S4 in the Supplemental

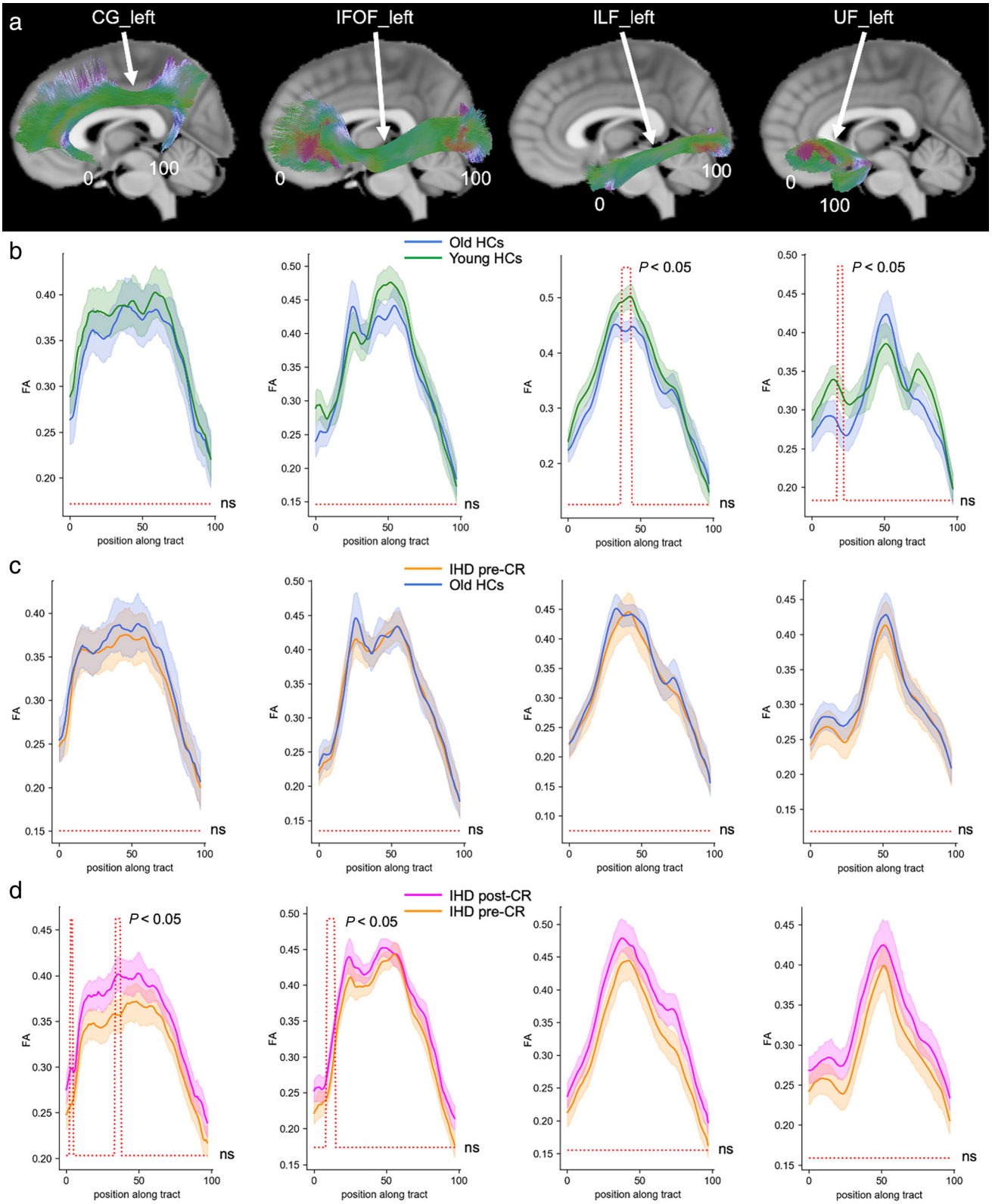

FIGURE 2: (a) Diffusion tractography visualization of left CG, IFOF, ILF, and UF white matter tractograms (colored lines) of a young healthy control (HC) overlaid onto an MNI T1 1.25-mm template. Corresponding group-wise tractometry plots comparing FA along each position of these WM bundles are shown in (b–d), including 95% confidence intervals (shaded area) and FWE-corrected $P < 0.05$ (red-dotted lines). (b) Older controls have decreased FA in left ILF and UF compared to younger controls. (c) No significant differences in FA are found between IHD patients at baseline and age-matched controls. (d) Relative to baseline, IHD patients following 6 months of cardiac rehabilitation have improved white matter integrity as evidenced by increased FA in left CG and IFOF.

