


# Cortical Disconnection of the Ipsilesional Primary Motor Cortex is Associated With Gait Speed and Upper Extremity Motor Impairment in Chronic Left Hemispheric Stroke

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**Abstract:** Advances in neuroimaging have enabled the mapping of white matter connections across the entire brain, allowing for a more thorough examination of the extent of white matter disconnection after stroke. To assess how cortical disconnection contributes to motor impairments, we examined the relationship between structural brain connectivity and upper and lower extremity motor function in individuals with chronic stroke. Forty-three participants [mean age: 59.7 ( $\pm$ 11.2) years; time poststroke: 64.4 ( $\pm$ 58.8) months] underwent clinical motor assessments and MRI scanning. Nonparametric correlation analyses were performed to examine the relationship between structural connectivity amid a subsection of the motor network and upper/lower extremity motor function. Standard multiple linear regression analyses were performed to examine the relationship between cortical necrosis and disconnection of three main cortical areas of motor control [primary motor cortex (M1), premotor cortex (PMC), and supplementary motor area (SMA)] and motor function. Anatomical connectivity between ipsilesional M1/SMA and the (1) cerebral peduncle, (2) thalamus, and (3) red nucleus were

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significantly correlated with upper and lower extremity motor performance ( $P \leq 0.003$ ). M1–M1 inter-hemispheric connectivity was also significantly correlated with gross manual dexterity of the affected upper extremity ( $P = 0.001$ ). Regression models with M1 lesion load and M1 disconnection (adjusted for time poststroke) explained a significant amount of variance in upper extremity motor performance ( $R^2 = 0.36$ – $0.46$ ) and gait speed ( $R^2 = 0.46$ ), with M1 disconnection an independent predictor of motor performance. Cortical disconnection, especially of ipsilesional M1, could significantly contribute to variability seen in locomotor and upper extremity motor function and recovery in chronic stroke. *Hum Brain Mapp* 39:120–132, 2018. © 2017 Wiley Periodicals, Inc.

**Key words:** stroke; motor; diffusion tensor imaging; connectome; upper extremity; gait

## INTRODUCTION

To improve prognosis of motor recovery following stroke and enhance targeting of therapeutic interventions, an increased understanding of the damage caused to both local and global neural networks poststroke is needed. Diffusion tensor imaging (DTI) enables the examination of the microstructural integrity and orientation of white matter in the brain *in vivo* by estimating the magnitude and directionality of water diffusion [Fung et al., 2011; Sundgren et al., 2004]. DTI can be used to visualize ischemic regions within motor tracts or to quantify remaining white matter integrity, thus offering important information for predicting motor impairment and recovery after stroke [Stinear et al., 2007]. Several studies using DTI techniques have demonstrated a correlation between upper extremity motor dysfunction and decreased integrity of the corticospinal tract (CST)—the major neural pathway for discrete voluntary movements, especially of the hands—in both acute [Feng et al., 2015; Jang et al., 2005a; Radlinska et al., 2010; Takenobu et al., 2014] and chronic [Chen and Schlaug, 2013; Lindenberg et al., 2010; Sterr et al., 2014; Zhu et al., 2010] stroke. However, more research needs to be performed to enhance our understanding of the relationship between the integrity of multiple motor tracts, not just the CST, and motor function in chronic stroke.

Motor recovery of the affected upper extremity has been highly studied, whereas less is known about motor recovery mechanisms involved with lower extremity and locomotor function after stroke. Human locomotion is a complex movement that requires a dynamic interplay between spinal central pattern generators and supraspinal locomotor centers. The extended brain network involved in locomotor control includes cortical (e.g., primary sensorimotor area, supplementary motor area, premotor cortex, anterior cingulate cortex, cingulate motor area, occipital visual areas), subcortical (e.g., basal ganglia, thalamus, midbrain tegmentum, cerebellum), and brainstem regions, highlighting the complex neuronal circuitry involved in locomotion [Jaeger et al., 2014; la Fougere et al., 2010; Takakusaki, 2017]. Some stroke survivors display locomotor ability despite complete lateral CST injury in the affected hemisphere [Ahn et al., 2006]. Indeed, while the

CST is necessary for fine movements of the hands [Davidoff, 1990; Stinear et al., 2007], locomotion and motor function of the legs is less dependent on the CST [Dawes et al., 2008; Jang et al., 2005b]. Other descending neural pathways such as the reticulospinal, rubrospinal, and vestibulospinal tracts also contribute to locomotor function.

Upper and lower extremity motor dysfunction and recovery poststroke can be variable among individuals with similar lesion size and location, as the full extent of white-matter injury may not be revealed by traditional structural MRI scans [Fridriksson et al., 2007; Thomalla et al., 2005]. Wallerian degeneration (WD), characterized by anterograde degeneration of the distal portion of axons after injury to the cell body and/or proximal nerve, commonly occurs after ischemic stroke. WD has been detected as early as within the first 2 weeks poststroke using DTI [Thomalla et al., 2004] and can eventually lead to fibrosis and atrophy of the fiber tracts. Several studies have examined WD of the CST in individuals with stroke and found that reduced fractional anisotropy (FA) and/or reduced signal (interpreted as a reflection of WD) along the CST were associated with increased motor impairment [Liang et al., 2008; Thomalla et al., 2004; Watanabe et al., 2001]. Wallerian degeneration may occur in other brain regions affected by the infarct, further impacting motor recovery after stroke.

In addition to altered white-matter integrity in the lesioned area, brain regions and motor tracts beyond the infarction site may also exhibit structural abnormalities. These nonlesioned areas can be indirectly affected by the loss of connections resulting from a stroke and can become dysfunctional [Cramer and Nudo, 2010], contributing to behavioral deficits. Advances in neuroimaging have enabled the mapping of white-matter connections across the entire brain (the brain connectome) [Bonilha et al., 2014a, 2014b] using diffusion MRI, allowing for a more thorough examination of the extent of white-matter disconnection after stroke.

