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Tract-Specific and Region of Interest Analysis of Corticospinal Tract Integrity in Subcortical Ischemic Stroke: Reliability and Correlation with Motor Function of Affected Lower Extremity

ORIGINAL RESEARCH

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BACKGROUND AND PURPOSE: TS analysis has been suggested as a useful method to evaluate the fiber integrity of white matter tracts. This study investigated the intrarater and interrater reliability and validity of a TS analysis for the CST and compared the results with those of a ROI-based analysis.

MATERIALS AND METHODS: Diffusion spectrum imaging was performed on 7 patients with subcortical ischemic stroke on a 3T MR imaging system. For the TS analysis, seed regions were placed at the cerebral peduncle and the medial portion of the primary motor cortex to reconstruct the tracts of the CST for motor control of the lower extremity. The mean GFA was measured at the PLIC by calculating the weighted sum of the GFAs sampled by the CST tracts at this segment. For the ROI-based analysis, the posterior two-thirds of the PLIC were enclosed on the GFA maps, and the mean GFA in this ROI was calculated.

RESULTS: The results showed good-to-excellent intrarater and interrater reliability on the seed region/ROI placement (mean κ values >0.80) and mean GFA values (ICCs >0.90) for both the TS and ROI-based analyses. Both the $GFA_{PLIC\text{-}TS}$ and $GFA_{PLIC\text{-}ROI}$ values were highly correlated with the motor function of the affected lower extremity ($r = 0.76$ and 0.80, respectively; $P < .05$).

CONCLUSIONS: We demonstrated good reliability and validity of the TS and ROI-based analyses of the CST corresponding to lower extremity motor control in patients with subcortical ischemic stroke.

ABBREVIATIONS: AH = affected hemisphere; BG = basal ganglia; BOLD = blood oxygen level–dependent; CP = cerebral peduncle; CST = corticospinal tract; CV = coefficient of variance; DSI = diffusion spectrum imaging; DTI = diffusion tensor imaging; FA = fractional anisotropy; FMA-LE = Fugl-Meyer assessment of lower extremity; GFA = generalized fractional anisotropy; $GFA_{PLIC\text{-}TS}$ = GFA value of the PLIC calculated by using the tract-specific method; $GFA_{PLIC\text{-}ROI}$ = GFA value of the PLIC calculated by using the ROI-based method; ICC = intraclass correlation coefficients; M1 = primary motor cortex/precentral gyrus; MMSE = Mini-Mental State Examination; NIHSS = National Institutes of Health Stroke Scale; PLIC = posterior limb of the internal capsule; ROI = region of interest; SD = standard deviation; TS = tract-specific; UH = unaffected hemisphere

BRAIN

ORIGINAL RESEARCH

Using MR DTI to assess the integrity of white matter tracts in patients with stroke is potentially valuable to correlate the motor impairments and to predict functional outcomes.[1,2] It has been reported that FA, which is a quantitative index of the directional anisotropy of water molecular diffusion derived from the diffusion tensor, is an effective measure of fiber integrity.[3] Decreases in FA have been found in the affected tracts at infarct regions and regions with wallerian degeneration.[1,4,5] Knowledge about tract integrity after stroke may allow for both the accurate stratification of functional recovery and the planning of effective customized rehabilitation programs for individual patients.

Most studies have used ROI-based analysis of FA maps to detect white matter changes in patients with stroke.[2,6,7] Using ROI-based analysis, researchers manually select certain white matter regions with the aid of anatomic landmarks. This approach depends on raters' familiarity with the brain anatomy and is thus subject to poor interrater and intrarater reproducibility.[8] Recently, several studies have suggested that TS analysis may be more objective, specific,[9-11] and reliable[11,12] than ROI-based analysis to evaluate the integrity of white matter fibers. The TS analysis method uses diffusion tractography as a guide to quantify the FA of a specific fiber tract bundle.[9,11,13-16] Compared with ROI-based analysis, TS analysis has the advantage of exploring the fiber integrity anywhere along a tract of interest, and thus, it is not limited to regions identifiable by anatomic landmarks.

Performing tractography of a long tract bundle such as the CST often encounters interruption of the tracts in patients

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Table 1: Demographics of stroke subjects

Subject	Sex	Age	Handedness	Footedness	Lesion Location	NIHSS (42)	Post-Onset Days	FMA-LE Sensation (24)	FMA-LE Range of Motion (22)	FMA-LE Motor (34)	MMSE (30)
1	M	59.2	R	R	R corona radiata	7	89	24	15	12	29
2	F	66.1	R	R	R BG, PLIC	5	99	24	22	34	28
3	M	49.3	R	R	L thalamus	8	102	24	22	28	29
4	F	65.4	R	R	R corona radiata	4	87	24	22	34	25
5	F	69.0	R	R	R corona radiata	5	89	24	22	34	26
6	M	54.6	R	R	L thalamus, PLIC	7	98	24	22	28	30
7	M	50.7	R	R	R corona radiata	2	91	24	22	34	30
Mean		59.2					93.6	24.0	21.0	29.1	28.1
SD		7.9					5.9	0.0	2.7	8.1	1.9

Note:—Numbers in parentheses indicate the highest possible score of the assessments.

