White Matter Integrity Is a Stronger Predictor of Motor Function Than BOLD Response in Patients With Stroke

Mingguo Qiu, Third Military Medical University
Warren G. Darling, University of Iowa
Robert J. Morecraft, University of South Dakota
Chun Chun Ni, Emory University
Justin Rajendra, Emory University
Andrew John Butler, Emory University

Journal Title: Neurorehabilitation and Neural Repair
Volume: Volume 25, Number 3
Publisher: SAGE Publications (UK and US) | 2011, Pages 275-284
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1177/1545968310389183
Permanent URL: http://pid.emory.edu/ark:/25593/f7fr9

Final published version: http://nnr.sagepub.com/content/25/3/275

Copyright information:
© The Author(s) 2011

Accessed November 7, 2019 9:38 AM EST
White Matter Integrity Is a Stronger Predictor of Motor Function Than BOLD Response in Patients With Stroke

Mingguo Qiu, MD1, Warren G. Darling, PhD2, Robert J. Morecraft, PhD3, Chun Chun Ni4, Justin Rajendra4,5, and Andrew J. Butler, PhD4,5
1Third Military Medical University, Chongqing, China
2The University of Iowa, Iowa City, IA, USA
3University of South Dakota, Vermillion, SD, USA
4Emory University, Atlanta, GA, USA
5Atlanta Veterans Administration Medical Center, Atlanta, GA, USA

Abstract

Objective—Neuroimaging techniques, such as diffusion tensor imaging (DTI) and blood oxygenation level–dependent (BOLD) functional magnetic resonance imaging (fMRI), provide insights into the functional reorganization of the cortical motor system after stroke. This study explores the relationship between upper extremity motor function, white matter integrity, and BOLD response of cortical motor areas.

Methods—Seventeen patients met study inclusion criteria; of these 12 completed DTI assessment of white matter integrity and 9 completed fMRI assessment of motor-related activation. Primary clinical outcome measures were the Wolf Motor Function Test (WMFT) and the upper limb portion of the Fugl-Meyer (FM) motor assessment. Structural integrity of the posterior limb of the internal capsule was assessed by examining the fractional anisotropy (FA) asymmetry in the PLIC. Laterality index of motor cortical areas was measured as the BOLD response in each patient during a finger pinch task. Linear regression analyses were performed to determine whether clinical outcome was associated with structural or functional MRI measures.

Results—There were strong relationships between clinical outcome measures and FA asymmetry (eg, FM score \( R^2 = .655, P = .001 \) and WMFT asymmetry score \( R^2 = .651, P < .002 \)) but relationships with fMRI measures were weaker.

Conclusion—Clinical motor function is more closely related to the white matter integrity of the internal capsule than to BOLD response of motor areas in patients 3 to 9 months after stroke. Thus, use of DTI to assess white matter integrity in the internal capsule may provide more useful information than fMRI to interpret motor deficits following supratentorial brain injury.

Keywords

magnetic resonance imaging; diffusion tensor imaging; fractional anisotropy; laterality index; motor functional outcome
Central mechanisms underlying upper limb motor recovery following stroke remain poorly understood. Clinical observations suggest that the initial levels of motor deficit and the course of recovery depend on corticofugal projection fiber integrity.\textsuperscript{1-5} Diffusion tensor imaging (DTI) can appraise the integrity of white matter tracts by recording the fractional anisotropy (FA), which is derived from the eigenvalues of the diffusion tensor, to localize changes in white matter integrity due to local tissue damage or Wallerian degeneration after stroke.\textsuperscript{6} Furthermore, comparing the FA value of a well-defined pathway on one side of the neuraxis with the homologous pathway on the opposite side for signs of asymmetry provides insight toward the integrity and general health of a potentially injured or structurally declining white matter pathway. For instance, studies examining stroke patients with small homogeneous subcortical infarcts have found that larger asymmetries in FA are associated with poor motor recovery of the limb subserved by the injured pathway.\textsuperscript{7} Indeed, recent observations suggest that the potential for motor function recovery declines with increasing corticospinal tract disruption in stroke patients,\textsuperscript{8,9} with no clinically meaningful gains appearing if DTI-derived FA asymmetry values exceed 0.25.\textsuperscript{10}

Functional magnetic resonance imaging (fMRI) has provided important insights into the reorganization of the motor cortices after stroke.\textsuperscript{11-13} The reported fMRI-derived patterns of motor system activation following stroke are variable and their interpretation regarding the recovery process is controversial.\textsuperscript{14-17} Some studies suggest that positive motor recovery correlates with activation of the ipsilesional lateral premotor and supplementary motor areas when performing movements of the affected limb following stroke, particularly when the primary motor cortex (M1) is involved in the damage.\textsuperscript{14,15} However, other reports suggest that bilateral patterns of cortical activity are associated with more favorable levels of motor recovery than ipsilesional activation alone, implicating a role for the contralesional motor areas in the recovery process.\textsuperscript{17,18} Patients with good upper limb recovery after stroke have a significantly lower laterality index (LI) during finger tapping\textsuperscript{19} (ie, higher contralesional activity) than able-bodied volunteers, indicating relatively greater activation and potential contribution of the unaffected primary sensorimotor cortex (SM1). Conversely, poorly recovered chronic stroke patients exhibit low LI values.\textsuperscript{20} However, these differences in LI values may subtend proportional differences in recovery stage since those in the Cramer et al\textsuperscript{19} study were 11 days to 15 months poststroke (combined acute and chronic phases or recovery), whereas Carey et al\textsuperscript{20} enrolled patients who were 10 months to 21 years poststroke (all in chronic phase of recovery).