To date, the connectivity-based approach developed by Bonilha et al. [2014b] has been used to examine overall structural disconnection in the lesioned hemisphere (vs the nonlesioned hemisphere) after ischemic stroke [Bonilha et al., 2014a] and to examine the relationship between

**TABLE I. Summary of demographic, behavioral, and imaging data**

Age, years	59.7 (11.2); 31–80
Female <sup>a</sup>	16 (37.2)
Time since stroke, months	64.4 (58.5); 10–284
M1 lesion load, % <sup>b</sup>	21.3 (23.3); 0–91.0
PMC lesion load, % <sup>b</sup>	15.3 (25.5); 0–98.4
SMA lesion load, % <sup>b</sup>	6.4 (14.8); 0–59.4
Box & Block Test <sub>Aff</sub>	30.6 (21.7); 0–64
Grip <sub>Aff</sub> , kg	23.46 (15.72); 0–56.67
Arm Motricity Index <sub>Aff</sub>	74.5 (29.2); 0–99
Leg Motricity Index <sub>Aff</sub>	76.2 (22.1); 28–99
Gait Speed, m/s	0.94 (0.31); 0.21–1.46

Values are presented as mean (SD); range.

<sup>a</sup>*n* (percentage).

<sup>b</sup>Ipsilesional hemisphere.

Abbreviations: yr, years; mo, months; M1, primary motor cortex; PMC, premotor cortex; SMA, supplementary motor area; <sub>Aff</sub>, affected extremity; kg, kilograms; m/s, meters per second.

language impairments and structural brain connectivity in individuals with chronic aphasia [Bonilha et al., 2014c]. Results showed intrahemispheric disconnection extending beyond the necrotic area in individuals with chronic stroke, highlighting that extent of reduced structural connectivity cannot be surmised based solely on necrotic tissue size or location [Bonilha et al., 2014a, 2014c]. Additionally, structural disconnection of Brodmann area 45 was independently associated with naming performance after controlling for necrotic tissue volume [Bonilha et al., 2014c]. This connectivity-based approach, however, has not yet been used to examine the relationship between *motor* impairments and impaired cortical connectivity in chronic stroke. By examining neural connectivity using the brain connectome, the extent of cortical disconnection beyond the lesion site may be more fully revealed, expanding our understanding of motor impairment–brain structure relationships after stroke.

The objective of this study was to examine the relationship between upper and lower extremity motor impairment and structural brain connectivity in individuals with chronic stroke using the connectome-mapping techniques recently developed by Bonilha et al. [2014c]. Selective disruption of corticofugal fibers from multiple cortical motor regions can impact functional reorganization and motor recovery following stroke [Newton et al., 2006]. Thus, we focused on cortico-cortico and interhemispheric connectivity between three main cortical areas of motor control [primary motor cortex (M1), premotor cortex (PMC), and supplementary motor area (SMA)]. Additionally, we examined cortico-subcortical connectivity between these three cortical areas and several important subcortical regions in motor control (e.g., cerebral peduncle, red nucleus, thalamus). Fibers from the CST originate from multiple cortical regions (mainly primary motor and premotor cortices) and

course through the cerebral peduncle of the midbrain [Davidoff, 1990]. Neuroplastic changes in the red nucleus of the affected hemisphere have also been found post-stroke [Dong et al., 2007; Yeo and Jang, 2010], which may indicate a compensatory role of this brain region in motor recovery. The thalamus is involved in the integration of sensory information and is closely linked to the cerebral cortex; it is a key relay station for sensory-motor neuronal loops involving the cerebellum and basal nuclei, which are important for voluntary movement [Afifi and Bergman, 1998]. We hypothesized that (1) structural connectivity between cortical/subcortical motor-relevant brain regions would be positively associated with upper and lower extremity motor performance, and (2) poorer performance on gait and upper and lower extremity motor measures would be associated with residual cortical necrosis and/or overall disconnection, or loss of connectivity, of ipsilesional cortical motor areas (i.e., M1, PMC, and SMA).

## METHODS

### Participants

Behavioral assessments were performed on 52 participants. Nine participants were excluded from analyses due to incomplete MRI data. A summary of demographic, clinical, and imaging data for the remaining 43 participants is presented in Table I. The mean age of participants (16 female, 27 male) was 59.7 years (range 31–80 years), with a mean time poststroke of 64.4 months (range 10–284 months). All participants gave written informed consent to participate in this study that was approved by the Institutional Review Board at the University of South Carolina. As this study was part of a larger study investigating a range of impairments—including speech and language processing—in individuals with chronic stroke, inclusion criteria consisted of (1) monolingual speaker of English (prestroke), (2) occurrence of a single left hemispheric ischemic or hemorrhagic stroke at least 6 months prior to study inclusion, (3) able to follow simple instructions, and (4) able to walk 8 m with or without an assistive device and no physical assistance. Exclusion criteria included contraindication for MRI (claustrophobia, pregnancy, metal implants, etc.), clinically reported history of dementia, alcohol abuse, psychiatric disorder, other neurological conditions (e.g., traumatic brain injury, Parkinson’s Disease), or extensive visual acuity or visual-spatial problems.

### Motor Assessment

All participants underwent a comprehensive behavioral assessment of upper and lower extremity motor function, both on the affected (Aff) and unaffected sides, and gait performed by a licensed physical therapist. The Box and Block Test (BBT) [Chen et al., 2009; Desrosiers et al., 1994] was used to assess gross manual dexterity of the hand,

and a handheld dynamometer was used to assess grip strength (average of 3 trials) [Bohannon, 1986; Riddle et al., 1989]. The Motricity Index (MI) [Collin and Wade, 1990; Demeurisse et al., 1980] was used to examine motor function/strength of the upper and lower extremities. Self-selected walking speed was determined using the GAITRite [CIR Systems Inc., USA] electronic walkway (average of 3 trials) [Lewek and Randall, 2011; Stokic et al., 2009]. Assistive devices and/or orthotics commonly used with community ambulation were allowed for the walking speed assessment.

### MRI Acquisition

All participants underwent scanning using a 3T Siemens Trio system with a 12-element head coil at the McCausland Center for Brain Imaging (Columbia, SC) within 2 days of behavioral testing. High-resolution 3D T<sub>1</sub>-MRI scans [repetition time (TR) = 2,250 ms, inversion time (TI) 925 ms, echo time (TE) = 4.15 ms, flip angle = 9°, field of view (FOV) = 256 mm and voxel size = 1.0 × 1.0 × 1.0 mm] and 3D T<sub>2</sub>-MRI scans [TR = 3,200 ms, TE = 212 ms, variable flip angle, FOV = 256 mm, and voxel size = 1.0 × 1.0 × 1.0 mm] were acquired for determination of lesion size and location. DTI was performed with a single shot gradient echo planar imaging (EPI) sequence using the following parameters: TR = 4,987 ms, TE = 79.2 ms, flip angle ( $\alpha$ ) = 90°, FOV = 207 mm, voxel size = 2.3 × 2.3 × 2.3 mm, slice thickness = 2.3 mm, 36 volumes with noncollinear diffusion directions at a  $b$  value of 1,000 s/mm<sup>2</sup> and 5 volumes with a  $b$  value of 0, number of slices = 50. This diffusion sequence was acquired twice, with the second series reversing the phase-encoding direction.