with stroke.[17-19] This is because the FA values tend to decrease, and the tensor orientations become disorganized in the infarct location and its surroundings. The tracking procedure of the tractography algorithm would come to a halt when the FA value or proceeding angle does not pass a default threshold. Even if the tractography is not interrupted, it is still difficult to obtain a minor branch of a tract bundle from the tractography because the tensor orientation is predominantly pointing toward the orientation of the major branches. Analysis of our unpublished laboratory data supported that these difficulties pose a great challenge to TS analysis of the CST if a minor branch, such as that corresponding to the lower extremity motor control originated from M1, is to be assessed. In this study, we used DSI to address these problems.[20,21] DSI entails the acquisition of >200 diffusion-weighted images over the whole brain, where each diffusion weighting corresponds to a specific encoding point in the *q*-space. DSI tractography has been demonstrated to differentiate the CST from other crossing fiber tracts, including the corpus callosum, superior longitudinal fasciculus, and middle cerebellar peduncle, and it has been shown to separate the branches arising from different cortical areas responsible for the movement of different body parts.[22,23]

Previous studies have investigated the reproducibility of TS analysis in patients with amyotrophic lateral sclerosis and in premature infants.[9,11] The same studies in patients with stroke are still lacking. Although there have been many studies by using ROI-based analysis to reveal the correlation between the FA and motor function in patients with stroke,[1,2,4,24,25] such functional correlation studies by using the TS quantitative analysis have not yet been established. As for diffusion tensor tractography, only a qualitative analysis of the CST has been performed to relate the degrees of tract interruption and functional outcomes.[17-19,26,27]

Therefore, the goal of this study was to establish the reliability and validity of the TS analysis method. We acquired DSI data from patients with subcortical ischemic stroke, reconstructed the whole CST originating from the M1 region corresponding to the lower extremity motor control, and quantified the GFA at the segments covering the PLIC. The purpose of this study was 2-fold. First, we investigated the reliability of TS analysis of the CST or, more specifically, the intrarater and interrater reliability of the GFA values. Second, we tested the validity of the TS analysis by correlating the GFA values with the clinical motor function scores of the affected lower limbs. In this study, the performance of the ROI-based analysis was also evaluated and compared with the TS analysis.

Materials and Methods

Subjects

Patients with stroke were recruited from the stroke registry of the Neurology Department at the National Taiwan University Hospital. The inclusion criteria of the patients to participate in this research were the following: 1) having first-ever ischemic stroke based on clinical imaging reports and physician diagnosis; 2) presenting subcortical stroke with unilateral hemiplegia or hemiparesis; 3) showing mild-to-moderate severity of stroke, corresponding to the NIHSS ≤15[28]; 4) being between 40 and 80 years old; and 5) having no contraindications for MR scanning, such as an electrical device implanted in the body or claustrophobia. Patients were excluded if they had cortical stroke, unstable medical conditions, impaired cognitive function, or were unable to communicate. All participants signed an informed consent form approved by the institutional review board.

We evaluated the function of cognition with the MMSE.[29] Impairment in sensation, range of motion, and motor function of the affected lower extremity were evaluated by using the FMA-LE.[30] We used Manual Muscle Testing[31] to check whether there was any muscle weakness of the unaffected lower extremity. The reliability and validity of these clinical assessments have been established.[32-34]

Seven patients with subcortical ischemic stroke participated in this study (4 men and 3 women; mean age, 59.2 ± 7.9 years; 5 with right subcortical lesions and 2 with left subcortical lesions). The 7 subjects were all right-handed and right-footed before their stroke episode. All of them showed early (within 3 days of onset) NIHSS scores ranging from 2 to 8, indicating mild to moderate stroke in the acute stage (Table 1). All patients had normal cognitive function (MMSE >24, out of a total of 30) and intact sensory function of the affected lower extremities (FMA-LE sensory score of 24, out of a total of 24). One participant had moderate range of motion limitation at the hip and ankle joints of the affected lower extremity. The FMA-LE motor score of the affected lower extremities of the subjects ranged from 12 to 34 (out of a total of 34), indicating mild-to-moderate residual motor impairment (Table 1). All of the patients underwent MR imaging scanning ~90 days (93.6 ± 5.9 days) after stroke onset.

MR Data Acquisition

Patients were scanned on a 3T MR imaging system (Magnetom Trio; Siemens, Erlangen, Germany) with an 8-channel phased-array head coil. Head movement was restricted with expandable foam cushions.

