Applications of Diffusion Tensor MRI to Predict Motor Recovery of Stroke Patients in the Chronic Stages

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Abstract

Within 2 to 5 months after stroke, patients recover variable degrees of function, depending on the initial deficit. An impaired hand function is one of the most serious disability in chronic stroke patients. Therefore, to evaluate the extent of motor dysfunction in the hemiplegic hand is important in stroke rehabilitation.

In this paper, motor recoveries in 8 chronic stroke patients with Fugl-Meyer (FM) and white matter changes before and after the training program with a designed bilateral symmetrical arm trainer (BSAT) system were examined. The training was performed at 1 hr/day, 5 days/week during 6 weeks. In all patients, FM was significantly improved after the 6-week training. Diffusion tensor imaging (DTI) results showed that fractional anisotropy ratio (FAR) and fiber tracking ratio (FTR) in the posterior internal capsule were significantly increased after the training. It seemed that the cortical reorganization was induced by the 6 week training with the BSAT. In all parameters proposed this study, a significant correlation was found between these parameters (FAR and FTR) and motor recoveries. This study demonstrated that DTI technique could be useful in predicting motor recovery in chronic hemiparetic patients.

Key words: chronic stroke patients, fugl-meyer (FM), diffusion tensor imaging (DTI), fractional anisotropy ratio (FAR), fiber tracking ratio (FTR)

I. INTRODUCTION

Stroke is the second leading cause of death in Korea, followed by the cancer. More than 100,000 new strokes occur in Korea. The hemiparesis is the most common deficit after stroke or brain injury, affecting more than 80% of subjects acutely and more than 40% of those patients remained at chronic condition [1]. Within 2 to 5 months after stroke, patients recover variable degrees of function, depending on the initial deficit. An impaired hand function is one of the most serious disability in chronic stroke patients. Therefore, predicting the extent of motor dysfunction in the hemiplegic upper limb is important for stroke rehabilitation.

Many studies have attempted to predict the prognosis of the hemiparetic hand following a stroke using clinical assessment, electrophysilogical studies or brain imaging methods [2-3]. Of the various brian imaging methods, diffusion tensor imaging (DTI) allows the orientation and the integrity of the white matter tracts to be determined by virtue of its ability to image water diffusion characteristics [4]. In the normal white matter, water molecules move relatively freely parallel to the nerve fiver tract, but their movements are restricted across the tracts, causing the diffusion anisotropy (DA) of the white matter. In MR diffusion, fractional anisotropy (FA), relative anisotropy (RA), the volume ratio (VR), and lattice index (LI) are commonly used to characterize the DA of a tissue [5]. Among them, FA is most widely referred as an anisotropic index. A tissue is considered to be fully isotropic when its FA is equal to 0, and fully anisotropic when its FA equal to 1.

An impairment of water diffusion in the white matter tracts may be correlated with the degree of damage to its structure. DTI can provide a quantitative measure of DA, and thus it can be used to obtain quantitative information about the microstructural integrity of the white matter tracts [6]. Since the introduction of DTI, several studies have shown that DA impairment may be correlated with motor dysfunction in early stage stroke patients [7]. However, few studies have shown that the degree of impairment of DA in the chronic stages of stroke can be used to predict the motor recovery of hemip-

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aretic upper limb [8].

3D white matter tractography is a powerful approach to anisotropic diffusion using DTI data. Fiber white tract maps can be created, based on similarities between neighbouring voxels in the shape and orientation of the diffusion ellipsoid, and can be used for in analysis of axonal networks in the brain [9].

Some studies on stroke analyzed invariant anisotropy demonstrated the reduced diffusion anisotropy in white matter ischemia [10,11]. However, whether stroke affects an important axonal projection such as the corticospinal tract when neurological deficits suggest its involvement. Precise imaging localization of stroke reinforces neurological findings, and demonstration of stroke and neuronal fiber tracts on the same images might be helpful. 3D white matter tractography can used to show axonal projections and other brain components simultaneously.

