Diffusion tensor imaging, permanent pyramidal tract damage, and outcome in subcortical stroke

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ABSTRACT

Background: Studies in chronic stroke patients suggest that diffusion tensor imaging (DTI) parameters of the pyramidal tract (PT) relate to residual motor function. We performed a prospective controlled study to evaluate if the DTI parameters tract volume (TV) and fractional anisotropy (FA) in patients with acute subcortical infarcts are correlated with permanent PT damage and clinical outcome after 6 months.

Methods: We acquired DTI in 18 stroke patients with subcortical ischemic infarcts either affecting the PT (PT group, $n = 12$) or not (non-PT group, $n = 6$) and in 7 age- and risk factor-matched controls at median times of 12 and 180 days. The PT was isolated using tractography and tract volume ratios (R_{TV}) and FA ratios (R_{FA}) were calculated (affected tract/unaffected tract). Ratios were compared within and between groups at initial and follow-up time points, as well as in tract portions above and below the infarcts, and were correlated to Rivermead Motor Function Test (RMFT) scores.

Results: Mean R_{FA} and R_{TV} of the PT group were smaller than those of both non-PT and control groups initially and at follow-up ($p < 0.01$). Tract portions above the infarct had lower R_{TV} than below ($p < 0.05$). There was no significant change in R_{FA} and R_{TV} over time for the whole tract or tract portions. R_{FA} and R_{TV} both were highly correlated with initial and follow-up RMFT scores.

Conclusions: DTI parameters of PT integrity acquired within the first weeks after acute subcortical stroke measure permanent ischemic PT damage and are highly correlated with residual motor function in the acute and chronic stage. *Neurology*® 2010;75:1048-1054

GLOSSARY

ANOVA = analysis of variance; **BI** = Barthel Index; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FACT** = Fiber Assignment by Continuous Tracking; **MD** = mean diffusivity; **NIHSS** = National Institute of Health Stroke Scale; **PT** = pyramidal tract; **PTV** = pyramidal tract volume; **RMFT** = Rivermead Motor Function Test; **ROI** = region of interest; **TE** = echo time; **TR** = repetition time; **TV** = tract volume; **WD** = Wallerian degeneration.

Studies investigating motor outcome after stroke have employed functional imaging to describe recovery-related changes in functional cortical networks.¹ The role of white matter damage for poststroke outcome is less well-understood. Acute effects of infarct-related damage to major axonal pathways can now be studied noninvasively using diffusion tensor imaging (DTI). DTI permits the imaging of major axonal pathways of the living brain² and provides information about tissue microstructure by measuring fractional anisotropy (FA). FA is an index of the diffusion characteristics of water molecules preferentially directed along the axis of major axonal pathways. Within stroke lesions, significant decreases in FA have been demonstrated as early as 7 to 14 hours poststroke.³ These changes are associated with secondary degeneration of the pyramidal tract (PT) distal to the infarct over a 12-week period.⁴ Reduced FA has traditionally been interpreted as evidence of Wallerian degeneration (WD) and axonal loss following stroke.⁵ However, little is known about specific changes in FA along the entire tract (i.e.,

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outside of the stroke lesion) in the acute post-stroke period because decreased FA in the infarct renders tracing of affected tracts based on anatomical landmarks difficult.⁶ Using our new method for tract tracing, this study seeks to determine whether DTI parameters such as pyramidal tract volume (PTV) and FA of the entire tract, acquired early after stroke, reflect acute and permanent damage to the PT and to determine how these parameters relate to clinical motor deficit and outcome.

METHODS Patients. Eighteen right-handed patients (13 female, 5 male; mean age 73.06 ± 12.99 years) were assessed and scanned within 3 weeks of stroke (median time 12 days) and at 6 months (median time 180 days). The control group consisted of 7 patients with TIA (2 female, 5 male; mean age 65.14 ± 6.18 years) and no structural lesion on the MRI. The PT group consisted of 12 patients (8 female, 4 male; mean age 76.00 ± 12.33 years) with subcortical ischemic infarct affecting the PT (as determined on T1-weighted MRI). The non-PT group consisted of 6 patients (5 female, 1 male; mean age 67.17 ± 13.32 years) with subcortical ischemic infarct outside of the PT. All groups were similar with respect to age and cardiovascular risk factors (table). Sample size was estimated based on recently published data on between-session reproducibility and between-subject variability of diffusion MRI and tractography measures of the PT.⁷ Following these data, a minimum sample size of 6 subjects per group is required to detect a 10% difference in FA of the PT between subjects with a power of 0.8 at $p = 0.05$.