### Image Preprocessing

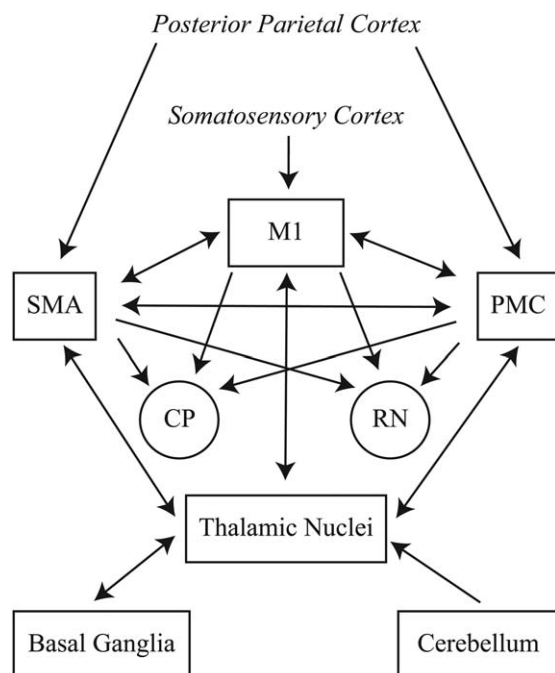
Stroke lesions were manually outlined by a neurologist (Bonilha) on the T<sub>2</sub> image, which was then coregistered to the T<sub>1</sub> image. T<sub>1</sub>-weighted images were normalized into standard MNI space utilizing enantiomorphic unified segmentation-normalization routines as part of the software Statistical Parametric Mapping (SPM) 12 [Rorden et al., 2012]. This step also provided probabilistic gray- and white-matter maps in standard space [Ashburner and Friston, 2005]. The inverse transformation was then applied to a John Hopkins University (JHU) template and to the gray and white matter probabilistic maps to transform these maps/template onto native T<sub>1</sub> space. The probabilistic gray-matter map (now in T<sub>1</sub> space) was then segmented into a map of cortical/subcortical JHU regions of interest (ROIs), excluding lesioned voxels. The percentage of necrotic lesion damage to each motor cortical ROI was calculated by overlaying the manually outlined lesion onto the segmented cortical map in native T<sub>1</sub> space. These steps were performed through in-house scripts written in

MATLAB and available online ([https://github.com/neuro-labusc/nii\\_preprocess](https://github.com/neuro-labusc/nii_preprocess)) [Bonilha et al., 2014c].

The diffusion images were undistorted using FSL's TOPUP and Eddy tools [Andersson et al., 2003; Andersson and Sotiropoulos, 2016] with excess scalp removed using the FSL BET tool. FSL's dtifit tool was used to compute a fractional anisotropy (FA) map. To improve registration between T<sub>1</sub> and DTI spaces, the scalp-stripped (based on segmentation estimates) T<sub>1</sub> image was nonlinearly normalized (using SPM12's "old normalization" function) to match the undistorted FA image. The same transformation matrix was applied to the map of segmented cortical ROIs and the probabilistic white-matter map (which were in T<sub>1</sub> space) to transform these maps into DTI space.

Probabilistic DTI tractography was performed using FDT's bedpostx and probtrackx [Behrens et al., 2007; Hernandez et al., 2013; Hernandez-Fernandez et al., 2016] (with 5,000 streamline samples) to determine the number of white matter streamlines connecting each JHU ROI. For each possible pair of cortical/subcortical ROIs  $i$  and  $j$ , the number of iterative streamlines connecting the pair was computed for the creation of a connectivity matrix  $A$ , where each  $A_{ij}$  entry represented the weighted link between ROIs (arriving at  $j$  when  $i$  was seeded and vice versa, with the streamlines being adjusted by distance travelled and the total number of streamlines divided by the sum of the volumes of the ROIs  $i$  and  $j$ ) [Bonilha et al., 2014c; Gleichgerrcht et al., 2017]. For our analyses, M1 corresponded to the JHU precentral gyrus ROI, PMC corresponded to the JHU middle frontal gyrus-posterior segment ROI, and SMA corresponded to the JHU superior frontal gyrus-posterior segment ROI. The weighted sum of all connections to these three cortical areas was computed to assess overall connectivity of these cortical regions (M1, PMC, and SMA). Loss of connectivity implies the weighted strength of connectivity of a specific node (brain region), irrespective of which other node each weighted link is connected to. The percentage of fibers compared to the homologous region in the unaffected hemisphere was calculated to assess fiber reduction in these motor areas in the affected hemisphere, and to normalize the final connectivity measure based on each subject's contralateral hemisphere.

To demonstrate the anatomical location of the most important white-matter connections, we reconstructed subcortical pathways in 59 healthy controls (45 female, mean age 54.7 ± 8.3 years) with a similar age distribution as the stroke survivors included in this study (DTI parameters: twice-refocused echo-planar imaging  $b = 0, 1,000, 30$  diffusion encoding directions, TR = 8,500 ms, TE = 98 ms, FOV = 222 × 222 mm<sup>2</sup>, matrix = 74 × 74, 3 mm slice thickness, and 40 axial slices; DSI studio: fiber reconstruction using Q-Space Diffeomorphic Reconstruction [Yeh and Tseng, 2011], 1.25 diffusion length sampling ratio, 2 mm output resolution). The white-matter tract was transferred to standard space using 7, 9, and 7 transformation



**Figure 1.**

Subsection of the motor network. SMA, supplementary motor area; M1, primary motor cortex; PMC, premotor cortex; CP, cerebral peduncle; RN, red nucleus.

parameters (Fourier basis) and then combined across subjects. The resulting bundle was interpolated into 100 segments and the center of mass for each segment was calculated. The streamlines whose segment-wise deviation from the center of mass was  $>0.5$  standard deviations were removed.