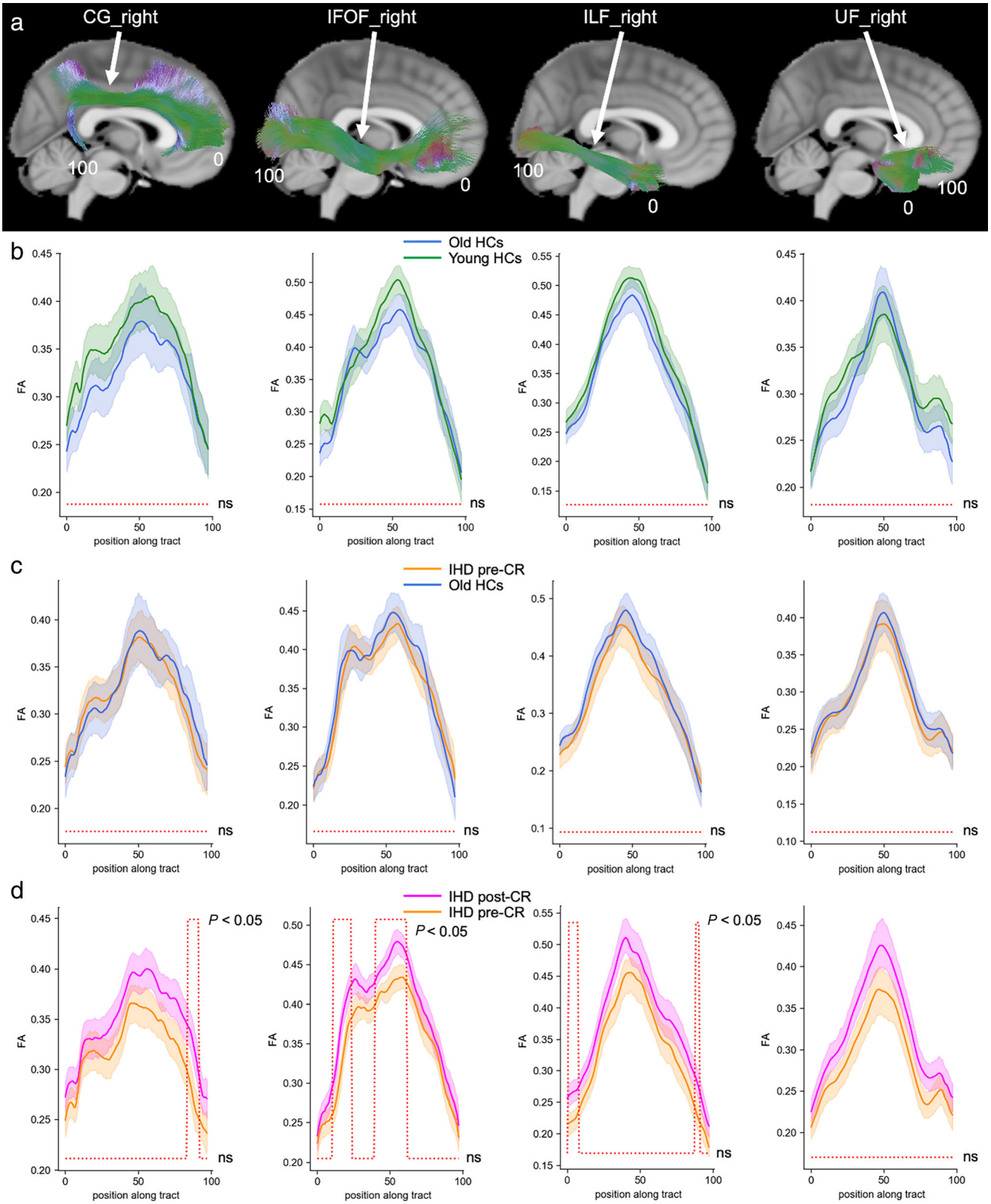

FIGURE 3: (a) Diffusion tractography visualization of right CG, IFOF, ILF, and UF white matter tractograms (colored lines) of a young healthy control (HC) overlaid onto an MNI T1 1.25-mm template. Corresponding group-wise tractometry plots comparing FA along each position of these WM bundles are shown in (b–d), including 95% confidence intervals (shaded area) and FWE-corrected $P < 0.05$ (red-dotted lines). No significant differences in FA are found (b) between older and younger controls, or (c) between IHD patients at baseline and age-matched controls. (d) Relative to baseline, IHD patients following 6 months of cardiac rehabilitation have improved white matter integrity as evidenced by increased FA in right CG, IFOF, and ILF.

