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Microstructural Status of Ipsilesional and Contralesional Corticospinal Tract Correlates with Motor Skill in Chronic Stroke Patients

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Abstract: Greater loss in structural integrity of the ipsilesional corticospinal tract (CST) is associated with poorer motor outcome in patients with hemiparetic stroke. Animal models of stroke have demonstrated that structural remodeling of white matter in the ipsilesional and contralesional hemispheres is associated with improved motor recovery. Accordingly, motor recovery in patients with stroke may relate to the relative strength of CST degeneration and remodeling. This study examined the relationship between microstructural status of brain white matter tracts, indexed by the fractional anisotropy (FA) metric derived from diffusion tensor imaging (DTI) data, and motor skill of the stroke-affected hand in patients with chronic stroke. Voxelwise analysis revealed that motor skill significantly and positively correlated with FA of the ipsilesional and contralesional CST in the patients. Additional voxelwise analyses showed that patients with poorer motor skill had reduced FA of bilateral CST compared to normal control subjects, whereas patients with better motor skill had elevated FA of bilateral CST compared to controls. These findings were confirmed using a DTI-tractography method applied to the CST in both hemispheres. The results of this study suggest that the level of motor skill recovery achieved in patients with hemiparetic stroke relates to microstructural status of the CST in both the ipsilesional and contralesional hemispheres, which may reflect the net effect of degeneration and remodeling of bilateral CST. *Hum Brain Mapp 30:3461–3474, 2009.*

Key words: diffusion tensor imaging; anisotropy; stroke recovery; hemiparesis; tractography; white matter

INTRODUCTION

Stroke commonly causes acute, contralateral loss of motor function. Poststroke recovery of this lost function typically occurs over the subsequent weeks to months, yet is variable among stroke survivors. Motor recovery has been shown to relate to reorganization of activity in the ipsilesional and contralesional sensorimotor cortices [Dij-

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khuizen et al., 2001; Jaillard et al., 2005; Ward et al., 2003]. Accumulating evidence from studies in animal models of stroke suggest that structural remodeling of white matter of the ipsilesional and contralesional hemispheres also plays a role in motor recovery [Brus-Ramer et al., 2007; Carmichael and Chesselet, 2002; Dancause et al., 2005; Liu et al., 2008; Stroemer et al., 1995]. Little is known about the relationship between white matter structure of the sensorimotor network and motor recovery in patients with stroke.

The relatively recent development of diffusion tensor imaging (DTI), a noninvasive magnetic resonance imaging (MRI) technology that measures the random motion of water molecules in brain tissue, enables examination of white matter microstructure in vivo. Fractional anisotropy (FA) is a metric derived from DTI data that quantifies the extent to which water diffusion is directionally restricted, and is influenced by a number of factors including axonal myelination, diameter, density, and orientational coherence [Beaulieu, 2002; Takahashi et al., 2002]. FA is currently the most commonly used metric to reflect microstructural status of white matter. During the first few weeks after stroke in patients who go on to recover relatively little motor function, the ipsilesional corticospinal tract (CST) undergoes progressive decline in FA due to loss of axonal integrity that leads to Wallerian degeneration [Moller et al., 2007; Watanabe et al., 2001]. In animals recovering from experimentally-induced stroke, FA of perilesional white matter declines during the first few days poststroke [van der Zijden et al., 2008], yet rises during subsequent weeks [Ding et al., 2008; Jiang et al., 2006; van der Zijden et al., 2008]. The rise in FA of perilesional white matter has been shown to colocalize with histological evidence of white matter reorganization [Ding et al., 2008; Jiang et al., 2006], increased angiogenesis and local cerebral blood flow [Ding et al., 2008], and enhanced neural connectivity with perilesional sensorimotor cortex based on manganese-enhanced MRI [van der Zijden et al., 2008]. Treatment of animals poststroke with certain cell-based or pharmacological agents enhances the rise in perilesional FA in association with improved motor recovery [Ding et al., 2008; Jiang et al., 2006]. Anatomical tracing studies in animals with experimental stroke have also shown that contralesional corticofugal axons sprout to make new connections with nuclei denervated due to stroke, and that this form of axonal remodeling is enhanced by certain poststroke treatments in association with improved motor recovery [Andrews et al., 2008; Carmichael and Chesselet, 2002; Chen et al., 2002; Lee et al., 2004; Liu et al., 2008; Ramic et al., 2006]. In patients with chronic stroke, a progressive increase in FA of normal-appearing, whole-brain white matter has been observed (from 3–6 to 24 months poststroke) [Wang et al., 2006]. Together, these findings suggest that structural changes of ipsilesional and contralesional white matter occur after stroke and relate to motor recovery. In this study, we sought to examine the relationship between motor outcome in patients with chronic stroke and microstructural status of brain white matter tracts as measured by FA.

To meet this aim, we employed a recently developed method called Tract-Based Spatial Statistics (TBSS) that optimally aligns major white matter tracts across subjects, thereby allowing for valid voxelwise analyses of FA of all major white matter tracts [Smith et al., 2006]. In addition, we focused on evaluating FA of the ipsilesional and contralesional CST using tractography. As the majority of research aimed at understanding the neural underpinnings of motor outcome in patients with stroke has focused on reorganization of gray matter activity, this study widens the lens of inquiry by investigating the influence of microstructural status of white matter.

MATERIALS AND METHODS

Subjects

Ten patients with chronic stroke, former in-patients in hospitals within the Greater Boston area, were enrolled (Table I). These patients fulfilled the following inclusion criteria: (1) first-ever ischemic stroke incurred $\geq$6 months earlier; (2) acute unilateral loss of hand strength to $\leq$4 on the Medical Research Council (MRC) scale (0–5, 5 = normal) [Medical Research Council, 1976] lasting $\geq$48 h, based on physician notes entered into the medical record of the initial hospitalization within $\sim$ 24 h after stroke; and (3) at the time of study enrollment, the stroke-affected hand had sufficient motor skill to permit measurement of manual dexterity and index finger tapping speed. Exclusion criteria were as follows: (1) prior or subsequent symptomatic stroke; (2) language or cognitive deficit that would impair cooperation with study procedures; (3) other disorder that impaired motor function of the stroke-affected hand; and (4) contraindication to MRI. All patients had received and completed poststroke physical rehabilitation. No patient had switched handedness from before the stroke to the time of study enrollment based on the Edinburgh Inventory [Oldfield, 1971].

