Detection and Predictive Value of Fractional Anisotropy Changes of the Corticospinal Tract in the Acute Phase of a Stroke

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Background and Purpose—A decrease in fractional anisotropy (FA) of the ipsilesional corticospinal tract (CST) distal to stroke lesions in the subacute (eg, 30 days) and chronic phase has been correlated with poor motor outcomes, but it is unclear whether FA values obtained within the acute stroke phase (here defined as 80 hours after onset) can predict later outcome.

Methods—Fifty-eight patients underwent an assessment of motor impairment in the acute phase and at 3 months using the upper extremity Fugl-Meyer assessment. FA values, obtained within 80 hours after stroke onset, were determined in 2 regions of interest: cerebral peduncle and a stretch of the CST caudal to each stroke lesion (nearest-5-slices).

Results—The FA laterality index for the cerebral peduncle-regions of interest was a poor predictor of 3-month outcome (R^2=0.044; P=0.137), whereas the slope over the FA laterality index of the nearest-5-slices showed a relatively weak but significant prediction (R^2=0.11; P=0.022) with the affected side having lower FA values. Initial upper extremity Fugl-Meyer (R^2=0.69; P<0.001) and the weighted CST lesion load (R^2=0.71; P<0.001) were strong predictors of 3-month outcome. In multivariate analyses, controlling for initial upper extremity Fugl-Meyer, weighted CST lesion load, and days-of-therapy, neither the FA laterality index of the cerebral peduncle nor the slope over the FA laterality index of the nearest-5-slices significantly contributed to the prediction of 86% of the variance in the upper extremity Fugl-Meyer at 3 months.

Conclusions—FA reductions of the CST can be detected near the ischemic lesion in the acute stroke phase, but offer minimal predictive value to motor outcomes at 3 months. (***Stroke*****. 2016;47:1520-1526. DOI: 10.1161/STROKEAHA.115.012088.)**

Key Words: corticospinal tract ■ diffusion tensor imaging ■ lesion load ■ lesion mapping ■ magnetic resonance imaging ■ outcomes assessment ■ stroke

Motor impairment is a common consequence after ischemic stroke, leading to major disability and poor quality of life.[1] Recovery after a stroke is variable and remains challenging to predict although recent studies have related recovery to the effect that a lesion has on the motor system.[2–4] The corticospinal tract (CST) is the primary descending motor pathway connecting cortical motor regions with neurons in the spinal cord. Injury from ischemic stroke leads to anterograde degeneration of axons and myelin sheaths of affected tracts, commonly known as Wallerian degeneration (WD).[5–7] Studies have shown that measures of the integrity of the CST in the chronic stroke phase closely correlate with motor outcome after stroke.[4,8–15] Furthermore, evidence of CST atrophy and other signal changes thought to be indicative of WD on conventional magnetic resonance imaging (MRI)[16] have been correlated with poor motor outcome in patients with chronic stroke.[17,18] It seems that these changes develop at later stages and might be too subtle to be quantified in the acute stroke phase and therefore might not be useful as a prognostic tool for clinicians, patients, and caregivers.[19] One prospective study found a decrease in the apparent diffusion coefficient (ADC) of the ipsilesional CST within 12 hours of stroke in patients with initial severe motor impairment,[20] but predictions of outcome were not strong. Another imaging marker, fractional anisotropy (FA), derived from diffusion tensor imaging, quantifies the organization (ie, degree of alignment) and integrity of white matter tracts in vivo using information about the predominant direction and degree of water diffusion. Variation of FA in normal tissue is expected and is related to the orientation of axonal membranes and myelin sheaths.[21,22] Studies of subacute and chronic stroke patients have demonstrated a decrease in FA of the CST distal to the infarct thought to be the result of WD, but previous studies did not find any FA changes in the CST distal to the stroke lesion at either 12 hours or 3 days after a stroke.[19,23–29]

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Other variables determined in the acute stroke phase, such as the initial motor impairment,[10,30] lesion size and location quantified as the CST lesion load (LL),[2,31] and CST integrity[24,32] determined at later stages have already been shown to correlate with poststroke motor outcome.[33] We found that the weighted CST (wCST) LL—a combined measure of the acute stroke lesion overlapped with a canonical CST—predicted poststroke motor outcomes at 3 months better than clinical measures of motor impairment, particularly for patients with severe initial motor impairment.[2]

However, it remains unclear whether FA, a direct diffusion tensor imaging–derived measure of the affected motor tract, measured in the acute phase of stroke, contributes to motor outcome predictions at 3 months when new and innovative ways of assessing signal changes are applied.