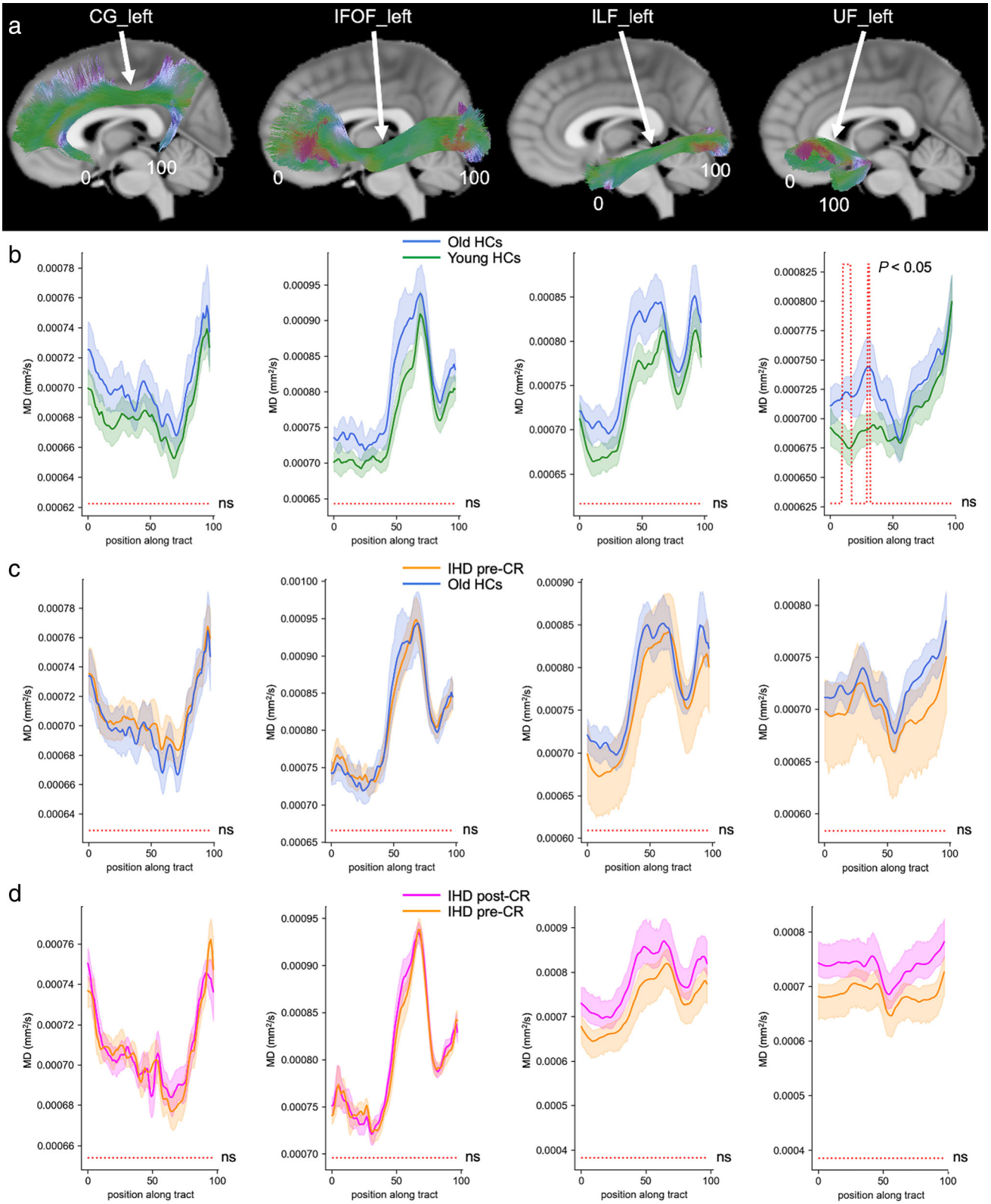

FIGURE 4: (a) Diffusion tractography visualization of left CG, IFOF, ILF, and UF white matter tractograms (colored lines) of a young healthy control (HC) overlaid onto an MNI T1 1.25-mm template. Corresponding group-wise tractometry plots comparing MD along each position of these WM bundles are shown in (**b–d**), including 95% confidence intervals (shaded area) and FWE-corrected $P < 0.05$ (red-dotted lines). (b) Older controls have increased MD in left UF compared to younger controls. No significant differences in MD are found (c) between IHD patients at baseline and age-matched controls, or (d) between IHD patients at baseline and following 6 months of cardiac rehabilitation.