Ten healthy adults with no history of stroke and a normal neurological examination were also enrolled. These subjects were well matched to the patients with stroke for handedness (controls and patients: 9 right hand dominant, 1 left hand dominant), age (controls: 60 $\pm$ 10 years; patients: 59 $\pm$ 11 years), and gender (controls: 3 females; patients: 4 females). This matching was done because handedness [Buchel et al., 2004], age [Pfefferbaum et al., 2000], and gender [Hsu et al., 2008] may affect FA of white matter in the sensorimotor network.

All subjects provided written informed consent in accordance with the Human Subjects Committee of the Partners Institutional Review Board.

TABLE I. Patient characteristics

Patient	Dominant hand	Stroke-affected hand	Age (yr)	Gender	Time post-stroke (yr)	Acute UL (hand) MRC score	Lesion location
1	R	L	52	M	0.5	3	R CR, BG, temporal lobe
2	R	R	47	M	3.9	0 (0)	L CR, BG, IC, inferior frontal lobe
3	R	R	41	F	5.9	0–3 (0)	L medial temporal lobe, PLIC
4	R	R	69	M	1.6	4	L CR, BG, temporal lobe
5	R	L	76	F	2	1 (0)	R CR, temporal lobe
6	R	R	62	F	1.2	3–4+ (3+)	L CR
7	R	L	48	F	1.7	0 (0)	R frontal and parietal lobe white matter
8	L	R	60	M	5.8	0–3 (0)	L CR, BG
9	R	R	61	M	2.2	0 (0)	L frontal lobe, parietal lobe
10	R	L	69	M	1.2	1–3 (1)	R BG, IC
Summary	9R/1L	6R/4L	59 ± 11	4F/6M	2.6 ± 1.9		

M, male; F, female; R, right; L, left; UL, upper limb; IC, internal capsule; PLIC, posterior limb of IC; BG, basal ganglia; CR, corona radiata. UL MRC scores are strength measures (scale 0–5; 0 = no power, 5 = normal) for muscles of the affected upper limb acutely after stroke, as reported in the medical record; hand MRC scores are given in parentheses if available. Summary values are mean ± SD.

Behavioral Testing

In patients with stroke and control subjects, manual dexterity of each hand was measured using the Purdue Pegboard test in 3 × 30 s trials [Desrosiers et al., 1995; Tiffin and Asher, 1948]. Maximum speed of index finger tapping was measured in 2 × 10 s trials [Shimoyama et al., 1990]. Test scores were averaged over trials. After verifying that test scores of the unaffected hand of patients were not significantly different from the comparable hand of controls, average test scores of the stroke-affected hand of patients were normalized by scores of the unaffected hand and are reported in percent. A principal component analysis was conducted on normalized dexterity and tapping scores from all patients using MATLAB (The Mathworks, v6.5.1). The resultant first principal component score for each patient was taken to be a composite measure of motor skill of the stroke-affected hand and used in subsequent analyses. To aid in interpreting results of regression analyses that examined motor skill in relation to white matter tract FA in the patients (see later), the patients were dichotomized into subgroups with poorer and better motor skill based on a median-split of the first principal component scores.

Image Acquisition

All images were acquired with a 3T Siemens Trio magnetic resonance scanner and a transmitter/receiver Bruker circular polarization head coil. A custom-formed bite bar was used to limit head motion.

Diffusion tensor image acquisition employed single-shot echo planar imaging with a twice-refocused spin echo pulse sequence optimized to minimize eddy current-induced image distortions [Reese et al., 2003] (repetition time (TR) = 10.7 s; echo time (TE) = 91 ms; flip angle (α) = 90°; field-of-view (FOV) = 256 mm × 256 mm; matrix size = 128 × 128; slice thickness = 2 mm; interslice gap = 0 mm; number of acquisitions = 70, 60 diffusion-weighted images along noncollinear directions with b-value = 700 s/mm^2, 10 T2-weighted images with b-value = 0 s/mm^2; voxel size = 2 mm × 2 mm × 2 mm; number of slices = 75). The slices were acquired parallel to the intercommissural plane using an automated, atlas-based alignment procedure [van der Kouwe et al., 2005].

High-resolution T2-weighted turbo spin-echo images (TR = 6,920 s; TE = 103 ms; α = 150°; FOV = 200 mm × 200 mm; matrix size = 256 × 256; slice thickness = 3 mm; interslice gap = 0.6 mm; voxel size = 0.78 mm × 0.78 mm × 3.6 mm; number of slices = 40) and T1-weighted magnetization prepared rapid gradient echo images (TR = 7 ms; TE = 3 ms; α = 7°; FOV = 256 mm × 256 mm; matrix size = 192 × 256; effective slice thickness = 1.33 mm) were also acquired.

Image Analysis

DTI

Diffusion tensor images were corrected for motion and eddy current distortion using FMRIB's (http://www.fmrib.ox.ac.uk/fsl) Linear Image Registration Tool by registering each image to the first acquired T2-weighted image of the volume using a 12 degree-of-freedom affine transformation and mutual information cost function [Jenkinson et al., 2002]. The data were then skull-stripped using FMRIB's Brain Extraction Tool. The diffusion tensor and associated eigensystem were estimated at each voxel using a linear least squares regression method from which our primary DTI metric of interest, FA, was calculated [Basser, 1995]. The FA metric reflects the fraction of the total magnitude of

the diffusion tensor ascribed to anisotropic diffusion, and scales from a value of 0 indicating isotropy to 1 indicating anisotropy. As FA depends on the relative magnitude of the eigenvalues, maps of axial diffusivity and radial diffusivity were also generated to examine the underlying principal diffusivities. Axial diffusivity is the first eigenvalue of the diffusion tensor and reflects the magnitude of diffusivity parallel to the direction of maximal diffusion. In white matter, axial diffusivity is in the direction parallel to axons, and is thought to relate largely to axonal properties [Song et al., 2003]. Radial diffusivity was calculated as the average of the second and third eigenvalues, and reflects the magnitude of diffusivity orthogonal to the direction of maximal diffusion [Song et al., 2002]. In white matter, radial diffusion is in the direction orthogonal to axons and is thought to be affected largely by the axolemma and myelin sheath [Song et al., 2002, 2003].