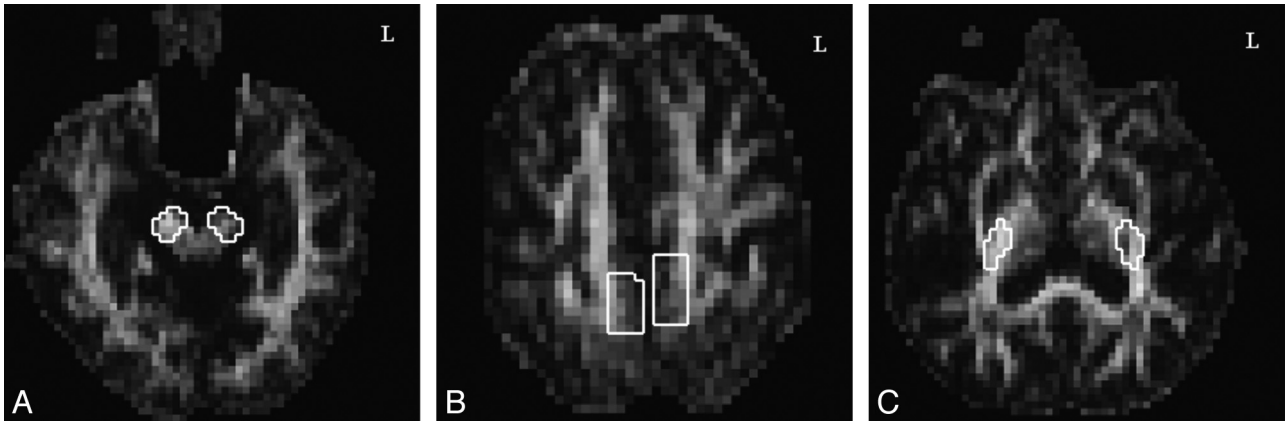

Fig 1. Seed region and ROI placement on GFA maps at the (*A*) CP and (*B*) M1 in the TS analysis and at the (*C*) PLIC in the ROI-based analysis of bilateral CSTs corresponding to the lower extremity motor control in a patient with moderate stroke.

An axial plane parallel to the anterior/posterior commissure line was determined for the section orientation of both the subsequent structural MR imaging and the DSI scans. To provide an anatomic reference, a T2-weighted fast spin-echo sequence was performed with 35 contiguous axial sections covering the whole brain (TR/TE = 5290/102 ms, flip angle = 150°, FOV = 250 × 250 mm^2, matrix = 256 × 256, section thickness = 3.9 mm). The DSI data were acquired by using a pulsed gradient twice-refocused spin-echo echo-planar imaging sequence.[35] In this study, 203 diffusion gradient vectors were applied, each corresponding to one of the isotropic 3D grid points in the *q*-space.[36] The maximum diffusion gradient was equivalent to the maximum diffusion sensitivity (b_{max}) of 6000 s/mm^2. The DSI data were obtained at 2.9 × 2.9 × 2.9 mm^3 isotropic resolution (TR/TE = 9100/142 ms, flip angle = 90°, FOV = 370 × 370 mm^2, matrix = 128 × 128, section thickness = 2.9 mm). As a result, a total of 203 diffusion-weighted brain volumes were acquired, where each volume consisted of 45 transaxial sections encompassing the whole brain. We used a standard procedure to stabilize the head and body of the participants during the scanning to minimize the problem of head motion. The total scan time was ~45 minutes for each participant. All participants were able to tolerate the whole scanning section.

MR Data Analysis

Two raters (Z.-A.L. and Y.-H.K.), who are licensed physical therapists specialized in neurologic physical therapy and had had 2 years of intensive training on MR data acquisition and analysis, were first trained by the set of analysis guidelines described below. The relatively fair spatial resolution of the GFA maps on which the seed region/ROI areas were selected may also affect the reliability of the seed region/ROI placement. To ameliorate this potential problem, the raters used the subjects' T2-weighted structure images to guide the identification of anatomic landmarks on the GFA maps.

TS Quantitative Analysis

Having acquired the DSI data, the probability attenuation function at each pixel was reconstructed by performing a Fourier transform of the signal intensity in the *q*-space. The orientation distribution function was then calculated by using the second moments of the probability attenuation function in different radial directions.[20] The GFA,[37] a quantitative index derived from the orientation distribution function to indicate diffusion anisotropy, was calculated at each pixel. The fiber vectors at each pixel were also defined by selecting the peak orientations of the orientation distribution function.[23]

The reconstruction of the CST tractography was performed by a modified streamline method[22] by using the in-house software DSI Studio (http://sites.google.com/a/labsolver.org/dsi-studio/). The seed points for initiating the fiber tracking were placed at 2 seed regions: the CP at the midbrain level (Fig 1*A*) and the M1 (Fig 1*B*). The CST corresponding to motor control of the lower extremity was obtained by tracking through the 2 seed regions. The selection of the seed region at the CP was outlined by choosing the 2 sections containing the CP at the midbrain and then enclosing the pixels containing the CP area. The seed region at the lower extremity region of the precentral gyrus was defined as follows. First, from the vertex downward, we selected the first 4 sections that allowed clear identification of the precentral sulcus, precentral gyrus, central sulcus, and postcentral gyrus. Second, we encompassed the region corresponding to motor control of the lower extremity in the precentral gyrus. The seed region that was thereby defined usually spanned 4 columns of pixels on each bank of the medial longitudinal fissure, and the seed region was typically located between the precentral sulcus and central sulcus. To determine the propagating direction of a fiber vector in the seed region, trilinear interpolation was applied on the fiber orientations of neighboring voxels at the 8 corners. If voxels contained multiple fiber orientations, the orientation closest to the previous propagating direction was selected for interpolation. The next point of the fiber tract was determined by the propagating direction. The procedures were performed recursively and terminated when the turning angle exceeded a specific threshold, 32°, or when the tract reached a voxel without fibers. Using this method, the fiber tracts passing through both seed regions were retained to represent the CST originating from the lower extremity motor control of the M1 (Fig 2). The sections showing the PLIC were determined on the GFA map, and the weighted-average of the GFA at the PLIC segment, denoted $GFA_{PLIC\text{-}TS}$, was calculated by multiplying the GFA of each pixel with a weighting factor proportional to the number of CST tracts passing through the same pixel. The measurement was performed in both the unaffected and affected hemispheres. We grouped the data according to affected and unaffected hemisphere in this study because previous research has suggested that handedness does not directly affect CST fiber characteristics[38] and that analysis of our own unpublished data of 10 healthy adults shows that neither handedness nor footedness has an effect on GFA values of the CSTs of the 2 hemispheres.

