Changes to White Matter Microstructure in Transient Ischemic Attack: A Longitudinal Diffusion Tensor Imaging Study

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Abstract: Transient ischemic attack (TIA) is associated with localized ischemic changes, identifiable by diffusion-weighted imaging. Past research has not considered whether TIA is also associated with diffuse changes to white matter microstructure; further past work has not tracked changes longitudinally. Here we examine whole-brain changes in fractional anisotropy (FA) in individuals with TIA presenting with sensorimotor symptoms. Twenty individuals with a recent (within 30 days) TIA and 12 healthy older adults were recruited. Participants underwent 3.0 T diffusion MRI at baseline; scans were repeated for the TIA group 90 days post-TIA. Track-based spatial statistics (TBSS) was used to conduct a voxel-wise analysis of FA between groups. FA was significantly lower in the TIA group relative to healthy controls, primarily in anterior white matter tracts including: forceps minor, anterior thalamic radiations, cingulum, inferior fronto-occipital fasciculus, and corticospinal tract. TBSS results informed an ROI-based longitudinal examination of FA in the TIA group. There were no changes to TBSS-identified clusters, forceps minor, or the corticospinal tract over time. There was lower FA in the anterior thalamic radiations in the TIA-affected hemisphere at baseline, but no difference between hemispheres at 90 days. In summary, individuals with TIA presenting with sensorimotor symptoms have decreased FA in tracts that are also implicated in sensorimotor function, which outlast the clinical symptoms associated with TIA. This suggests a more profound type of brain damage associated with TIA than has been typically described in past work. Diffusion tensor imaging may have utility as a marker of TIA-associated changes to white matter pathways. *Hum Brain Mapp* 38:5795–5803, 2017. © 2017 Wiley Periodicals, Inc.

Key words: DTI; MRI; FA; TBSS; TIA

INTRODUCTION

Transient ischemic attack (TIA) increases the risk of recurrent stroke, particularly within the early high-risk period post-event [Giles and Rothwell, 2007; Rothwell et al., 2006]. Recurrent stroke presents a serious concern to rehabilitation as it is associated with poorer functional outcomes and higher rates of disability than first-time stroke [Jørgensen et al., 1997; Rohweder et al., 2015]. Management of secondary stroke prevention depends on the accurate identification of individuals with TIA [Rothwell et al., 2007].

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Currently, TIA diagnosis relies primarily on clinical assessment and the presence of vascular comorbidities that increase stroke risk [Castle et al., 2010]. Diffusion-weighted imaging (DWI) has been useful in TIA and minor stroke to detect evidence of early ischemic changes [Souillard-Sce-mama et al., 2015]. Although the presence of DWI+ lesions is an indicator of TIA, up to half of individuals with suspected TIA do not demonstrate abnormalities on DWI [Bou-langer et al., 2007; Mlynash et al., 2009]. Other neurological markers may be associated with TIA, which could inform further development of imaging approaches to discriminate TIA from other transient neurological conditions.

Diffusion tensor imaging (DTI) characterizes microstructural properties of white matter tracts. Fractional anisotropy (FA) is a commonly employed DTI metric that measures the degree of directionality in voxel diffusion, with higher values indicating greater degree of organization or axonal density in underlying white matter tracts [Jones et al., 2013]. DTI has been widely used in stroke research on sensorimotor function, and FA of the corticospinal tract has emerged as a key predictor of upper-limb motor recovery [Kumar et al., 2016; Stinear et al., 2012]. Regional FA measures may be similarly informative for the evaluation of TIA with sensorimotor symptoms. FA is affected by vascular comorbidities, such as hypertension [Gons et al., 2010] and diabetes [van Bloemendaal et al., 2016], which are also clinical indicators of recurrent stroke risk in TIA populations [Wardlaw et al., 2015]. A recent paper from the Rotterdam study found global FA measures were predictive of future stroke [Evans et al., 2016]; within a mixed sample of individuals with TIA or minor stroke, FA values in frontal white matter tracts were related to measures of cognitive impairment [Zamboni et al., 2017]. FA also discriminates TIA from minor stroke at the ischemic site [Tong et al., 2011]. However, whether FA values are changed in TIA relative to healthy controls is unknown.

