

# Fractional Anisotropy and Tractography in Diffusion Tensor Imaging for the Prediction of Upper Limb Motor Recovery After Stroke

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## Abstract

**Purpose:** Diffusion tensor imaging (DTI) has garnered attention regarding the prediction of patient outcomes following stroke and its application in clinical practice is expected. Here, we evaluated the usefulness of combination analysis with fractional anisotropy (FA) and tractography parameters in order to build an optimal DTI protocol to predict motor recovery after stroke.

**Subjects and Methods:** We recruited 35 consecutive patients with supratentorial hemorrhagic or ischemic stroke. DTI examination took place 14–16 days after stroke onset and the bilateral cerebral peduncles were regions of interest for the FA and tractography analyses. Three months after stroke, Brunnstrom recovery stage (BRS) scoring of the upper limb and fingers was performed. We tested correlations between the FA ratio (rFA) of the bilateral cerebral peduncles, tractography findings, and BRS scores.

**Results:** A significant correlation was identified between rFA and 3-month BRS score ( $r = 0.465$ ,  $p = 0.008$ ). The pattern of tractography was divided into 2 groups (complete-disrupted type and incomplete-disrupted type). The patients with the incomplete-disrupted type had significantly higher rFA ( $p = 0.008$ ) and BRS scores ( $p < 0.001$ ). After excluding patients with the complete-disrupted type who had high rFA, we observed statistically significant strong positive correlations between rFA and the BRS scores ( $r = 0.728$ ,  $p < 0.001$ ).

**Conclusions:** Combination analysis with FA and tractography may be a useful predictor of motor recovery in the acute phase of stroke.

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## INTRODUCTION

Paralysis is a critical problem for patients with stroke, which markedly reduces quality of life. Recently, studies have emphasized the importance of rehabilitation (i.e., adopting a team approach involving physicians, nurses, and physical and occupational therapists along with other professionals), and particularly of adequate physical and occupational therapy, in the acute phase of stroke. The prediction of

motor recovery in the acute stage is an important step toward the identification of an appropriate rehabilitation strategy in patients with stroke<sup>1)</sup>. Motor paralysis in the upper limb is especially important and has considerable effects on activities of daily living (ADL) and instrumental ADL<sup>2)</sup>. The early prediction of prognosis of upper limb motor paralysis is expected to be valuable in rehabilitation for stroke. Previous studies have reported the utility of motor impairment

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score (Fugl-Meyer assessment: FMA)<sup>3,4)</sup>, neuroimaging (Magnetic Resonance Imaging: MRI)<sup>3,5)</sup>, and neurophysiological assessment (Transcranial magnetic stimulation: TMS)<sup>3,6)</sup> for the prediction of motor paralysis following stroke. However, these approaches have not been widely used in clinical practice. Currently, there is poor clinical reproducibility in the prognosis of upper limb paralysis because it depends on the experience of the therapist. Therefore, a useful and feasible modality with better reproducibility for the prediction of motor paralysis recovery is in demand in the clinic. To this end, several studies have reported the utility of diffusion tensor imaging (DTI) for the prediction of patient outcomes following brain injury<sup>7-16)</sup>. Koyama et al. demonstrated that fractional anisotropy (FA) within the cerebral peduncle was highly correlated with the long-term outcome of hemiparesis after intracerebral hemorrhage<sup>11,12)</sup>. Jung et al. reported that diffusion tensor tractography was also able to predict motor recovery after intracerebral hemorrhage<sup>9)</sup>. These reports suggest that DTI allows the prediction of motor recovery with high accuracy in some patient sub-populations after stroke. However, to our knowledge, a combinational analysis using FA and tractography parameters has not yet been reported. Therefore, our analysis used a combination of FA and tractography DTI sequences in patients with supratentorial stroke in order to determine the usefulness of DTI for the prediction of upper limb motor outcomes after the acute phase of stroke. We aimed to establish a method for prognosis prediction of upper-limb motor paralysis with better reproducibility in clinical practice.

