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Technical Note

Clinical applicability of automated tractography for stroke rehabilitation: Z-score conversion of fractional anisotropy

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Abstract. [Purpose] To expand the applicability of diffusion-tensor tractography fractional anisotropy for stroke rehabilitation, this study aimed to provide references for representative neural tracts from non-lesioned hemispheres. Therefore, we applied the assessment of neural integrity to representative stroke patients using Z-score conversion. [Participants and Methods] Fractional anisotropy values were assessed in neural tracts, including the corticospinal tract, inferior fronto-occipital fasciculus, uncinate fasciculus, and anterior thalamic radiation, of stroke patients receiving acute care. [Results] Data were collected from 60 patients for the non-lesioned right hemisphere and 68 patients for the non-lesioned left hemisphere. Mean fractional anisotropy values in the corticospinal tract and inferior fronto-occipital fasciculus were notably elevated, reaching approximately 0.6 and 0.5, respectively. The mean fractional anisotropy values for other neural tracts were approximately 0.4, and, the overall standard deviations were approximately 0.04. In two typical stroke patients assessed using Z-scores, the scores in the corticospinal tract corresponded to the severity of the hemiparesis. The scores in the anterior thalamic radiation and inferior fronto-occipital fasciculus were associated with more significant brain dysfunction, including inattention and aphasia. [Conclusion] In this study, the Z-score findings related to stroke symptoms align with those reported in the literature, indicating the appropriateness of the methodology used and its potential in future applications.

Key words: Evaluation, Normative, Tract

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INTRODUCTION

Neuroimaging is a crucial diagnostic tool in stroke rehabilitation[1)]. Among the various neuroimaging modalities, diffusion-tensor imaging (DTI) stands out due to its unique ability to evaluate neural fiber integrity *in vivo*[2)]. Tractography is an analytical DTI methodology that enables the visualization of neural tracts. However, it requires a start point (seed) and end point (target), which are usually defined by a time-consuming manual process[3)]. Consequently, it is subjective and has lower reproducibility than other analytical DTI methodologies such as tract-based spatial statistics[4)]. To address these shortcomings, an automated procedure known as XTRACT has been developed[5)]. This method uses predetermined parameter settings for the tractography analyses, including seed, target, exclusion masks, and number of samples, which allows for 42 representative neural tracts within the whole brain to be evaluated in only 1 hour[6)].

Of various parameters derived from tractography, fractional anisotropy (FA) is commonly used as an indicator of neural integrity within the brain, particularly as a marker of Wallerian degeneration[7)]. In our previous studies, we successfully

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*Corresponding author. Tetsuo Koyama (E-mail: ytkoyama@bd6.so-net.ne.jp) demonstrated the clinical applicability of this newly developed automated tractography approach in relation to hemiparesis and aphasia due to stroke[8–11]. To further expand the ability of this new method to assess the neural tracts within the brain, we conducted the present study to provide reference FA values for the neural tracts that are commonly involved in stroke pathology. In particular, we assessed neural integrity by using Z-scores obtained from the FA values of non-lesioned hemispheres.

PARTICIPANTS AND METHODS

This retrospective cohort study was conducted using data obtained from medical records. The study cohort comprised patients admitted to Nishinomiya Kyoritsu Neurosurgical Hospital for stroke treatment between April 2022 and September 2023. Stroke management followed the Japanese Guidelines for the Management of Stroke 2021[12], which include a rehabilitative regimen. To account for potential confounds arising from variations in pre-stroke health status and lesion sites, our sample was limited to first-ever stroke patients with unilateral supratentorial lesions who were functionally independent in activities of daily living (ADLs) before the stroke[8–11]. We also excluded patients who subsequently showed a deterioration in neurological manifestations and other medical conditions during acute care. Informed consent was obtained through the opt-out method, and the study protocol received approval from the Institutional Review Board of Hyogo Medical University (No. 4546).

As in our previous studies[8–11], DTI scans were typically conducted in the second week after admission to our acute care service. The scans were obtained using a 3.0-Tesla scanner (MAGNETOM Trio; Siemens AG, Erlangen, Germany) equipped with a 32-channel head coil. DTI data were acquired using a single-shot echo-planar imaging sequence in the anterior-to-posterior direction and comprised 30 images with non-collinear diffusion gradients (b=1,500 s/mm^2) and one non-diffusion-weighted imaging scan (b=0 s/mm^2). For each patient, 80 contiguous axial slices were obtained with a field of view of 256 mm × 256 mm, an acquisition matrix of 128 × 128, and a slice thickness of 2 mm. The echo time was 96 ms, the repetition time was 10,900 ms, and the flip angle was 90°. To address eddy current-induced and echo-planar imaging-induced distortions, two additional non-diffusion-weighted imaging scans were acquired in the anterior-to-posterior direction and two in the posterior-to-anterior direction. In addition, T1-weighted images were acquired using a three-dimensional fast gradient imaging sequence to capture the anatomical details of patients' brains. For each patient, a total of 176 contiguous sagittal slices were acquired with a field of view of 256 mm × 256 mm, an acquisition matrix of 256 × 256, and a slice thickness of 1 mm. The echo time was 2.52 ms, the repetition time was 1,900 ms, and the flip angle was 10°.