Specific aims of this article were to (1) characterize alterations to white matter microstructure in sensorimotor TIA with a voxelwise analysis of FA, comparing to a group of matched healthy controls; (2) conduct a region of interest (ROI)-based analysis of FA in tracts relevant for sensorimotor recovery, comparing to healthy controls; and (3) examine longitudinal changes in FA after TIA in the immediate to early-period post-TIA in regions of interest. We hypothesized that individuals with TIA with sensorimotor symptoms would show lower FA in sensorimotor tracts compared to matched healthy controls. We further hypothesized that tracts with low FA in the TIA group would show a decline in FA levels from the immediate to the early period post-TIA.

METHODS

Participants

Individuals between the ages of 30 and 85 with a recent (within 30 days) TIA were recruited from the Stroke

Prevention Clinic at the Vancouver General Hospital. Inclusion criteria for the TIA group were a recent (within 30 days) diagnosis of TIA presenting with unilateral sensory or motor symptoms, confirmed by the evaluating physician. Healthy older adults were recruited from the community and all healthy participants were right-hand dominant. For both the TIA and healthy control (HC) groups, participants were excluded if they (1) reported a history of stroke, seizure/epilepsy, head trauma, neurodegenerative disease, or major psychiatric disorders; (2) had any contraindications to MRI; and (3) were outside of the age range of 30–85. Informed consent was obtained for each participant in accordance with the Declaration of Helsinki. The University of British Columbia research ethics board approved all aspects of the study protocol.

Clinical Measures

All participants in the TIA group were evaluated by a neurologist at the Vancouver General Hospital Stroke Prevention Clinic prior to participation in the study. The evaluating physician confirmed diagnosis of TIA presenting with unilateral sensory or motor symptoms. All clinical symptoms were fully resolved before participation in the study, and no structural lesions were present on conventional imaging scans (e.g., CT or MRI). When possible, ABCD² scores were calculated for each participant based on chart review for age, recorded blood pressure, clinical symptoms, and prior diabetes status [Johnston et al., 2007].

Magnetic Resonance Imaging (MRI) Acquisition and Preprocessing

MR acquisition was conducted at the University of British Columbia MRI research center on a Philips Achieva 3.0 T whole-body MRI scanner (Philips Healthcare, Best, The Netherlands), using an eight-channel sensitivity encoding head coil (SENSE factor = 2.4) and parallel imaging. Diffusion scans were performed using a single-shot spin echo DwiSE sequence ($T_R = 7465$ ms, $T_E = 60$ ms, FOV = 212×1312 mm, 60 slices, voxel dimensions = $2.2 \times 2.2 \times 2.2$ mm³). Diffusion weighting was applied across 16 independent noncollinear orientations ($b = 1000$ s/mm²) with one unweighted image ($b = 0$ s/mm²). Scans were performed within 30 days of the TIA event, and repeated at 90 days after the TIA event.

Diffusion data were processed using FSL v5.0.9 (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). Images were visually inspected, and corrected for motion and eddy currents with the Eddy tool. The unweighted diffusion volume ($b = 0$) was skull stripped using the Brain Extraction Tool (BET). DTIFIT was used to reconstruct tensors and produce FA maps. In line with established practice in individuals with TIA or stroke [Schaapsmeeders et al., 2016; Schaechter et al., 2009; Takenobu et al., 2014], where the TIA affected the left hemisphere, FA maps were flipped

Figure 1.

ROIs derived from the JHU white matter atlas [Hua et al., 2008; Wakana et al., 2007]. ROIs were converted to binary masks and applied to FA maps. **(A)** Forceps minor; **(B)** corticospinal tract; **(C)** anterior thalamic radiations.

using the `fslswapdim` tool, so that the TIA-affected hemisphere was on the right, to correspond with the nondominant hemisphere in the healthy control group.