Although these studies have provided insight into recovery mechanisms after stroke, the specific neural substrates mediating recovery of hand motor function are not completely understood. Recent data suggest that pyramidal tract integrity is a strong predictor for focusing activation within affected primary sensorimotor cortex.\textsuperscript{21} The question remains as to the relative importance of the contribution of the cortical motor areas and their corticofugal projection systems to upper limb recovery following stroke. Furthermore, the relationship between motor system activation and white matter integrity remains poorly understood.\textsuperscript{13} The aim of the present study was to test the hypothesis that FA asymmetry in the posterior limb of the internal capsule (PLIC) and LI of the cortical motor areas are associated with upper limb motor functional outcomes in hemiparetic patients following stroke. Indeed, it is well known that the corticofugal projection from the frontal motor cortices to cervical spinal cord levels reside within the PLIC\textsuperscript{1,22} and PLIC damage in humans results in upper extremity functional deficits.\textsuperscript{1,4,5} We hypothesized that the degree of affected upper limb motor function will be correlated with FA asymmetry of PLIC and laterality of activated voxels in primary motor cortex in hemiplegic patients with moderate motor impairment 3 to 9 months poststroke. Specifically, superior motor function with the
hemiplegic hand will be associated with lower FA asymmetry (ie, better integrity of PLIC) and higher LI (ie, higher ipsilesional activity).

**Materials and Methods**

**Participants**

This study was approved by the local institutional review board and examined the outcomes of 17 chronic stroke patients (3-9 months since the stroke) with residual upper limb hemiparesis. Prior to enrollment, written informed consent was obtained. Five patients withdrew or did not complete both DTI and fMRI studies primarily due to transportation difficulties, thus final data are reported on 12 volunteers (Table 1).

**Inclusion and Exclusion Criteria**

Patients with upper limb hemiparesis following ischemic or hemorrhagic stroke were recruited. Participants were excluded if they had a history of epilepsy, psychiatric disorders, fracture in the upper extremity within the past 2 years, diaphoresis, severe spasticity (greater than grade 4 on the modified Ashworth Spasticity Scale), tendonitis in the upper extremity within the past 3 months, migraine headaches within the past 6 months, or attention deficit hyper-activity disorder. Stimulant or relaxant medications (including antispasticity medication or pharmacological injections) were not permitted.

**Clinical Assessments**

Each patient underwent an extensive clinical evaluation by the same licensed occupational therapist. Clinical outcomes measures included a laboratory-based measure of upper extremity motor function (Wolf Motor Function Test [WMFT]) and an evaluation of motor function, balance, sensation, and joint function (Fugl-Meyer assessment [FM]).

The FM is a comprehensive assessment of sensation and motor function (reflexes, volitional movement assessment, flexor synergy, extensor synergy, movement combining synergies, movement out of synergy, normal reflex assessment, wrist movement, hand movement, and coordination and speed). The upper extremity portion includes 33 items, scored on a scale of 0 to 2, with a total possible score of 66.

The WMFT is a comprehensive assessment tool with established reliability and validity and has been used extensively to evaluate upper extremity motor function in constraint-induced movement therapy trials. The test contains 15 timed movement tasks ordered from simple to complex and 2 strength tasks: pushing a weighted sandbag against the outer wrist joint across a table by extending the elbow (ie, maximum weight score) and maximum handgrip strength (ie, grip strength) assessed as the average of 3 trials using a calibrated dynamometer (Jamar, Asimow Engineering Co, Santa Monica, California), with the elbow flexed to 90°.

Participants were asked to perform all tasks in the correct manner as quickly as possible. If a patient took more than 2 minutes to perform a task, the time was truncated at 121 seconds. A WMFT asymmetry score was calculated using the 15 timed tasks performed with each upper limb:

\[
\frac{\text{WMFT}_{\text{aff}} - \text{WMFT}_{\text{unaff}}}{\text{WMFT}_{\text{aff}} + \text{WMFT}_{\text{unaff}}}
\]

Values can range from –1.0 to +1.0, with positive values indicating greater impairment of affected hand and negative values indicating better performance of the impaired hand. Weight score asymmetry is calculated from the weight score (task 4 of WMFT), and grip
strength asymmetry is calculated from the maximum handgrip grip strength (task 14 of WMFT). Handgrip strength asymmetry was calculated as

\[
\frac{\text{Grip}_{\text{unaff}} - \text{Grip}_{\text{aff}}}{\text{Grip}_{\text{unaff}} + \text{Grip}_{\text{aff}}}
\]

Values range from \(-1.0\) to \(+1.0\), with negative values indicating greater handgrip force in the affected hand, and a value of \(0.0\) indicating symmetrical handgrip force. The calculations of the end-range values assume zero values can occur, which are possible for the affected hand but not for the unaffected hand.