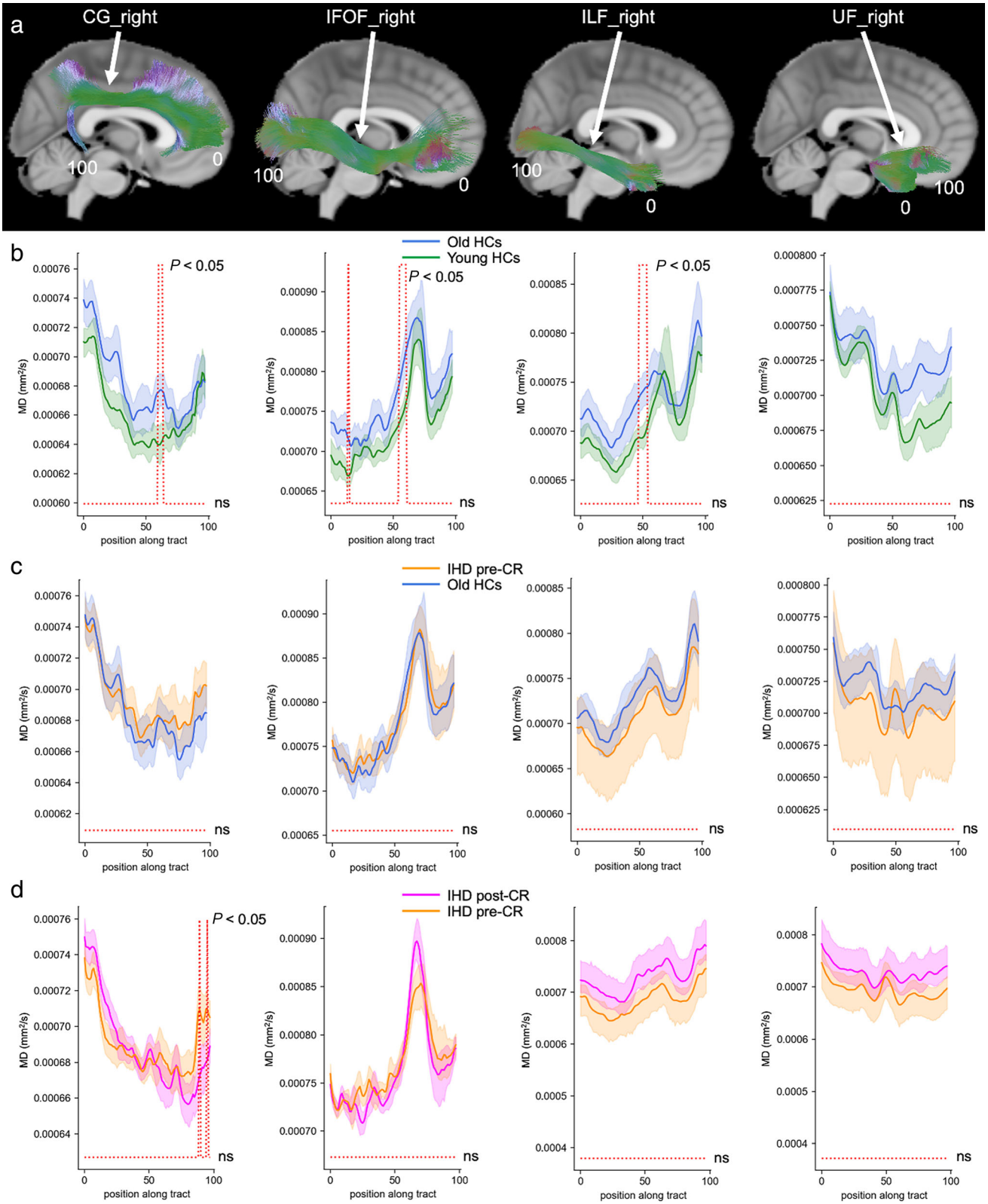

FIGURE 5: (a) Diffusion tractography visualization of right CG, IFOF, ILF, and UF white matter tractograms (colored lines) of a young healthy control (HC) overlaid onto an MNI T1 1.25-mm template. Corresponding group-wise tractometry plots comparing MD along each position of these WM bundles are shown in (b–d), including 95% confidence intervals (shaded area) and FWE-corrected $P < 0.05$ (red-dotted lines). (b) Older controls have increased MD in right CG, IFOF, and ILF compared to younger controls. (c) No significant differences in MD are found between IHD patients at baseline and age-matched controls. (d) Relative to baseline, IHD patients following 6 months of cardiac rehabilitation have improved white matter integrity as evidenced by decreased MD in right CG.

Material). No significant differences in AD in any of the WM bundles were observed between older and younger controls ($P = 0.39$).

IHD PATIENTS PRE-CR VS. AGE-MATCHED HEALTHY CONTROLS. Compared to age-matched controls, IHD patients pre-CR showed non-significant increases in MD in the left AF ($P = 0.52$) and non-significant increases in RD in the left CG ($P = 0.38$) (see Fig. S3 in the Supplemental Material). There were no significant differences in FA or AD in any of the WM bundles between IHD patients at baseline and age-matched controls ($P = 0.08$). Pearson correlational analysis between regional DTI tractometry measurements and MoCA scores across all IHD patients pre-CR and age-matched controls showed a weak negative association between MD and MoCA in the left AF, right AF, right IFOF, left SLF III, and right SLF III ($r = -0.20$).

