Lesion Load of the Corticospinal Tract Predicts Motor Impairment in Chronic Stroke

Lin L. Zhu, BS; Robert Lindenberg, MD; Michael P. Alexander, MD; Gottfried Schlaug, MD, PhD

Background and Purpose—Previous studies have shown motor impairment after a stroke relates to lesion size and location, but unexplained variability in recovery still exists. In this study, we used lesion-mapping techniques in combination with diffusion tensor imaging to quantitatively test the hypothesis that motor recovery in patients with chronic stroke is inversely related to the proportion of the corticospinal tract (CST) affected by the lesion.

Methods—We studied 50 patients with chronic stroke, all of whom presented with moderate to severe motor impairments in the acute stage, using high-resolution anatomic MRI. We evaluated the degree of motor impairment with the Upper Extremity module of the Fugl-Meyer Assessment. To analyze the relationship between CST damage and impairment scores, we calculated a CST-lesion load for each patient by overlaying the patient’s lesion map with a probabilistic tract derived from diffusion tensor images of age-matched healthy subjects.

Results—CST-lesion load was a significant predictor of motor deficit. Infarct size, despite correlating with motor scores, did not significantly predict impairment.

Conclusions—Our results show the degree of functional motor deficit after a stroke is highly dependent on the overlap of the lesion with the CST and not lesion size per se. In the future, automated calculation of CST-lesion load may allow more precise prediction of motor impairment after stroke. (Stroke. 2010;41:910-915.)

Key Words: corticospinal tract ■ diffusion tensor imaging ■ lesion mapping ■ motor recovery
the study (12 women; mean age 58.6±13.9 years; median time poststroke 17.1 months, interquartile range 6.5 to 37.5 months; 21 right hemisphere and 29 left hemisphere strokes; 48 right-handed and 2 left-handed individuals). Each patient had a Medical Research Council strength grade ≤3/5 in the extensor muscles of the affected upper extremity in the first 24 hours after symptom onset. All patients in this study required inpatient rehabilitation, which consisted of standard physical and occupational therapy. Exclusion criteria were: bihemispheric or brain stem infarcts, primary intracerebral hemorrhages, history of stroke or consecutive stroke, or other concomitant neurological diseases. Patients were assessed using the Upper Extremity module of the Fugl-Meyer Assessment (UE-FM). The UE-FM is a 30-item motor function assessment with scores ranging from 0 to 66; higher scores reflect more complete functional recovery. It is the most frequently used clinical motor impairment test in stroke rehabilitation research. An additional 10 healthy subjects were enrolled as age-matched control subjects (4 men; mean age 58.2±12.2 years); age at assessment for this study did not differ significantly between the patient group and the healthy control group (F(1,58)=0.006, P=0.940). All control subjects were right-handed and had no history of stroke or other neurological or psychiatric diseases. Routine MRI of their brains did not show any focal abnormalities and there was no evidence of clinically silent strokes. This study was approved by the local Institutional Review Board, and all participants gave written informed consent.

MRI Acquisition and Preprocessing

All patients were scanned on a 3-T GE scanner using a standard radiofrequency head coil. Head motion was minimized by foam padding and forehead-restraining straps. T1-weighted high-resolution scan (voxel resolution: 0.93×0.93×1.5 mm³) and a set of axial fluid-attenuated inversion recovery images (0.5×0.5×5 mm³) were acquired. T1-weighted and fluid-attenuated inversion recovery images were realigned and spatially normalized into images of isotropic voxel size (2×2×2 mm³) using SPM5 (Wellcome Department of Neurology, London, UK) implemented in Matlab (The Mathworks Inc, Natick, Mass.). For patients with extensive lesions, the infarct was excluded from the cost function calculation of the spatial normalization process37 using lesion masks drawn in MRicron.38

Lesion Mapping

We used MRicron38 to define the lesions in the spatially normalized T1-weighted images. For each patient, we manually outlined the lesion area on each slice of the normalized T1-weighted images while using the fluid-attenuated inversion recovery images as an additional guide to confirm the extent of the lesion. In cases with marked ventricular dilatation due to extensive ischemic lesions and consequent hemispheric atrophy, no part of the dilated ventricle was included in the lesion area. Lesions were drawn by a single rater who was blinded to the patients’ UE-FM scores. A second blinded rater drew lesions in a subset of 10 patients to calculate an interobserver reliability (R²=0.92). To display all lesions on the same side during final calculations, right hemispheric lesion maps (n=21) were mirrored across the midsagittal axis.