Thus, this study aimed to examine FA differences (when compared with a matched control group and when compared with the unaffected hemisphere) in the approximate location of the CST (using a canonical tract incorporated into each patient's routine clinical MRIs done within the acute stroke phase) and to examine how those differences can predict motor outcomes at 3 months either alone or in combination with other variables (eg, wCST-LL).

Methods

Subjects

This is a retrospective analysis of a prospectively collected cohort of patients with varying degrees of initial motor impairment after first-time ischemic hemispheric stroke. The study was approved by the local institutional review board. Inclusion criteria for this study were as follows: (1) first-time, acute, hemispheric ischemic stroke; (2) age >18 years old; (3) MRI with diffusion-weighted imaging, diffusion-tensor imaging, and fluid attenuation inversion recovery (FLAIR) sequences obtained within 80 hours after stroke onset; (4) at least mild upper extremity motor impairment, defined as upper extremity Fugl-Meyer[31] (UE-FM) score <60 measured between 2 and 6 days after stroke onset; and (5) completed follow-up assessment ≈3 months after their stroke (mean follow-up was 90±18 days [SD]). Patients were excluded if they met any of the following: (1) primary intraparenchymal hemorrhage or subarachnoid/subdural/epidural hemorrhage; (2) bihemispheric strokes; (3) stroke lesion affecting the brain stem; (4) history of prior stroke demonstrated on computed tomography or MRI, or the medical record; (5) documented history of dementia, medically uncontrolled depression, or any nonstroke neurological disorder causing motor impairment; (6) clinical evidence for a recurrent stroke before the follow-up visit.

Twelve healthy right-handed control subjects served as an age-matched control group (9 men; mean age, 56.5±14.8 years). They were scanned using a 3T GE MRI scanner with image parameters identical to those described in a previous publication.[31]

MRI Protocol

All patient images used for analysis were standard-of-care, clinical MRI scans (on a 1.5 Tesla GE MRI scanner) obtained within 80 hours (mean, 25.7 hours [±14]) after stroke onset. Diffusion tensor images were obtained using single-shot spin-echo EPI sequence with 2.5×2.5×5 mm^3 voxel resolution, with 24 slices in total, and 30 non-collinear directions with a *b*-value of 1000 s/mm^2. Reconstructed FA maps were used for analyses. FLAIR image sequence had resolution of 1.3×0.8×5.0 mm^3, slice thickness 5 mm, and a total of 24 slices.