IHD PATIENTS POST-CR VS. PRE-CR. Potential favorable effects of exercise training on cerebral WM microstructure were observed in IHD patients post-CR. This was supported by increased FA and increased AD in multiple WM bundles linked to cognitive functions including the bilateral CG and bilateral IFOF (Figs. 2d and 3d; see Figs. S1 and S2 in the Supplemental Material). In IHD patients post-CR, FA was also increased in the right ILF and splenium of CC, and AD was also increased in the left AF. Compared to pre-CR, IHD patients post-CR had decreased MD and decreased RD in the right CG (Fig. 5d; see Fig. S4 in the Supplemental Material). In IHD patients post-CR, RD was also decreased in the right IFOF.

Discussion

This study used two DTI analysis approaches, TBSS and tractometry, to assess changes in WM microstructure in IHD related to ischemic cardiac injury independent of brain aging, and evaluate the sensitivity of detecting localized WM changes using an intervention model—exercise-based CR. TBSS showed age-related WM changes in brains of older adults matched in age to IHD patients, evidence of ischemic cardiac disease effects on WM integrity and WM plasticity following an exercise-based intervention. Thereby, this study demonstrated the utility of a novel advanced tractometry approach in quantifying localized changes along WM bundles linked to higher-order cognitive functions (executive function, information processing speed, verbal memory) in IHD post-MI. Taken together, these findings suggest that both brain aging and cardiovascular disease may contribute to WM disruptions and WM-related cognitive impairment in IHD, and the IHD-related WM disruptions may be favorably modified by exercise-based CR.