Voxelwise analysis of white matter tract FA

To perform voxelwise analysis of the DTI data, images from the four patients with a right-sided stroke (Patient no. 1, 5, 7, 10) were flipped about the midsagittal plane, thereby lateralizing the stroke to the left hemisphere in all patients. Because some voxelwise analyses compared FA in patients to that in controls, the DTI data from the control subjects matched to these patients were also flipped midsagittally.

Statistical analyses of FA were performed using FMRIB's TBSS (v1.0) [Smith et al., 2006]. The FA volume from each patient and control was aligned to the within-group target volume that was closest to the group mean using a nonlinear registration algorithm (http://www.doc.ic.ac.uk/~dr/software) [Rueckert et al., 1999], followed by a 12 degree-of-freedom affine registration from the target FA volume to the Montreal Neurological Institute brain template (MNI152). Visual inspection of each subject's registered FA volume compared to the MNI152 template revealed no noticeable misalignment. A mean FA volume was created and used to generate an FA skeleton that corresponds to the center of major white matter tracts common to the group. Each subject's FA data were mapped to the skeleton by searching perpendicular to the skeleton, finding the highest FA value, and assigning that value to the skeleton.

We distinguished the portion of the FA skeleton in which FA values were mapped from a site of chronic infarction from the remainder of the skeleton. To do this, the T2-weighted images of the DTI volume were aligned across all patients using the same transformation matrices determined to align their FA volumes. The lesion in each patient was then marked on the spatially normalized T2-weighted images using MRIcro software [Rorden and Brett, 2000], and the total lesion volume was recorded. Subsequently, the same mapping used to map each patient's FA data to the skeleton was applied to the lesion mask, thereby identifying voxels of the skeleton that contained FA values from lesioned white matter. These voxels, which were 8% of all skeleton voxels, were considered to be within the lesion zone. The remainder of skeleton voxels was considered to be remote from the lesion (see Supporting Information Fig. 1).

The correlation between motor skill of the stroke-affected hand (first principal component score) and FA in patients was tested voxelwise in the lesion zone and, separately, remote from the lesion. The regression model included age as a nuisance regressor because the patients were of varying age (Table I) and increasing age has been shown to correlate with widespread reductions in brain white matter FA [Pfefferbaum et al., 2000].

To further probe the relationship between motor skill and microstructural status of white matter tracts, we tested for differences in FA between normal controls and patient subgroups with better and poorer motor skill of the affected hand (based on a median-split of first principal component scores) using unpaired *t*-tests. As there was no significant difference in age among the three groups (controls, better-recovered patients, poorer-recovered patients; $P = 0.42$, analysis of variance (ANOVA)), between-group comparisons were not adjusted for subject age.

Each statistical map was corrected to a cluster-wise significance level of $P < 0.001$. A significant cluster was defined as a set of contiguous voxels, each having a *P*-value of less than 0.05, with a size that occurred by chance less than once in 1,000 times, determined by Monte Carlo simulations (10,000 iterations) on synthesized noise entered into the group analysis. Noise values were uniformly distributed from 0 to 1 to reflect the range of FA values. We report the size of significant clusters as well as the *P*-value and MNI coordinates of the voxel within the cluster with the maximum significance. The anatomical location of significant clusters was determined by expert knowledge (author N.M.). To ease visualization of significant clusters of the FA skeleton, they are shown after thickening circumferentially by 2 mm.

For each cluster exhibiting significant between-group differences in FA, underlying axial and radial diffusivities were examined. To do this, mean axial and radial diffusivities were calculated for each subject of the patient subgroup and normal controls. Between-group differences in these diffusivities were tested using two-tailed, unpaired *t*-tests.

Tractography-based analysis of CST FA

A tractography method called Path-of-Interest statistics (POIstats v1.4), a tool within the FreeSurfer software library (http://surfer.nmr.mgh.harvard.edu), was used for CST reconstruction using each subject's native space DTI volume. The right and left CST were reconstructed between the precentral gyrus and ipsilateral cerebral peduncle. The hand region of the precentral gyrus was labeled on the single axial T2-weighted image in which the hand knob region [Yousry et al., 1997] was most

noticeable (14–20 mm inferior from the vertex of the brain). Borders of this label were the precentral sulcus (anterior), central sulcus (posterior), line extending posterior from the superior frontal sulcus (medial), and brain surface (lateral). The cerebral peduncle was labeled on the single axial T2-weighted image in which the region was most prominent.

Path reconstruction used a replica-exchange Monte Carlo method [Hansmann, 1997; Hukushima and Nemoto, 1996; Swendsen and Wang, 1986] in which multiple path replicas, each with a different value of the "temperature bath" parameter, connected the endpoint labels by a spline curve through the diffusion tensor volume. To remove the influence of voxels containing cerebrospinal fluid on path reconstruction, we masked out voxels with trace value >6 mm^2/s that characterizes the high level of total diffusivity of cerebrospinal fluid in ventricles and/or the site of chronic infarct. In search of the path replica with the lowest energy configuration, each path replica was perturbed at control points of the spline curve in a random direction and random, though bounded, distance. The energy of each path replica was determined using the relationship between the direction of each path line segment and the orientation distribution function [Kimmich and Weber, 1993; Tuch et al., 2003] calculated from the underlying diffusion tensor data. Replica exchange was implemented to guard against path replicas becoming trapped in local minima, with the decision to exchange replicas governed by the Metropolis update probability function [Metropolis et al., 1953]. Path replica perturbation and exchange were halted when the mean energy of successive replica sets was stable for 10 iterations. The optimal path among the final set of path replicas was assigned to the replica with the least energy overall. To account for the anatomic fact that white matter tracts have cross-sectional extent, a probability density volume was constructed around the optimal path such that the value at each voxel was inversely proportionate to the square of the distance from the optimal path. A threshold of 5×10^{-4} was applied to the probability density volume, and the resulting volume was considered to be the reconstructed CST (see Supporting Information Fig. 2). The location of the reconstructed CST in the ipsilesional hemisphere of patients was found to be symmetric to that in the contralesional hemisphere, indicating that the presence of the lesion did not interfere with performance of the tractography method. Applying a threshold of 1×10^{-3} to the probability density volume to yield the reconstructed CST did not change results of subsequent analyses.