The imaging process used has been described in detail elsewhere[8–11]. In brief, the initial steps included the elimination of the Gibbs ringing artifact, correction of distortions induced by eddy currents and echo-planar imaging, and application of bias field corrections by using MRtrix software[13] and the FMRIB Software Library (FSL)[14]. Brain masks were subsequently derived from the bias field-corrected images. After the preparatory stage, we used the XTRACT[5] function within FSL[14] for fiber tracking. This facilitated the generation of tractography data for 42 predefined sets of neural bundles. Parameter estimates including FA values were extracted using a threshold set at 0.01, in line with our previous studies[8–11]. For clarity, we concentrated on the neural tracts that are frequently impaired by stroke lesions[15–17]: the corticospinal tract (CST), the superior longitudinal fasciculus parts 1, 2, and 3 (SLF1–3), the frontal aslant (FAS), the anterior thalamic radiation (ATR), the inferior fronto-occipital fasciculus (IFOF), the inferior longitudinal fasciculus (ILF), and the uncinate fasciculus (UNF).

To evaluate neural tract damage, we first assessed the distribution of FA values in the non-lesioned hemispheres of the above-mentioned nine tracts as normative references. In the second step, the targeted neural tracts were then evaluated by FA distribution. To better characterize neural damage in reference to normative values, we used Z-score conversions. The Z-score was calculated using the following formula:

$$Z=(X-\mu)/\sigma,$$

where X is the individual data point, μ is the mean of the data set, and σ is the standard deviation of the data set. To assess the clinical utility of this methodology, we sampled two typical stroke patients who exhibited hemiparesis and/or higher brain dysfunctions such as aphasia. Neural tracts with Z-scores smaller than −1.96 (in the bottom 2.5% of a normal distribution) were considered potentially damaged.

Clinical manifestations were assessed using the motor component of the Stroke Impairment Assessment Set (SIAS-motor)[18] and the Functional Independence Measure (FIM)[19]. The SIAS-motor comprises five components that assess arm, finger, hip, knee, and ankle functions, with each scored on a scale from null to full (0 to 5). The FIM, a widely adopted tool for evaluating independence in ADLs, comprises a motor component (13 items) and a cognition component (5 items). Each item is scored on a 7-point scale (1=total assistance; 7=complete independence). Total scores for both FIM-motor (scale range, 13–91) and FIM-cognition (scale range, 5–35) are commonly used in stroke rehabilitation.

RESULTS

During the study period, we sampled 128 patients for the analytical database: 60 stroke patients with left hemisphere lesions and 68 stroke patients with right hemisphere lesions. Consequently, we obtained 60 samples for the non-lesioned right hemisphere and 68 samples for the non-lesioned left hemisphere. The demographic details of our samples are summarized in Table 1. The mean and standard deviation data for the nine target tracts in the non-lesioned right and left hemispheres are shown in Table 2. The mean FA values within the CST were notably higher, at around 0.6, with quite narrow deviation ranges, and appeared elevated compared to the mean values of the other neural tracts. These FA values were followed by those of the IFOF (approximately 0.5). The mean FA values of the other neural tracts investigated were around 0.4 with standard deviations of approximately 0.04.

The Z-scores derived from the FA distributions of the two typical cases are shown in Table 2. Case 1 was an 80-year-old male patient who was admitted to our acute care service due to a sudden onset of severe hemiparesis in his left extremities. Computed tomography images taken in the acute care unit revealed high-density areas in the right thalamus (Fig. 1). He underwent conservative treatment with antihypertension medication. On day 9, DTI were acquired, and tractography images were generated using the automated methodology (Fig. 2). Raw FA values and Z-score conversions are shown in Table 3 and indicate neural damage in the right CST (Z=−4.764) and right ATR (Z=−1.981). Consistent with the low Z-scores in the CST and ATR, the patient had severe hemiparesis and attentional disorders such as unilateral spatial neglect. He was transferred to our affiliated convalescent rehabilitation hospital on day 28 for ongoing inpatient rehabilitation, but the hemiparesis persisted. Upon discharge to home on day 176, he had a SIAS-motor assessment of 0-1-2-1-0, a FIM-motor score of 59, and a FIM-cognition score of 30, indicating that he required some assistance in ADLs, primarily in the motor component.