Stroke patients were screened for inclusion and exclusion criteria on admittance to the stroke unit of the Jewish General Hospital, Montreal. All patients were right-handed, having had a first-ever subcortical stroke affecting white matter only. Exclusion criteria included prior stroke or history of other neurologic

disease, alcohol or drug abuse, and contraindications for MRI. Inclusion and exclusion criteria were chosen as to yield a homogenous sample of subcortical strokes sparing the cortex. Seventy-seven stroke patients who met these criteria were approached to participate. PT involvement was determined from initial and follow-up T1-weighted images by 2 independent raters (A.T. and J.M.), both experienced stroke neurologists blinded to patient presentation. There was 100% agreement on patient classification by the raters.

Standard protocol approvals, registrations, and patient consents. The protocol was approved by the McGill and JGH institutional review boards and written informed consent was obtained from all participants.

Behavioral testing. All patients were assessed for clinical stroke severity in addition to physical and neurologic examination in the acute poststroke phase. Stroke-related neurologic disability was evaluated using the National Institute of Health Stroke Scale (NIHSS) and performance on activities of daily living using the Barthel Index (BI).⁸ The degree of handicap was assessed with the modified Rankin Scale⁹ and upper limb motor function was assessed with the arm subsection of the Rivermead Motor Function Test (RMFT) (table). Since the infarcts were restricted to white matter, most of our patients had mild to moderate deficits (brachio-facial hemiparesis). These deficits are better reflected in the specific arm subset of the RMFT than in more global scales and the RMFT was thus used as primary outcome measure.

Data acquisition. T1-weighted and diffusion-weighted images were acquired on a 3-Tesla Siemens Trio Scanner, first with a quadrature single channel head coil, then with a 12-channel phased-array head coil. Diffusion encoding was achieved using a single-shot spin-echo echoplanar sequence with twice-refocused balanced diffusion encoding gradients.¹⁰ Two datasets designed for high angular resolution reconstruction were acquired with 50, then 64, diffusion encoding directions, 2 mm isotropic voxel size, 63 slices, $b = 1,000 \text{ s/mm}^2$, echo time (TE) = 121 ms, repetition time (TR) = 11.1 s, and GRAPPA parallel reconstruction. This inevitable change in the number of diffusion directions has been shown to have a negligible effect on FA values of the PT.⁷ Furthermore, the same number of directions was acquired at initial and follow-up time points for each subject. The T1-weighted anatomical scan acquired was of 1-mm isotropic resolution (spoiled gradient echo, TR = 9.7 msec, TE = 4 ms, $\alpha = 12^\circ$).

Data analysis. DTI datasets were processed using in-house MINC suite tools (McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Quebec, Canada; <http://www2.bic.mni.mcgill.ca/>). Datasets were concatenated and registered to the first frame of the set, then realigned to the T1-weighted anatomical scan using a mutual information-based algorithm.¹¹ Mean diffusivity (MD), FA, eigenvectors, and eigenvalues of the diffusion tensor were then calculated at each voxel of the 4D image. Fiber tracking was performed by the Fiber Assignment by Continuous Tracking (FACT) algorithm¹² and initiated in all voxels in the volume on a $3 \times 3 \times 3$ grid of start points within each voxel in order to facilitate branching. Only tracts that passed through 2 tract-delineating regions of interest (ROIs) in each hemisphere were retained. Tracking in the anterior direction (from infarct through peduncle ROI to brainstem) continued to the most inferior slice of the acquired data volume. In the opposite direction (from infarct to motor cortex) tracking was stopped if the FA was less than 0.2 or the

Table	Patient demographics and behavioral test scores			
	PT group	Non-PT group	Controls	p
No.	12	6	7	
Median age, y (range)	80.5 (42-86)	71.5 (49-82)	65 (57-75)	0.107
Hypertension, n (%)	11 (92)	5 (83)	5 (71)	0.933
Diabetes, n (%)	5 (42)	2 (33)	1 (14)	0.533
Median time to MRI, d (range)	12 (3-15)	11.0 (6-20)	—	0.506
Initial mean NIHSS, 34 (poor)-0 (good) (SD)	4.4 (4.05) ^a	1.7 (1.37)	0 (0) ^a	<0.001
Initial mean Barthel Index, 0 (poor)-100 (good) (SD)	68.7 (36.81) ^a	98.3 (4.08)	100 (0) ^a	0.01
Initial mean modified Rankin Scale, 6 (poor)-0 (good) (SD)	2.9 (1.62) ^a	1.3 (0.52)	0 (0) ^a	<0.001
Initial mean RMFT, 0 (poor)-15 (good) (SD)	9.6 (5.13) ^a	13.7 (1.51)	15 (0) ^a	<0.001
Follow-up mean RMFT, 0 (poor)-15 (good) (SD)	10.5 (5.58) ^b	14.3 (0.82)	—	0.085

Abbreviations: NIHSS = National Institute of Health Stroke Scale; PT = pyramidal tract; RMFT = Rivermead Motor Function Test.