Two analyses were conducted utilizing FA of the reconstructed CST, each paralleling voxelwise analyses of FA. One analysis tested the correlation between motor skill of the affected hand (first principal component score) and mean FA of the reconstructed CST (separate analyses for ipsilesional and contralesional CST) with adjustment for patient age. The second analysis computed mean FA of each axial slice along the length of a reconstructed CST in patients and controls. The mean FA data were then interpolated to cover 50 *z*-positions, bringing the CST data reconstructed in native space into spatial correspondence across subjects. The interpolated FA data from patient subgroups were compared to those from normal controls using a functional data analysis (FDA) approach. FDA is a set of statistical procedures that considers data points as samples from a continuous curve in a function space [Ramsay and Dalzell, 1991; Ramsay and Silverman, 1997]. FDA is in contrast to conventional multivariate statistical methods that consider data points on a curve as multivariate data in a finite-dimensional space, which presents challenging issues related to multiple comparisons of spatially correlated data. Considering the interpolated CST FA data as a curve accounts for the underlying continuity and spatial correlation of the data.

Specifically, using the FDA toolbox in the R statistical analysis package (www.r-project.org), the interpolated CST FA data from each subject and hemisphere were fit using B-splines with each curve smoothed to achieve 15 degrees of freedom. This level of smoothing was chosen empirically to maintain local features of the interpolated FA data (see Supporting Information Fig. 3). Functional unpaired *t*-tests were performed to compare curves of CST FA from patient subgroups with poorer and better motor skill to those from controls. Curves were considered to be significantly different if they differed over any interval at the two-tailed 0.05 level. A difference between curves at a level greater than 0.05 and less than 0.10 was considered a nonsignificant trend. We report intervals of the curves that showed a significant, or trending toward a significant, difference between groups.

White matter hyperintensity volume

The severity of white matter disease affects functional outcome after stroke [Arsava et al., in press; Kissela et al., 2009] and relates to microstructural status of white matter as measured by FA [Jones et al., 1999]. Accordingly, we questioned whether the differences in white matter tract FA we observed between patient subgroups and controls (see Results) could relate to between-group differences in white matter disease. Therefore, we quantified the volume of white matter hyperintensity in the subjects based on the high-resolution T2-weighted images according to the semi-automated method described previously [Gurol et al., 2006] using MRIcro software [Rorden and Brett, 2000]. To avoid potential confound due to stroke, the volume of signal hyperintensity was measured in the contralesional hemisphere of the patients, and in the comparable hemisphere of the matched control subjects. White matter hyperintensity volumes were normalized by intracranial size measured using the high-resolution T1-weighted images. Normalized volumes of white matter hyperintensity among better-recovered patients, poorer-recovered patients, and controls were compared using one-way ANOVA.

TABLE II. Results of behavioral testing of stroke-affected hand of patients

Patient	Motor skill test		Composite motor skill score (1st principal component)	Patient subgroup
	Purdue Pegboard (% unaffected hand)	Index finger tapping (% unaffected hand)		
1	82.3	79.8	7.80	Better
2	39.4	34.1	−54.81	Poorer
3	97.7	107.1	37.86	Better
4	112.4	91.3	37.42	Better
5	52.8	58.2	−28.42	Poorer
6	88.0	59.3	−2.37	Poorer
7	92.5	98.8	28.35	Better
8	50.8	85.3	−10.99	Poorer
9	100.0	93.3	29.90	Better
10	48.5	39.2	−44.73	Poorer
Mean ± SD	76.4 ± 26.0	74.6 ± 25.4		

Patient subgroup determined by median-split of 1st principal component scores.

TABLE III. White matter tract regions exhibiting significant correlation between FA and motor skill of stroke-affected hand of patients

WM region	Tract(s)	Cluster size (mm^3)	Max P, 10^{-x}	MNI coordinates (mm)		
				X	Y	Z
Lesion zone						
Positive correlation						
IL precentral gyrus[a]	CST and SLF	122	5.8	−50	−3	31
IL superior/anterior corona radiata[a]	CST and SLF	1,379	4.9	−29	−1	36
IL superior corona radiata[a]	CST and SLF	305	4.5	−40	−29	31
IL orbitofrontal region	Uncinate fasciculus	77	4.1	−34	31	−11
Negative correlation						
IL temporal lobe	Inferior longitudinal fasciculus	71	2.8	−39	7	−42
Remote from lesion						
Positive correlation						
IL precentral gyrus	CST and SLF	116	4.6	−49	−1	31
IL rostral PLIC, cerebral peduncle, genu IC	CST and corticobulbar tract	212	4.4	−11	−5	−7
IL middle PLIC, cerebral peduncle[a]	CST	126	3.0	−18	−21	−7
IL superior/anterior corona radiata[a]	SLF	581	4.6	−24	23	24
IL superior corona radiata	SLF	113	3.7	−15	4	52
IL external/extreme capsule	Corticostriate fibers and temporo-parieto-frontal fibers	123	2.6	−25	23	1
CL superior PLIC[a]	CST	213	3.2	30	−26	23
CL middle PLIC, cerebral peduncle	CST	94	4.5	22	−11	−7
CL orbitofrontal region	Cingulum bundle and uncinate fasciculus	243	4.0	13	43	−16
Negative correlation						
IL posterior corona radiata	SLF and inferior longitudinal fasciculus	114	3.9	−28	−64	22

IL, ipsilesional; CL, contralesional; IC internal capsule; PLIC posterior limb of internal capsule; CST corticospinal tract; SLF superior longitudinal fasiculus.
[a]Region shown in Figure 1.