**MRI Acquisition**

Twelve direction diffusion tensor images were acquired using a Siemens 3T Trio whole-body scanner (Siemens Medical Solutions, Malvern, Pennsylvania), using a standard quadrature headcoil. Functional images with blood oxygenation level–dependent (BOLD) contrast were acquired using a T2*-weighted single-shot gradient-recalled echoplanar imaging (EPI) sequence. Axial slices of 3 mm thickness were acquired to provide full-brain coverage (35 slices for each subject) with the following parameters: repetition time (TR) 2350 ms, echo time (TE) 28 ms, in-plane resolution 3.0 mm × 3.0 mm, in-plane matrix 64 × 64, field of view (FoV) 220 mm. High-resolution anatomic images were acquired using a 3-dimensional (3D) magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence (TR 2300 ms, TE 3.02 ms, inversion time 1100 ms, flip angle 8°, FoV 220 mm) consisting of 176 sagittal slices of 1 mm thickness (in-plane resolution 1 mm × 1 mm, in-plane matrix 256 × 256).

The participant lay supine in the scanner with both arms outstretched close to the body with the hand located at the flared magnet aperture and unimpeded by the magnet bore in moving their fingers and thumb. A mirror positioned above the person's eyes provided unobstructed visualization of images projected on a screen at the magnet's rear aperture. Head restraint straps and foam blocks were used to minimize head movement, and sound-attenuating headphones muffled scanner noise.

**fMRI Task**

All patients were introduced to the task outside the scanner and allowed to practice until comfortable with the procedure. The task consisted of tracking a visually displayed target sinusoidal force wave by pinching a force transducer (Mini-40 Model; ATI Industrial Automation, Garner, North Carolina) between the thumb and index finger of the more impaired hand. The amplitude of the force was set between 5% and 25% of the individual’s maximum pinch force, and both the target force and pinch force produced by the subject were displayed on a computer monitor. Patients were instructed to track the sinusoidal waveform as accurately as possible. Visual feedback of both the force and sinusoidal waveform ensured that each person performed the task at the same pace while inside the scanner.

A block design was used in which 30-second blocks of baseline and 30-second blocks of the task alternated, with nonstimulation (baseline) blocks beginning and ending each run; there were 3 stimulation blocks per run. Volunteers were asked to track the sinusoidal wave by exerting graded precision pinch forces by compressing the transducer that was embedded in acrylic. The tracking task was performed on separate runs using the affected and unaffected hand while inside the scanner.
A visual signal ("PINCH" or "REST") prompted the participants to start each task. The entire scanning session lasted about 1 hour. To ensure that no finger movements occurred during rest, the experimenter remained near the patient during each run, and the force trace was monitored continuously so that no pinch force was produced during a rest block. When performance was unacceptable from pinch forces produced during the rest period, the patient was informed and the scan was repeated, thus ensuring compliance on all task performances.

Data Analysis

Performance of the force tracking task was quantified by calculating 3 measures of relative tracking error between the target signal and the measured response: the relative root mean squared error (RRMSE—Equation 1, note that error is normalized to force), the time within range 2.5% above and below target force (TWR—higher values indicate better performance), and the coefficient of coordination ($K_c$—Equation 2). RRMSE values close to zero suggest more accurate grip force control resulting in greater hand functionality. $K_c$ is the correlation coefficient between the target signal and the force response and the correlation coefficients for the corresponding time rates. A $K_c$ value close to 1.0 suggests better coordination of grip force. Full details of the grip force data analysis methods are described in Kurillo et al.

\[
RRMSE = \sqrt{\frac{1}{T} \sum_{t=2}^{T} \frac{(F_t(t) - F_{\alpha}(t))^2}{\max(F_{\alpha})^2}}, \quad (1)
\]

\[
K_c = \rho(F_{\alpha}, F_{\gamma}) \cdot \rho \left( \frac{dF_{\alpha}}{dt}, \frac{dF_{\gamma}}{dt} \right), \quad (2)
\]

Image Processing

Postprocessing included eddy current correction and computation of diffusion tensor elements. White matter integrity was investigated on FA maps generated by the FDT toolbox of the (FMRIB) Software library (FSL) (http://www.fmrib.ox.ac.uk/fsl). Regions were drawn by hand in each hemisphere of each T1 brain image individually by a single investigator (MQ) and checked by another (AB). To estimate interrater reliability the 2 investigators independently drew regions of interest (ROIs) of the PLIC on the affected side and calculated the volume. The intraclass correlation coefficient for PLIC volume in the affected hemisphere was .993 with a 95% confidence interval of 0.971 to 0.998 ($P < .000$). For each participant, the PLIC was delineated bilaterally, from the level of the anterior commissure to the base of the corona radiata, with reference to FA RGB images and the MRI Atlas of Human White Matter. FA was computed for the affected and unaffected PLIC and used to calculate the FA asymmetry. FA asymmetry was defined as

\[
\frac{FA_{\text{unaff}} - FA_{\text{aff}}}{FA_{\text{unaff}} + FA_{\text{aff}}},
\]