^a $p < 0.05$.

^b $n = 10$.

Figure 1 Definition of pyramidal tract (PT)

Illustration of PT delineation in (A) PT group patient, (B) non-PT group patient, and (C) control. (A) (a) Infarct region delineated in native space, (b) native brain and infarct region of interest (ROI) are transformed into stereotactic space, and (c) mirrored along the z axis. (B, C) (c) Posterior limb of the internal capsule delineated in both hemispheres. (A–C) (d) Cerebral peduncle delineated in both hemispheres, (e) posterior limb/stroke and peduncle ROIs put together in native space, (f) fiber tracking carried out separately in each hemisphere, (g, h) exclusion masks added to avoid fibers crossing into the contralateral hemisphere and branching into the cerebellum, (i) left and right PT fibers overlaid on an anatomical T1-weighted MRI, (j) PT fibers overlaid on the fractional anisotropy (FA) mask, (k, l) left and right PT fibers separated into regions above and below the infarct ROIs, (m) fibers above and below infarct regions overlaid on the FA mask and evaluated separately.

curvature from one voxel to the next was greater than 40°. In non-PT and control groups, ROIs consisted of the anatomically defined posterior limb of the internal capsule and the cerebral peduncle in both hemispheres. These ROIs have been shown to correspond to reliable marking points along the length of the PT.¹³ In the PT group, cerebral peduncle ROIs were defined in the same way. Since the internal capsule was often affected by the stroke in these patients, the infarct region itself was used as second ROI in the affected hemisphere. For PT group nonaffected hemisphere ROIs, infarct regions were mirrored from the affected side. In some cases, exclusion masks were used to avoid the crossing and branching of fibers into the contralateral hemisphere and into the cerebellum, despite the curvature constraint

of 40°, which only limits the change in angle from one voxel to the next but not a progressive curvature over several voxels. Figure 1 illustrates the analysis. Using the infarct as seed ROI in the PT group had no effect on the absolute volume of the tract in the unaffected hemisphere. It was not significantly different from the tract volumes in the non-PT group and controls (mean $PTV_{unaffected}$ in PT group $6,956.0 \pm 930.74$, in non-PT/control group $7,039.9 \pm 814.39$) where the internal capsule was used instead.

Full tract R_{TV} and R_{FA} were calculated as ratios of affected and nonaffected hemisphere PTV and FA in the PT and non-PT groups, and as left/right hemisphere PTV and FA ratios in the control group. In the PT group, tracts were subdivided into an-

terograde (i.e., below the stroke) and retrograde (i.e., above the stroke) portions relative to the lesion site to test if R_{TV} and R_{FA} are differentially affected. Statistical analyses were performed using SigmaStat 3.5 and SigmaPlot 10.0 (Systat Software, Inc., SigmaStat Executable) using appropriate parametric and non-parametric tests for within- and between-group differences as specified below.

RESULTS The PT was successfully traced from the pons to the motor cortex in both the affected and nonaffected hemispheres of all PT group patients (except one) and non-PT group patients, as well as in the left and right hemispheres of all controls initially and at follow-up (figure 1). Follow-up data were not available for 2 patients in the PT group who discontinued the study due to loss of interest. One patient with the infarct in the subcortical white mat-

ter directly under the motor cortex had no significant tract portion above the infarct.

Behavioral data. Motor function as measured by the RMFT was initially more impaired in PT group patients (rank-sum test, $p = 0.041$) than in the non-PT group. PT group patients had higher RMFT scores at follow-up than initially (Wilcoxon test, $p = 0.047$) (table).

Whole tract volume (R_{TV}) and FA ratios (R_{FA}). For R_{FA} , a 2-factor repeated-measures analysis of variance (ANOVA) with group (PT, non-PT, control) and time (initial, follow-up) as factors was significant for factor group but not for time ($p < 0.006$). Post hoc single-pair comparisons (Holm-Sidak) indicated that R_{FA} was smaller in the PT group when compared to the non-PT and control groups ($p < 0.023$) (figure 2A). There were no significant differences between control and non-PT groups.

The same results were obtained with the same ANOVA for R_{TV} . There was a group effect ($p < 0.01$) with R_{TV} being smaller in the PT group as compared to the others (Holm-Sidak). Again, no significant difference was noted for non-PT and control groups (figure 2B).