Case 2 was an 80-year-old female patient who experienced loss of consciousness and was transferred to our acute care unit by ambulance. Magnetic resonance diffusion-weighted images upon admission revealed high-intensity areas in the left frontal operculum encompassing the left insular cortex (Fig. 1). Subsequently, mechanical thrombectomy was performed and anticoagulant medication was prescribed. There was no loss in upper or lower extremity functions, but the patient had severe aphasia: she could not comprehend simple verbal commands and could speak only in simple words. On day 9, DTI was acquired, and tractography images were then generated (Fig. 2). Raw FA values and Z-score conversions are shown in Table 3 and indicate neural damage in the left FAS (Z=−2.538), left IFOF (Z=−2.411), and left UNF (Z=−3.471). These low Z-scores corresponded to the observed clinical symptoms of severe aphasia. On day 11, the patient was transferred to our affiliated convalescent rehabilitation hospital to continue rehabilitation for aphasia. Her aphasia symptoms gradually improved, and she began to verbally communicate with medical staff, using short sentences of approximately 2 to 3 words. On day 57, she was discharged to home with a SIAS-motor assessment of 5-5-5-5-5, a FIM-motor score of 85, and a FIM-cognition score of 15. She exhibited no signs of hemiparesis, and the motor-related components of ADLs resumed almost independently. However, cognitive decline was still evident due to persistent aphasia at discharge from our convalescent rehabilitation hospital.

Table 1. Sample profiles (N=128)

	Non-lesioned right hemisphere	Non-lesioned left hemisphere
Total number	60	68
Sex (male/female)	37/23	41/27
Age (years)	67.8 ± 11.1	70.2 ± 12.0
Type of stroke (hemorrhagic/ischemic)	21/39	25/43

Data for age are shown as mean ± standard deviation.

Table 2. Distributions of fractional anisotropy (FA) values in the non-lesioned hemispheres of stroke patients

Tract	Right hemisphere (n=60)	Left hemisphere (n=68)
CST	0.588 ± 0.038	0.579 ± 0.036
SLF1	0.436 ± 0.037	0.422 ± 0.046
SLF2	0.387 ± 0.032	0.361 ± 0.036
SLF3	0.412 ± 0.039	0.400 ± 0.042
FAS	0.406 ± 0.041	0.405 ± 0.043
ATR	0.407 ± 0.042	0.399 ± 0.048
IFOF	0.492 ± 0.026	0.484 ± 0.043
ILF	0.431 ± 0.035	0.420 ± 0.037
UNF	0.430 ± 0.040	0.410 ± 0.048

Data are presented as mean ± standard deviation. ATR: anterior thalamic radiation; CST: corticospinal tract; FAS: frontal aslant; IFOF: inferior fronto-occipital fasciculus; ILF: inferior longitudinal fasciculus; SLF1: superior longitudinal fasciculus part 1; SLF2: superior longitudinal fasciculus part 2; SLF3: superior longitudinal fasciculus part 3; UNF: uncinate fasciculus.

DISCUSSION

In this study, we assessed the distribution of FA values in various neural tracts within the non-lesioned hemispheres of stroke patients. The targeted neural tracts were the CST, SLF1, SLF2, SLF3, FAS, ATR, IFOF, ILF, and UNF. Notably, the mean FA values in the CST and the IFOF were elevated, reaching approximately 0.6 and 0.5, respectively. Despite the higher mean values, the FA distributions of these two tracts exhibited relatively small ranges in standard deviation. The mean FA values for the other neural tracts examined were around 0.4, with an approximate standard deviation of 0.04. Then, the Z-