WM changes with age[5] and disease.[10] Furthermore, aging is considered a risk factor for cerebrovascular disease.[11] Therefore, to distinguish vascular disease-related effects from age-related effects in IHD, it was important in this study to first establish if brain aging could be, at least, partly responsible for some of the WM changes observed in the IHD cohort. Consistent with these findings, past studies have reported decreases in FA accompanied by increases in diffusivities (MD, AD, RD) to indicate WM breakdown in the healthy aging human brain.[28,29] Specifically, decreased FA is considered a primary biomarker of decreased WM integrity and is associated with loss of directional preference of water diffusion along WM axons.[5] In addition, secondary biomarkers of WM impairment such as increased MD, increased AD, and increased RD have been thought to reflect increased extracellular water content (i.e., edema), loss of axonal integrity, and demyelination, respectively.[30] In this study, WM changes associated with normal brain aging were observed in older healthy adults relative to younger healthy adults, especially in the CG, IFOF, ILF, and UF which have previously been shown to be linked to higher-order cognitive functions.[31,32] These findings show that aging can affect WM microstructural integrity and is, therefore, an important consideration when assessing structural integrity of cerebral WM pathways in the brains of IHD patients undergoing both aging and vascular-related changes.

A few studies have assessed DTI changes in WM microstructure in vascular diseases.[33–35] Fu et al found that patients with subcortical ischemic vascular disease had decreased FA and increased apparent diffusion coefficient values in the genu and splenium of the CC, IFOF, and SLF compared to healthy controls.[33] Qiao et al performed atlas-based ROI analysis of FA, MD, AD, and RD values in patients with early subcortical vascular cognitive impairment and found WM changes (decreased FA, increased MD, increased AD, increased RD) in several WM tracts including the anterior corona radiata, IFOF, and ILF.[34] Interestingly, Biesbroek et al found that DTI changes in the right SLF and left UF—WM bundles linked to executive function and verbal memory—can provide added value in explaining variance of cognitive outcomes in patients with vascular brain injury on top of conventional macroscopic WM imaging techniques (i.e., T2-weighted FLAIR MRI).[35] This study observed early signs of subtle WM disruptions in the brains of IHD patients pre-CR who have had a recent vascular-related ischemic injury and whose brains are also undergoing normal aging.

Most notably, there was evidence of cardiovascular disease-related WM changes (decreased FA) in the fornix of IHD patients pre-CR with WM plasticity given by improvements in all four DTI metrics (increased FA, decreased MD, increased AD, decreased RD) observed in the fornix following CR. Given the crucial involvement of the fornix in cognition and the limbic system,[36] and its vulnerability to WM degeneration in brain aging, dementia, and vascular disease including heart failure,[30,37–39] these findings suggest that the fornix

may be a brain region susceptible to WM disruptions post-ischemic cardiac injury, and that these changes can be favorably modified following CR. However, it is worth noting that the DTI changes could also be attributable to the fornix consisting of a small densely packed unidirectional population of axons that make it less susceptible to the so-called "crossing fiber and bottleneck problems" (multiple WM bundles within a single voxel or brain region) and subtle changes in WM more detectable than other WM regions.[40] In addition to the FA changes in the fornix, increases in MD were also observed in the body of the CC, left superior corona radiata, and left SFOF, suggesting an additive effect of age and IHD on brain WM microstructure. One study by Santiago et al assessed DTI changes in WM microstructure in IHD.[3] Specifically, Santiago et al found that increased FA was associated with increased executive function in the left CG and left IFOF of patients with coronary artery disease.[3] Although this study did not assess changes in specific cognitive domains (i.e., executive functions), a weak association between regional increases in MD and decreases in global cognitive performance was observed in IHD patients pre-CR. However, it should be noted that this IHD cohort is in a relatively early stage of cardiovascular disease which could explain why a strong correlation between DTI metrics and cognitive function was not observed in this study. Future larger population longitudinal DTI studies in IHD using cognitive test batteries targeting more specific cognitive domains could shed further insight into vascular-related cognitive decline in IHD.