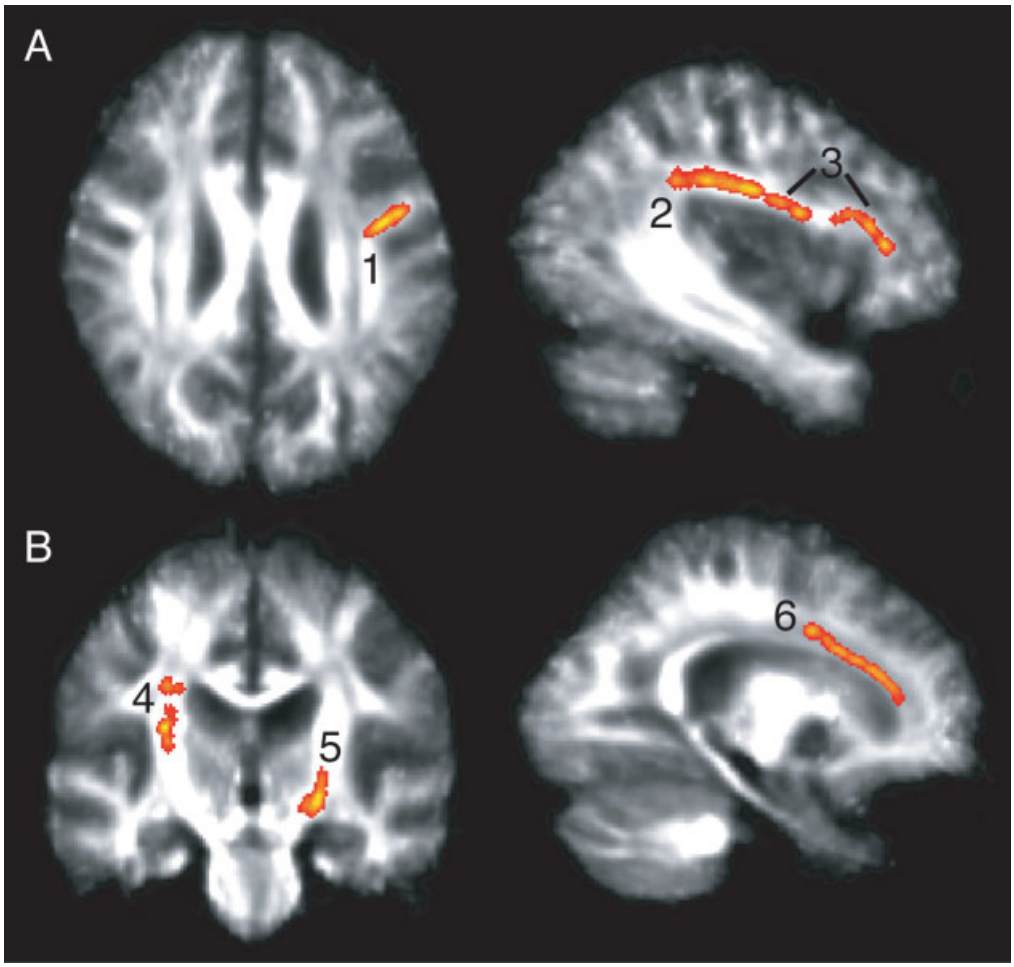

Figure 1.
White matter tract regions exhibiting significant (clusterwise $P < 0.001$) positive correlation between FA and motor skill in patients with chronic stroke. (**A**) Regions in lesion zone. (**B**) Regions remote from lesion. Shown are clusters in: 1, ipsilesional precentral gyrus; 2, ipsilesional superior corona radiata; 3, ipsilesional superior/anterior corona radiata; 4, contralesional superior posterior limb of internal capsule; 5, ipsilesional middle posterior limb of internal capsule, cerebral peduncle; 6, ipsilesional superior/anterior corona radiata. Clusters shown overlaying mean FA image from patients with stroke.

RESULTS

Behavioral Testing

The patients with chronic stroke exhibited a range (fair to excellent) in motor skill of the stroke-affected hand (Table II). Measures of dexterity (Purdue Pegboard scores) and index finger tapping speed were strongly correlated in the patients (Pearson's $r = 0.77$, $P < 0.01$). The first principal component of the behavioral measures accounted for 88.5% of the variability within the patient data, justifying its use as a composite score reflecting motor skill of the stroke-affected hand. Patient subgroups with poorer and better motor skill had significantly different dexterity (poorer: 56% ± 19% (SD), better: 97% ± 11%, $P < 0.01$, unpaired *t*-test) and index finger tapping speed (poorer: 55% ± 20%, better: 94% ± 10%, $P < 0.01$), indicating that the two patient subgroups represented two levels of motor skill.

Voxelwise Analysis of White Matter Tract FA

Voxelwise regression analysis revealed that within the lesion zone, FA of the CST and association tracts, primarily the superior longitudinal fasciculas (SLF), significantly and positively correlated with motor skill of the affected hand in the chronic stroke patients (Table III; Fig. 1). In the ipsilesional hemisphere remote from the lesion, a significant FA-behavior correlation was observed in regions of the CST and SLF and extended into neighboring white matter tract regions (e.g., genu of internal capsule, external/extreme capsule). Notably, in the contralesional hemisphere, a significant positive correlation between FA and motor skill was largely specific to regions of the CST, with the contralesional orbitofrontal region also exhibiting a significant FA-behavior correlation.

To further interrogate the observed FA-behavior association revealed by the regression analysis, white matter tract FA in patient subgroups (i.e., poorer and better motor skill) was compared to that in normal controls. Patients with poorer motor skill showed significantly reduced FA of the CST, SLF, and neighboring white matter tracts that extended from the lesion zone into ipsilesional regions remote from the lesion (Table IV, Fig. 2A). These patients also showed reduced FA along the contralesional CST. The reductions in white matter tract FA were associated with

TABLE IV. White matter tract regions exhibiting significant difference in FA in patients with poorer motor skill compared to controls

WM region	Tract(s)	Cluster size (mm^3)	Max P, 10^{-x}	MNI coordinates (mm)			Diffusivity	
				X	Y	Z	Axial	Radial
Lesion zone								
Patients < controls								
IL precentral gyrus[a]	CST and SLF	1,244	5.7	−22	−5	36		↑[b]
Anterior/superior corona radiata	CST and SLF							
Genu IC	Corticobulbar tract							
Anterior limb IC	Anterior thalamic radiation and frontopontine fibers							
IL precentral gyrus	CST and SLF	88	3.5	−45	−8	35		↑[b]
IL superior corona radiata	SLF	152	2.6	−41	−18	29		
IL superior corona radiata	SLF	75	2.3	−37	−33	35	↓[b]	↑[c]
IL external/extreme capsule	Corticostriate fibers and temporo-parieto-frontal fibers	324	5.7	−30	13	2		↑[c]
Remote from lesion								
Patients < controls								
IL PLIC, cerebral peduncle	CST	645	4.8	−18	−7	3		↑[d]
Genu IC	Corticobulbar tract							
Anterior limb IC[a]	Anterior thalamic radiation and frontopontine fibers							
IL ventral pons	CST	152	2.7	−10	−21	−26		↑[d]
IL dorsal pons	Pontocerebellar fibers	145	4.1	−7	−38	−45		↑[c]
IL anterior/superior corona radiata[a]	CST and SLF	292	4.2	−28	1	30		↑[b]
IL external/extreme capsule	Corticostriate fibers and temporo-parieto-frontal fibers	273	6.2	−28	18	2		↑[d]
IL internal capsule, retrolenticular part	Inferior longitudinal fasciculus	173	2.8	−38	−34	0		↑[d]
CL PLIC, cerebral peduncle[a]	CST	563	4.8	24	−5	8		↑[c]