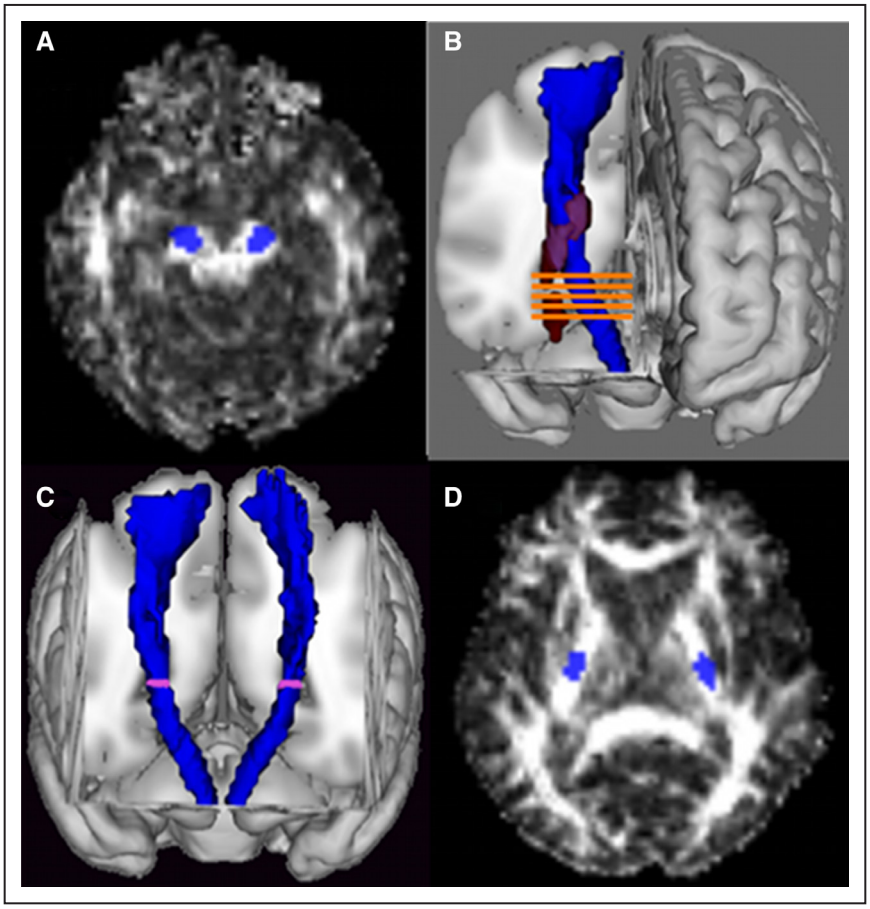

Figure 1. Region of interest (ROI) definition. **A**, Cerebral peduncle ROI. **B**, Nearest-5-slices ROI. Lesion is shown in red and canonical corticospinal tract (CST) is shown in blue. **C**, The canonical CST (shown in blue) with the first slice of the nearest-5-slices marked (**D**). The mean lowest slice of overlap for the patient group, shown here, was found to lie within the posterior limb of the internal capsule.

Image Processing

All MRI sequences for patients and control subjects were normalized to the same standardized space using SPM5 (Wellcome Department of Neurology, London, United Kingdom) implemented in MATLAB (The Mathworks, Inc, Natick, MA). Appropriate SPM5 templates with isotropic voxels (2×2×2 mm) were used for each set of images (details of the normalization process are available in the study of Feng et al[2]).

Lesion maps were manually drawn for each patient on the normalized diffusion-weighted imaging using MRIcro (http://www.mccauslandcenter.sc.edu/mricro/mricro/index.html) by investigators who were blind to the motor impairment of the patients.

Construction of the Canonical CST and wCST-LL

Construction of the canonical CST and wCST-LL was done as previously described.[2] For the selection of ROIs described below, a threshold was applied to these tracts such that each contained only those voxels shared by at least 8 of the 12 individual tracts.[31] Lesion maps were overlaid onto the CST mask to calculate a weighted LL value for each patient.[2,31]

Image Analysis

The canonical CSTs were overlaid on the spatially normalized images for each patient and each control subject to define 2 regions of interest (ROIs) bilaterally (Figure 1): the cerebral peduncle (CP)-ROI and the nearest-5-slices (N5S) ROI. The CP-ROI was used because the posterior limb of the internal capsule (another region used in the literature) was involved in the lesion in several patients and because the course of the CST in the CP can be easily identified.

The N5S ROI was defined as follows. The lesion map for each patient was overlaid with the canonical CST, and the lowest axial slice where the lesion overlapped with the CST was determined. Two axial slices below this overlapping slice (ie, leaving at least a one slice buffer between the lesion and the N5S ROI), the entire cross-sectional area of the CST on this slice and the subsequent 4 slices were used to define a N5S ROI on both hemispheres. To explore whether a trend could be seen moving along the CST distal to the lesion, a calculation of the FA laterality index (LI) for the nearest slice ROI and the next 4 descending slices was constructed for each patient. A slope across the LI of the 5 slices was calculated. We refer to this variable as the slope of the N5S (S-N5S) FA LI. We first calculated an FA LI for each of the N5S, then we regressed the FA LI across the 5 slices, and finally extracted the slope value from the regression equation.

Average FA, ADC, and FLAIR values were calculated for all CP-ROIs. To compare the stroke-affected hemisphere (A) with the unaffected hemisphere (U), a LI was calculated for each CP-ROI/sequence comparison using the following formula, shown here for FA: $(FA_A-FA_U)/(FA_A+FA_U)$. Resulting values fall between −1 and 1, with positive LIs indicating a higher FA on the affected hemisphere and negative LIs indicating a higher FA on the unaffected hemisphere.