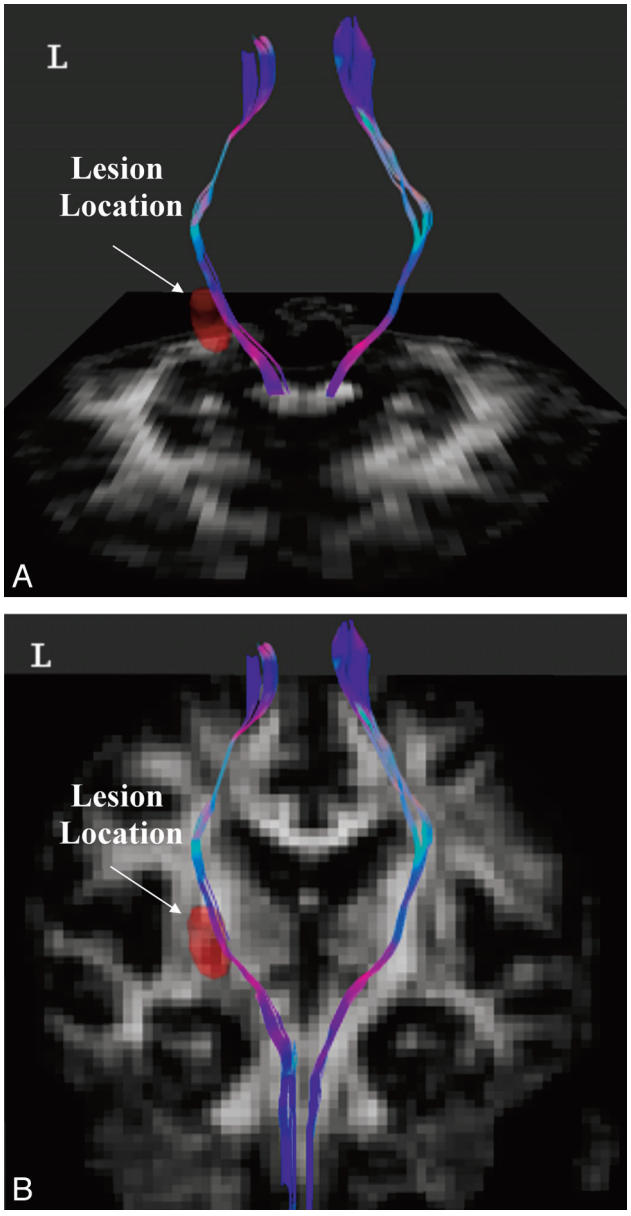

Fig 2. Tractography of bilateral CSTs corresponding to lower extremity motor control in a patient with ischemic stroke at the left PLIC (red area). *A*, The axial view of the bilateral CSTs passing through the CP; (*B*) the coronal view of the bilateral CSTs. For fiber direction, red indicates the left-right direction, green indicates the anteroposterior direction, and blue indicates the inferior-superior direction. The background images are GFA maps.

ROI-Based Analysis

The mean GFA values at the PLIC segments were also calculated by using the ROI-based analysis. On all sections containing the PLIC on the GFA map, the posterior two-thirds of the PLIC were selected as the ROI to represent the lower extremity motor control area (Fig 1*C*). We obtained the GFA values of all selected pixels and calculated the mean GFA of the ROI at the PLIC, denoted $GFA_{PLIC\text{-}ROI}$. The measurement was also performed in both the unaffected hemisphere and affected hemisphere.

Statistical Analysis

To establish the intrarater and interrater reliabilities of the TS and ROI-based analyses, 2 raters (Y.-H.K. and Z.-A.L.) analyzed the data twice with a 1-week interanalysis interval. The intrarater and interrater reliabilities were investigated on the seed region placement for the TS analysis and ROI placement for the ROI-based analysis. The κ statistics were used to evaluate the agreement of pixel coordinates for both the seeds at the CP and the motor control of the lower extremity at the M1 for the TS analysis, as well as at the PLIC for the ROI-based analysis. A κ value >0.80 was considered excellent agreement, and κ between 0.60 and 0.80 represented substantial levels of agreement.[39] The intrarater and interrater reliabilities for the mean $GFA_{PLIC\text{-}TS}$ and mean $GFA_{PLIC\text{-}ROI}$ were evaluated by $ICC_{3,1}$[40] and the standard error of measurement.[41] An ICC value >0.75 was regarded as good reliability.[41] The standard error of measurement ($S_x\sqrt{1-r_{xx}}$, where S_x is the standard deviation of the set of observed values and r_{xx} is the reliability of coefficient of the measure) is the standard deviation of the measurement errors, and thus smaller standard errors of measurement corresponds to better reliability of the GFA measures.[41]