In this study, we measured diffusion anisotropy to examine changes of FA of chronic stroke patients before and after 6-week rehabilitative training. In addition, we examined changes amount of fiber tracking using 3D white matter tractography before and after 6-week training. Finally, we determined the correlation with these parameters and upper-limb motor function recovery to demonstrate whether DTI predicts motor recovery in chronic stroke patients

II. MATERIALS AND METHODS

A. Subjects

Eight hemiparetic patients (5males and 3females) participated in an open clinical study approved by written consent. Inclusion criteria were first hemorrhagic stroke with an interval of at least 20 months post-stroke; severe upper-arm paresis, that is, the patients could only protract their paretic shoulder girdle, hold their extended arm while lying or flex, and extend their elbow slightly; at least moderate upper-limb flexor spasticity or joint stiffness on the affected side (modified Ashworth's scale: MAS<3) mild or no impairment of sensation of the affected upper extremity, tested for touch, pain as prothopatic and position sense; no additional peripheral paresis of the both upper extremities; no additional orthopedic disease (eg. Arthritis, arthrosis) of both upper extremities; no severe impairment of cognition and communication; no involved in other upper-limb rehabilitation in hospital or home now. The original Ashworth scale was modified because the lower end of the scale was indiscrete (Table 1). Stroke patients were at an age of 43.9±11.0years (range 33~67 years). The mean stroke interval was 67.5 months (range 24~142 months). Five subjects had right hemiparesis and three had left hemiparesis. Characteristics of eight patients are listed in Table 2.

Table 1. Modified Ashworth scale for grading spastcity

Grade	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part is moved in flexion of extension
2	More marked increase in muscle tone through most of the range of motion, but affected part easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part rigid in flexion or extension

Table 2. Demographics and pathology of 8 patients with stroke

Patient	Age/Sex	Lesson type	Paretic hand	Time of stroke (months)
1	44/M	ICH in right BG, TH	Lt.	38
2	37/M	ICH in right BG, TH	Lt.	58
3	49/M	ICH in left BG, IC	Rt.	24
4	33/M	ICH in left TH, IC	Rt.	58
5	67/M	ICH in left TH, IC	Rt.	142
6	57/F	ICH in right BG,TH	Rt.	72
7	48/F	ICH in right TH, IC	Lt.	120
8	36/F	ICH in left BG, TH	Rt.	28

ICH=Intracerebral hemorrhage, BG=basal ganglia, TH=thalamus, IC=internal capsule

B. Bilateral Symmetric Arm Trainer (BSAT)

A designed system consists of 2 independent handles that move symmetrically. Both handles of the training system were connected to two serial spur gears. The system provides both handles with symmetric motions such as forearm pronation/supination or wrist flexion/extension. Therefore, the affected side can be passively controlled with the symmetrical movement according to the active motion of the unaffected side [8] (Fig. 1).

Subjects were seated in a chair in front of a height-adjustable table, with their forearms in the mid-position between pronation and supination into an arm trough. Each hand of each subject grasped a handle that was 3cm in diameter and was tapered at the top for ease in insulting into the paretic hand. The hand was held in place by a 6cm Velcro strap.

C. Rehabilitative Training Program

Each training with BSAT takes at his/her home, and was performed 5 times per week during 6 weeks. Each patient grasps the handles or the affected hand is strapped to the handle depending on the severity of the deficits. Patients trained both forearm pronation/supination or wrist flexion/extension each 30 minutes, respectively. The whole training program consisted of four 15 minute session with BSATand 10 minute rest was given at every session.

D. Fugl-Meyer (FM) Assessment

Fugl-Meyer (FM) assessment has been shown to be valid and reliable and it correlates well with inter-joint upper-limb coordination measurements in the upper-limb of patients after stroke [12]. During the 6-week training with the BSAT, FM in participated patients was measured every two weeks. All tests were measured by a physical therapist. The initial analyses were one-way t-test to compare measures on the dependent reliables before and after training at 6 weeks of training. In FM score, significant results were further investigated post hoc (Tukey honestly significant difference). Data of ordinal scales were presented as median and interquartile ranges, any within group differences before and after training were calculated within the help of nonparametric the Wilcoxon test. An alpha level of <0.05 was used as the level of significance. All statistical analyses were performed by SPSS 10.0 (SPSS, Chicago, USA).