TBSS Analysis

Track-based spatial statistics (TBSS) is a DTI analysis provided by FSL, which performs a whole-brain voxelwise analysis of FA values [Smith et al., 2006]. TBSS was performed according to standard processing pipelines [Smith et al., 2006]. Briefly, nonlinear registration was performed to bring each individuals' scan into standard space using FSL's `FNIRT` function [Andersson et al., 2007a,b]. FA maps were combined to create a mean FA map across the sample. The mean FA map was thresholded to an FA of 0.2, to generate a mean FA skeleton. The FA skeleton represents regions of high FA that are common across the sample. Each individual scan was projected onto the mean skeleton before generating voxel-wise cross-subjects statistics. Differences between groups across the FA skeleton were examined using an independent sample *t* test with FSL's `randomize` tool, with 5000 random permutations. The threshold for significance was set at $P < 0.05$, correcting for multiple comparisons using threshold-free cluster enhancement [Smith and Nichols, 2009]. Significant clusters identified by TBSS were used as regions of interest (ROIs) in subsequent longitudinal analyses; clusters < 100 voxels in size were excluded from longitudinal analyses.

ROI/Longitudinal FA Analyses

TBSS allows for the identification of significant clusters of FA difference between groups; however, these clusters are not region-specific. Therefore, we used the results of the TBSS analysis to inform ROI analyses of white matter tracts were relevant for sensorimotor function in this TIA population. All FA maps were nonlinearly registered to standard space with FSL's `FLIRT` function [Andersson et al., 2007a,b]. Tracts of interest were generated from the JHU white matter atlas [Hua et al., 2008; Wakana et al., 2007]; atlas regions were converted to binary masks and

applied to FA maps. ROIs included in the analyses were clusters identified by TBSS that were > 100 voxels in size, forceps minor, bilateral corticospinal tract (CST), and bilateral anterior thalamic radiations. See Figure 1 for included ROIs. Mean FA was extracted from each ROI, and analyzed using SPSS software (V23). Normality of the data was confirmed by the Shapiro-Wilk test. Significance was set at $P \leq 0.05$ for all analyses.

We performed an ROI analysis comparing TIA and healthy control scans at baseline to identify region-specific changes in FA after TIA. One-way ANOVA was performed to compare FA in forceps minor between TIA and healthy controls. Mixed model two-way ANOVAs were used to examine differences in FA in bilateral ROIs (CST, anterior thalamic radiations) between HC and TIA groups with within-subjects factor hemisphere (affected/unaffected) and between-subjects factor group (TIA/HC).

Next, longitudinal analyses were performed on the TIA group to evaluate whether significant changes in FA were present between baseline and 90 days post-TIA in ROIs that were significantly different between TIA and HC groups at baseline. One-way ANOVAs were used to examine differences between timepoints in clusters identified by the TBSS analysis, and in forceps minor. Repeated-measures two-way ANOVAs were used to examine differences in bilateral tracts (anterior thalamic radiations) with within-subjects factors hemisphere (affected/unaffected) and time (30 days/90 days). Significant interactions were tested *post hoc* with Tukey's HSD.

RESULTS

Twenty individuals with TIA were recruited within 30 days of the TIA event (means $\pm$ SD: age: 61.2 ± 12.9 ; time since TIA (days): 16.5 ± 7.0 ; ABCD²: 3.7 ± 1.4); 12 of these individuals were scanned again at 90 days post-TIA (means $\pm$ SD: age: 62.3 ± 13.1 ; time since TIA (days): 89.4 ± 9.2 ; ABCD²: 3.7 ± 1.5). Twelve healthy controls were recruited from the community (means $\pm$ SD: age: 57.2 ± 9.7). TIA and healthy control groups did not differ