[a]Region shown in Figure 2A.
[b]$P < 0.05$ patients versus controls, unpaired t-test.
[c]$P < 0.01$.
[d]$P < 0.001$.

significant elevations in radial diffusivity. In contradistinction, patients with better motor skill showed elevated FA of the ipsilesional and contralesional CST remote from the lesion, and the ipsilesional SLF in the lesion zone (Table V, Fig. 2B). The elevations in white matter tract FA were associated with significant reductions in radial diffusivity. Patients with better motor skill also exhibited significantly reduced white matter tract FA in the temporal lobe of the lesion zone and ipsilesionally remote from the lesion.

There was no significant difference between the number of skeleton voxels contributing to the lesion zone in patients with poorer versus better motor skill (poorer: 1,459 ± 2,820 voxels, better: 722 ± 494 voxels; $P = 0.58$, unpaired t-test). Further, no significant difference was found between patient subgroups in total lesion volume (poorer: 20 ± 40 cm^3, better: 18 ± 16 cm^3; $P = 0.88$). These results indicate that the observed differences in white matter tract FA in the patient subgroups relative to controls are neither directly attributable to between-group differences in primary damage to white matter tracts nor total lesion volume.

Tractography-Based Analysis of CST FA

Regression analyses revealed a significant positive correlation between motor skill and mean FA of the ipsilesional reconstructed CST ($P < 0.05$) and contralesional reconstructed CST ($P < 0.05$). These tractography results are consistent with those found by the voxelwise regression analysis, both indicating that microstructural status of the ipsilesional and contralesional CST correlates with motor skill of the affected hand in patients with chronic stroke.

Figure 3 shows results of FDA of FA curves of the ipsilesional and contralesional CST in patient subgroups and normal controls. In patients with poorer motor skill, FA was significantly reduced along much of the length of the ipsilesional CST, as well as from the level of the posterior limb of the internal capsule to the cerebral peduncle of the contralesional CST. Notably, patients with better motor skill showed a nonsignificant trend toward an elevation in FA of the ipsilesional CST at the level of the posterior limb of the internal capsule, and a significant elevation in FA of

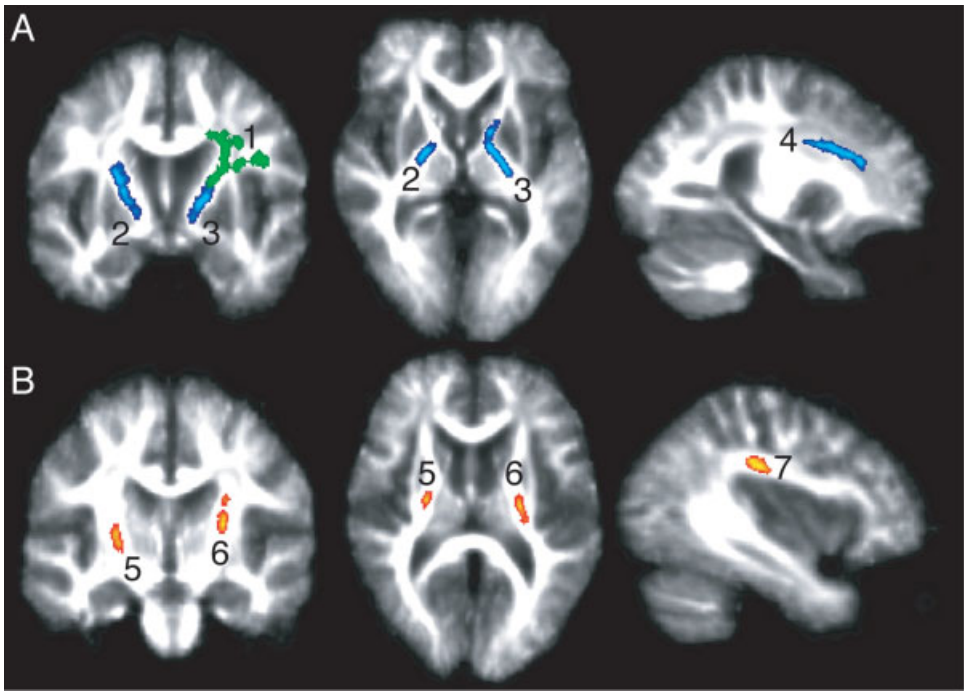

Figure 2.

White matter tract regions exhibiting significant (clusterwise $P < 0.001$) differences in FA in patient subgroups compared to normal controls. (**A**) Regions of reduced FA in patients with poorer motor skill. (**B**) Regions of elevated FA in patients with better motor skill. Shown are clusters in: 1, lesion zone involving precentral gyrus, superior/anterior corona radiata, genu of internal capsule and anterior limb of internal capsule; 2, remote from lesion in contralesional posterior limb of internal capsule, cerebral peduncle; 3, remote from lesion in ipsilesional posterior limb of internal capsule, cerebral peduncle, genu of internal capsule and anterior limb of internal capsule; 4, remote from lesion in ipsilesional superior/anterior corona radiata; 5, remote from lesion in contralesional PLIC; 6, remote from lesion in ipsilesional posterior limb of internal capsule; 7, remote from lesion in ipsilesional superior corona radiata. Clusters shown overlaying mean FA image from all subjects.

the contralesional CST in the region between the posterior limb of the internal capsule and cerebral peduncle.

White Matter Hyperintensity Volume

Normalized volume of white matter hyperintensity was not significantly different among patient subgroups and controls (poorer-recovered patients: 1.0 ± 0.8 cm^3; better-recovered patients: 0.7 ± 1.1 cm^3; controls: 1.1 ± 1.5 cm^3, $P = 0.85$, ANOVA). These results indicate that the observed between-group differences in FA of the ipsilesional and contralesional white matter tracts detected by voxelwise TBSS and tractography analyses are not attributable to differences in the severity of white matter disease.