E. Diffusion Tensor Imaging (DTI)

Diffusion tensor imaging (DTI) was performed before and after the 6-week training program with the BSAT. For the anatomic image, conventional T2-weighted images were acquired, and a single shot spin echo planner imaging DTI sequence was used to produce diffusion tensor images. For diffusion tensor imaging, 33 contiguous axial images were acquired at the internal capsule level and the imaging parameters were: TR/TE/NEX=12000ms/93ms/1, slice thickness =4mm, matrix=256×256, FOV=250×250mm^2 and b=1000s/mm^2. Fractional anisotropy (FA) maps were obtained by using dTVII, Version 1.72 (VOLUME-ONE, University of Tokyo Hospital, Tokyo, Japan). The FA for analyzing to extent of the injured corticospinal tract was determined by measuring the region of interest (ROI) in the FA map. The FA was measured in the posterior limb of the internal capsule (Plic) in an unaffected site (a) and in the affected site (b). The injury to the internal capsule at the affected site was determined by calculating the ratio of the affected site to the unaffected site using both FAs. In other words, the FA ratio was calculated from 'FA ratio (FAR)(%)=b/a×100', and this reflected the conserved FA level of the affected site's posterior limb of the internal capsule (Fig 2).

From the DTI, brain fiber tracking was performed using the

(a) (b)

Fig. 1. Bilateral symmetric arm trainer (BSAT): (a) wrist flexion/extension, (b) forearm pronation/supination

free software Volume-One and dTVII (VOLUME-ONE, University of Tokyo Hospital, Tokyo, Japan) to composed the tractography. The seed area was set as the ROI was drawn around the posterior of the internal capsule on the axial image of the axially reformatted FA map.

We also evaluated fiber connectivity using fiber assignment by continuous tracking (FACT) [13]. Fiber tracking was stopped when the FA values was <0.18 and an angle change >45° according to a previous study for the optimal trackability threshold of FA [14]. FT measured the amount of fiber pass through posterior limb of the internal capsule (Plic) before and after the training with the BSAT, when seed point were selected as 161 point which draw circular ROI using the dTVII software. The seed point for analyzing the extent of the injured corticospinal tract was determined by measuring the region of ROI in the color map. So We draw a region of interest as sees on an uninvolved region of the corticospinal tract in the affected cerebral hemisphere which could detected in the posterior limb of the internal capsule. The same seed point was applied to all Images of patient.

The posterior limb was identified by its characteristic shape which forms a narrow strip between the thalamus and the putamen and globus pallidus on a 2-D FA color map (Fig 2). In every case, a section was selected in which the lesion appear most impaired.

The FT was measured in the Plic in an unaffected site (a) and in the affected site (b). The injury to the internal capsule at

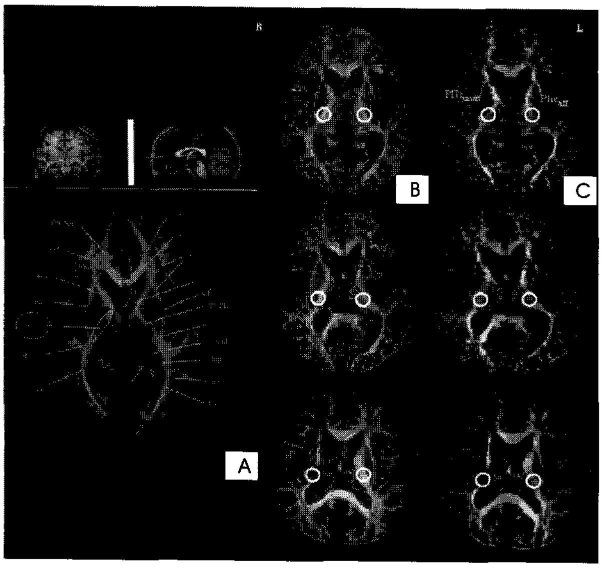

Fig. 2. Posterior limb of internal capsule (Plic) in atlas of brain white matter in axial color map (A), axial fractional anisotropy (FA) maps (B) and axial color maps (C), B, C slice positions showing the locations of typical regions of interest (round marks) used in this study (yellow: affected side, white: unaffected side)