TABLE I. Demographic characteristic of study participants

Subject ID	Age	Sex	ABCD ² score	Affected hem	Time since TIA, Scan 1	Time since TIA, Scan 2
T01	52	F	4	LH	18	67
T02	47	F	1	LH	29	-
T03	55	M	4	LH	14	-
T04	43	M	3	LH	16	86
T05	65	M	1	RH	15	85
T06	68	M	-	RH	15	96
T07	51	M	4	LH	26	-
T08	56	M	2	RH	23	101
T09	75	F	5	LH	9	100
T10	36	M	4	RH	11	92
T11	61	M	-	RH	12	92
T12	75	F	5	LH	17	-
T13	62	M	-	LH	9	-
T14	71	F	-	LH	7	97
T15	74	M	6	LH	30	86
T16	71	M	4	LH	14	85
T17	76	M	4	RH	8	86
T18	77	M	-	RH	18	-
T19	41	M	3	RH	26	-
T20	68	F	5	LH	13	-
HC01	55	F				
HC02	54	F				
HC03	66	F				
HC04	64	M				
HC05	31	F				
HC06	51	F				
HC07	53	F				
HC08	64	F				
HC09	64	M				
HC10	64	M				
HC11	59	M				
HC12	61	F				

TIA: TIA group; HC: healthy control; F: female; M: male; LH: left hemisphere; RH: right hemisphere. Time since TIA is in days.

in age ($t_{30} = -0.936$; $P = 0.357$). Demographic characteristics for participants are presented in Table I.

TBSS Analysis

The TBSS analysis generated several clusters where FA in the white matter skeleton was significantly lower in TIA group relative to healthy controls (TIA < HC). Cluster data are presented in Table II and clusters are visualized in Figure 2. Clusters occurred diffusively throughout the brain. Clusters 4 and 5 were >100 voxels in size, and thus were included in subsequent ROI-based analyses. Cluster 4 was located in forceps major, and the left anterior thalamic radiations, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and superior longitudinal fasciculus. Areas of low FA occurred in the corticospinal tract, notably affecting the hand-knob region of primary motor cortex in the right hemisphere. Cluster 5 was localized in forceps minor, and bilateral anterior thalamic radiations, cingulum, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus; superior longitudinal fasciculus;

uncinate fasciculus, and bilateral corticospinal tract (Fig. 2). There was also involvement of the right primary somatosensory cortex. There were no significant clusters where FA was higher in the TIA group relative to the healthy control group (TIA > HC).

ROI Analysis

ROI analyses were performed between HC and TIA groups at baseline to examine differences in specific white matter tracts of interest (Fig. 3). One-way ANOVA revealed significantly lower FA in individuals with TIA compared to healthy controls in forceps minor: ($F_{1,30} = 2.173$, $P = 0.044$). Two-way mixed model ANOVA showed no main effects of Group or Hemisphere in CST and no significant Hemisphere by Group interaction (Group: $F_{1,30} = 2.196$, $P = 0.149$; Hem: $F_{1,30} = 0.089$, $P = 0.767$; Hem $\times$ Group: $F_{1,30} = 1.367$, $P = 0.251$). The TIA group had significantly lower FA in anterior thalamic radiations compared to the HC group ($F_{1,30} = 4.535$, $P = 0.042$), and there was a main effect of Hemisphere across groups,

TABLE II. Clusters identified by TBSS, with significantly lower FA in TIA relative to healthy controls at baseline

Cluster index	Voxels	MAX	MAX X (mm)	MAX Y (mm)	MAX Z (mm)	Atlas regions
5	9,879	0.989	21	42	6	L+R Ant thalamic radiations; L+R CST; L+R cingulum; forceps minor; L+R Inf fronto-occipital fasciculus; L+R Inf longitudinal fasciculus; L+R Sup longitudinal fasciculus; L+R uncinate
4	196	0.954	-29	-71	10	L Ant thalamic radiations; Forceps minor; L Inf fronto-occipital fasciculus; L Inf longitudinal fasciculus; L Sup longitudinal fasciculus
3	85	0.957	-28	-24	5	L CST; L Inf fronto-occipital fasciculus; L Inf longitudinal fasciculus; L Sup longitudinal fasciculus
2	49	0.954	-46	-20	-5	L Inf fronto-occipital fasciculus; L Inf longitudinal fasciculus; L Sup longitudinal fasciculus
1	47	0.953	-41	-12	-15	L Ant thalamic radiations; forceps minor; L Inf fronto-occipital fasciculus; L Inf longitudinal fasciculus; L Sup longitudinal fasciculus; L uncinate fasciculus

Atlas regions are from the JHU white-matter atlas, based off of the TBSS skeleton.