Because it was not known whether a normal control group would show a hemispheric laterality in the measures of interest, we calculated an LI for each CP-ROI/sequence comparison for each control subject, using the following formula: $(FA_L-FA_R)/(FA_L+FA_R)$. Positive LIs indicate a higher FA on the left (L) and negative LIs indicate a higher FA on the right (R). To create a suitable N5S ROI in the control group, a distribution of the slices was derived for each patient. The mean axial slice±1 SD of this distribution was determined for the patient group; the mean axial slice was located at the level of the internal capsule (z=8.2, Montreal Neurological Institute [MNI]) and a total of 17 slices (8 slices superior and 8 slices inferior to this mean axial slice) were used to define a comparable N5S ROI in the healthy control group. An LI was calculated for each of these 17 slices, and the LIs were averaged across these 17 slices for each control subject. For S-N5S values, each slice FA LI was corrected for laterality differences before calculating overall slope for each subject over the 5 slices (described in detail in the Statistical Analysis section of this article).

Statistical Analysis

All values are reported as mean±SD. Fifty-eight patients met criteria for inclusion; three subjects were identified as extreme outliers in the wCST-LL values in the regression diagnostics and excluded. To test for significant hemispheric asymmetry in FA and FLAIR signal intensity in control subjects, a 1-sample t test was used to compare left versus right LI with an expected mean LI=0 for both the CP-ROI and N5S ROI. For all sequence type/ROI combinations in which a significant left versus right difference was found in controls, each patient's affected versus unaffected LI was adjusted by mean left versus right LI determined in controls to correct for this normal hemispheric asymmetry. In these cases, the LI of a patient with a left hemisphere lesion was determined by subtracting the mean LI of the normal control group from the patient's LI. For patients with right hemisphere lesions, the LI ratio was determined as described for left hemisphere lesion patients, but then multiplied by −1 so that the affected FA was uniform on the same side for all patients. For all sequence type/ROI combinations in which no significant side-to-side difference was found in the control group, each patient's uncorrected affected versus unaffected hemisphere LI was used.

Kruskal–Wallis 1-way ANOVA was used to test for an effect of imaging days post stroke on imaging variables.

Univariate regression analysis was used to test the predictive value of several variables with regard to 3-month UE-FM score. Multiple regression analysis was subsequently done to test whether the imaging variable (FA LI) could improve on the predictive value of the initial UE-FM after controlling for effects of other variables.

Results

Demographic and clinical characteristics are shown in Table 1. Mean lesion volume was 39.0 (±53.4) mL and mean

Table 1. Patients' Demographical and Clinical Data Characteristics

	All Patients
No. of patients	58
Age, y	61.3±14.2
Sex, % (women)	34
Lesion side, % (right)	64
Lesion volume, mL	39.01±53.44
Weighted CST-LL, mL	4.02±2.94
Handedness, % (right)	97
NIHSS, baseline	10.5±7.4
NIHSS, 3 mo	4.3±5.0
UE-FM, baseline	25.7±19.2
UE-FM, 3 mo	42.5±23.5
Imaging hours poststroke	26.4±14.0
tPA/reperfusion therapy, %	39
Hypertension, %	73
Hyperlipidemia, %	63
Diabetes mellitus, %	44
Coronary artery disease, %	15
Atrial fibrillation, %	19
Smoking, %	37

CST-LL indicates corticospinal tract-lesion load; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue-type plasminogen activator; and UE-FM, upper extremity Fugl-Meyer.

Table 2. Laterality Index Analysis in Controls and Patients

	Controls*	Patients†
CP		
FA	−0.028±0.019‡	−0.016±0.047§
ADC	−0.028±0.048	0.019±0.128
FLAIR	0.004±0.013	−0.018±0.044
Slope of LIs of nearest 5-slices		
FA	−0.031±0.010‡	0.011±0.021‡,§
ADC	0.001±0.014	−0.004±0.017
FLAIR	0.007±0.012	0.001±0.012

ADC indicates apparent diffusion coefficient; CP, cerebral peduncle; FA, fractional anisotropy; FLAIR, fluid attenuation inversion recovery; L, left; LI, laterality index; and R, right.

*LI calculated using $(FA_L-FA_R)/(FA_L+FA_R)$.

†LI calculated using $(FA_A-FA_U)/(FA_A+FA_U)$.

‡Significantly different from zero with $P<0.05$.