the affected site was determined by calculating the ratio of the affected site to the unaffected site using both FTs. In other words, the FT ratio was calculated from 'FT ratio (FTR) (%)=b/a×100', and this reflected the conserved FT level of the affected site's posterior limb of the internal capsule. On these images, injured nerve fibers of the affected site could be compared to those of the unaffected site by dimensional visualization. The final DTI was checked by two of clinical doctor (Dr. S.Y Lee and Dr. C.H Sohn in Keimyung Medical Center) to obtain their consent about the quality.

In order to illustrate the impact of a stroke on the unaffected hemisphere of the patient group, the FA in the Plic was also measured in the unaffected hemisphere. To investigate changes of the FAR and FTR before and after training (at 6 weeks of training using the BSAT), one-way repeated ANOVA was used. Spearman's correlation coefficients describing the bi-variate relationship between FA ratio and motor recovery were calculated. In addition, we estimated the correlation with the amount of draw line and motor recovery in white matter fiber tracking. An alpha level of <0.05 was used as the level of significance.

Ⅲ. RESULTS

A. Fugl-Meyer (FM) Assessment

Table 3 shows changes in motor function such as FM score during the 6-week training. In all eight patients, FM (range: 0-66) of the affected hands were significantly improved after the 6-week training program ($p < 0.05$).

B. DTI Analysis

Changes of FAR Before and After the Training

Table 4 shows FA ratio before and after the training with the BSAT. In all patients, the FA ratio significantly increased after the training ($p < 0.05$).

Correlation Between FAR and FM Score

The relationship between FM and FAR of the patients was examined. As shown in Fig. 3, the FM of patient 6 was the lowest at 15 and 22 points before and after training, respectively, but FAR, measured by 55.00% and 62.38%, was not lower than patient 3, 7, and 8. On the other hand, patient 6 had the lowest FM at 15 points, but higher FAR than patient 3, 4, 7, and 8. FAR from the initial and final DTI did not show a linear correlation with motor impairment.

Fig. 4 shows the relationship between the initial FAR and the upper-limb motor recovery after 6-week training with the BSAT. In patients 5 and 6, whose initial FAR were 81.67% and 55.00%, respectively, motor recovery was not found in the

Table 3. Changes in clinical score of FM

Patient	FM 0-2-4-6 (week)	dFM
1	25 - 29 - 33 - 34	9
2	35 - 49 - 54 - 56	21
3	20 - 25 - 27 - 32	12
4	26 - 27 - 37 - 38	12
5	43 - 44 - 46 - 49	6
6	15 - 17 - 21 - 22	7
7	18 - 18 - 25 - 28	10
8	23 - 23 - 27 - 33	10
Mean	25.8 - 27.8 - 33.8 - 36.5	10.9

dFM = last FM score-initial FM score

Table 4. Changes of FAR before and after training with the BSAT

Patient	Before			After			dFAR
	FAunaf.	FAaff.	FAR (%)	FAunaf.	FAaff.	FAR (%)	
1	0.61	0.33	54.10	0.61	0.41	67.21	13.11
2	0.62	0.34	54.84	0.62	0.48	77.42	22.58
3	0.66	0.25	37.88	0.66	0.35	53.03	15.15
4	0.65	0.25	38.46	0.66	0.32	48.48	10.02
5	0.60	0.49	81.67	0.58	0.50	86.21	4.54
6	0.60	0.33	55.00	0.61	0.38	62.30	7.30
7	0.62	0.28	45.16	0.68	0.39	57.35	12.19
8	0.62	0.28	45.16	0.69	0.36	52.17	7.01
Mean	0.62	0.32	51.53	0.64	0.40	63.02	12.49

unaff.=unaffected side, aff.=affected side, FRA=fractional anisotropy ratio ((FAaff./FAunaf.)×100), dFAR= last FAR-initial FAR

upper limb, with scores of 6 and 7 points, respectively. Initial FAR did not show a linear correlation with motor recovery.