This calculation yielded a value between -1.0 and +1.0, where positive values indicate reduced FA in the affected PLIC and a value of 0.0 indicates symmetrical FA in the PLIC. The ROI volumes of the affected and unaffected PLICs were equal. In participants with complete destruction of the affected PLIC (S1, S5, and S7), the volume of interest was estimated as a mirror image of the unaffected PLIC.
Functional image processing was performed using the Analysis of Functional NeuroImages software package. Prior to statistical analysis, the functional images were motion-corrected, intensity-normalized, spatially smoothed using a 3D Gaussian kernel (full-width at half-maximum = 3 mm) and aligned to the structural data. Motion parameters were stored and used as nuisance variables in the generalized linear model analysis. Every experimental run used a blocked design and task-related activity was modeled using a boxcar regressor convolved with a canonical hemodynamic response function. High-resolution T1-weighted structural MR images were spatially coregistered into Talairach space and used to generate ROIs for each individual subject. ROIs were created for primary motor area (M1), premotor cortex (PMC), and supplementary motor area (SMA) based on anatomical definitions of the functional areas. 

Activation clusters within each ROI were measured in bilateral motor regions using an uncorrected threshold of $P < .001$. Lateralization of cortical activity during affected hand pinch was calculated from the number of active voxels in each ROI bilaterally. The LI was calculated as

$$LI = \frac{I - C}{I + C}$$

where $I$ is the active voxel count for the specified region in the ipsilesional hemisphere and $C$ is the active voxel count for the region in the contralesional hemisphere while performing the task with the affected hand. LI values range between $-1.0$ and $+1.0$, where $+1.0$ indicates that all the cortical activity occurred within the ipsilesional ROI and $-1.0$ indicates that all the cortical activity occurred within the contralesional cortical motor areas.

To create group maps, a random-effects model was used. For each subject, the regression model provided a single estimate of the response to the task in each voxel. After stereotactic normalization to Talairach space, activation maps during affected hand pinch were flipped so that the lesioned hemisphere was on the same side for each subject for the purposes of averaging. One-sample $t$ tests and one-way analysis of variance (ANOVA) was performed on each voxel in standard space to compare the 4 within-subjects conditions. Planned contrasts on task type were undertaken (fixed effect), with each individual subject serving as the repeated measure (random effect).

### Statistical Analysis

Simple linear regression (SLR) models were used to examine the relationships between clinical outcome measures and FA asymmetry and LI of M1, PMC, and SMA. Separate linear regression analyses were performed to investigate the relationships between FA asymmetry (independent variable) with WMFT asymmetry, FM score, weight score asymmetry, and the log WMFT of the affected hand (dependent variables). Multiple linear regression (MLR) analyses were performed to identify the physiologic measure most predictive for clinical outcome. FM score or WMFT asymmetry was the dependent variable, whereas the FA asymmetry and LIs for each ROI were independent variables. The normality of each measure was checked using the Kolmogorov–Smirnov test. Because of the skewed distribution of the WMFT, a logarithmic transformation was performed on the 15 time-based WMFT measures. All results are quoted as 2-sided $P$ values. $P < .05$ was considered statistically significant. All statistical analyses were performed using SPSS for Windows v17.0 (SPSS Inc, Chicago, Illinois).

### Results

All patients were right-hand dominant prior to the stroke. Clinical and demographic information on the stroke patients are presented in Table 1 along with FA asymmetry values.
and clinical motor functional outcomes. Three patients exhibited neurologic deficits resulting from brain ischemia in the territory supplied by the middle cerebral artery (MCA), indicating possible involvement of cortical motor areas. T2-weighted MRI of Subject04 showed vague areas of restricted diffusion in the right hemisphere, suggesting watershed ischemia in the deep white matter, with some involvement of the temporal and parietal lobes. The T2-weighted image of Subject05 showed bright signal on white matter tracts, deep to the insular cortex as well as within the external capsule and in the white matter just adjacent to the occipital horn of the left lateral ventricle. Axial and sagittal T1-weighted image of Subject12 revealed increased signal along the precentral gyrus at the junction of the left frontal and the parietal lobes.