By correlating the mean $GFA_{PLIC\text{-}TS}$ and $GFA_{PLIC\text{-}ROI}$ of the affected hemisphere analyzed by rater 1 (Z.-A.L.) with the FMA-LE rated by rater 2 (Y.-H.K.), by using the Pearson correlation coefficients, we measured the relationships between the fiber integrity of the CST of the affected hemisphere and the motor function of the affected lower extremity.

The comparisons between the mean $GFA_{PLIC\text{-}TS}$ and $GFA_{PLIC\text{-}ROI}$, between their SDs, and between their CVs (= SD/mean) were performed by using a 2-tailed paired *t* test. Statistical significance was considered for $P < .05$.

Results

Reliability

For the TS analysis, the κ values of intrarater reliability for the coordinates of the seeds in both the unaffected hemisphere and affected hemisphere ranged from 0.87 to 0.97 for rater 1 and from 0.79 to 0.95 for rater 2 (Table 2). The κ values of interrater reliability ranged from 0.81 to 0.90 for the unaffected hemisphere and from 0.86 to 0.98 for the affected hemisphere (Table 2). These results indicated substantial-to-excellent intrarater and interrater agreement on the seed region placement at the CP and the motor control of the lower extremity at the M1.

The ICCs for intrarater reliability for the mean $GFA_{PLIC\text{-}TS}$ in both the unaffected hemisphere and affected hemisphere ranged from 0.83 to 1.00 for rater 1 ($P < .05$) and from 0.96 to 1.00 for rater 2 (Table 3). The ICCs for interrater reliability for the mean $GFA_{PLIC\text{-}TS}$ were 0.85 for the unaffected hemisphere and 1.00 for the affected hemisphere (Table 3). The standard error of measurements of the mean $GFA_{PLIC\text{-}TS}$ in all intrarater and interrater analyses were ≤ 0.01 (Table 3). The high ICCs and small standard error of measurements indicated excellent intrarater and interrater reliability for the mean $GFA_{PLIC\text{-}TS}$ values.

For the ROI-based analysis, the κ values of intrarater reliability for the coordinates of the ROIs in both the unaffected hemisphere and affected hemisphere ranged from 0.93 to 0.98 for rater 1 and from 0.76 to 1.00 for rater 2 (Table 2). The mean κ values for interrater reliability were 0.90 for the unaffected hemisphere and 0.91 for the affected hemisphere (Table 2). The results indicated excellent intrarater and interrater agreement for the ROI placement at the PLIC.

The ICCs for intrarater reliability for the mean $GFA_{PLIC\text{-}ROI}$ values in both the unaffected hemisphere and

Table 2: Kappa values for agreement on the seed region and ROI placement in the TS and ROI-based analyses

	TS Analysis						ROI-Based Analysis					
	Intrarater				Interrater:		Intrarater				Interrater:	
	Rater 1		Rater 2		Raters 1 and 2		Rater 1		Rater 2		Raters 1 and 2	
Subject	UH	AH	UH	AH	UH	AH	UH	AH	UH	AH	UH	AH
1	0.93	0.93	0.95	0.82	0.85	0.90	0.95	0.93	0.91	0.95	0.87	0.84
2	0.97	0.97	0.87	0.82	0.87	0.90	0.95	0.95	0.93	0.99	0.93	0.93
3	0.94	0.87	0.93	0.89	0.82	0.87	0.93	0.94	0.91	0.89	0.86	0.92
4	0.92	0.88	0.79	0.83	0.81	0.98	0.95	0.95	0.84	0.89	0.89	0.93
5	0.96	0.93	0.93	0.91	0.90	0.90	0.95	0.95	1.00	0.76	0.92	0.91
6	0.97	0.94	0.92	0.92	0.89	0.86	0.98	0.94	0.89	0.82	0.91	0.90
7	0.93	0.97	0.89	0.93	0.84	0.92	0.95	0.97	0.91	1.00	0.89	0.94
Mean	0.95	0.93	0.90	0.87	0.85	0.90	0.95	0.95	0.91	0.90	0.90	0.91
SD	0.02	0.04	0.05	0.05	0.03	0.04	0.01	0.01	0.05	0.09	0.03	0.03

Table 3: $ICC_{(3,1)}$ and standard error of measurement of the $GFA_{PLIC\text{-}TS}$ and $GFA_{PLIC\text{-}ROI}$ for intra- and interrater reliability in stroke subjects

	$GFA_{PLIC\text{-}TS}$		$GFA_{PLIC\text{-}ROI}$	
	Unaffected Hemisphere	Affected Hemisphere	Unaffected Hemisphere	Affected Hemisphere
ICC (95% CI)				
Intrarater reliability				
Rater 1	0.97* (0.83–0.99)	1.00* (0.99–1.00)	0.99* (0.94–1.00)	1.00* (0.99–1.00)
Rater 2	1.00* (1.00–1.00)	0.99* (0.96–1.00)	1.00* (0.97–1.00)	1.00* (0.99–1.00)
Interrater reliability				
Raters 1 and 2	0.85* (0.14–0.98)	1.00* (0.99–1.00)	1.00* (0.99–1.00)	1.00* (0.99–1.00)
Standard error of measurement				
Intrarater reliability				
Rater 1	0.01	0.01	0.01	0.01
Rater 2	0.00	0.01	0.01	0.01
Interrater reliability				
Raters 1 and 2	0.01	0.01	0.01	0.01

*$P < .05$ indicates significance.