### Statistical Analyses

Two-tailed paired  $t$  tests (or Wilcoxon signed rank tests if data were not normally distributed) were used to evaluate differences in motor scores between the affected and unaffected extremities, and hemispheric differences in anatomical connectivity among a subsection of the motor network (Fig. 1). Spearman's correlation analyses were performed to examine the relationship between structural connectivity amid these *a priori* ROIs (including interhemispheric connectivity between homologous regions) and motor function. Correlations were interpreted as poor ( $<0.25$ ), fair ( $0.25-0.5$ ), moderate ( $0.5-0.75$ ), and strong ( $>0.75$ ) [Portney and Watkins, 2000]. Significance level was set at  $P < 0.05$ , corrected for multiple comparisons (corrected  $P \leq 0.003$ ).

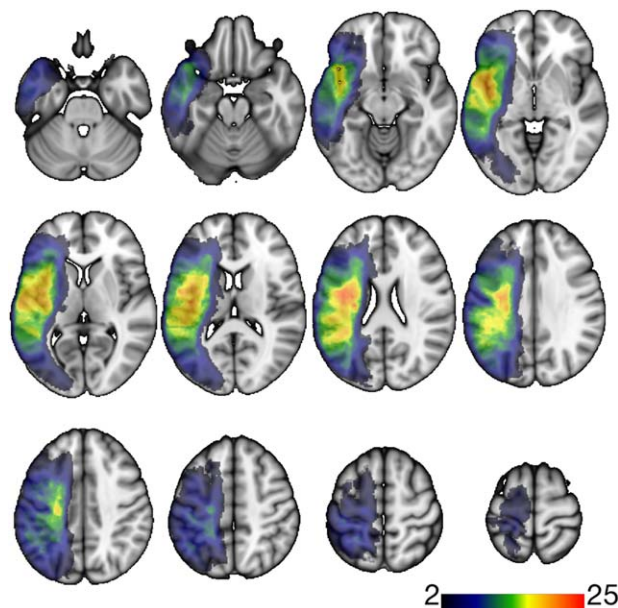
Standard multiple linear regression analyses were performed to examine the relationship between cortical necrosis and disconnection of M1, PMC, and SMA and upper/lower extremity motor performance. To normalize data for

regression analyses, participants who scored 0 on BBT were removed as the BBT has a known floor effect [Chen et al., 2009; Desrosiers et al., 1994]. Similarly, participants who scored 99 on the MI for the affected upper/lower extremity were removed due to a ceiling effect [Collin and Wade, 1990; Demeurisse et al., 1980]. A reflect and square root transformation was then used with Arm  $MI_{Aff}$  data to obtain a normal distribution. Separate multiple linear regressions were performed for each behavioral measure, and included the clinical score as the dependent variable with the following independent variables: (1) percentage of necrotic lesion damage to each motor area and (2) percentage fiber number of each motor area. Each cortical motor area was analyzed separately. Significance level was set at  $P < 0.05$ , corrected based on the number ( $n = 5$ ) of behavioral measures assessed (corrected  $P \leq 0.01$ ).

## RESULTS

### Behavioral Measures

Individuals showed reduced gross manual dexterity of the affected hand [median  $BBT_{Aff}$  score = 34.5 (interquartile range (IQR), 7.25–46.5), median  $BBT_{Unaffected}$  score = 51.0 (IQR, 44.0–56.25),  $P < 0.001$ ], decreased grip strength ( $Grip_{Aff} = 23.46 \pm 15.72$  kg,  $Grip_{Unaffected} = 34.64 \pm 10.51$  kg,  $P < 0.001$ ), and impaired upper extremity motor function [median Arm  $MI_{Aff}$  score = 88 (IQR, 56.5–100), median Arm  $MI_{Unaffected}$  score = 100 (IQR, 100–100),  $P < 0.001$ ]. The



**Figure 2.**

Lesion overlay. This figure demonstrates the overlay of the lesions in standard space from all subjects included in this study. The colored areas indicate the number of subjects whose lesions encompassed that voxel.

**TABLE II. Nonparametric correlations between motor function and structural connectivity of *a priori* ROIs**

Structural connectivity of <i>a priori</i> ROIs	Behavioral measures				
	BBT <sub>Aff</sub> ( <i>n</i> = 42)	Grip <sub>Aff</sub> ( <i>n</i> = 42)	Arm MI <sub>Aff</sub> ( <i>n</i> = 40)	Leg MI <sub>Aff</sub> ( <i>n</i> = 42)	Gait speed ( <i>n</i> = 40)
<i>Ipsilesional Hemisphere</i>					
M1 ↔ PMC	0.35	0.24	0.28	0.17	0.10
M1 ↔ SMA	0.42*	0.46*	0.41	0.38	0.25
PMC ↔ SMA	0.31	0.22	0.22	0.14	-0.05
M1 ↔ CP	0.74*	0.67*	0.67*	0.63*	0.55*
PMC ↔ CP	0.45*	0.30	0.45*	0.41	0.34
SMA ↔ CP	0.66*	0.56*	0.63*	0.63*	0.54*
M1 ↔ RN	0.53*	0.49*	0.49*	0.43*	0.24
PMC ↔ RN	0.35	0.28	0.35	0.34	0.23
SMA ↔ RN	0.52*	0.42*	0.46*	0.45*	0.38
M1 ↔ Thalamus	0.65*	0.56*	0.61*	0.66*	0.54*
PMC ↔ Thalamus	0.39	0.21	0.37	0.37	0.23
SMA ↔ Thalamus	0.65*	0.57*	0.63*	0.64*	0.46*
<i>Basal Ganglia &amp; Cerebellum</i>					
Caudate ↔ Thalamus	0.05	-0.07	0.10	0.10	-0.09
Putamen ↔ Thalamus	0.37	0.36	0.27	0.40	0.43*
GP ↔ Thalamus	0.23	0.29	0.25	0.33	0.36
Cerebellum ↔ Thalamus	0.50*	0.51*	0.43*	0.48*	0.39
<i>Interhemispheric Connectivity</i>					
M1 ↔ M1	0.46*	0.30	0.31	0.30	0.14
PMC ↔ PMC	0.24	0.01	0.16	0.08	0.06
SMA ↔ SMA	0.35	0.14	0.22	0.21	0.23

Values in the table are Spearman's coefficients (*r*).