MAX: coordinates for voxel of maximum difference in MNI space. L: left hemisphere; R: right hemisphere; Ant: anterior; Inf: inferior; Sup: superior.

with significantly lower FA in the TIA-affected/nondominant hemisphere (Hem: $F_{1,30} = 153.486$, $P \leq 0.001$).

We examined longitudinal changes in ROIs in the TIA group, between baseline and 90 days post-TIA (Fig. 4). Results of the one-way ANOVA showed no change in TBSS clusters or in forceps minor over time (Cluster 5: $F_{1,11} = 3.839$, $P = 0.076$; Cluster 4: $F_{1,11} = 0.593$, $P = 0.458$; Forceps minor: $F_{1,11} = 0.201$, $P = 0.663$). Two-way repeated measures ANOVA revealed a significant hemisphere $\times$ time interaction in the anterior thalamic radiations (Hem: $F_{1,11} = 10.436$, $P = 0.008$; time: $F_{1,11} = 0.162$, $P = 0.695$, Hem $\times$ time: $F_{1,11} = 5.929$, $P = 0.033$). Post hoc analyses revealed a significant difference between cerebral hemispheres at baseline, with lower FA in the TIA-affected hemisphere ($P = 0.018$), but no difference between hemispheres at

90 days ($P = 0.997$). Within hemispheres, there were no statistically significant differences between baseline and 90 day FA (affected: $P = 0.498$; unaffected: $P = 0.247$) (Fig. 5).

DISCUSSION

To our knowledge, this is the first study of a transient ischemic attack population that employed longitudinal DTI measures to index changes. All individuals in our TIA sample presented with unilateral sensorimotor symptoms. Despite symptom resolution at the time of scanning and an absence of overt lesions, there were diffuse reductions to FA in anterior sensorimotor, association, and commissural white matter tracts. Many of these tracts are also

Figure 2.

TBSS-identified clusters where FA in the TIA group is lower than healthy controls. **(A)** Serial axial slices of TBSS results. **(B)** Serial coronal slices of TBSS results. Color bar represents significance as $1 - p$, with lighter colors indicating a greater between-group difference in FA values.

Figure 3.

Region of interest (ROI) analysis of fractional anisotropy (FA) in tracts that are relevant for sensorimotor recovery between TIA and healthy control (HC) groups. Ant. thal: anterior thalamic radiations; CST: corticospinal tract; affected: TIA-affected hemisphere/dominant hemisphere; unaffected: TIA-unaffected hemisphere/nondominant hemisphere. Error bars are SEM. * $P < 0.05$; *** $P < 0.001$.

implicated in sensorimotor outcomes after stroke. With the exception of the anterior thalamic radiations, FA levels in TIA-affected tracts remained stable between <30 days and 90 days post-TIA. This is consistent with previous work from our group showing TIA results in persistent changes to cortical excitability during the early high-risk period post-TIA [Edwards et al., 2011], which parallel intracortical excitability changes seen after stroke [Edwards et al., 2013]. Our findings could inform the development of diagnostic biomarkers of TIA.