§Adjusted for significant L vs R asymmetry in control group.

wCST-LL was 4.02 (±2.94) nL. MRI occurred 25.7 (±14.0) hours post stroke. Regression analysis of MRI time after stroke onset showed no effect of imaging day post stroke for any FA LI sequence/ROI combination (data not shown, all $P>0.05$). Four FA images were of poor quality, and four FA images could not be normalized due to imaging artifacts, leaving 50 of 58 (86%) FA images available for analysis. Two ADC images were of poor quality and an additional 7 ADC images could not be normalized because of imaging artifacts, leaving 51 of 58 (88%) ADC images available for analysis. Seven FLAIR images could not be satisfactorily normalized because of distortions, leaving 51 of 58 (88%) FLAIR images available for analysis.

Laterality Indices in Controls and Patients

In controls, there was a subtle, but significant hemispheric asymmetry in FA for both the CP and nearest slice equivalent, with LIs indicating slightly higher FA values on the right for both ROIs. All controls were right-handed; thus, the higher FA values indicated that more alignment was seen in the nondominant CST. There was no significant asymmetry in ADC or FLAIR for either ROI (Table 2).

In patients, there was a significant difference in mean FA LI for the N5S slope indicating lower FA of the ipsilesional CST (Figure 2). There was no significant difference between groups for any other sequence/ROI combination (all $P>0.05$).

Mean difference of FA laterality between the nearest slice (slice 1) and the furthest slice (slice 5) was significantly different when assessed with a paired t test ($P<0.001$; Figure 2A).