Abbreviations: ROIs, regions of interest; BBT<sub>Aff</sub>, Box and Block Test (affected extremity); Grip<sub>Aff</sub>, grip strength (affected extremity); Arm MI<sub>Aff</sub>, Arm Motricity Index score (affected extremity); Leg MI<sub>Aff</sub>, Leg Motricity Index score (affected extremity); M1, primary motor cortex; PMC, premotor cortex; SMA, supplementary motor area; CP, cerebral peduncle; RN, red nucleus; GP, globus pallidus.

\*Significant at corrected  $P \leq 0.003$ .

affected lower extremity also exhibited significant residual motor impairment [median Leg MI<sub>Aff</sub> score = 79 (IQR, 59–100), median Leg MI<sub>Unaffected</sub> score = 100 (IQR, 100–100),  $P < 0.001$ ]. Average gait speed was  $0.94 \pm 0.31$  m/s.

For the subgroup of participants with normalized data for the regression analyses, average BBT<sub>Aff</sub> score was  $37.8 \pm 17.4$  ( $n = 34$ ), average Arm MI<sub>Aff</sub> score was  $59.8 \pm 28.1$  ( $n = 25$ ), and average Leg MI<sub>Aff</sub> score was  $64.9 \pm 18.4$  ( $n = 28$ ).

### Lesion Location

All participants exhibited a cortical/subcortical lesion in the left hemisphere, broadly distributed within the territory of the middle cerebral artery. For one participant, the lesion was too small to adequately outline; all other lesions were clearly visible on T2-weighted images. Locations of maximal lesion overlap were the extranuclear and subgyral areas (Fig. 2).

### Lesion Size and Motor Impairment

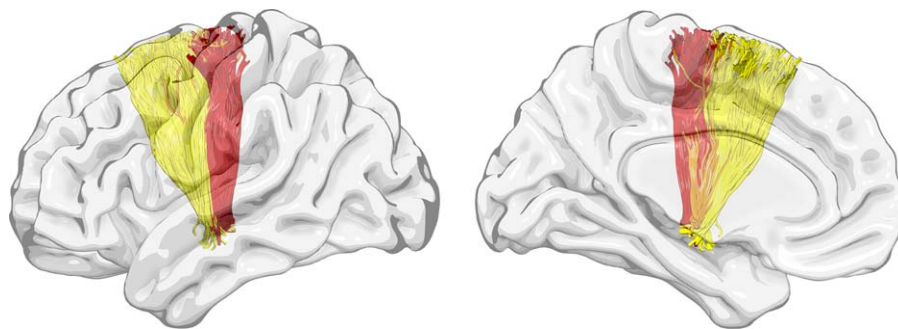
Total lesion volume was not significantly correlated (Spearman's rho) with motor function of the affected extremity on BBT ( $r = -0.17$ ,  $P = 0.29$ ), grip strength ( $r = 0.10$ ,

$P = 0.54$ ), arm MI ( $r = -0.15$ ,  $P = 0.37$ ), leg MI ( $r = -0.06$ ,  $P = 0.71$ ), or with gait speed ( $r = 0.15$ ,  $P = 0.35$ ).

### Cortical/Subcortical Connectivity and Motor Impairment

Anatomical reciprocal connectivity within the lesioned hemisphere between the following *a priori* ROIs was decreased overall compared with the homologous connectivity in the nonlesioned hemisphere: M1 ↔ thalamus ( $P = 0.002$ ); PMC ↔ thalamus ( $P = 0.001$ ); SMA ↔ thalamus ( $P < 0.001$ ); M1 ↔ cerebral peduncle ( $P = 0.002$ ); SMA ↔ cerebral peduncle ( $P = 0.001$ ); M1 ↔ PMC ( $P < 0.001$ ); and caudate nucleus ↔ thalamus ( $P < 0.001$ ). Connectivity between the remaining ROIs was not significantly different between hemispheres ( $P > 0.003$ ).

Correlations between motor function and structural connectivity of *a priori* ROIs (lesioned hemisphere and interhemispheric) are presented in Table II. Anatomical connectivity between ROIs corresponding to two cortical motor areas (M1 and SMA) and the (1) cerebral peduncle and (2) thalamus were significantly correlated with motor performance across all behavioral measures ( $P \leq 0.003$ ), with BBT<sub>Aff</sub> exhibiting the strongest correlations. Structural



**Figure 3.**

Tracts. Using reconstructed pathways from a normative non-stroke database of 59 healthy controls, this figure demonstrates the anatomical location of the white-matter tracts most significantly associated with upper and lower extremity motor function abnormalities (e.g.,  $BBT_{Aff}$ , gait speed). The tracts colored red are the connections from M1 (precentral gyrus) to the CP,

those in orange from M1 (precentral gyrus) to the RN, and those in yellow from SMA (superior frontal gyrus) to the CP.  $BBT_{Aff}$ , Box and Block Test (affected extremity); M1, primary motor cortex; CP, cerebral peduncle; RN, red nucleus; SMA, supplementary motor area.

connectivity between M1/SMA and the RN was significantly correlated with motor performance across all upper extremity measures and one lower extremity measure (Leg  $MI_{Aff}$ ). In terms of basal ganglia connectivity, anatomical connectivity between the putamen and thalamus was significantly correlated with walking function (gait speed,  $r = 0.43$ ,  $P = 0.003$ ). Cortico-cortico connectivity analyses revealed a significant correlation between M1 ↔ SMA connectivity and grip strength ( $r = 0.46$ ,  $P = 0.001$ ) and  $BBT_{Aff}$  ( $r = 0.42$ ,  $P = 0.003$ ). Interhemispheric connectivity between M1 ↔ M1 was also significantly correlated with gross manual dexterity of the affected upper extremity ( $BBT_{Aff}$ ,  $r = 0.46$ ,  $P = 0.001$ ). Using a normative nonstroke database with a similar age distribution as our stroke sample, Figure 3 depicts the anatomical location of the white-matter tracts most significantly associated with motor function abnormalities.