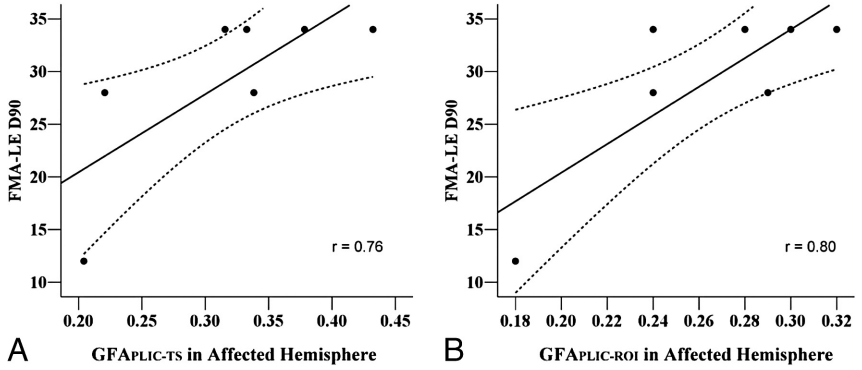

Fig 3. Scatterplots of the correlation between (*A*) the $GFA_{PLIC\text{-}TS}$ of the affected hemisphere and the FMA-LE motor score ($r = 0.76$), and (*B*) the $GFA_{PLIC\text{-}ROI}$ of the affected hemisphere and the FMA-LE motor score ($r = 0.80$).

affected hemisphere were 0.99 or 1.00 ($P < .05$) for both raters. The ICCs for interrater reliability were 1.00 for both the unaffected hemisphere and affected hemisphere (Table 3). The standard errors of measurements were 0.01 for all intrarater and interrater reliability with the ROI-based analysis (Table 3). Therefore, there was excellent intrarater and interrater reliability for the mean $GFA_{PLIC\text{-}ROI}$ values.

Clinical Correlation of Motor Function of the Lower Extremities

We used the data analyzed by rater 1 to calculate the correlations between the GFA values of the affected hemisphere and the FMA-LE motor scores. The results showed significantly high correlations of the FMA-LE motor score with the $GFA_{PLIC\text{-}TS}$ ($r = 0.76$, $P < .05$) (Fig 3*A*) and with the $GFA_{PLIC\text{-}ROI}$ ($r = 0.80$, $P < .05$) (Fig 3*B*).

Comparison of $GFA_{PLIC\text{-}TS}$ and $GFA_{PLIC\text{-}ROI}$

We used the data analyzed by rater 1 to compare the differences between the $GFA_{PLIC\text{-}TS}$ and $GFA_{PLIC\text{-}ROI}$ (Table 4). The $GFA_{PLIC\text{-}TS}$ was highly correlated with the $GFA_{PLIC\text{-}ROI}$ for the affected hemisphere ($r = 0.90$, $P < .05$), but not for the unaffected hemisphere ($r = -0.15$, $P > .05$). The values for the mean $GFA_{PLIC\text{-}TS}$ of the unaffected hemisphere (0.43 ± 0.02)

Table 4: Mean, SD, and CV of the GFA values by TS analysis and ROI-based analysis (rater 1)

	$GFA_{PLIC\text{-}TS}$						$GFA_{PLIC\text{-}ROI}$					
	Unaffected Hemisphere			Affected Hemisphere			Unaffected Hemisphere			Affected Hemisphere		
Subject	Mean	SD	CV	Mean	SD	CV	Mean	SD	CV	Mean	SD	CV
1	0.43	0.03	0.07	0.20	0.04	0.21	0.41	0.07	0.17	0.18	0.08	0.44
2	0.44	0.04	0.09	0.33	0.05	0.16	0.40	0.08	0.20	0.24	0.13	0.54
3	0.42	0.02	0.05	0.34	0.07	0.22	0.37	0.07	0.19	0.29	0.10	0.34
4	0.40	0.05	0.13	0.38	0.02	0.06	0.33	0.09	0.27	0.30	0.08	0.27
5	0.41	0.03	0.07	0.43	0.03	0.07	0.36	0.09	0.25	0.32	0.10	0.31
6	0.45	0.03	0.07	0.22	0.08	0.36	0.34	0.10	0.29	0.24	0.10	0.42
7	0.46	0.03	0.07	0.32	0.03	0.10	0.31	0.08	0.26	0.28	0.08	0.29
Group mean	0.43*	0.03*	0.08*	0.32*	0.05*	0.17*	0.36	0.08	0.23	0.26	0.10	0.37
Group SD	0.02	0.01	0.03	0.08	0.02	0.10	0.04	0.01	0.05	0.05	0.02	0.10