Behavioral Data During Scanning
Subjects performed the tracking task with reasonable accuracy. The mean RRMSE during force tracking with the affected hand while in the scanner was 4.44 (SD = 5.94); the mean TWR, indicating the time the participant stayed within the range of 5% above or below the target force, was 3.28 seconds (SD = 2.46); and the coordination of tracking represented by the mean $K_c$ was 0.204 (SD = 0.186). By comparison, age-matched healthy controls (data not presented) typically exhibit higher accuracy and coordination in the same paradigm (RRMSE = 0.46, SD = 0.09; TWR = 12.16 seconds, SD = 2.48; $K_c$ = 0.807, SD = 0.055).

fMRI Data
Because of excessive head motion artifact, fMRI data from only 9 subjects were analyzed (Subject01, Subject13, and Subject14 were excluded). The fMRI results showed that the principal ROIs activated during affected finger pinching varied among subjects (Figure 1). There were bilateral M1 and PMC activations in Subject2, Subject11, Subject12, Subject15, and Subject17 (eg, Subject12; Figure 2A.2); contralateral M1 and PMC activation in Subject04; bilateral SMA activation in Subject02, Subject04, Subject12, Subject15, and Subject16, but primarily ipsilesional activation of M1 and PMC in Subject05 and Subject07 (eg, Subject05; Figure 2B.2).

Negative LIs were usually observed in stroke patients during affected hand pinching, although there was considerable intersubject variability (ie, average M1 LI = –0.21, range = −0.84 to 0.72; PMC LI = −0.28, range = –0.86 to 0.65; SMA LI = −0.14, range = −0.63 to 0.56). The average activation map indicated greater activation of motor areas in the contralesional hemisphere during the affected hand pinching (Figure 3). LIs for M1 and PMC were weakly correlated with WMFT asymmetry but not with FM score.

Relationship Between Clinical Scores and Imaging Data
Linear regression—Clinical function test scores for the affected limb were closely correlated with white matter damage as indicated by FA asymmetry. SLR revealed strong linear relationships between FA asymmetry and upper limb FM score (Table 2A, Figure 4A), WMFT asymmetry (Table 2B), and log WMFT score of the affected hand (Figure 4B). There was a weaker linear relationship between FA asymmetry and grip strength asymmetry (Figure 4B, $R^2 = .414, P = .02$), indicating that lower FA asymmetry is associated with greater grip strength exerted by the affected hand. There was a weak but significant relationship between FA asymmetry and LI of MI and PMC (Table 2C). However, there were no significant relationships between FA asymmetry and the weight score asymmetry ($P > .05$) and no relationship between FA asymmetry and the amount of weight displaced by the affected or unaffected hand.

Adding the LI of M1, PMC, or SMA as predictors into stepwise MLR models resulted in only a slight improvement in the model fits (as indicated by $R^2$). Moreover, there were
indications of overfitting as adjusted $R^2$ values decreased by greater than 0.05 in all cases. Adding LI SMA to FA asymmetry did explain an additional 13% of the variance ($P = .016$), and the adjusted $R^2$ increased by 10%. FA asymmetry alone accounted for 59% of the variance for 9 subjects. Thus, we performed SLR to test whether LIs were predictive of FM score (Table 2A—no significant relationships) and WMFT asymmetry (Table 2B—only one significant relationship with LI M1; $P = .039$).

Discussion

We have shown that the degree of affected upper limb motor function is more closely related to the white matter integrity of the internal capsule than to BOLD response of cortical motor areas in patients 3 to 9 months after stroke. Specifically, we found FA to be strongly predictive of affected arm upper limb FM score and WMFT asymmetry. Lower FA asymmetries were associated with better motor function in patients with moderate upper extremity impairment after stroke. Furthermore, BOLD-derived LI measures for motor areas were not correlated with FM scores and were only weakly correlated with WMFT asymmetry. To our knowledge, this is the first demonstration of a stronger correlation of upper limb motor function with FA asymmetry than with BOLD-derived laterality index for frontal lobe motor areas, in the same patients 3 to 9 months after stroke.

Predicting potential behavioral gains in patients recovering from stroke using measures of structural integrity may help rehabilitationists design restorative therapeutic approaches to better achieve individual patient's functional recovery goals. FA asymmetry is a measure of the degree of damage in the affected PLIC versus the unaffected PLIC. Higher FA asymmetry values are associated with poorer integrity of the PLIC on the damaged side. Our results show strong linear relationships between FA asymmetry in PLIC and affected upper limb FM score, WMFT asymmetry, and log WMFT times of the affected upper limb. This is consistent with previous reports that clinical motor function (FM score) is strongly correlated with FA asymmetry in PLIC. However, Stinear et al also reported that FA asymmetry in PLIC had no power to predict clinical upper limb motor behavior in patients in whom MEPs could be elicited by stimulation over motor cortex.

Our motor behavioral results showed a weak linear relationship between FA asymmetry and grip strength asymmetry, with lower FA asymmetry associated with greater grip force of the affected hand in patients after stroke. However, there were no significant relationships between FA asymmetry and asymmetry of weights displaced by the affected and unaffected hand. These findings suggest that activation of distal muscles for handgrip force production depends strongly on intact transmission from cortical motor areas to spinal motor neurons but activation of proximal musculature to forcefully extend the elbow is less dependent on an intact corticospinal tract.