DTI: Image Acquisition and Analysis

The control subjects underwent DTI using a single-shot, spin-echo echoplanar image sequence with the following parameters: TR=10 seconds, TE=86.9 ms, resolution 2.6×2.6×2.6 mm³, 30 noncollinear linear diffusion directions with a b value of 1000 s/mm², and 6 acquisitions with a value of 0 s/mm². A total of 56 slices covered the entire brain, including the brain stem. Fractional anisotropy, a measure of the degree of directional preference of water diffusion, was calculated for each brain voxel.

Diffusion tensors were calculated for every voxel using MedINRIA 1.7,19 which performs the estimation with least squares on the linearized version of the Stejskal and Tanner diffusion equation.20 After estimation, nonpositive tensors were detected and replaced by the Log-Euclidian average of all positive–definite neighboring tensors. Log-Euclidian interpolation21 has been shown to preserve tensor volume (ie, interpolation of tensor volume is monotonic) and, consequently, to not introduce more diffusion than there is initially (no swelling effect22).

Tractography was then applied to the DTI data to reconstruct white matter tracts by successively following the path of preferred direction of water diffusion. Fiber tracts were traced using tensor lines,23 a modified streamline algorithm that connects adjacent voxels with similar principal eigenvectors while simultaneously using advection vectors to stabilize propagation through regions with nonlinear preferential diffusion. Trilinear Log-Euclidian interpolation21 was used throughout tracking to produce fibers with smoother trajectories.

We applied a threshold fractional anisotropy value of 0.2 and a smoothness factor24 of 0.2 for continuous fiber reconstruction; these parameters are similar to those reported by other researchers who have obtained continuous CSTs with this method.23,24 Three regions of interest (ROIs) were drawn on each patient’s fractional anisotropy images. The analysis was started with an ROI in the posterior limb of the internal capsule (at a level corresponding to z=8 of a spatially normalized brain in Talairach space25). A second ROI was drawn in the anteriorpons (basis pontis; z=−24), where neuroanatomical26 and tractography studies27 locate the fiber bundle constituting the pyramidal tract. A logical AND function was added so that only fibers passing through both the posterior limb of the internal capsule and basis pontis were considered for further analysis. A third ROI included the precentral gyrus along with its underlying white matter (z=50). A logical AND function was also added for this ROI so that only those fibers originating in the precentral gyrus and passing through both the posterior limb of the internal capsule and thepons were designated as part of the CST. Fibers that went to the cerebellum were excluded by drawing ROIs in the superior cerebellar peduncle and the middle cerebellar peduncle and applying a logical NOT function in conjunction with the other ROIs.

The reconstructed fiber tract of each control subject was transformed into a binary image and spatially normalized using SPM5. We obtained continuous CSTs because their structurally abnormal tracts would have varied greatly due to the ischemic lesions and subsequent Wallerian degeneration.28,29

Calculation of Lesion–CST Overlap

After normalization, the binary CSTs of the 10 healthy control subjects were summed to generate a fiber map using Matlab (Figure 1). Voxel intensities ranged from I=0 (ie, voxel is not part of the CST in any of the subjects) to I=10 (ie, voxel is part of the CST in all 10 subjects); thus, the probability that a particular voxel would be part of the CST was calculated as one tenth of the voxel’s intensity.