## METHODS

### Subjects

The study population comprised patients with hemorrhagic or ischemic supratentorial stroke ( $n = 35$ ) who were treated at our hospital between May 2012 and April 2013. Neurosurgeons performed the diagnosis of stroke based on computed tomography (CT) and diffusion-weighted (DW) MRI examination findings. We included patients who had no history of stroke and no pre-existing lesions as assessed using primary cranial CT and MRI. All patients had no physical disabilities prior to the onset of stroke. We excluded patients with lesions limited to the cerebral cortex or lesions extending to the brainstem. We also excluded patients who were not provided with sufficient rehabilitation due to complications such as severe

pneumonia. All included patients completed a CT scan 24 hours after admission and subsequently underwent early, intensive, and long-term rehabilitation. They received conventional acute rehabilitation and Kaifukuki rehabilitation (i.e., muscle strengthening, ADL, and walking exercises and neuromuscular facilitation). They received rehabilitation for 2–3 hours/day in the Kaifukuki rehabilitation ward after while transferred to rehabilitation hospital. All patients who were included in this study provided informed consent. The study protocol was approved by the Institutional Review Board of Juzenkai Hospital.

### DTI Acquisition

DTI was performed on days 14–16 after admission using a 1.5-TMR scanner (Signa HD1.5, GE Healthcare, USA) with a 32-channel head coil. Using a single-shot echo-planar imaging sequence, the DTI scheme acquired 12 images with non-collinear diffusion gradients and 1 non-diffusion-weighted image. Typical acquisition parameters were as follows: repetition field of view =  $26 \times 26$ ; matrix =  $256 \times 192$ ; slice thickness = 5 mm; interslice gap = 5 mm, repetition time/echo time = 8300/101.9 ms, b value = 1000 s/mm<sup>2</sup>; number of excitations = 3.

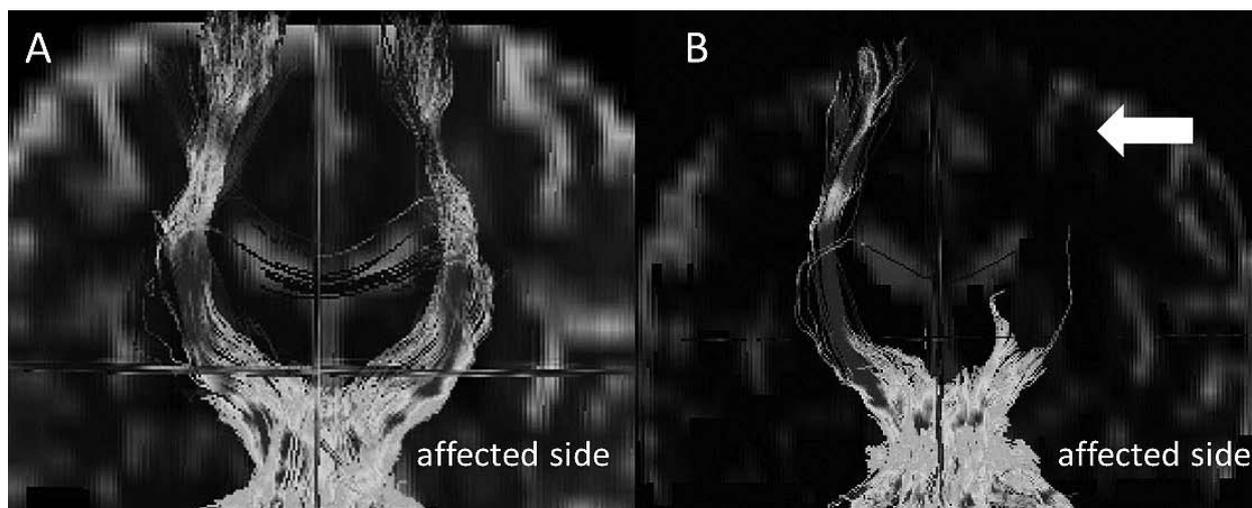
### Image Processing

Functool was used for DTI analysis, which is the internal analysis software of the SIGNAL.5HD. The regions of interest (ROIs) were placed on axial slices over the bilateral cerebral peduncles according to a similar method previously described<sup>6)</sup>. A radiologist blinded to the aims of the study mapped all ROIs, measured FA values, and calculated rFA values as the FA ratios of the bilateral cerebral peduncles in each patient. Tractography was constructed using the ROIs outlined above. The pattern of tractography was divided into 2 groups (complete-disrupted type and incomplete-disrupted type) by a neurosurgeon who was blinded to the clinical characteristics of patients (Fig 1). The incomplete-disrupted type was characterized by the presence of fibers that successfully contacted the cerebral cortex, whereas the complete-disrupted type was characterized by the presence of fibers that disappeared proximal to the lesion.