Tract portions within PT group. A 2-factor repeated-measures ANOVA with factors time (initial and follow-up) and tract portion (above and below the infarct) was not significant for R_{FA} (figure 3A). The same analysis for R_{TV} resulted in a significant effect of tract portion. R_{TV} above the infarct was smaller than below the infarct for both time points, thus indicating a stronger effect of the lesion on the retrograde tract portion (Holm-Sidak, $p < 0.01$, figure 3B). There was no significant change over time.

Correlation analyses. Both initial R_{FA} and initial R_{TV} were linearly correlated with RMFT scores in the acute phase ($p = 0.019$ for R_{TV} and $p < 0.001$ for R_{FA} , figure 4A) and at 6-month follow-up ($p < 0.01$ for R_{TV} and R_{FA} , figure 4B). This indicates that the extent of acute tract damage is not only related to the initial clinical deficit but is also associated with long-term outcome. Regression coefficients were higher at both timepoints for R_{FA} ($r = 0.87$ initially and at follow-up) than for R_{TV} ($r = 0.72$ initially and $r = 0.77$ at follow-up).

DISCUSSION In this longitudinal prospective study, we explored the acute and long-term effects of subcortical stroke on morphologic PT fiber integrity by investigating changes in mean FA and tract volume (PTV) within 20 days and after 6 months of stroke onset. We present a methodology to achieve full-length fiber tract tracing in patients having had

Figure 2 Diffusion parameters of the entire tract

Fractional anisotropy ratio (R_{FA} , A) and tract volume ratio (R_{TV} , B) initially and at follow-up for control subjects and patients with subcortical stroke affecting (PT) and not affecting (non-PT) the pyramidal tract (PT). Significant comparisons of repeated-measures analysis of variance with Holm-Sidak post hoc test. (A) **PT group R_{FA} was significantly different from control group R_{FA} at both time points. (B) **PT group R_{TV} was significantly different from control group R_{TV} at both time points, *PT group R_{TV} was significantly different from non-PT group R_{TV} at both time points.

Figure 3 Diffusion parameters of tract portions

Fractional anisotropy ratio (R_{FA} , A) and tract volume ratio (R_{TV} , B) initially and at follow-up for tract portions retrograde (above) and anterograde (below) to the infarct in patients where the infarct affected the pyramidal tract. Significant comparisons of repeated-measures analysis of variance with Holm-Sidak post hoc test. (A) There were no significant differences between R_{FA} above and R_{FA} below the lesion at either time point. (B) **In the PT group, R_{TV} above the lesion was significantly smaller than R_{TV} below the lesion at both time points.

acute subcortical stroke along the PT. DTI-based fiber tracking algorithms, such as FACT,¹² can be used to reliably delineate individual tracts of interest in healthy populations. Indeed, the reproducibility of longitudinal measurements of FA and tract volume within the same subjects has systematically been studied.^{7,14,15} In stroke patients, however, the lesion site produces a region of significantly reduced FA, which renders comprehensive demarcation of affected tracts difficult to achieve.⁶ Despite causing significant damage to the affected tract, we have shown that the lesion itself can nevertheless be used as a seed region for fiber tracking given that there remain intact fibers within and around the infarcted area. We were able to delineate the PT in its entirety from the motor cortex to the pons in all but one patient (in whom there was a complete transection of the PT at the level of the basal ganglia and who had the worst

clinical outcome). This makes it possible to map fiber tracts in stroke patients in a standardized way and constitutes a significant improvement in methodology given that recent work has mainly focused on fiber-tract interruption and mean FA along incomplete fibers to predict motor outcome.^{13,16} Furthermore, by using the mirror region of the infarct as a seed for fiber tracing in the contralesional hemisphere, we were able to investigate changes in PT volume in the acute and chronic poststroke phases alongside changes in FA. Based on tract tracings, we found significant reductions in both mean FA and PTV along the entire PT relative to the nonaffected hemisphere tracts, as well as compared to patients with strokes outside of the PT and controls. Decreases in PTV were seen even within the earliest of these cases, 3 days poststroke ($R_{TV} = 0.42$). To our knowledge, these represent the earliest reported changes in apparent tract volume and FA in noninfarcted white matter as measured by DTI to date. Diffusion changes in the infarct itself have been reported to stabilize after 7 hours.³ Especially the comparison to patients with strokes outside of the PT demonstrates that changes in FA and PTV are specifically caused by the tract-affecting infarct, rather than being secondary to nonspecific subcortical infarcts anywhere in the white matter of the affected hemisphere.