For each lesion, a raw lesion–tract overlap volume (Vraw) was calculated by overlaying the lesion map onto the probabilistic CST and summing the intensities of all intersecting voxels. This calculation is denoted by the following equation:

\[
V_{\text{raw}} = \sum_{n=1}^{n_{\text{max}}} \frac{1}{10} I(n) \times (\text{voxel volume}),
\]

where nmax is the total number of intersecting voxels between the lesion map and fiber map and I(n) is the intensity of the nth voxel (as represented in the fiber map). It should be noted that this method weighs voxels according to their individual probabilities of being part of the CST as opposed to treating all voxels with intensities above a certain threshold equally (ie, using isocountours20,31). A weighted lesion–tract overlap volume was then calculated for each lesion using a method similar to the previously used proportional grid system.3 This weighted overlap accounts for the narrowing of the CST as it descends from the motor cortex to the posterior limb of the internal capsule by multiplying the lesion–tract overlap on each slice by the ratio of the maximum cross-sectional area of the tract to the cross-sectional area of the tract on that particular slice.
Although the proportional grid system—which used the Talairach and Tournoux atlas22 as a reference—arbitrarily divided the region between the motor cortex and the intercommissural plane into 5 levels (1 cortical and 4 subcortical layers) and assigned a different weighting factor to each layer, we instead chose to calculate a different weighting factor for each individual slice (x) at every intensity level (I). For a particular slice x containing m(x, I) voxels with intensity ≥I, a weighting factor f(x, I) was calculated as:

\[
f(x, I) = \frac{m(x^*, I)}{m(x, I)},
\]

where \(m(x^*, I)\) denotes the number of voxels on the slice \(x^*\) that contains the most voxels of intensity ≥I. Thus, for any intensity I, the slice \((x^*)\) with the most voxels ≥I was assigned a weighting factor of \(f(x^*, I)=1\). For each patient, a weighted lesion–CST volume was then calculated using the following equation:

\[
V_{\text{weighted}} = \frac{1}{n_{\text{max}}} \sum_{n=1}^{n_{\text{max}}} V_{\text{raw}} f(x(n), I(n))
\]

\[
- \frac{1}{n_{\text{max}}} I(n) (\text{voxel volume}) f(x(n), I(n)),
\]

where \(n_{\text{max}}\) is the total number of intersecting voxels between the lesion map and fiber map, \(I(n)\) is the intensity of the \(n^{th}\) voxel located on slice \(x(n)\), and \(f(x(n), I(n))\) is the weighting factor for the voxel. We will refer to the variables \(V_{\text{raw}}\) and \(V_{\text{weighted}}\) as raw and weighted CST-lesion load, respectively.

### Results

Motor impairment correlated significantly with raw CST-lesion load \(R^2=0.664, P<0.001;\) Figure 2A), weighted CST-lesion load \(R^2=0.724, P<0.001;\) Figure 2B), and lesion size \(R^2=0.307, P<0.001;\) Figure 2C).

A regression analysis was first conducted using raw CST-lesion load and lesion size as predictors of motor impairment (adjusted \(R^2=0.656, P<0.001)\). Whereas raw CST-lesion load significantly predicted UE-FM scores (partial \(R^2=0.524, P<0.001)\), lesion size was shown not to be a significant predictor of motor impairment (partial \(R^2=0.016, P=0.383)\). A second regression analysis was then conducted using weighted CST-lesion load and lesion size as predictors of motor impairment (adjusted \(R^2=0.720, P<0.001)\). Again, lesion size did not significantly predict motor impairment (partial \(R^2=0.023, P=0.302)\), whereas the weighted CST-lesion load did (partial \(R^2=0.613, P<0.001)\).

A final regression analysis was conducted using lesion size and both raw and weighted CST-lesion load as predictors of UE-FM score (adjusted \(R^2=0.727, P<0.001)\). Weighted CST-lesion load was shown to be a better predictor (partial \(R^2=0.223, P=0.001)\) than either raw CST-lesion load (partial \(R^2=0.045, P=0.147)\) or lesion size (partial \(R^2=0.007, P=0.568)\).

### Discussion

We used lesion–behavior mapping techniques to analyze the relationship between motor function and lesion load of the CST in patients with chronic stroke. Our results inform a longstanding debate regarding the relationship between infarct size and clinical outcome measures of stroke. Although several studies have reported significant but moderate correlations between motor impairment and lesion size, others have argued that no statistically significant relationship exists.32 In our study, infarct size, despite correlating with
UE-FM score, did not predict motor impairment. In contrast, the partial correlations of CST-lesion load with UE-FM scores remained highly significant in the regression analyses, which suggest that, in fact, infarct size is merely masking the effect of lesion damage within the CST (Figure 3).