### Outcome Measurements

To evaluate motor outcomes, a physical therapist or occupational therapist assessed the Brunnstrom recovery stage (BRS) of the affected upper limb and fingers at 3 months after stroke<sup>17,18)</sup> (Table 1<sup>19)</sup>). BRS is a popular evaluation tool for motor paralysis in Japan and Europe, developed in England. It is included

in the Stroke Guideline Grade B in Japan<sup>20)</sup>.



**Figure 1.** Representative images of sub-population types on diffusion tensor imaging tractography. (A) The incomplete-disrupted type as characterized by the presence of fibers that contacted the cerebral cortex. (B) The complete-disrupted type as characterized by the presence of fibers that did not contact the cerebral cortex (white arrow).

**Table 1.** Brunnstrom Stages and Clinical Observations

Stage I	Immediately after the acute episode, flaccidity is present and voluntary movements of the limbs can be initiated.
Stage II	The basic limb synergies, or some of their components, may appear as associated reaction or minimal voluntary movement responses. At this time, spasticity begins to develop.
Stage III	The patient gains voluntary control of the movement synergies, though the full range of all synergy components does not necessarily develop. Spasticity has further increased and may become severe.
Stage IV	Some movement combinations that do not follow the paths of either synergy are mastered, first with difficulty, then with more ease, and spasticity begins to decline.
Stage V	If progress continues, more difficult movement combinations are learned as the basic limb synergies lose their dominance over motor acts.
Stage VI	With the disappearance of spasticity, individual joint movements become possible and coordination approaches normality.

**Table 2.** Characteristics of Study Subjects

Characteristics	Subjects (n=35)
Age (y)	68.9 ± 10.9
M/F	15/20
Ischemic/hemorrhagic	16/19
Stroke location	
cortex	10
thalamus	7
putamen	13
corona radiata	1
gyru angulaires	1
nucleus bassalis	2
gyri insulae	1
Surgery	10/35
tractography type	
incomplete-disrupted type	19
complete-disrupted type	16
NIHSS	12.8 ± 9
rFA	0.81 ± 0.1
3-month BRS score	7.3 ± 3.1

Tractography and the ratio of fractional anisotropy (rFA) values were assessed at 14 – 16 days post stroke onset. Brunnstrom stage (BRS) was assessed at 3 months post stroke onset. M: male, F: female, rFA: ratio of fractional anisotropy, BRS: Brunnstrom recovery stage.

Statistical Analysis

Spearman rank correlation analysis was used to examine the relationship between rFA value and motor outcome as assessed by BRS scoring. Independent t-tests were used to examine differences in patients with complete-disrupted type and incomplete-disrupted type strokes. All statistical analyses were performed using the SPSS software package version 19.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The mean patient age was  $68.9 \pm 10.1$  years (range = 50–88 years). Out of 35 included patients, 16 had ischemic stroke and 19 had hemispheric stroke (Table 2). Medical history included respiratory disease (n = 1), heart diseases (n = 8), fractures (n = 3), and cancer (n = 2). Complications included aspiration pneumonia (n = 2), urinary-tract infection (n = 7), and hemorrhagic infarction (n = 1). Three patients reported having experienced exacerbation in motor paralysis after stroke onset. The median BRS score was 7 (range = 2–12). On DTI, a meaningful correlation was identified between rFA and BRS scores (Fig 2,  $r = 0.465$ ,  $p = 0.008$ ). Regarding tractography, 16 patients were categorized into the complete-disrupted type and 19 patients were categorized into the incomplete-disrupted type. Fourteen out of 19 patients with the incomplete-disrupted pattern had total BRS score higher than 10 points. The rFA of the patients who were categorized into the incomplete-disrupted type was significantly higher than that observed in patients categorized into the complete-disrupted type (Mean  $\pm$  SD: incomplete disrupted type =  $0.88 \pm 0.15$ ,