However, in patients with higher change of FAR, like patients 2 and 3, motor recovery was greatly improved by 21 and 12 points, respectively. A significant correlation was found between the change of FAR and the motor recovery in the posterior limb of IC (r=0.88, p=0.002) (Fig. 5).

Three-Dimensional Fiber Tracking Analysis

Table 5 shows the amount of fiber pass through Plic before and after the training with the BSAT, when seed point were selected as 161 point. In all patients, the fiber tracking ratio

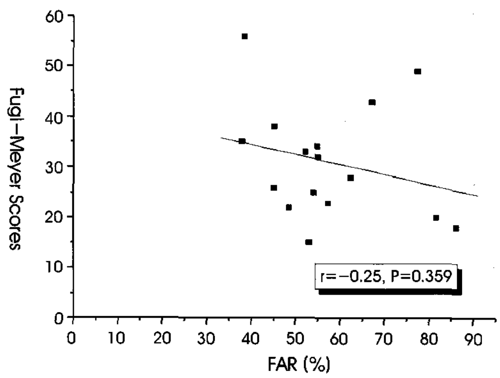

Fig. 3. The relationship between the fractional anisotropy ratio and FM

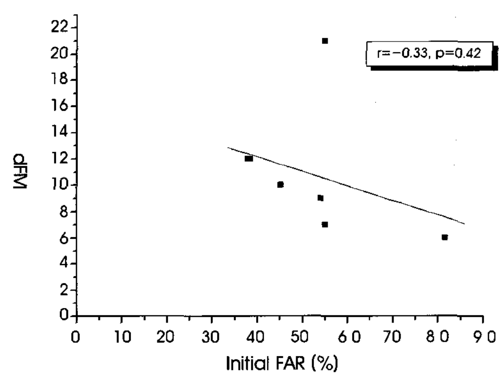

Fig. 4. The relationship of the initial fractional anisotropy ratio to the extent of improvement

Table 5. Changes of FTR before and after training with the BSAT

Patient	Before			After			dFTR
	$FT_{unaf.}$	$FT_{aff.}$	FTR (%)	$FT_{unaf.}$	$FT_{aff.}$	FTR (%)	
1	161	73	45.34	161	110	68.32	22.98
2	161	89	77.02	161	150	93.17	37.89
3	161	69	42.86	161	113	70.19	27.33
4	161	52	32.30	161	98	60.87	28.57
5	161	115	71.43	161	143	88.82	17.39
6	161	63	39.13	161	109	67.70	28.57
7	161	53	32.92	161	94	58.39	25.47
8	161	62	38.51	161	101	62.73	24.22
Mean	161	72.00	47.44	161	114.75	71.27	26.55

unaff.=unaffected side, aff.=affected side, FTA=fiber tracking ratio ((FTaff/FTunaf.) ×100), dFTR= last FTR−initial FTR

(FTR) significantly increased after the training ($p < 0.05$).

Correlation Between FM and FTR

Fig. 6 shows the relationship between the FTR and FAR before and after 6-week training with the BSAT. A significant correlation was found between the change of FTR and FAR in the posterior limb of IC (r=0.80, p=0.001).

Fig. 7 shows the relationship between the FTR and FM score after 6-week training with the BSAT. In patients 1 and 5, whose initial FTR were 22.98% and 17.39%, respectively, motor recovery was found in the upper limb, with scores of 9 and 6 points, respectively. Therefore, FTR show a linear correlation with motor recovery (r=0.87, p=0.05).

Fig. 8 show 3-dimensional tractography in Patient 5 before and after 6-weeks training with the BSAT. Tactography shows the corticospinal tract form various angles such as the axial, sagittal and coronal view. In eight patients, 3D fiber tract maps showed corticospinal tract in close proximity to the hemorrhage but not to pass through it. Before the training, there was little corticospinal tract in the affected side relative to the unaffected side in all patients. After 6 weeks trainng, almost all sides of the corticospinal tract were conserved in Patient 2, 5, and 8, although there was a little displacement by hemorrhage.