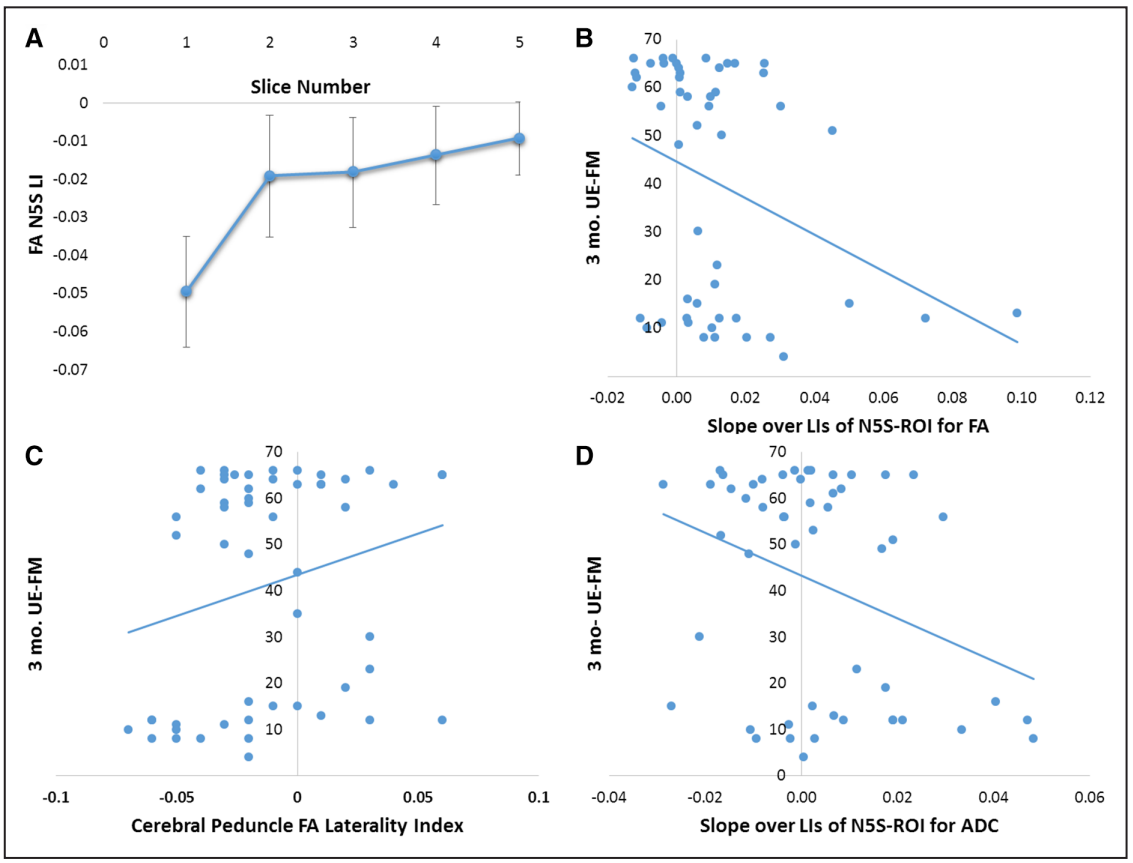

Figure 2. Fractional anisotropy (FA) laterality indices and 3-month upper extremity Fugl-Meyer (UE-FM) outcome. FA laterality indices are shown for each slice of the nearest-5-slices (N5S) region of interest (ROI; **A**). Slice 1 is the slice closest to the lesion. The 3-month UE-FM scores are plotted against the slope of the laterality index (LIs) of the N5S for the FA (**B**), as well as against the FA laterality index of the cerebral peduncle ROI (**C**), and against the slope of the LIs of the N5S for the apparent diffusion coefficient (ADC; **D**). Negative FA or ADC laterality indices indicate lower values on the lesional hemisphere compared with the unaffected hemisphere.

Table 3. Regression Analyses for Predicting 3-Month UE-FM Score

	n	*R*	*P* Value
Variable, univariate			
Initial UE-FM	58	0.687	<0.001
S-N5S FA LI	50	0.105	0.022
FA LI CP	50	0.044	0.137
DoT	56	0.247	<0.001
wCST lesion load	55	0.710	<0.001
S-N5S ADC LI	51	0.113	0.02
Variables, multivariate			
DoT‡, wCST-LL, initial UE-FM, + S-N5S FA LI		0.859	<0.001*, 0.249†
DoT‡, wCST-LL, initial UE-FM, + S-N5S ADC LI		0.849	<0.001*, 0.334†

ADC indicates apparent diffusion coefficient; CP, cerebral peduncle; wCST-LL, weighted corticospinal tract-lesion load; DoT, days of therapy; FA, fractional anisotropy; LI, laterality index; S-N5S, slope of the nearest-5-slices; and UE-FM, upper extremity Fugl-Meyer.

*Both models were significant in predicting 3-month outcome controlling for DoT, wCST-LL, and initial UE-FM.

†Partial regression *P* value (which was nonsignificant); this *P* value assesses whether there is unique or significant contribution in the model for outcome prediction for the slope of the LIs of the N5S for FA or ADC after controlling for the effect of all other variables in the multivariate model.

‡DoT, wCST-LL, and initial UE-FM were controlled for in the multivariate regression analyses.

Motor Outcome Prediction

Table 3 and Figures 2B to 2D and 3A to 3C show the results of the regression analyses. The slope of the FA LI for the N5S ROI showed a weak, significant trend (Figure 2B) as a predictor of 3-month UE-FM score in univariate analysis (R^2=0.105; P=0.02), whereas the FA LI for the CP ROI did not show any trend (R^2=0.044; P=0.14; Figure 2C). The slope of the ADC LI for the N5S ROI was also weakly predictive of 3-month outcome (R^2=0.113; P=0.02; Figure 2D). No other variable was predictive of 3-month outcome (P>0.05, data not shown). However, the FA and ADC variables contributed only modestly and the regressions seemed highly susceptible to outliers. Initial UE-FM (R^2=0.69; P<0.001) was a much better predictor than any FA or ADC variable in univariate analysis, comparable with the wCST-LL prediction (R^2=0.71; P<0.001; Figure 3A and 3B). Days of therapy also significantly predicted motor outcome (R^2=0.249; P<0.001; Figure 3C) although much less than initial UE-FM and wCST-LL.

In multivariate analyses, neither the slopes over the LIs of the N5S for the FA nor for the ADC significantly improved the R^2 of our overall model including initial UE-FM, days of therapy, and wCST-LL for predicting 3-month UE-FM (FA: overall R^2=0.859; P<0.001; slope over LIs of N5S for FA partial P=0.25; ADC: overall R^2=0.849, P<0.001; slope over LIs of N5S for ADC partial P=0.33; Table 3).

Discussion

We demonstrated that subtle changes in asymmetry of FA values derived from a canonical tract of the CST incorporated into a patient's brain imaging were detectable (close to the lesion) early after ischemic stroke, but not in the CP. In particular, the most pronounced FA asymmetry was detected in the slice that was closest to the ischemic lesion. The slope of the FA laterality indices of the N5S and the slope of the ADC laterality indices of the N5S were weak, significant predictors of 3-month UE-FM score, but neither measure significantly improved on the predictive value of initial UE-FM for 3-month motor outcome in a multivariate analysis. We did not find significant changes in FLAIR signal in any of the ROIs.