complete-disrupted type =  $0.72 \pm 0.18$ , respectively,  $p = 0.008$ , t-test). The same was true for the BRS scores (Mean  $\pm$  SD: incomplete disrupted type =  $10 \pm 1.02$ , complete-disrupted type =  $4.18 \pm 1.048$ , respectively,  $p < 0.001$ , t-test). From these results, we excluded patients with the complete-disrupted type who had high rFA from the correlation analysis between rFA and BRS. Then, we observed statistically significant strong positive correlations between rFA and the BRS scores (fingers and upper limb) (Fig 3,  $r = 0.728$ ,  $p < 0.001$ ).

DISCUSSION

In the present study, we evaluated the usefulness of combination analysis with FA and tractography parameters in order to build an optimal DTI protocol to predict motor recovery after stroke. Our results showed changes in the correlations between motor function and rFA values between the acute and chronic phases of stroke. At 3 months after stroke, a significant correlation was observed with regard to the upper limbs and fingers <sup>11,21</sup>. The rFA values were statistically significantly different between tractography types, suggesting an association between these variables. Indeed, we observed statistically significant strong positive correlations between rFA and the BRS scores when patients with the complete-disrupted type who had high rFA were excluded. Given the likelihood that each sequence offers different insight relative to the prediction of motor recovery after stroke, the development of a combined tractography and rFA analysis method may improve the predictive utility of DTI in patients with stroke. Combination analysis

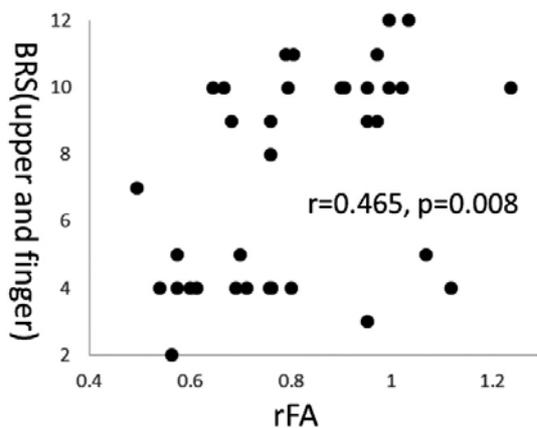


Figure 2. A significant correlation was identified between the ratio of fractional anisotropy and the Brunnstrom stage score .

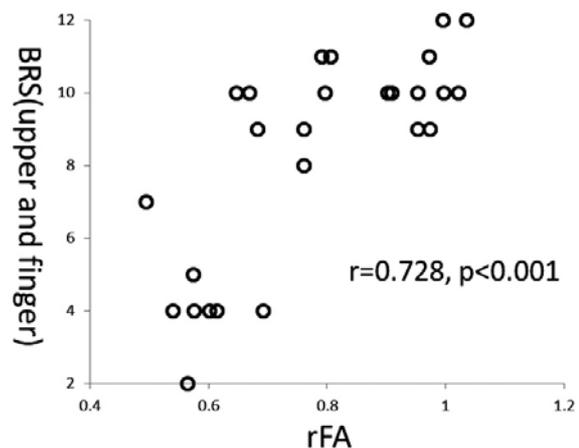


Figure 3. The modified correlation between the ratio of fractional anisotropy and the Brunnstrom stage score at 3 months post stroke onset.

with FA and tractography may be a useful predictor of motor recovery in the acute phase of stroke and could be used to solve the issue with poor clinical reproducibility.

Several studies have reported on the prediction of motor recovery using DTI<sup>7,9,11,12,14,16,22-26</sup>. DTI has several distinct advantages over MRI or physical examination for the prediction of motor recovery, as it independently allows the assessment of the corticospinal tract. Furthermore, previous reports have shown that DTI is capable of detecting Wallerian degeneration in the acute phase of stroke in a manner that correlates with long-term outcome<sup>27</sup>. Koyama et al demonstrated that FA values within the cerebral peduncle are tightly associated with the long-term functional outcomes of the upper limb and fingers<sup>11,12,24</sup>, and similarly Puig et al demonstrated that FA values within the pons are tightly correlated with long-term motor outcome after stroke<sup>26,28</sup>. Our findings are in agreement with those of these previous studies. FA is superior to other DTI sequences for the prediction of motor recovery in terms of quantity and high reproducibility because it has been validated in the literature by several reports and has shown high reproducibility. However, the acquisition protocol and analysis for rFA values is relatively complicated because changes in FA after injury are strongly influenced by the distance between the ROI and the lesion<sup>26,29-32</sup>.