### Multiple Regression Analyses

Results of the regression analyses are summarized in Table III. For upper extremity motor performance, a model composed of M1 lesion load and M1 disconnection (adjusted for time poststroke) explained a significant amount of variance in  $BBT_{Aff}$  score [ $R^2 = 0.46$ ,  $F(3,29) = 8.25$ ,  $P < 0.001$ ;  $\beta_{LL} = -0.085$ ,  $P = 0.57$ ;  $\beta_{disconnection} = 0.531$ ,  $P = 0.001$ ], Grip $_{Aff}$  strength [ $R^2 = 0.36$ ,  $F(3,37) = 7.04$ ,  $P = 0.001$ ;  $\beta_{LL} = 0.051$ ,  $P = 0.76$ ;  $\beta_{disconnection} = 0.611$ ,  $P < 0.001$ ], and arm  $MI_{Aff}$  score [ $R^2 = 0.43$ ,  $F(3,20) = 5.02$ ,  $P = 0.009$ ;  $\beta_{LL} = 0.031$ ,  $P = 0.88$ ;  $\beta_{disconnection} = -0.560$ ,  $P = 0.007$ ]. Whereas M1 disconnection was an independent predictor of upper extremity motor performance across all three measures, M1 lesion load was not independently associated with upper extremity motor performance. Moreover, the  $R^2$  for M1 disconnection was higher than those for most connections between M1 and relevant motor regions reported in the previous section. We also

observed a trend toward significance between  $BBT_{Aff}$  score and a model composed of SMA lesion load and SMA disconnection [ $R^2 = 0.31$ ,  $F(3,27) = 4.09$ ,  $P = 0.016$ ;  $\beta_{LL} = -0.203$ ,  $P = 0.38$ ;  $\beta_{disconnection} = 0.253$ ,  $P = 0.167$ ]; however, neither SMA lesion load or disconnection was an independent predictor of  $BBT_{Aff}$  score. Upper extremity motor performance was not associated with a model composed of PMC lesion load and disconnection.

In terms of lower extremity motor performance, a significant relationship was found between gait speed and a model composed of M1 lesion load and M1 disconnection (adjusted for time poststroke) [ $R^2 = 0.46$ ,  $F(3,35) = 9.75$ ,  $P < 0.001$ ;  $\beta_{LL} = 0.398$ ,  $P = 0.011$ ;  $\beta_{disconnection} = 0.557$ ,  $P < 0.001$ ]. Both lesion load and disconnection were independent predictors of gait speed. Necrosis and disconnection of PMC or SMA were not associated with lower extremity motor performance.

### DISCUSSION

Preservation of the integrity of the CST and additional corticofugal fibers is important for motor recovery in chronic stroke [Lindenberg et al., 2010; Sterr et al., 2014; Ward et al., 2006]. In addition to direct disruption of these tracts by lesioned necrotic tissue, broader structural changes have been shown to occur in the nonlesioned motor network following stroke [Lindenberg et al., 2012; Liu et al., 2015; Schaechter et al., 2009]. In this study, we demonstrated that both upper and lower extremity motor performance in chronic stroke was positively associated with structural connectivity between several ipsilesional brain regions involved in motor control (e.g., M1/SMA and the cerebral peduncle, red nucleus, and thalamus). Furthermore, cortical disconnection of M1 was independently associated with motor function of the affected

**TABLE III. Multiple regression analyses of cortical necrosis and disconnection and upper/lower extremity motor performance (adjusted for time post-stroke)**

Behavioral measure	Predictors	$R^2$	$F$ statistic	$P$ value for $F$	$\beta_{LL}$	$\beta_{disconnection}$
BBT <sub>Aff</sub> ( $n = 33$ )						
M1	LL <sub>M1</sub> , % fiber number <sub>M1</sub>	0.46	8.25	0.000 <sup>†</sup>	-0.085	0.531**
PMC <sup>b</sup>	LL <sub>PMC</sub> , % fiber number <sub>PMC</sub>	0.11	1.13	0.353	0.085	-0.019
SMA <sup>c</sup>	LL <sub>SMA</sub> , % fiber number <sub>SMA</sub>	0.31	4.09	0.016	-0.203	0.253
Grip <sub>Aff</sub> ( $n = 41$ )						
M1	LL <sub>M1</sub> , % fiber number <sub>M1</sub>	0.36	7.04	0.001 <sup>†</sup>	0.051	0.611**
PMC <sup>d</sup>	LL <sub>PMC</sub> , % fiber number <sub>PMC</sub>	0.08	1.00	0.404	0.240	0.127
SMA	LL <sub>SMA</sub> , % fiber number <sub>MA</sub>	0.19	2.88	0.049	-0.045	0.388*
Arm MI <sub>Aff</sub> ( $n = 24$ ) <sup>a</sup>						
M1	LL <sub>M1</sub> , % fiber number <sub>M1</sub>	0.43	5.02	0.009 <sup>†</sup>	0.031	-0.560**
PMC <sup>b</sup>	LL <sub>PMC</sub> , % fiber number <sub>PMC</sub>	0.32	2.99	0.057	0.500	0.455
SMA	LL <sub>SMA</sub> , % fiber number <sub>SMA</sub>	0.35	3.62	0.031	0.365	-0.254
Leg MI <sub>Aff</sub> ( $n=27$ )						
M1	LL <sub>M1</sub> , % fiber number <sub>M1</sub>	0.18	1.63	0.209	0.112	0.464*
PMC	LL <sub>PMC</sub> , % fiber number <sub>PMC</sub>	0.02	0.15	0.929	0.043	0.041
SMA	LL <sub>SMA</sub> , % fiber number <sub>SMA</sub>	0.07	0.58	0.634	-0.167	0.151
Gait speed ( $n = 39$ )						
M1	LL <sub>M1</sub> , % fiber number <sub>M1</sub>	0.46	9.75	0.000 <sup>†</sup>	0.398*	0.557**
PMC	LL <sub>PMC</sub> , % fiber number <sub>PMC</sub>	0.23	3.43	0.027	0.408	0.099
SMA <sup>c</sup>	LL <sub>SMA</sub> , % fiber number <sub>SMA</sub>	0.19	2.65	0.065	-0.273	0.163

Abbreviations: BBT<sub>Aff</sub>, Box and Block Test (affected extremity); Grip<sub>Aff</sub>, grip strength (affected extremity); Arm MI<sub>Aff</sub>, Arm Motricity Index score (affected extremity); Leg MI<sub>Aff</sub>, Leg Motricity Index score (affected extremity); M1, primary motor cortex; PMC, premotor cortex; SMA, supplementary motor area; LL, lesion load.

<sup>†</sup>Significant at corrected  $P \leq 0.01$ ; \*\* $P \leq 0.01$ ; \* $P \leq 0.05$ .

<sup>a</sup>Arm MI<sub>Aff</sub> behavioral scores reflect and square root transformed to normalize behavioral data.