TBSS was ideally suited to our investigation of FA values changes in TIA individuals, as it is a whole-brain, hypothesis-free approach. This allowed us to explore regional changes in FA values between the TIA and healthy controls groups. TBSS identified multiple regions within the white matter skeleton with reduced FA in the TIA group, including the anterior portion of the corpus callosum, bilateral anterior thalamic radiations, inferior fronto-occipital fasciculus, inferior and superior longitudinal fasciculus, and the corticospinal tract. In each of these regions, FA was lower in the TIA group relative to the HC group, indicating that sensorimotor TIA affects multiple white matter tracts, primarily in anterior regions of the brain. This finding is consistent with patterns of frontal cerebral atrophy seen in previous work on small vessel disease and vascular dementia (for review see: Kalara [2016]). Our findings are further supported by a recent report from Zamboni et al. [2017], demonstrating that FA in frontal white matter pathways is related to cognitive

impairment in individuals with TIA or minor stroke [Zamboni et al., 2017]. Taken together, our work contributes to a growing body of evidence suggesting that frontal circuits are particularly vulnerable to damage in high-vascular-risk populations.

TBSS cluster FA did not change over the course of the early high-risk period in the TIA group. Cluster 5 was the largest cluster identified by TBSS, spanning multiple white matter tracts; this finding suggests regional variability in the impact of TIA on FA values. Thus, our region-specific analysis of sensorimotor tracts provided a nuanced assessment of TIA-related differences in FA, compared to the TBSS results alone. The anterior thalamic radiations form a portion of the anterior limb of the internal capsule, and connect limbic and hypothalamic circuits from the thalamus to the prefrontal cortex [Mori et al., 2005]. The anterior thalamic radiations have principally been implicated in cognitive functions, for example, small-vessel damage to the anterior thalamic radiations is associated with vascular cognitive impairment [Duering et al., 2011]. However, previous work has also found FA of the anterior thalamic radiations relates to upper-limb motor skill in individuals with chronic stroke [Schaechter et al., 2009], suggesting these pathways may be important in cognitive and sensorimotor outcomes in overt stroke. The anterior thalamic radiations may also be susceptible to cardiometabolic risk factors; low FA in anterior thalamic radiations

Figure 4.

Region of interest (ROI) longitudinal analysis of change in fractional anisotropy (FA) values in the TIA group, between <30 days (baseline) and 90 days post-TIA. Clusters 5,4: clusters identified by TBSS analyses as significantly different between TIA group and healthy control group at baseline. Clusters spanned multiple bilateral brain regions, including forceps minor, anterior thalamic radiations, cingulum, superior and inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and corticospinal tract. Error bars are SEM. * $P < 0.05$.

Figure 5.

Longitudinal analysis of change in anterior thalamic radiation FA values in the TIA group between <30 days (baseline) and 90 days post-TIA. Affected: TIA-affected hemisphere; unaffected: TIA-unaffected hemisphere. Error bars are SEM. * $P < 0.05$.

has previously been identified using TBSS in patients with type-2 diabetes [Zhang et al., 2014]. In the present report, not only was anterior thalamic radiation FA reduced overall in the TIA group at baseline, there was also a hemispheric asymmetry in thalamic FA, with significantly lower FA in the TIA-affected hemisphere at baseline. At 90 days post-TIA thalamic FA levels had normalized, such that this hemispheric asymmetry resolved. The observed change in thalamic FA over a relatively short time course suggests that the TIA event may be affecting FA levels in this tract; though without premorbid FA measures, we cannot confirm this speculation. Anterior thalamic radiations may therefore represent a clinically sensitive pathway in TIA, and are a possible TIA biomarker to explore in future work.

Corpus callosum FA is known to be impacted by stroke resulting in sensorimotor impairments [Borich et al., 2012; Wang et al., 2012], even when the stroke lesion does not directly involve the corpus callosum [Gupta et al., 2006]. Forceps minor of the corpus callosum is connected to prefrontal cortical regions [Hua et al., 2009; Zarei et al., 2006]. Reduced FA in forceps minor has also been found in individuals with silent lacunar lesions [Chen et al., 2015], and low FA in forceps minor discriminates vascular dementia from Alzheimer's disease [Zarei et al., 2009]. In our report, forceps minor of the corpus callosum was lower in the TIA group, and FA levels did not change over time. Taken together, this suggests that anterior regions of the corpus callosum are particularly vulnerable to vascular disturbances and cardiovascular risk factors. Previous work from our group has shown that the integrity of the anterior region of the corpus callosum predicts variability in upper-limb outcomes in chronic stroke populations [Mang et al., 2015]. Thus, reduced FA in forceps minor may

predispose TIA populations to worse recovery outcomes in the event of a stroke resulting in motor impairment.