DISCUSSION

The main finding of this study is that motor skill of the stroke-affected hand significantly and positively correlated with microstructural status, indexed by FA, of the ipsilesional CST and the contralesional CST in patients with chronic stroke. A correlation between FA of bilateral CST and behavior was detected using a voxelwise approach that was unbiased with respect to location of major white matter tracts and confirmed using a tractography approach applied to the CST. The finding of a relationship between microstructural status of the ipsilesional CST and motor skill is consistent with the established role of the CST in fine motor control [Hepp-Reymond and Wiesendanger, 1972; Wiesendanger, 1984] and prior studies showing that greater sparing of the ipsilesional CST is associated with better motor outcome of the paretic limb of patients with stroke [Pendlebury et al., 1999; Pineiro et al., 2000; Schaechter et al., 2008]. The finding that the FA-behavior correlation occurred at regions along the contralesional CST supports prior suggestions that the contralesional CST may play a role in motor recovery after unilateral stroke [Ago et al., 2003; Brus-Ramer et al., 2007; Caramia et al., 2000; Fisher, 1992; Jankowska and Edgley, 2006; Johansen-Berg et al., 2002; Liu et al., 2008]. Given the close proximity of the CST with other corticofugal fibers (e.g.,

TABLE V. White matter tract regions exhibiting significant difference in FA in patients with better motor skill compared to controls

WM region	Tract(s)	Cluster size (mm^3)	Max P, 10^{-x}	MNI coordinates (mm)			Diffusivity	
				X	Y	Z	Axial	Radial
Lesion zone								
Patients > controls								
IL superior corona radiata[a]	SLF	80	3.8	−40	−27	32		↓[b]
Patients < controls								
IL temporal lobe	Inferior longitudinal fasciculus	96	3.2	−46	11	−33		
Remote from lesion								
Patients > controls								
IL PLIC[a]	CST	145	3.7	−27	−19	25		↓[c]
IL middle cerebellar peduncle	Pontocerebellar fibers	113	2.7	−7	−69	−37		↓[c]
IL orbitofrontal region	Cingulum bundle and uncinate fasciculus	112	2.8	19	48	−4		↓[c]
CL PLIC[a]	CST	108	2.7	28	−14	8		↓[d]
Patients < controls								
IL temporal lobe	Inferior longitudinal fasciculus	478	4.3	−48	−57	−2		↑[c]

[a]Region shown in Figure 2B.
[b]$P < 0.05$ patients versus controls, unpaired t-test.
[c]$P < 0.01$.
[d]$P < 0.001$.

corticopontine, corticorubral) in the cerebral hemispheres, FA of these other descending tracts may have contributed to the correlation between CST FA and motor skill. We interpret the observed FA-behavior correlation as suggesting that biophysical properties that affect white matter FA, such as axonal density, diameter, myelination, and orientation coherence [Beaulieu, 2002; Takahashi et al., 2002], relate to the efficacy of communication along the CST, which in turn relate to the level of motor skill in chronic stroke patients. Prior studies in healthy adults have shown a correlation between performance on perceptual-motor tasks and FA along functionally-relevant white matter tracts [Bohr et al., 2007; Bucur et al., 2008; Tuch et al., 2005]. To our knowledge, this is the first report

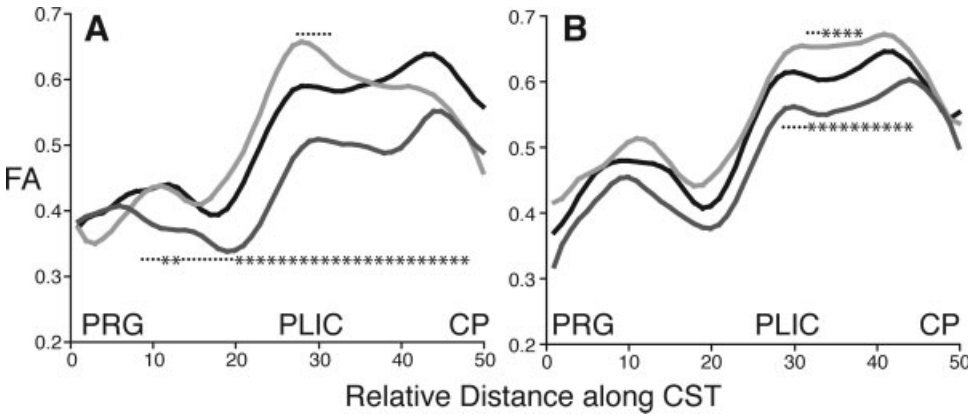

Figure 3.

FA curves of the ipsilesional CST (**A**) and contralesional CST (**B**) in patients with chronic stroke with better (light gray line) and poorer (dark gray line) motor skill of the affected hand and normal control subjects (black line). The tracts were reconstructed between the precentral gyrus (PRG) and cerebral peduncle (CP), extending through the posterior limb of internal capsule (PLIC). FA curves are smoothed versions of interpolated FA data. Asterisks indicate the interval of the curve at which the patient subgroup differed from controls at $P < 0.05$ based on FDA. Dots indicate the interval of the curve at which the patient subgroup differed from controls at $0.05 < P < 0.10$. Confidence intervals are not shown for ease of visualization.

demonstrating that FA of bilateral CST correlates with motor performance of the affected hand in stroke patients.

The CST FA-behavior correlation was associated with reduced FA of the ipsilesional CST in patients with poorer motor skill compared to normal controls. The finding of reduced FA of the ipsilesional CST in this patient subgroup is consistent with prior reports, and likely represents primary (in the lesion zone) and secondary (remote from the lesion) axonal degeneration and gliosis [Pierpaoli et al., 2001; Werring et al., 2000]. Reduced FA of the ipsilesional CST was found to be associated with elevated radial diffusivity, suggesting that loss in integrity of the axolemma and/or myelin sheath contributed to the reduced anisotropy. Changes in axial diffusivity have been shown to occur at regions of primary degeneration (i.e., elevation) and secondary degeneration (i.e., reduction) of the ipsilesional CST [Pierpaoli et al., 2001]. That we observed little or no significant elevation in axial diffusivity in the lesion zone may have been due to our operational definition of this FA skeleton region (see Materials and Methods section); reductions in axial diffusivity due to mapping from voxels of chronic infarction may have been diluted by mapping from voxels of undamaged white matter. The lack of significant reduction in axial diffusivity of the ipsilesional CST remote from the lesion may indicate relatively little axonal loss in these patients.