Cortical activity tended to be weakly lateralized toward the ipsilesional hemisphere in patients with intact ipsilesional cortical motor areas during affected hand use, but more likely lateralized toward the contralesional hemisphere in patients with motor cortex damage. The current study showed weak but significant relationships of the LI of the motor cortical areas (M1, PMC) with the FA asymmetry and WMFT asymmetry (LI M1), suggesting that the LI is a weak predictor of existing upper limb motor function in patients 3 to 9 months poststroke. Stinear et al also found a relationship between the lateralization of cortical activity in area BA4p (M1) during affected hand use and clinical score in patients in whom MEPs could not be elicited by TMS over cortical motor areas. Specifically, higher FM scores were predicted by stronger lateralization of cortical activity toward the ipsilesional M1. It must be noted that the patients enrolled in the current study were 3 to 9 months poststroke, whereas the study by Stinear et al consisted of patients 6 to 144 months.
poststroke. Functional motor outcomes generally improve over time poststroke, and it is likely that FA asymmetry improves and laterality of activation changes with time since stroke.

We manually drew ROIs (as opposed to using automated detection methods) because we were working with a small sample and could confirm the PLIC using the intact PLIC. Future development in techniques to automatically detect white matter tracts such as the PLIC may improve the overall validity of the method and improve the accuracy of estimation as well as permitting application in large populations of stroke patients. The rather small sample size, missing data (n = 9 for fMRI), and time since stroke (3-9 months) limits the use of complex regression modeling and generalizability to the entire stroke population. However, the inclusion of patients with both cortical and subcortical stroke allows us to draw broad conclusions concerning the hemiparetic stroke population. We have confirmed previous reports that FA asymmetry is strongly correlated with upper limb FM score, a measure of paresis, in post–acute stroke patients. Moreover, we have extended these findings to show that FA asymmetry is also strongly correlated with WMFT, a comprehensive time-based assessment tool of upper limb movement control, and that the fMRI measure of LI is only weakly correlated with these measures of motor impairment. Therefore, these preliminary data serve as a basis for further investigations on the functional recovery mechanisms in the human brain after stroke and a larger study will be needed to confirm these initial observations.

**Acknowledgments**

We gratefully thank the therapists, coordinators, and research assistants for invaluable work during data collection.

**Funding**

The author(s) disclosed receipt of the following financial support for the research and/or authorship of this article: This study was sponsored by the National Institutes of Health (Grant Number NCCAM R21 AT-002138-03 to AJB) and NSFC (30670595).

**References**


Figure 1.
Activated voxel counts (in numbers of voxels) in the principal ROIs for affected finger pinching varied among subjects. Abbreviations: M1, primary motor cortex; PMC, premotor cortex; SMA, supplementary motor area.
Figure 2.

(A.1) Subject12 (left middle cerebral artery [MCA]) diffusion tensor imaging (DTI) showed slightly decreased fractional anisotropy (FA) in L-PLIC (posterior limb of the internal capsule; indicated by white circle) compared with R-PLIC. FA asymmetry was low (0.09), indicating integrity of damaged L-PLIC was only slightly worse than that of the R-PLIC because R-PLIC FA was in the normal range. R, right; L, left. Combined FA and directional map. Color hue indicates direction as follows: red, medial–lateral; green, anterior–posterior; blue, superior–inferior. This convention applies to all the directional maps. Brightness is proportional to FA. (A.2) Subject12 functional magnetic resonance imaging (fMRI) showed bilateral activation of M1, supplementary motor area (SMA), premotor cortex (PMC), and BA7 during affected hand (right) pinch. Clinical motor functions tests showed moderate impairment of the right hand in this subject (Fugl-Meyer motor assessment [FM] = 34, Wolf Motor Function Test [WMFT] asymmetry = 0.52, log affected WMFT = 0.86). The statistical threshold was set at a threshold of $P < .05$ corrected. The color map shows the $t$ scores. Pinching-specific activity is shown as higher $t$ scores, or reddish-orange.

(B.1) Subject5 (left MCA) DTI showed low FA in L-PLIC (indicated by white circle) due to obvious disruption of white matter in this region. The high FA asymmetry (0.32) indicates less integrity of L-PLIC compared with the R-PLIC, which was associated with low motor scores for the right hand (FM = 28, WMFT asymmetry = 0.82, log WMFT = 1.99). R, right; L, left. (B.2) Subject5 fMRI showed ipsilesional activation of M1 and PMC during affected hand (right) pinch. The statistical threshold was set at a threshold of $P < .05$ corrected. The color map shows the $t$ scores. Pinching-specific activity is shown as higher $t$ scores, or reddish-orange.
Figure 3.
Average cortex activation map of cortical motor areas for all subjects, showing more activation in contralesional hemisphere (unaffected side, ipsilateral to the affected hand) during affected hand pinch. Group analysis results, with threshold set at $P < .05$ ($n = 9$, corrected for multiple comparisons) are shown. The color map shows the $t$ scores. Pinching-specific activity is shown as higher $t$ score, or reddish-orange. The central sulcus is depicted as a green line. Abbreviations: SMA, supplementary motor area; PMC, premotor cortex; PPC, posterior parietal cortex; M1, primary motor cortex; A, anterior; P, posterior.
Figure 4.
(A) A significant negative linear relationship between FA asymmetry and FM score ($R^2 = 0.655$, $P < .002$). Higher FA asymmetry is associated with lower FM scores, whereas lower FA asymmetry is associated with greater FM scores. (B) A significant positive linear relationship between FA asymmetry with WMFT asymmetry ($R^2 = 0.651$, $P = .002$), log affected WMFT ($R^2 = 0.636$, $P = .002$), and grip asymmetry ($R^2 = 0.414$, $P = .02$). Lower FA asymmetry is associated with lower WMFT time asymmetry, superior log WMFT performance times, and greater grip force of affected hand. Abbreviations: FA, fractional anisotropy; FM, Fugl-Meyer motor assessment; WMFT, Wolf Motor Function Test
### Table 1