*$P < .05$ indicates significant differences between the TS- and ROI-based analyses.

and affected hemisphere (0.32 ± 0.08) were significantly greater than the mean $GFA_{PLIC\text{-}ROI}$ of the unaffected hemisphere (0.36 ± 0.04) and affected hemisphere (0.26 ± 0.05) ($P < .05$). The CVs for the mean $GFA_{PLIC\text{-}TS}$ of the unaffected hemisphere (mean CVs = 0.08) and affected hemisphere (mean CVs = 0.17) were significantly smaller than those of the mean $GFA_{PLIC\text{-}ROI}$ (mean CVs = 0.23 for the unaffected hemisphere, 0.37 for the affected hemisphere) ($P < .05$).

Discussion

By analyzing the DSI data of the patients with subcortical ischemic stroke, we investigated the reliability and validity of TS analysis on the CST, and we compared the performance with that of the ROI-based analysis. We found excellent intrarater and interrater reliability for both TS- and ROI-based analyses in the seed region or ROI placement and in the mean GFA values. In the affected hemisphere, the mean GFA measured from both analyses showed high correlation with the motor function of the affected lower extremity. Although the GFA values measured by both analyses were correlated, the TS analysis yielded significantly higher mean GFA and lower variance than did the ROI-based analysis.

Several factors may affect the agreement on seed region and ROI placement. The rater's knowledge and familiarity with brain anatomy is a key factor in determining the proper selection of the seed region and ROI, which in turn influences the reliability of the seed region and ROI placement.[8] In this study, using a set of guidelines and the T2-weighted template, in addition to adequate personnel training, may have helped us establish excellent reliability in both analyses.

Our excellent intrarater and interrater reliability for the seed region and ROI placement have led to the excellent reliability of the measured GFA values. Hong et al[9] used both TS- and ROI-based analyses to investigate the interrater reliability of the FA values of the pyramidal tracts at the CP in patients with amyotrophic lateral sclerosis. Hong et al[9] found significantly higher interrater reliability of FA values in the TS analysis (Spearman correlation coefficient $r_s = 0.91$) compared with those in the ROI-based analysis ($r_s = 0.70$). In contrast, our results did not show poorer reliability of the $GFA_{PLIC\text{-}ROI}$ as compared with that of the $GFA_{PLIC\text{-}TS}$. This discrepancy may be due to the relatively clearer boundary of the CST at the PLIC region than at the CP. Furthermore, the pyramidal tracts in the brain stem are close to the space containing the CSF[9] and to other crossing tracts.[22] Therefore, the ROI-based analysis at the brain stem region is more subject to partial volume effects than at the PLIC region.

Ozturk et al[8] investigated the intrarater and interrater reliability of the FA at the PLIC region by using ROI-based analysis in 5 healthy controls and 7 subjects with closed-head injuries. They reported a low level ($\kappa = 0.08$) of intrarater reliability and a fair level ($\kappa = 0.31$) of interrater reliability, which may be related to the long interanalysis interval (4–12 weeks) and no use of a template for ROI delineation. In summary, according to our results, both the TS quantitative analysis and the ROI-based analyses are reliable approaches for DSI data analysis and may be performed in future clinical DSI studies. The set of clear guidelines, adequate training of raters, and better ROI delineation at the PLIC region may lead to better results for reliability than the previous reports.

In this study, we found significantly good-to-excellent correlation of the $GFA_{PLIC\text{-}TS}$ or $GFA_{PLIC\text{-}ROI}$ with the FMA-LE. Previously, similar studies have been performed by using ROI-based analysis of DTI data to show a high correlation between the FA values and the overall muscle strength of the affected extremities (by using the total score of Manual Muscle Testing or Motricity Index)[2,42] and the hand function [6,7] in patients with subacute or chronic ischemic stroke. Using the TS analysis, we have successfully demonstrated that the fiber integrity of the affected CST corresponding to the lower extremity motor control originating from the M1 is strongly correlated with the motor function of the affected lower extremity ($r > 0.75$). Our findings suggest that the integrity of the CST fibers originating from the M1 plays an important role in lower extremity motor recovery. Our approach may allow future research using the TS analysis to study the relationships between the fiber integrity of a particular fiber tract and the motor function of a particular body part.

Our findings that the correlation between the $GFA_{PLIC\text{-}ROI}$ and the FMA-LE of the affected lower extremity ($r = 0.80$) was slightly higher than that between the $GFA_{PLIC\text{-}TS}$ and the FMA-LE ($r = 0.76$) may be due to differences in the CST fibers selected by the 2 analyses. Studies by using functional MR imaging in patients with ischemic stroke have found that the brain activation areas during unilateral movement of the affected lower extremity include the ipsilesional M1, supplementary motor area, and secondary sensorimotor cortices.[43,44] The descending motor fibers originating from these areas all pass through the PLIC region. Our TS quantitative analysis included only the spared CST fibers originating from

the M1 area. Our ROI-based method enclosed the posterior two-thirds of the PLIC, which included not only spared CST fibers originating from the M1 but also those originating from other secondary cortical motor areas. Because all of these fibers contribute to motor recovery, this might lead to a slightly higher correlation between the $GFA_{PLIC\text{-}ROI}$ and the FMA-LE.