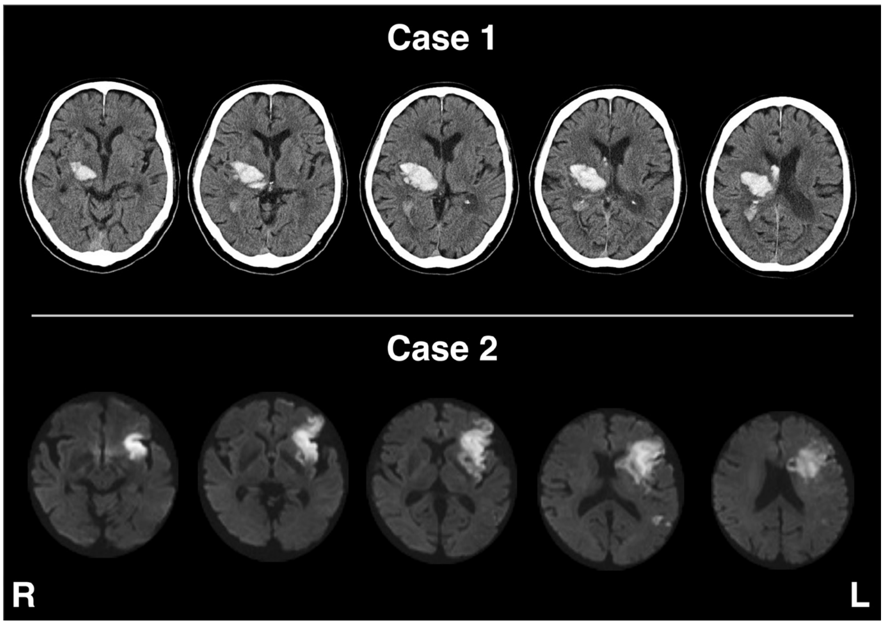

Fig. 1. Computed tomography images (Case 1) and diffusion-weighted magnetic resonance images (Case 2) obtained during the acute stage. L: left; R: right.

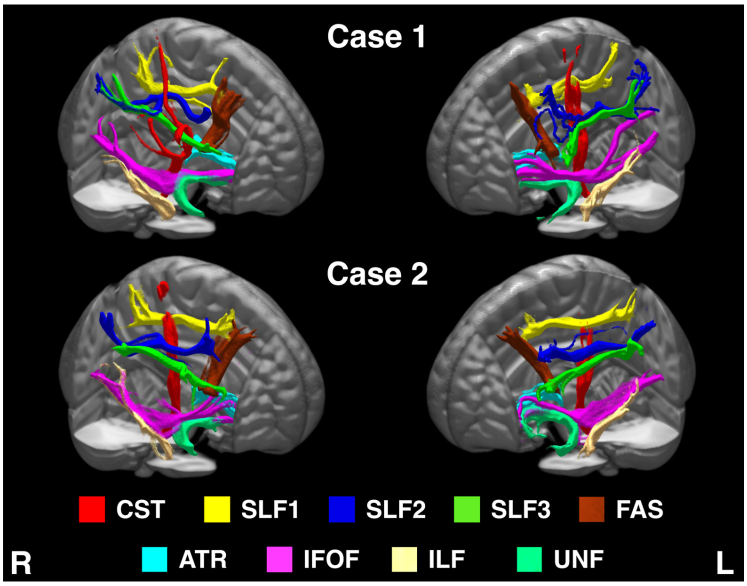

Fig. 2. Three-dimensional images generated by automated tractography.
ATR: anterior thalamic radiation; CST: corticospinal tract; FAS: frontal aslant; IFOF: inferior fronto-occipital fasciculus; ILF: inferior longitudinal fasciculus; SLF1: superior longitudinal fasciculus part 1; SLF2: superior longitudinal fasciculus part 2; SLF3: superior longitudinal fasciculus part 3; UNF: uncinate fasciculus; L: left; R: right.

Table 3. Raw fractional anisotropy (FA) values and Z-score conversions of the neural tracts investigated in two representative stroke cases

Tract	Case 1		Case 2	
	Right hemisphere	Left hemisphere	Right hemisphere	Left hemisphere
CST	**0.409 (Z=−4.764)**	0.598 (Z=0.486)	0.589 (Z=0.023)	0.575 (Z=−0.134)
SLF1	0.467 (Z=0.838)	0.489 (Z=1.465)	0.458 (Z=0.614)	0.395 (Z=−0.608)
SLF2	0.363 (Z=−0.739)	0.376 (Z=0.398)	0.384 (Z=−0.101)	0.346 (Z=−0.424)
SLF3	0.396 (Z=−0.416)	0.383 (Z=−0.415)	0.383 (Z=−0.754)	0.349 (Z=−1.236)
FAS	0.409 (Z=0.075)	0.443 (Z=0.894)	0.352 (Z=−1.308)	**0.291 (Z=−2.667)**
ATR	**0.324 (Z=−1.981)**	0.432 (Z=0.670)	0.339 (Z=−1.639)	0.321 (Z=−1.643)
IFOF	0.461 (Z=−1.172)	0.461 (Z=−0.555)	0.474 (Z=−0.708)	**0.378 (Z=−2.502)**
ILF	0.417 (Z=−0.416)	0.445 (Z=0.650)	0.470 (Z=1.106)	0.381 (Z=−1.065)
UNF	0.379 (Z=−1.271)	0.389 (Z=−0.434)	0.356 (Z=−1.834)	**0.245 (Z=−3.448)**