Ⅳ. DISCUSSION

The FA is a popular index to quantify degree of DA, and has been used as an indicator of white matter integrity at the microstructural level [6]. In this study, the FA in the affected side was significantly smaller than that in the unaffected side. Several investigators have tried to demonstrate that the microstructural abnormalities, such as the degree of DA impairment, reflect motor dysfunction at the time of DA evaluation in stroke patients [7,15]. More recently, the role of DTI as a potential marker to predict motor recovery in stroke patients has been suggested [16,17]. Watanabe et al. [16] demonstrated that a three dimensional axonograph using the DTI method in the early stages of stroke may be useful to predict the prognosis of motor function. The FA of the

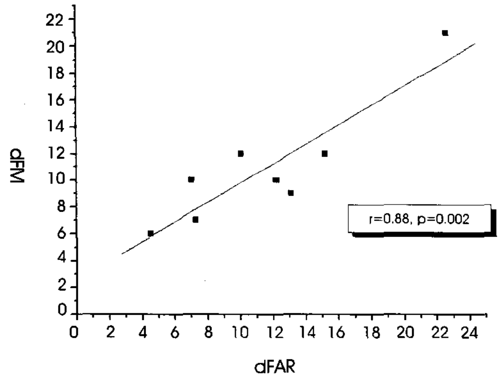

Fig. 5. The relationship of the fractional anisotropy ratio change to the extent of improvement

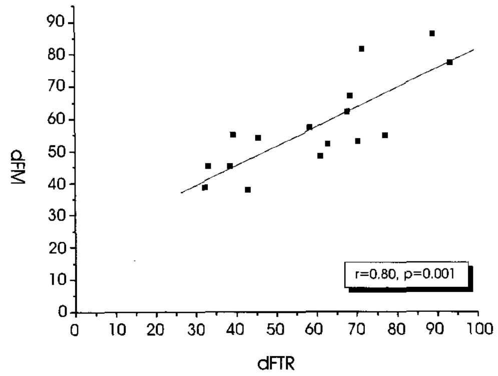

Fig. 6. The relationship between FAR and FTR

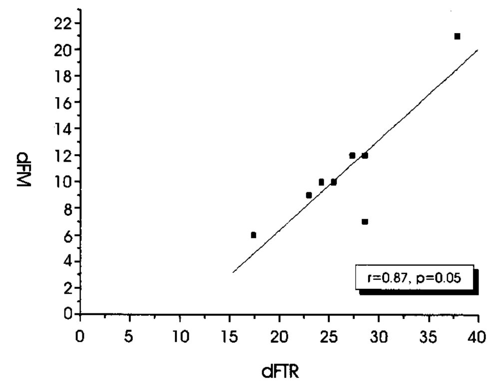

Fig. 7. The relationship of the fiber tracking ratio to the extent of improvement

unaffected side in hemiparetic patients was significantly smaller than that of control subjects. Reasons for this phenomenon might be the inter-hemispheric influence of the motor system or the immobilization effect. Many studies have demonstrated that the affected motor cortex can affect the unaffected contralateral motor cortex via transcallosal pathway or by some other pathways [15]. Schmithorst and Wilke [18] have demonstrated that the long-term forced use of a hand can increase the DA of white matter. Jang et al. [19] and Cho et al. [20] demonstrated the degree of impairment in diffusion anisotropy during the early stages of stroke appears to have the potential to predict motor recovery.

3D white matter tractography, the first method which allows us to show axonal projections non-invasively in living human beings, is currently being used to assess normative functional connections. Application to certain types of pathology such as brain tumors or stroke haves begun [21,22].

We showed the corticospinal tract repeatedly and symmetrically in involved of uninvolved hemispheres. Its cause was consistent with anatomical descriptions, and we inferred that what we were showing did indeed represent the corticospinal tracts and that 3D white matter tractography was thus suitable for demonstrating it. The technique provided unique information which could not be obtained from axial images alone, displaying the corticospinal tract and infarcts or hemorrhages simultaneously, so that the involvement of the former could be assessed by eye. This may be useful in stroke, which frequently affects the internal capsule and corona radiate. The observed correlation between involvement of the tract and prognosis indicates that amount of fiber tracking relationships of the corticospinal tract to an infarcts or hemorrhage might affect with recovery of motor function.