The highly significant linear correlation demonstrated between raw CST-lesion load and UE-FM score is in accordance with previous studies that have quantitatively examined the relationship between CST involvement within the ischemic lesion and motor outcome. One such study analyzed infarct size with respect to CST involvement by overlaying a hand-drawn mask of descending motor tracts onto T2-weighted MR images. The greatest proportional intersection of lesion with this mask on any single slice was found to be more highly correlated with motor impairment than lesion size; however, this maximum ratio of lesion to mask cross-sectional area was not found to be a significantly superior predictor of motor impairment as compared with infarct size, which the authors attributed to their rather small patient sample (n=18). Two studies that used variations of this approach resulted in comparable findings. In the first study, the slices of greatest proportional overlap were determined by overlaying lesion maps of 3 patients with motor tracts derived from diffusion tensor images of healthy subjects; disconnections of the tracts were associated with differing hand-grip responses displayed by the patients. In another study, lesion maps of 18 patients with mild to moderate impairments of the lower limb were overlaid onto a probabilistic fiber map derived from diffusion tensor images of 8 healthy, nonage-matched control subjects. Although gait parameters showed trends for correlation with both maximal cross-sectional overlap as well as total lesion overlap, in contrast to our study, none of the correlations reached statistical significance. Our study complements these investigations by overlaying lesion maps from a large sample of patients with stroke onto a probabilistic, nonisocontour CST map derived from age-matched control subjects.

Our approach further expounds on the relationship between CST-lesion overlap and impairment by accounting for the narrowing of the CST as it descends from the precentral gyrus. We applied slicewise weighting factors to our probabilistic fiber map similar to those utilized in the previously used proportional grid system and, as such, were able to more realistically model the anatomic topography of the CST. Consequently, the weighted CST-lesion load, which quantifies motor impairment in terms of tract geometry, was shown to be an even better predictor of motor impairment than the raw overlap variable.

Future longitudinal studies may wish to use CST-lesion load measured in the acute phase to examine the relationship between CST involvement and subsequent motor impairment. One study showed integrity of the CST—as classified using acute-phase DTI scans—to predict motor outcome at 6 months in patients with pontine infarcts; whether or not a similar causal relationship exists between acute/subacute lesion–tract overlap in hemispheric strokes and motor outcome in the chronic phase has not yet been determined.

Our study is not without its limitations; we have generated our probabilistic CST map using fibers that were tracked using a modified streamline algorithm. Although this single-fiber method has been shown to be able to traverse regions of oblate tensors and, thus, reconstruct some crossing fibers,

**Figure 2.** Regression analyses. UE-FM scores are plotted as functions of (A) raw CST-lesion load, (B) weighted CST-lesion load, and (C) lesion size.
future studies may wish to use other tractography methods that might be better suited for fiber reconstruction in regions of complex crossings (eg, multitenor or q-ball analysis). Multifiber probabilistic models may be particularly useful for researchers examining motor functions represented more laterally on the cortex or behaviors served by nondominant fiber pathways. Finally, by including the entire precentral gyrus as a cortical ROI, we have inevitably also tracked corticospinal fibers originating from the premotor cortex. Nevertheless, our approach, which is consistent with methods used in previous DTI studies, is reliable and easily reproduced because the precentral gyrus can be easily identified. In contrast, no clear macroanatomic landmarks indicate the border between the primary motor and premotor cortices.

In conclusion, we have shown CST-lesion load—a new variable that combines lesion size and CST involvement into a single quantitative measure—to be a statistically significant predictor of motor impairment in patients with chronic stroke. The value of this new variable can be enhanced by using weighting factors to account for the narrowing of the CST as it descends from the precentral gyrus. The superiority of CST-lesion load as a predictor of motor deficit reinforces the notion that infarct localization and fiber tract integrity play critical roles in functional impairment. Our method, which complements established lesion mapping and DTI techniques, could be automated in the future to assist clinicians and researchers in making accurate prognoses of motor impairment after stroke.

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Disclosures
None.

References


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