The CST FA-behavior correlation was also associated, rather unexpectedly, with reduced FA of the contralesional CST in patients with poorer motor skill compared to normal controls. Contralesional CST regions of reduced FA had elevated radial diffusivity, suggesting a similar loss in integrity of the axolemma and/or myelin sheath as along the ipsilesional CST. The cross-sectional design of our study precludes definitive conclusions about the antecedent of these between-group differences. However, several findings, in sum, suggest that loss in microstructural status of the contralesional CST more likely evolved poststroke than was present prestroke. The control subjects in our study were well matched to the patients for age, handedness, and gender, excluding these factors as responsible for possible prestroke differences in contralesional CST FA and radial diffusivity. We also found no between-group differences in the severity of white matter disease, which could theoretically affect susceptibility of the CST, both ipsilesional and contralesional, to poststroke degenerative changes. Further, a previous study showed progressive loss in FA of contralesional white matter over the first 6 months poststroke that paralleled the loss of ipsilesional CST FA [Buffon et al., 2005], supporting the possibility that our findings reflect poststroke change in microstructural status of the contralesional CST in the patients with poorer motor skill.

The CST FA-behavior correlation was associated with elevated FA of bilateral CST in patients with better motor skill compared to controls. Accumulating evidence, largely from studies in animal models of stroke, suggests that white matter remodeling occurs in the ipsilesional and contralesional hemispheres during the recovery period after stroke. In the ipsilesional hemisphere of animals with experimental stroke, increased FA of white matter in the lesion borderzone has been shown to correspond spatially to histological evidence of white matter reorganization [Ding et al., 2008; Jiang et al., 2006] and MRI evidence of neural connectivity with perilesional sensorimotor cortex [van der Zijden et al., 2008]. In the contralesional hemisphere, CST axons have been demonstrated to sprout and form new connections with denervated motor nuclei in the brainstem and spinal cord spontaneously after experimental stroke, and this structural remodeling is enhanced by certain post-stroke treatments (i.e., cell-based, electrical stimulation, pharmacological paired with rehabilitation) that improve motor recovery [Andrews et al., 2008; Brus-Ramer et al., 2007; Chen et al., 2002; Lee et al., 2004; Liu et al., 2008; Ramic et al., 2006]. Immunohistochemical studies suggest increases in oligodendrocyte myelinating activity in ipsilesional and contralesional white matter after experimental stroke [Gregersen et al., 2001; Ishiguro et al., 1993; Tanaka et al., 2003]. Our finding that the regions of bilateral CST exhibiting elevated FA had reduced radial diffusivity is consistent with the possibility that increased myelination underlies CST axonal remodeling in the stroke patients with better motor skill. DTI studies in patient populations other than stroke have similarly provided evidence of structural remodeling of functionally-relevant white matter tracts. An increase in the number of tractography-reconstructed fibers of the contralesional corticobulbar tract and an increase in FA at regions of the contralesional CST have been reported in patients with congenital hemiparesis due to unilateral periventricular white matter injury [Thomas et al., 2005]. Patients with multiple sclerosis early after clinical onset who had white matter damage in the working memory network yet little or no working memory impairment, showed an increase in the number of tractography-reconstructed fibers between the right and left thalami [Audoin et al., 2007]. These reports, together with our findings, suggest that structural remodeling of functionally-relevant white matter tracts may be an adaptive response that compensates for injury to the human brain.

Voxelwise regression analysis revealed that FA of association tracts of the ipsilesional hemisphere, primarily the SLF, correlated with motor skill in the patients with chronic stroke. The SLF, a multicomponent fiber bundle [Makris et al., 2005], includes parieto-frontal fibers that are critical to exchanging information about the perception of the body in space for the planning, initiation, and updating of goal-directed movement [Fuster, 2004]. The functional role of this SLF component is consistent with the observed FA-behavior correlation. However, the functional role of the other association tracts exhibiting the FA-behavior correlation (e.g., inferior longitudinal fasciculus, extreme capsule) is related to high-level cognition and emotion and not linked tightly to motor function. Accordingly, the correlation between motor skill and FA of these

association tracts may have been epiphenomenal, resulting from stroke-induced reduction in FA of similar magnitude as that occurring along the neighboring ipsilesional CST. The patients in this study did not undergo testing of high-level cognition and emotion. Such testing might have allowed us to determine the relative strength of correlation among various functions (i.e., motor, cognitive, emotional) and white matter tract FA.

Voxelwise regression analysis also revealed that FA of the contralesional orbitofrontal region correlated with motor skill in the patients. Interestingly, the orbitofrontal gyrus is a region of the adult human brain that has one of the highest levels of GAP-43, a presynaptic protein strongly implicated in axonal remodeling after injury [Ng et al., 1988]. We speculate that the observed correlation between FA of the orbitofrontal region and motor skill among the patients may relate to the propensity for axonal remodeling in response to brain injury, and not be specifically tied to motor function.

A technical aspect of this study deserves comment. The voxelwise TBSS method involves automated alignment of each subject's FA volume to the template FA volume. Stroke-induced tissue necrosis and cavitation can result in structural and signal intensity abnormalities that could cause poor alignment to the template brain and lead to inaccurate results of voxelwise analyses. However, visual inspection of each brain after spatial alignment revealed no noticeable errors, indicating that our results from voxelwise analyses were not due to misalignment of the FA volumes. Further, with regard to the CST, results of analyses of FA of the CST reconstructed using tractography, an independent approach conducted without spatial alignment of brain image volumes, were qualitatively similar to those using the TBSS approach, supporting the veracity of results of the voxelwise analyses.

CONCLUSION

The findings of this DTI study demonstrate that microstructural status of the ipsilesional and contralesional CST correlates with motor skill of the affected hand in chronic stroke patients. The relative strength of poststroke degeneration of bilateral CST tending to limit motor recovery and poststroke remodeling of bilateral CST tending to improve motor recovery may underlie the FA-behavior relationship we observed at the chronic time-point. The determinants of the relative strength of degenerative versus restorative changes of the CST are unknown, yet could involve genetic variations that affect responses to ischemic brain damage. A prospective serial study that examines the evolution of poststroke changes in CST microstructure is required to better understand the underpinnings of the FA-behavior correlation observed in this study. The results of the current study broaden our view of the factors that may play a role in motor recovery after stroke in patients, from one focused on reorganization of activity of the sensorimotor cortices to including the contribution of changes in microstructural status of bilateral CST.

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