Patient Demographic Information

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Sex</th>
<th>Age, y</th>
<th>Hemi</th>
<th>Time Point</th>
<th>Site of Lesion</th>
<th>FA ASY</th>
<th>FM</th>
<th>LOG WMFT</th>
<th>WMFT ASY</th>
<th>GRIP ASY</th>
<th>LI M1</th>
<th>LI PMC</th>
<th>LI SMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject01</td>
<td>F</td>
<td>58</td>
<td>R</td>
<td>5</td>
<td>L thalamus</td>
<td>0.34</td>
<td>27</td>
<td>1.26</td>
<td>0.78</td>
<td>0.89</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Subject02</td>
<td>M</td>
<td>57</td>
<td>R</td>
<td>3</td>
<td>L basal ganglia</td>
<td>0.13</td>
<td>50</td>
<td>0.38</td>
<td>0.12</td>
<td>0.37</td>
<td>-0.47</td>
<td>-0.57</td>
<td>-0.16</td>
</tr>
<tr>
<td>Subject04</td>
<td>F</td>
<td>76</td>
<td>L</td>
<td>9</td>
<td>R MCA</td>
<td>0.19</td>
<td>32</td>
<td>1.64</td>
<td>0.67</td>
<td>0.61</td>
<td>-0.84</td>
<td>-0.86</td>
<td>-0.22</td>
</tr>
<tr>
<td>Subject05</td>
<td>F</td>
<td>67</td>
<td>R</td>
<td>6</td>
<td>L MCA</td>
<td>0.32</td>
<td>28</td>
<td>1.99</td>
<td>0.82</td>
<td>0.85</td>
<td>0.68</td>
<td>0.65</td>
<td>-0.19</td>
</tr>
<tr>
<td>Subject07</td>
<td>M</td>
<td>56</td>
<td>L</td>
<td>9</td>
<td>R basal ganglia</td>
<td>0.35</td>
<td>29</td>
<td>1.61</td>
<td>0.89</td>
<td>0.63</td>
<td>0.72</td>
<td>0.61</td>
<td>0.06</td>
</tr>
<tr>
<td>Subject11</td>
<td>M</td>
<td>52</td>
<td>L</td>
<td>5</td>
<td>R pallidum</td>
<td>0.27</td>
<td>30</td>
<td>0.70</td>
<td>0.50</td>
<td>0.69</td>
<td>-0.46</td>
<td>-0.40</td>
<td>0.56</td>
</tr>
<tr>
<td>Subject12</td>
<td>F</td>
<td>70</td>
<td>R</td>
<td>8</td>
<td>L MCA</td>
<td>0.09</td>
<td>34</td>
<td>0.86</td>
<td>0.52</td>
<td>0.51</td>
<td>-0.48</td>
<td>-0.36</td>
<td>-0.18</td>
</tr>
<tr>
<td>Subject13</td>
<td>M</td>
<td>64</td>
<td>L</td>
<td>7</td>
<td>R thalamus</td>
<td>0.28</td>
<td>30</td>
<td>1.61</td>
<td>0.89</td>
<td>0.49</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Subject14</td>
<td>M</td>
<td>59</td>
<td>R</td>
<td>9</td>
<td>L lower pons</td>
<td>0.02</td>
<td>40</td>
<td>0.33</td>
<td>0.42</td>
<td>0.67</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Subject15</td>
<td>M</td>
<td>43</td>
<td>L</td>
<td>5</td>
<td>R pontine</td>
<td>0.01</td>
<td>46</td>
<td>0.30</td>
<td>0.27</td>
<td>0.48</td>
<td>-0.39</td>
<td>-0.48</td>
<td>-0.23</td>
</tr>
<tr>
<td>Subject16</td>
<td>M</td>
<td>55</td>
<td>R</td>
<td>7</td>
<td>L IC</td>
<td>0.02</td>
<td>42</td>
<td>0.53</td>
<td>0.22</td>
<td>0.16</td>
<td>-0.70</td>
<td>-0.59</td>
<td>-0.25</td>
</tr>
<tr>
<td>Subject17</td>
<td>M</td>
<td>62</td>
<td>R</td>
<td>7</td>
<td>L thalamus</td>
<td>0.12</td>
<td>36</td>
<td>0.87</td>
<td>0.61</td>
<td>0.56</td>
<td>0.09</td>
<td>-0.54</td>
<td>-0.63</td>
</tr>
</tbody>
</table>