Tractometry showed no statistically significant differences in DTI metrics in WM bundles between IHD patients pre-CR and age-matched controls, which are similar to the correlational analysis findings and could also reflect an early stage of cardiovascular disease in the IHD cohort. Tractometry detected non-significant changes in MD and RD in the left AF and left CG respectively. Nevertheless, because these IHD patients either had an MI or were at risk for MI, the tractometry analysis was focused on specific WM bundles linked to vascular-related decline of higher-order cognitive functions (executive function, information processing speed, verbal memory) in IHD post-MI.[1–3] Furthermore, investigation of these a priori WM regions in IHD is especially important because MI is known to precede dementia by roughly 7 years.[1,2] These findings show that advanced diffusion MRI techniques, such as tractometry, can identify subtle WM changes in brains of older adults at risk for cognitive decline.

An exercise-based cardiovascular intervention program can improve cognitive function and overall health of older adults at risk for vascular-related cognitive decline.[41,42] These neural adaptations might be related to increased gray matter volume and cerebral blood flow that was observed in this IHD group undergoing a low-to-moderate intensity aerobic exercise-based CR program.[17,18] Here, in the same IHD cohort, widespread improvements were found in WM microstructure, especially in WM regions linked to higher-order cognitive functions (CG, IFOF, ILF, UF) in patients following 6 months of the CR program. Interestingly, tractometry showed that the increases in FA observed in IHD patients post-CR seem to be primarily driven by increases in AD, suggesting improved axonal integrity in IHD following CR. Future DTI studies in larger cohorts using a higher intensity exercise-based CR program could help further explain potential biophysiological mechanisms behind longitudinal DTI changes in IHD patients following CR. Nevertheless, this study has demonstrated that CR can favorably modify WM microstructure, suggesting that CR is a promising neuromodulator of WM microstructure in IHD.

Limitations

Brain MRI images in this retrospective single-center study were acquired using a single field strength (3 T) scanner and in a relatively small IHD cohort, which may have limited the ability to detect acute cardiovascular disease-related WM changes in this cohort following a cardiac event. Also, it is well established that DTI is a simplistic model for characterizing water diffusion in the brain.[43] Future IHD studies using more advanced diffusion MRI techniques such as diffusion kurtosis imaging[43] or high-angular resolution diffusion imaging[44] could provide superior characterization of WM pathways in the brain, especially in crossing fiber regions where FA is known to be underestimated. Although this study was limited to DTI-based analysis based on DWI acquisition parameters, constrained spherical deconvolution (CSD) tractography was used to improve the accuracy of tractography and tractometry results. Of note, some of the WM changes observed in this study showed lateralization of DTI parameters (right WM disruptions more than left) between groups. While left WM fiber bundles have been reported to show asymmetry in DTI findings at all ages[45] and in cognitively impaired individuals,[46,47] the reasons for lateralization are largely unknown and could be explored in IHD within a larger group of participants in future DTI studies. Cardiac event severity, patient outcome, and the presence of brain WM hyperintensities were not clinically assessed in the IHD cohort, therefore no conclusions regarding potential associations between these variables and WM microstructural changes in IHD can be drawn from this study. It is possible that other factors could have played a role in the WM changes observed in this IHD cohort following CR, including spontaneous WM recovery, change in diet, and psychosocial support. Nevertheless, these findings support the broad benefits of an exercise-based CR program that include favorable effects on brain structure in IHD.

Conclusion

This study demonstrated that DTI can reveal brain WM disruptions in older adults undergoing aging and vascular-related

changes. DTI showed improvement in measures of brain WM integrity in IHD patients following a 6-month exercise-based CR program. Additionally, this study demonstrated the utility of a novel advanced tractometry technique in probing localized changes in WM microstructure in IHD beyond the level of traditional voxel-wise DTI analysis approaches (TBSS) and providing complementary information regarding WM integrity in IHD following ischemic vascular injury. In IHD, both brain aging and cardiovascular disease may contribute to WM disruptions and WM-related cognitive decline, and the IHD-related WM disruptions may be favorably modified by CR.

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Conflict of Interest

All authors declare that they have no competing interests.

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