In this study, we demonstrated both FAR and FTR in DTI were significant increase after 6 week training with the BSAT. In addition, changes of FAR and FTR show a linear correlation with motor recovery. However, some technical limitations should be noted. We used 256×256 matrix in plane resolution and 4 mm, contiguous slices for DTI, leading to substantial orientations volume averaging of multiple fibers with different orientations in a voxel for which interpolation could not compensate. The tract shown reflects only major trajectories with abundant fiber bundles and does not necessarily represent the whole tract. We traced the corticospinal tract based on its known anatomical characteristics. Accurate tracking is more difficult in the brain stem because of both susceptibility and fiber crossing. Using high resolution and thin slice images

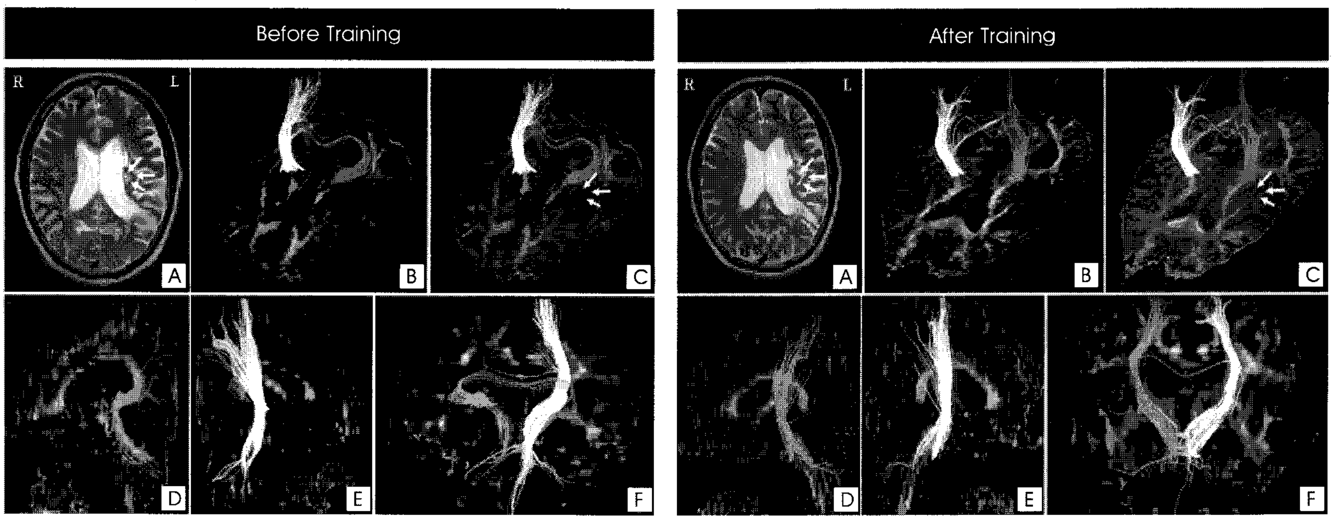

Fig. 8. Tractography in Patient 5, A: axial T2-weighted image, B: 3D tractograpy superimposed onan axial color map, C: 3D tractograpy superimposed on an axial FA map, D: 3D tractograpy superimposed on a left sagittal color map, E: 3D tractograpy superimposed on a right sagittal color map, F: 3D tractograpy superimposed on a coronal color map. Corticospinal tract of the affected side: red lines, unaffected side: yellow lines

may be one way to solve these problems, but it takes longer and is more subject to motion artifacts.

In DTI, despite these limitations, the clinical correlations we have shown are encouraging. Although further studies are needed, it seems likely that favorable recovery of gross motor functions could be expected in patients without obvious involvement on 3D white matter tractography.

V. CONCLUSION

In this study, motor recovery of upper-limb function in chronic hemiparetic patients after 6 week motor training with a BSAT was evaluated.

DTI seems suitable for qualitative assessment of quantitative or spatial relationships of the corticospinal tract an infarcts or hemorrhages, which might be helpful in prognosis of patients with chronic stroke.

Further studies with long-term follow up and degree of functional change, and type and location of the lesions may give more insight.

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