FA of the corticospinal tract is reduced in the ipsilesional hemisphere in sensorimotor stroke [Borich et al., 2014; Schaechter et al., 2009], and has emerged as a key predictor of sensorimotor recovery [Jang, 2010; Stinear et al., 2007]. We observed reduced FA in the corticospinal tract bilaterally in the TIA group; however, these results only occurred in the TBSS results and did not survive the regional FA analysis. CST FA levels should be examined further in sensorimotor TIA, as this may be an indicator of persistent damage from a transient ischemic event.

The strengths of this study include the use of multiple DTI approaches to explore global FA changes, and identify specific regional variability in FA levels. Our use of longitudinal measures enabled us to identify whether TIA-related disruptions to white matter microstructure change over a clinically sensitive time frame. Our study also has several limitations. First, it is possible that our TIA sample includes individuals who are TIA mimics, which can occur in conditions such as migraine [Prabhakaran et al., 2008]. We have increased the reliability of our TIA categorization by having a stroke neurologist diagnose the participants, and only recruiting subjects with unilateral sensorimotor symptoms. Second, as we do not have data on cardiovascular risk factors in the healthy control group, it is difficult to ascertain whether decreases in FA values are the result of the TIA event or whether they are the result of a higher prevalence of comorbid conditions in the TIA group. In particular, it is possible that anterior callosal and thalamic FA are influenced by these comorbid conditions based on the strength of support in previous literature [Chen et al., 2015; Schaechter et al., 2009; Zarei et al., 2009; Zhang et al., 2014]. However, TIA populations can be conceptualized as a high cardiovascular risk group, and thus the present results remain informative to understanding the health implications of TIA. Third, in this article, we flipped 8 out of the 20 TIA scans to move all the TIA-affected hemispheres to the left side. We hope our results will inform future studies with a larger sample sizes that will examine hemispheric interactions after TIA. Finally, our diffusion sequence used only 16 gradients, which is no longer the standard in DTI research. We addressed this limitation by using TBSS and atlas-based ROIs to examine FA data, rather than using a tractography approach. These methods both rely on a mean FA map and thus should be less sensitive to a lower number of diffusion gradients. The lower number of diffusion gradients was employed to mimic the imaging capacity of most clinical 1.5 T MRI scanners; if our findings ultimately inform the development of a clinical biomarker of TIA they will need to be robust with a low number of diffusion gradients in order to be clinically practical.

In conclusion, TIA is associated with disruptions to white matter microstructure, primarily in frontal white-matter tracts. Furthermore, these changes occur in the

absence of overt lesions and appear to substantially outlast the duration of clinical symptoms; the first MRI scanning session was completed on average at 16 days post-TIA. These findings contribute to a growing body of evidence of persistent neurological changes after TIA. The involvement of sensorimotor pathways may suggest that TIA results in disturbances to pathways that are directly affected in the transient ischemic episode. Alternately, this finding could indicate that individuals who experience a sensorimotor TIA have reductions to FA levels that could ultimately influence recovery in the event of an overt stroke. While the majority of our measures remained stable over the early high-risk period post-TIA, anterior thalamic radiations showed low FA in the TIA-affected hemisphere, which normalized at the 90-day time point. Anterior thalamic radiations may therefore be sensitive to the effects of TIA, and may provide a novel marker of TIA-related changes to white-matter pathways. These findings may have predictive utility for examining recovery processes in the event of a symptomatic ischemic event. Our data suggest that TIA should not be considered a benign neurological event; TIA may confer persistent changes to white matter health that could influence trajectories of recovery after recurrent stroke.

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