We also analyzed tractography, which allows the visual assessment of corticospinal tract functional integrity. A previous study indicated that the tractography volume of the affected side is reduced after stroke<sup>32</sup>, and other studies have reported that tractography type (i.e., the condition of the corticospinal tract around the intracerebral hematoma) correlates with functional motor outcome after stroke<sup>10,34</sup>. Consistent with the results of these previous studies, we found that tractography was statistically able to distinguish between patients who were expected to show recovery and those who were not expected to show recovery, independent of lesion location. However, some patients showed good recovery despite the indication of complete tract disruption on tractography. To this end, it is important to consider that tractography has some limitations. Some reports have suggested a correlation between tractography findings and motor function in the acute phase but not in the chronic phase after stroke<sup>21</sup>. Additionally, tractography has lower quantity and reproducibility relative to the FA method.

Apart from motor paralysis, some patients also had sensory disorders and higher cortical dysfunction, as well as pre-existing diseases. Due consideration should be given on the effects these risks can have on motor recovery after stroke. This study focused on assessing the corticospinal tract to predict upper limb motor recovery after stroke using DTI because of the paramount importance of the relationship between motor paralysis and the corticospinal tract. In the future, prediction of upper limb motor recovery after stroke, including all associated physical and mental aspects will be required. Hence, it is necessary to accumulate evidence from a larger number of studies.

A major limitation of this study was the small sample size of the cohort, which did not allow for a subgroup analysis between supratentorial hemorrhagic and ischemic strokes. In addition, we could not perform a subgroup analysis based on demographics. As a result, we did not examine aspects, such as physical activity level or occupational history and pre-existing diseases before onset. This will be our future research task.

In summary, both rFA and tractography results were significantly correlated with functional motor outcome after stroke, which could address the issue with poor clinical reproducibility. However, the FA and tractography DTI sequences have particular advantages relative to one another; thus, further investigation is warranted to determine the exact clinical utility of specific DTI methods for predicting motor recovery after stroke. Progress in this field of research is expected in the future.

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## 拡散テンソル画像を用いた脳卒中後の運動麻痺の予後予測

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## 要 旨

目的：脳卒中後の運動麻痺の予後を予測する方法として拡散テンソル画像（DTI）が注目されており，その臨床応用が期待されている．そこで本研究では，脳卒中後の運動麻痺の予後予測における最適なDTIプロトコルを構築するために拡散異方性（FA）と tractography の組み合わせによる解析の有用性を検証した．

方法：本研究では脳出血，脳梗塞を呈した35名を対象とした．DTI は脳卒中発症14～16病日目に撮像し，大脳脚を関心領域としFA及び tractography を抽出した．また身体機能は脳卒中発症3か月後に上肢と手指のBrunnstrom stage（BRS）を用いて評価した．解析は，tractography による皮質脊髄路の評価とrFA（両側大脳脚のFA比）を組み合わせ，BRSとの相関関係を調査した．

結果：rFAと3ヶ月後のBRSスコアとの間には，有意な正の相関を認めた（ $r=0.465$ ,  $p=0.008$ ）．Tractographyは2群（complete-disrupted type and incomplete-disrupted type）に分けられ，complete-disrupted type に比べincomplete-disrupted type は，rFA（ $p=0.008$ ）およびBRSスコア（ $p<0.001$ ）が有意に高かった．高いrFAを有するcomplete-disrupted type の患者を除外した後のrFAとBRSスコアの間には，より強い正の相関を認めた（ $r=0.728$ ,  $p<0.001$ ）．

結論：FAと tractography を組み合わせて解析することは，急性期脳卒中患者における運動麻痺の有用な予測因子である可能性が示唆された．

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