As in most tractography experiments, the actual volume of the delineated tract may be influenced by the choice of fiber reconstruction technique and the tracking algorithm. More specifically, because a single fiber response was chosen for each voxel, tractography was limited by more complex subvoxel geometry such as crossings and fanning. These types of fiber structures occur particularly in more proximal portions of the PT, where partial volume effects are also an issue. The choice of the FA threshold might also influence the tract volume, whereby voxels within the tract but below the threshold are excluded. However, because the same FA threshold of 0.2 was used for both the ipsilateral and the contralateral hemispheres and we analyzed ratios of tract volumes, the observed differences are unlikely to be significantly influenced by the choice of the threshold. In addition, although the choice of seed region will inevitably affect tractography, careful delineation of the tract through the placement of anatomical ROIs and mirroring of the stroke region to the contralateral side ensures consistency. Finally, despite possible effects on actual tract size, the tractography procedure is identical in both the affected and nonaffected hemispheres and the parameter of interest is the ratios rather than absolute volume measurements.

Given that our findings are thus unlikely to be explained on methodologic grounds, 2 biologic interpretations may be considered. The first possibility

Figure 4 Diffusion parameters and outcome

Correlation of initial (A) and follow-up (B) Rivermead Motor Function Test with fractional anisotropy ratio (R_{FA} , A) and tract volume ratio (R_{TV} , B) in patients where the infarct affected the pyramidal tract.

is to interpret these volumetric changes as true degeneration. Reduced FA within ROIs anterograde to the lesion site, such as in the cerebral peduncle, have traditionally been attributed to ongoing axonal degeneration and thus been taken as an indication of WD.^{13,16-19} Based on animal and human experiments,²⁰⁻²³ WD is thought to advance at 1 to 3 mm per day following axonal injury. However, we recorded changes along the full length of the PT within a median of 12 days following infarct. Indeed, in a rodent model, the breakdown into ovoids of teased phrenic nerve fibers has been reported within just 25.6–45 hours, advancing at a speed of 46–250

mm/day.²⁴ Degeneration at this speed may indeed be detectable as early as 3 days post stroke onset.

However, inconsistent with the interpretation of WD is the fact that in our study R_{FA} was equally affected anterograde and retrograde to the infarct initially. No significant decrease was observed over the following 6 months for both tract portions. PTV measurements also gave no evidence for a significant contribution of degeneration beyond the initial damage: R_{TV} anterograde to the infarct did not decrease over time. Retrograde R_{TV} was significantly lower than anterograde R_{TV} , which might be caused by the algorithm due to more branching and crossing fibers above than below the infarct, thus leading to lower FA values.

The second possible biologic interpretation is that the changes in FA and PTV may not be associated with WD in a narrow sense, but rather reflect a different process also caused by the ischemic injury to the axons, such as the disruption of axonal transport. Lesion studies of peripheral neurons indicate that an interruption of axonal transport causes significant changes to both the distal and proximal parts of the axon. This disturbance of directed axonal protoplasmic flow may cause the change in FA. However, based on work with the squid giant axon,²⁵ it has been argued that the neurofilamentary cytoskeleton does not play a significant role in producing diffusion anisotropy and suggested that axonal membranes are the primary determinant of anisotropic diffusion along nerve fibers. Thus the microstructural basis for the changes in FA and PTV is beyond the scope of the current study and awaits further investigation.

Both decreases in R_{FA} and R_{PTV} within the PT group patients were significantly correlated with motor function initially and at follow-up. This finding expands on previous reports in chronic stroke where FA values²⁶ and PT volume²⁷ were found to be related to the clinical deficit because it demonstrates for the first time that measurements of DWI parameters in the acute phase may not only predict morphologic, permanent damage but also permanent motor function outcome. Whether these correlations in the acute phase can be improved by including so-called alternative motor pathways, as in chronic patients,²⁷ requires further investigation. Our results are also in line with animal data in a rat stroke model, where recovery of forelimb function was related to the density of corticospinal fibers ipsilateral to the lesion.²⁸

This prospective controlled longitudinal study provides evidence that DTI parameters of PT integrity acquired within the first 2 weeks after acute subcortical stroke measure permanent ischemic PT

damage and are highly correlated with residual motor function in the acute and chronic stages. These changes occur along affected fibers both anterograde and retrograde to the infarct location and are stable during the 6-month observation period, thus indicating that initial ischemic damage contributes more to the DWI parameters than WD. DWI parameters may thus become clinically useful surrogate outcome markers in subcortical stroke.

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DISCLOSURE

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