Neural tracts with Z-scores smaller than −1.96 are shown in bold. ATR: anterior thalamic radiation; CST: corticospinal tract; FAS: frontal aslant; IFOF: inferior fronto-occipital fasciculus; ILF: inferior longitudinal fasciculus; SLF1: superior longitudinal fasciculus part 1; SLF2: superior longitudinal fasciculus part 2; SLF3: superior longitudinal fasciculus part 3; UNF: uncinate fasciculus.

scores derived from the FA distributions in two typical stroke patients revealed that the Z-scores in the CST corresponded to the severity of hemiparesis, while the lower Z-scores in association fibers such as the ATR, IFOF, and UNF corresponded to higher brain dysfunction, such as attentional disorder and aphasia. These findings align well with those in the literature20–22), indicating the appropriateness of the methodology applied in the present study.

We sampled FA values from non-lesioned hemispheres in stroke patients in this study and considered them normative FA values. Such data would usually be obtained from healthy controls in an age-matched cohort23). However, we struggled to recruit healthy controls for this study due to the constraints of conducting it in a local community hospital and therefore we decided to sample FA values from non-lesioned hemispheres. This methodology has both advantages and disadvantages. The advantage is that data collection can proceed smoothly in daily clinical practice, facilitated by the widespread use of DTI in the field of stroke rehabilitation. Nevertheless, it is essential to acknowledge a potential disadvantage: considering the underlying diseases associated with stroke, such as hypertension24), diabetes25), and lipid metabolism disorder26), the brain tissue in the non-lesioned hemisphere may not be perfectly intact. It is worth noting that such underlying diseases were not uncommon in the studied population.

We focused on the typical symptoms resulting from stroke in this study. Case 1 had severe hemiparesis in combination with spatial neglect, while Case 2 had severe aphasia without hemiparesis. The present findings indicate that the assessment of neural tracts using Z-score conversions of FA values reflects the clinical manifestations. In terms of hemiparesis, our previous study demonstrated a strong correlation between raw FA values in the CST and severity of the hemiparesis8). In patients with hemorrhagic stroke with thalamic and/or putaminal hematoma, the estimated correlation coefficient was approximately 0.88). On the other hand, in terms of aphasia, another of our previous studies demonstrated low FA values in the neural tracts, including the IFOF, ILF, and UNF, of patients with some types of aphasia10). However, we could not obtain numerical evaluations (e.g., correlation coefficients) for the relationships between the severity of aphasia and reductions in FA values because the severity of aphasia cannot be assessed by simple numbers. The thresholding of Z-scores for the assessment of stroke-related symptoms should be clarified in future studies.

There are some challenges to the clinical application of tractography methodology. Conventionally, tractography requires the manual definition of a start point (seed) and an end point (target), which is time-consuming and subjective and has lower reproducibility. To address these concerns, we have integrated the newly developed automated tractography pipeline known as XTRACT5) into our daily clinical practice8–11). This automated approach incorporates predetermined parameter settings crucial for tractography analyses, including seed and target points, exclusion masks, and number of samples5) and is reproducible. Its reproducibility enabled us to successfully obtain reference FA values from non-lesioned hemispheres in this study. The Z-score conversions of these reference FA values may further contribute to the rehabilitative diagnosis, such as outcome prediction.

This study has several limitations. First, the FA values depend on the threshold setting. In this study, we established the threshold at 0.01, consistent with our previous publications within a series of tractography studies8–11). Nevertheless, there is currently a lack of consensus regarding this specific setting. Second, although the XTRACT5) function automatically generates 42 neural tracts, we omitted certain commissural fibers (e.g., the forceps minor) and the cingulum bundles in this study for clarity. However, stroke patients with anterior cerebral artery disorders often exhibit lesions within these neural tracts. We plan to publish data for these neural tracts in future case series reports. Third, for the sake of clarity, this study examined only representative cases of first-ever stroke with unilateral lesions. Because the present data sets may serve as normative references, the methodology used in this study could, in theory, be applied to cases of recurrent stroke with bilateral lesions. However, the focus in this study on only first-ever stroke with unilateral lesions should be noted.

In conclusion, the findings of this study suggest that the Z-score conversions of reference FA values derived from the non-lesioned hemisphere may contribute to rehabilitative diagnosis, including outcome prediction.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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