<sup>b</sup>One outlier removed.

<sup>c</sup>Two outliers removed.

<sup>d</sup>Four outliers removed.

upper extremity and gait speed. This study is novel in that it used innovative methodology to examine cortical/sub-cortical disconnection, and showed that cortical disconnection (controlling for extent of necrosis) contributes to both upper and lower extremity motor impairments in individuals with chronic stroke.

### Structural Connectivity of Ipsilesional Motor Network

Anatomical reciprocal connectivity within the lesioned hemisphere was significantly reduced (vs the nonlesioned hemisphere) between cortical motor areas and the cerebral peduncle and thalamus. There were no significant hemispheric differences, however, in connectivity between cortical regions and the red nucleus, as well as between SMA and M1/PMC. This may reflect adaptive changes in structural connectivity between these three cortical regions and the red nucleus, as well as changes in cortico-cortico connectivity in the lesioned hemisphere following stroke. The

red nucleus is the origin of the rubrospinal tract, which is less defined, but still present, in humans compared to non-human primates [Mamata et al., 2002; Yang et al., 2011]. Afferent input to the red nucleus includes fibers from the cerebral cortex and cerebellum, and it is believed the rubrospinal tract is an indirect pathway by which the cortex and cerebellum can influence motor neurons in the spinal cord [Snell, 2001; Yeo and Jang, 2010]. Previous studies in both nonhuman primates [Belhaj-Saif and Cheney, 2000; Sinkjaer et al., 1995] and humans [Ruber et al., 2012; Takenobu et al., 2014] suggest that remodeling and neuroplastic changes occur in the red nucleus during the early stages of stroke (and possibly later) and are still evident in the chronic stage. These changes may indicate compensation for CST injury and contribute to motor recovery. Our results showed that variability in upper and lower extremity motor function was associated with variability in structural connectivity between ipsilesional M1/SMA and the red nucleus, suggesting that connectivity between these cortical regions and midbrain nucleus may play a role in motor recovery in chronic stroke.



### Correlation With Motor Status

Connectivity between ipsilesional M1/SMA and the cerebral peduncle positively correlated with motor function across all upper/lower extremity behavioral measures, while connectivity between PMC and the cerebral peduncle only correlated with upper extremity motor function (BBT<sub>Aff</sub> and Arm MI<sub>Aff</sub>). These results are consistent with previous studies demonstrating selective disruption of corticofugal fibers from multiple motor regions can impact functional reorganization and motor recovery following stroke [Newton et al., 2006]. Microstructural integrity of CST pathways originating from primary and secondary cortical motor areas in the affected hemisphere have been shown to be reduced in chronic stroke, with grip strength strongly related to the integrity of fibers originating from the primary motor and (to a lesser extent) dorsal premotor cortices [Schulz et al., 2012]. Additionally, we found structural connectivity between ipsilesional M1/SMA and the thalamus was significantly correlated with motor function across all behavioral measures. This finding is not surprising, as the thalamus is a main relay station for sensory-motor neuronal loops and is closely connected to the cerebral cortex [Afifi and Bergman, 1998].

Investigation of the influence of basal nuclei connectivity on motor performance revealed a significant correlation only between gait speed and structural connectivity between the ipsilesional putamen and thalamus, indicating a potential role of the basal ganglia in lower extremity motor recovery following stroke. These nuclei have extensive connections with many different regions of the brain and are known to play an important role in postural control and voluntary movement [Afifi and Bergman, 1998]. Previous research has demonstrated increased putamen activation during imagined standing and walking in healthy adults [Jahn et al., 2004]. Moreover, damage to the putamen has been associated with temporal gait asymmetry [Alexander et al., 2009] and decreased walking speed [Reynolds et al., 2014] in individuals with chronic stroke, highlighting basal ganglia involvement in modulation of gait.

The findings of this study provide further support to the current knowledge of brain regions involved in locomotor control. Afferent input converges on subcortical (e.g., thalamus) and cortical regions and is then transmitted to motor regions (e.g., SMA) to produce or modify motor programs [Takakusaki, 2017]. Cortical locomotor commands occur primarily from the primary motor cortex, while other brain regions such as prefrontal supplementary motor areas and basal ganglia may provide an indirect pathway for planning and modulation of locomotion [la Fougere et al., 2010]. Thus, structural connectivity between these brain regions is important for supraspinal control of locomotion.

Interhemispheric structural connectivity between M1s was also significantly and positively correlated with upper extremity dexterity (BBT<sub>Aff</sub> score), suggesting that communication

between primary motor cortices is important for upper extremity movement and dexterity of the hand post-stroke. Structural connectivity between M1s is crucial for interhemispheric inhibition, a process in which activity in M1 of one hemisphere inhibits activity in the homologous region of the opposite hemisphere to execute unimanual movements and coordinated bimanual tasks [Duque et al., 2005; Johansen-Berg et al., 2007; Perez and Cohen, 2009]. Previous studies have found chronic upper extremity motor impairment is associated with reduced white-matter integrity of transcallosal fibers [Chen and Schlaug, 2013; Lindenberg et al., 2012]. Functional neuroimaging studies have also demonstrated decreased functional connectivity [Carter et al., 2010; Wang et al., 2012] and impaired interhemispheric inhibition [Murase et al., 2004; Perez and Cohen, 2009] between motor cortices is associated with upper extremity motor impairment poststroke. Our results could also suggest a role for contralesional M1 involvement in upper extremity motor recovery, which is supported by previous studies investigating functional connectivity and cortical reorganization following stroke [Lotze et al., 2012; Schaechter et al., 2008].

### Cortical Disconnection and Motor Performance

Our findings reveal that cortical disconnection occurs alongside cortical necrosis, and that cortical disconnection is independently associated with upper/lower extremity motor performance. We observed that grip strength and motor function (BBT and MI) of the affected upper extremity was associated with preservation of cortical integrity and connectivity of ipsilesional M1; gross manual dexterity (BBT) of the affected hand also trended toward an association with preservation of SMA cortical integrity and connectivity. Furthermore, preserved cortical connectivity of M1 was an independent predictor of upper extremity motor performance across all measures, after controlling for lesion load. As the CST is the major neural pathway for skilled, discrete voluntary movements (especially for fine movements of the hands) [Davidoff, 1990], preservation of white-matter fibers supporting ipsilesional M1 is important as approximately one-third of CST fibers arise from M1 [Snell, 2001]. The SMA is connected directly via bidirectional pathways with the ipsilateral primary motor, premotor, and somatosensory cortices and indirectly receives subcortical input mainly from the basal ganglia via corticothalamic pathways [Afifi and Bergman, 1998]. It has direct connections with spinal motor neurons which innervate the hand [Dum and Strick, 2002], and therefore can play an augmented functional role in producing simple hand movements poststroke. The SMA is important in the temporal/sequential organization of movement and becomes more significant in the execution of simple motor tasks if the primary motor cortex is injured [Afifi and Bergman, 1998; Mintzopoulos et al., 2009].