Abbreviations: Hemi, side of hemiparesis; time point (months), the time point of scanning and clinical assessment for each patient since stroke; L, left; R, right; MCA, middle cerebral artery; IC, internal capsule; FM, Fugl-Meyer upper limb score (maximum score 66); FA ASY, fractional anisotropy asymmetry calculated at the level of the posterior limb of internal capsule; WMFT ASY, Wolf Motor Function Test Time asymmetry; LOG WMFT, log WMFT time of affected hand in seconds; GRIP ASY, grip force asymmetry; LI M1, laterality index of M1 during the affected hand pinching task; LI PMC, laterality index of the premotor cortex during the affected hand pinching task; LI SMA, laterality index of the SMA during the affected hand pinching.

*An asterisk indicates omitted data due to excessive head motion artifact. SUBJECT01 and SUBJECT17 had hemorrhagic stroke, all remaining subjects were diagnosed with ischemic stroke.*
Table 2

Linear Regression of Upper Limb FM Score, WMFT Asymmetry, and FA Asymmetry on FA Asymmetry, LI M1, LI PMC, and LI SMA

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Independent Variables</th>
<th>N</th>
<th>Coefficient of Determination ($R^2$)</th>
<th>Adjusted $R^2$</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FM score</td>
<td>FA asymmetry</td>
<td>12</td>
<td>0.655</td>
<td>0.620</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>FA asymmetry</td>
<td>9</td>
<td>0.587</td>
<td>0.528</td>
<td>.016</td>
</tr>
<tr>
<td></td>
<td>FA asymmetry + LI M1</td>
<td>9</td>
<td>0.589</td>
<td>0.452</td>
<td>.069</td>
</tr>
<tr>
<td></td>
<td>FA asymmetry + LI PMC</td>
<td>9</td>
<td>0.588</td>
<td>0.450</td>
<td>.070</td>
</tr>
<tr>
<td></td>
<td>FA asymmetry + LI SMA</td>
<td>9</td>
<td>0.591</td>
<td>0.454</td>
<td>.069</td>
</tr>
<tr>
<td></td>
<td>LI M1</td>
<td>9</td>
<td>0.233</td>
<td>0.123</td>
<td>.188</td>
</tr>
<tr>
<td></td>
<td>LI PMC</td>
<td>9</td>
<td>0.294</td>
<td>0.193</td>
<td>.132</td>
</tr>
<tr>
<td></td>
<td>LI SMA</td>
<td>9</td>
<td>0.110</td>
<td>-0.017</td>
<td>.383</td>
</tr>
<tr>
<td>WMFT asymmetry</td>
<td>FA asymmetry</td>
<td>12</td>
<td>0.651</td>
<td>0.616</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td>FA asymmetry</td>
<td>9</td>
<td>0.618</td>
<td>0.564</td>
<td>.012</td>
</tr>
<tr>
<td></td>
<td>FA asymmetry + LI M1</td>
<td>9</td>
<td>0.667</td>
<td>0.556</td>
<td>.037</td>
</tr>
<tr>
<td></td>
<td>FA asymmetry + LI PMC</td>
<td>9</td>
<td>0.637</td>
<td>0.516</td>
<td>.048</td>
</tr>
<tr>
<td></td>
<td>FA asymmetry + LI SMA</td>
<td>9</td>
<td>0.748</td>
<td>0.664</td>
<td>.016</td>
</tr>
<tr>
<td></td>
<td>LI M1</td>
<td>9</td>
<td>0.478</td>
<td>0.404</td>
<td>.039</td>
</tr>
<tr>
<td></td>
<td>LI PMC</td>
<td>9</td>
<td>0.439</td>
<td>0.359</td>
<td>.052</td>
</tr>
<tr>
<td></td>
<td>LI SMA</td>
<td>9</td>
<td>0.006</td>
<td>-0.136</td>
<td>.842</td>
</tr>
<tr>
<td>FA asymmetry</td>
<td>LI M1</td>
<td>9</td>
<td>0.452</td>
<td>0.373</td>
<td>.047</td>
</tr>
<tr>
<td></td>
<td>LI PMC</td>
<td>9</td>
<td>0.522</td>
<td>0.453</td>
<td>.028</td>
</tr>
<tr>
<td></td>
<td>LI SMA</td>
<td>9</td>
<td>0.247</td>
<td>0.139</td>
<td>.174</td>
</tr>
</tbody>
</table>

Abbreviations: FM, Fugl-Meyer motor assessment; WMFT, Wolf Motor Function Test; FA, fractional anisotropy; LI, laterality index; M1, primary motor cortex; PMC, premotor cortex; SMA, supplementary motor area; N, number of subjects in model.