There is evidence in the literature that FA values are lower in the affected CST in the chronic stage after stroke because of the beginning of WD of the tract.[23–27] There is a correlation between the degree of FA asymmetry and the motor deficit at a chronic time point.[25,27] It has not been established how early this process begins in humans and whether imaging markers can detect subtle effects of WD in the acute stroke phase. Pathological evidence suggests that the process of tract degeneration begins early, with axonal degeneration and myelin degradation demonstrated as early as 2 days after stroke in an experimental animal model.[5] In contrast, studies in humans did not find such evidence for WD so early. A study of 9 patients by Thomalla et al[28] was the first one to show a decrease in FA in the affected descending CST at the level of the CP at 9 days after stroke onset, but patients were scanned on average 9 days after stroke. A prospective study by Puig et al[19] found absolute and relative FA decreases at 30 days

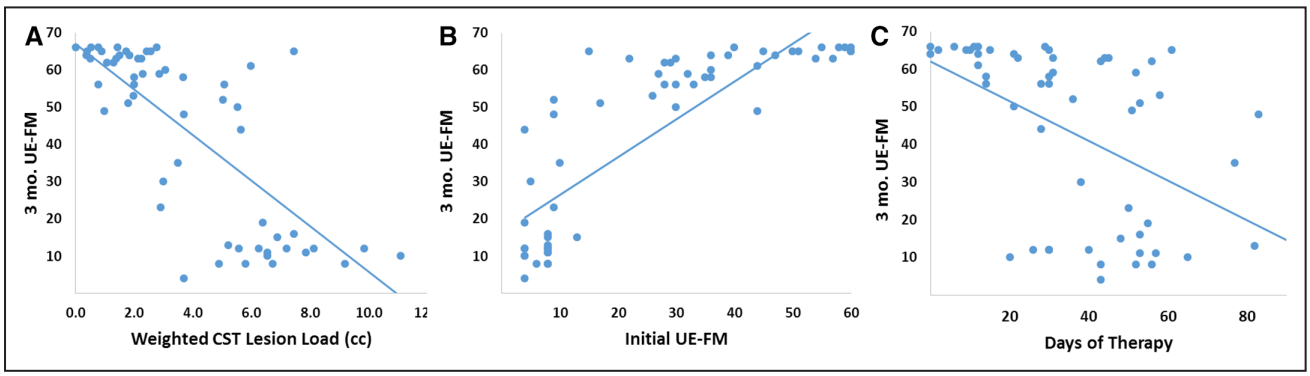

Figure 3. Weighted corticospinal tract (CST)-lesion load (**A**), initial upper extremity Fugl-Meyer (UE-FM; **B**), and days-of-therapy (**C**) regressed against 3-month UE-FM outcome.

after stroke, but not at 12 hours or 3 days after stroke. Both of these studies, however, examined FA changes at the level of the brain stem only, relatively far away from the ischemic lesion. The lack of an effect in the CP ROI in our study is in agreement with these earlier publications.

We were able to detect subtle changes in FA earlier than previous studies on routine clinical MRIs done on average 26 (±14) hours after an ischemic stroke by placing ROIs closer to the lesion, using our N5S ROI, and calculating the slope over these 5 laterality indices of the FA and the ADC. Without pathological correlation, it is not possible to state with certainty that the changes detected in this study represent early WD. The lack of significant differences in hemispheric asymmetry of FLAIR signal for our slope of N5S does, however, suggest that our findings are not simply because of perilesional edema or an increase in cellularity secondary to inflammation within the tract and could potentially reflect early disintegration of white matter fibers (either myelin sheath disintegration or axon collapse).

The degree of hemispheric asymmetry in the slope of the N5S FA LI was not a good predictor of 3-month motor outcome. Statistically, the additional predictive value offered by any FA value is null, and other predictors such as the initial UE-FM and the CST-LL are so strong that regional FA could not contribute anything to their predictive value.

Our study has several limitations. First, we used high-resolution diffusion tensor imaging for ROI definitions and FA comparisons in control subjects, but our clinical MRIs had lower resolution. This is unlikely to introduce bias to our results because the main FA data were derived from the patient group. Second, we chose to use only laterality indices, rather than absolute FA values, for the analyses to avoid inappropriate comparisons between the different imaging techniques. Third, we included only patients with their first ischemic hemispheric stroke, which may limit somewhat the generalizability of our findings to a broader group of patients with acute stroke.

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Disclosures

None.

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