Previous data are mixed concerning the relationship between lesion volume and motor impairment and

function. Several studies have found motor impairment after stroke is associated with lesion size, [Saver et al., 1999; Schiemanck et al., 2006] while others have not found a significant correlation [Page et al., 2013; Sterr et al., 2014]. Degree of lesion overlap with the CST is often a much better predictor of motor impairment and function than overall lesion volume [Pineiro et al., 2000; Zhu et al., 2010]. There is great variability, however, in clinical manifestation and recovery from stroke in the chronic phase. Our results found that lesion size alone was not correlated with chronic motor impairment, and that cortical disconnection of motor regions, especially of ipsilesional M1, could significantly contribute to the variability seen in upper extremity motor function/recovery. The extent of brain damage poststroke may therefore be underestimated by examination of the necrotic tissue alone if more salient, global effects on the motor network are not taken into account.

Gait speed was also associated with preservation of cortical integrity and connectivity of ipsilesional M1. Both lesion load and connectivity of this brain region were independently associated with gait speed, with cortical disconnection being a stronger predictor. Motor recovery of the affected upper extremity has been highly studied, whereas less is known about the motor recovery mechanisms involved with lower extremity and locomotor function after stroke. While the CST is necessary for fine movements of the hands [Davidoff, 1990; Stinear et al., 2007], locomotion and motor function of the legs is less dependent on the CST [Ahn et al., 2006; Dawes et al., 2008; Jang et al., 2005b]. Some studies have suggested that the lateral CST does not play a central role in basic locomotor function in primates or humans [Ahn et al., 2006; Jang, 2010] but rather it is involved in “skilled walking,” or the adaption of gait kinematics to environmental demands [Jang, 2009], and may be more strongly associated with temporal parameters of gait [Capaday, 2002; Dawes et al., 2008]. Other descending neural pathways such as the corticoreticulospinal, rubrospinal, and vestibulospinal tracts could contribute to locomotor function [Barthelemy et al., 2015; Jang et al., 2013]. Furthermore, the neural control of upper and lower limb movements is not analogous, as spinal interneurons play a more important role in the central pattern generation of gait [Barbeau and Rossignol, 1987; Lovely et al., 1986] while fine hand movements are primarily under cerebral control. Cortical reorganization following stroke, therefore, is most likely different for lower limb function compared to what has been demonstrated with upper limb function. Our results suggest that while we might not know the precise pathways that play a role in locomotor recovery, preservation of white matter fibers supporting ipsilesional M1 is important for locomotor function in individuals with chronic stroke.

Overall, these results complement the findings of Bonilha et al. [2014c] related to language impairments and cortical disconnection after stroke, and further highlight the discrepancy of brain regions that appear intact on structural scans but actually exhibit reduced structural

connectivity that may contribute to motor impairments poststroke. Improving our insight and understanding of the broader structural and functional changes that occur beyond the direct lesion can help improve motor recovery prognosis and target therapeutic interventions in a more tailored fashion for stroke survivors, thereby improving the clinical management of chronic mobility impairments in this patient population. More research needs to be performed to clarify the mechanisms that underlie changes in structural integrity and connectivity poststroke, and examine training-induced changes in structural connectivity of motor networks in both subacute and chronic stroke.

This study is one of the first to incorporate a large sample size with left hemisphere necrotic damage when examining the relationship between motor function and structural brain connectivity in chronic stroke. Motor attention [Rushworth et al., 2003], action selection [Stewart et al., 2014], and task complexity [Haaland et al., 2004] are predominantly associated with activation in the left rather than right hemisphere. Left hemispheric lesions are particularly disruptive to more complex movement sequences [Haaland and Harrington, 1996] and selection of movements [Rushworth et al., 1998]. Therefore, our findings related to ipsilesional motor network integrity and connectivity and the relationship to motor function involving more complex tasks (e.g., Box and Block Test, locomotion) may not generalize to right hemispheric stroke. Examining structural brain connectivity and correlates of motor function in persons with right hemispheric stroke is also imperative. The results of our study, however, should be interpreted in the context of the limitations of DTI tractography (e.g., false tracking in low anisotropic areas and/or regions with fiber complexity and crossing) [Assaf and Pasternak, 2008; Tuch et al., 2002]. Additionally, our ROIs were defined by the atlas we used, thus limiting our ability to examine certain structures in more detail (e.g., dividing the thalamus into separate nuclei). Other studies have used alternative analysis techniques that incorporate different ROI parameters or evaluate different subsections of white matter tracts and/or brain regions [Lindenberg et al., 2010; Schaechter et al., 2009]. Lastly, as this study was part of a larger study investigating lesion-impairment mapping of speech and language processing in individuals with chronic stroke, the majority of participants had lesions involving language regions of the brain resulting in a large number of subjects with minimal motor impairment. Future studies involving lesions primarily distributed in sensorimotor areas may provide a broader range of motor impairments and enable the examination of structural disconnection related to more direct necrotic lesion damage to the motor network.

## CONCLUSIONS

Our findings demonstrate that ipsilesional structural connectivity between several brain regions involved in the

motor network (particularly between M1/SMA and the cerebral peduncle, red nucleus, and thalamus) is associated with both upper and lower extremity motor performance in individuals with chronic stroke. Furthermore, upper extremity motor function of the affected extremity and gait speed is dependent on the preservation of cortical integrity and connectivity of ipsilesional M1, with cortical disconnection of M1 being an independent predictor of motor function. Our findings highlight the importance of examining structural changes and cortical disconnection in the broader motor network poststroke. Such insight could enhance our understanding of the underlying factors contributing to motor impairments after stroke. Future research examining treatment-induced changes in structural integrity and connectivity may provide insight into more global patterns of structural brain plasticity that could help clinicians and researchers better target therapeutic interventions to enhance motor recovery potential.

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