Although the $GFA_{PLIC\text{-}TS}$ and $GFA_{PLIC\text{-}ROI}$ in the affected hemisphere were highly correlated with each other and both values were correlated with the motor function of the affected lower extremity, the TS analysis yielded higher mean GFA values and less variability, as revealed by the lower standard deviation and coefficient of variance of GFA values, than did the ROI-based analysis. One reason for this discrepancy may be that the ROI-based method possibly includes pixels with evidently low GFA values, whereas the tractography preferentially passes through the relatively spared regions and samples pixels with relatively higher GFA values. Another reason may be due to the method for calculating the mean GFA values. In our TS analysis, the mean $GFA_{PLIC\text{-}TS}$ was calculated as the weighted sum of the GFA values of each individual pixel, with the weighting factors scaled to the number of tracts passing through the same pixel. This was to give more weighting to pixels with a greater number of fibers passing through than to those with fewer fibers passing through. In contrast, in our ROI-based analysis, the GFA values of the selected pixels were averaged with equal weights, which was consistent with conventional ROI analysis.[2,6,7]

Generally speaking, due to the inherent differences in the GFA sampling and calculation, the ROI analysis focuses more on functional-related regions of white matter, whereas the TS analysis allows for investigation of fiber properties of tract-specific regions and provides information about properties of particular fiber tracts of interest. The strength of the ROI-based analysis is that the obtained $GFA_{PLIC\text{-}ROI}$ values can be considered to represent the overall integrity of a white matter region, where both injured and spared fibers involved in lower extremity motor control are enclosed. Thus, the $GFA_{PLIC\text{-}ROI}$ would show a high correlation with a more general clinical outcome measure, such as the FMA-LE, of lower extremity motor control. Using ROI-based analysis, however, may potentially enclose fibers originating from different cortical motor areas, which makes it difficult to differentiate the degree of contributions from different motor areas to the recovery of lower extremity motor control. On the other hand, the TS analysis has the advantage of specifically evaluating the degree of integrity in the relatively spared tract region of the CST fibers originating from the lower extremity motor control region of the M1. This method also has the potential to allow researchers to examine other specific fibers of interest, such as those originating from secondary motor cortical areas. With this specificity of the fibers reconstructed by using the TS analysis, the $GFA_{PLIC\text{-}TS}$ may inevitably yield a slightly smaller correlation with the global clinical outcome measure FMA-LE than the $GFA_{PLIC\text{-}ROI}$. Therefore, the decision regarding which method to be used in a study will depend on the purpose of the study.

There are a few limitations of this study. First, the sample size may be too small for the generalization of our results on rater comparison. We have performed similar rater comparison on DSI data of 10 healthy subjects by using the same analysis algorithm. The results yielded the similarly high intra- and interrater reliabilities. Second, the success of the TS analysis relies mainly on the accurate reconstruction of the tractography over the entire CST. The tractography may be interrupted in severe stroke, where low GFA values involve a large area, or in hemorrhagic stroke, where some derivatives of hemoglobin may induce severe magnetic susceptibilities. Further research on patients with greater stroke severity will be needed. Third, scan time required to acquire DSI data may potentially increase the likelihood of patient motion, which then can cause blurring of the image data and reduce the angular resolution of the orientation distribution function,[45] consequently resulting in the failure of the tractography reconstruction. In this study, all participants tolerated the scan time well and presented little head motion during the scan. The tractography of the CST was successfully reconstructed from all of the participants, but difficulties may arise when it is applied to patients with a wider range of clinical problems.

In this study, the seeds/ROI placement is selected manually by following a set of guidelines. An emerging method of reconstructing white matter fibers is by using functional MR imaging-guided fiber tracking technology. This technology has been performed in healthy participants[46] and in patients with brain tumors[47,48] by using DTI. This methodology has potential to be used in patients with stroke for mapping the cortical representations for upper and lower extremity motor function and guiding the placement of seeds for reconstructing CST fibers associated with upper and lower extremity motor function. However, we also foresee 2 major difficulties when applying this technology in patients with stroke. First, patients with stroke may have difficulty performing isolated joint movements without any associated movements or spasticity, which then may cause larger head motion during MR imaging.[44,49] Second, the BOLD signals in ipsilesional M1 may be significantly decreased or even absent while patients with stroke perform movements with the affected upper or lower extremity.[50-53] Movement-related BOLD signals may shift from the primary motor cortex to secondary association motor networks or even the contralesional hemisphere in response to stroke lesions.[53,54] More research will be needed to validate the usage of this new technology in patients with stroke.

Conclusions

In this study, we have demonstrated good reliability and validity of the TS analysis method and ROI-based analysis method of the CST. Both analysis methods indicate that the GFA values at the PLIC segments of the CST in the affected hemisphere are highly correlated with motor function of the affected lower extremity in patients with ischemic stroke. The different mean GFA and its variance derived from the 2 methods imply that the inherent differences in sampling and calculation of the 2 methods might provide different information about the tract integrity.

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