Interhemispheric Structural Connectivity Underlies Motor Recovery after Stroke

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Objective: Although ample evidence highlights that the ipsilesional corticospinal tract (CST) plays a crucial role in motor recovery after stroke, studies on cortico-cortical motor connections remain scarce and provide inconclusive results. Given their unique potential to serve as structural reserve enabling motor network reorganization, the question arises whether cortico-cortical connections may facilitate motor control depending on CST damage.
Methods: Diffusion spectrum imaging (DSI) and a novel compartment-wise analysis approach were used to quantify structural connectivity between bilateral cortical core motor regions in chronic stroke patients. Basal and complex motor control were differentially assessed.
Results: Both basal and complex motor performance were correlated with structural connectivity between bilateral premotor areas and ipsilesional primary motor cortex (M1) as well as interhemispheric M1 to M1 connectivity. Whereas complex motor skills depended on CST integrity, a strong association between M1 to M1 connectivity and basal motor control was observed independent of CST integrity especially in patients who underwent substantial motor recovery. Harnessing the informational wealth of cortico-cortical connectivity facilitated the explanation of both basal and complex motor control.
Interpretation: We demonstrate for the first time that distinct aspects of cortical structural reserve enable basal and complex motor control after stroke. In particular, recovery of basal motor control may be supported via an alternative route through contralesional M1 and non-crossing fibers of the contralesional CST. Our findings help to explain previous conflicting interpretations regarding the functional role of the contralesional M1 and highlight the potential of cortico-cortical structural connectivity as a future biomarker for motor recovery post-stroke.

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Diffusion magnetic resonance imaging (dMRI) is commonly used to characterize white matter (WM) alterations associated with motor impairment following stroke.[1] It is well-established that the capacity for motor control depends on the microstructural integrity of descending motor tracts, such as the ipsilesional corticospinal tract (CST).[2] At the same time, very little attention has been devoted to cortico-cortical structural connectivity, even though functional imaging studies suggest a pivotal role of interactions between cortical motor areas for motor performance in healthy individuals and stroke patients.[3,4] Functional MRI (fMRI)-based cortico-cortical connectivity has repeatedly been shown to relate to motor impairment in the acute and chronic stages post-stroke.[5–8] Given the assumed structure–function relationships,[9] structural connectivity of the cortical motor network might play a seminal role in motor control after stroke. The premorbid level of structural connectivity likely predetermines the capacity for functional

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reorganization, which can be considered as the motor system's structural reserve.[10]

However, studies on cortico-cortical structure–function relationships remain surprisingly scarce. Existing evidence suggests that motor performance relates to structural connectivity between bilateral primary motor cortex (M1).[11–16] Studies investigating ipsilesional premotor-M1 connectivity have reported inconclusive findings.[11,17,18] Moreover, data on the role of interhemispheric premotor-M1 connections are missing. Whereas whole-brain analyses principally include these connections, typical atlas parcellations do not isolate known premotor areas, limiting their interpretability.[19,20] Moreover, most studies commonly focus on either CST integrity or cortical connectivity. Hence, it remains unknown how motor reorganization is facilitated by cortico-cortical connectivity or whether it primarily depends on the ipsilesional CST.

To address these issues, we assessed diffusion spectrum imaging (DSI) data in a sample of patients with chronic stroke, that is, in the stable phase of motor network reorganization longer than 6 months post-stroke.[21] Using a novel compartment-wise analysis approach,[22] structural integrity of specific cortico-cortical motor tracts was quantified and associations with basal and complex motor functions were assessed. Whereas basal motor skills were conceptualized as simple movements relying on the recruitment of isolated muscle groups, complex motor skills were defined as sophisticated movements, such as reaching and object manipulation. In line with fMRI findings, we expected bilateral premotor – ipsilesional M1 and interhemispheric M1 to M1 connectivity to be indicative of both basal and complex motor skills.[5,7,8,23] Importantly, partial correlation analyses were used to assess the dependence of the relationship between cortico-cortical connectivity and motor control on ipsilesional CST integrity. We hypothesized less dependence on ipsilesional CST integrity for basal than for complex motor skills given that basal motor commands might be compensated via alternative routes, such as non-crossing fibers of the contralesional CST.[24] Finally, we addressed whether structural connectivity differed in patients with substantial compared to patients with nonsubstantial motor recovery. This approach allowed us to identify features of cortico-cortical structural connectivity associated with successful motor recovery. Advancing our understanding of motor recovery will help to lay the foundation for targeted therapeutic interventions and to identify structural cortico-cortical connections that might serve as potential future biomarkers.

Materials and Methods

Subjects

Twenty-five chronic stroke patients (mean age = 66.68 years, SD = 11.25, 5 women and 20 men) formerly hospitalized at the University Hospital Cologne, Department of Neurology, were included (for detailed demographic and clinical information, see Table 1). Inclusion criteria were (1) age between 40 and 90 years, (2) first-ever ischemic stroke more than 6 months ago, and (3) initial unilateral impairment of upper limb motor function. Exclusion criteria were (1) any contraindications to MRI, (2) bihemispheric infarctions, (3) cerebral hemorrhage, (4) reinfarction or other neurological diseases, and (5) persistence of severe aphasia or neglect. All subjects provided informed consent. The study was approved by the ethics committee of the Medical Faculty of the University of Cologne and was conducted in accordance with the Declaration of Helsinki. Although data from the current patient cohort were included in a previous publication focusing on descending corticospinal and extrapyramidal pathways,[22] there is no overlap with the current analyses assessing cortico-cortical connectivity.

Behavioral Motor Tests

To differentially quantify the impairment of basal and complex motor control involving proximal and distal arm movements, motor impairment was assessed using the Action Research Arm Test (ARAT)[25] and the Motricity Index (MI)-arm score.[26] The ARAT probes the execution of activities of daily living and therefore requires the complex interplay of motor synergies, emphasizing distal control of hand motor functions, such as reaching, grasping, and object manipulation. In contrast, the MI-arm reflects more basal motor control with a focus on proximal and some distal upper limb movements (Fig 1). The National Institutes of Health Stroke Scale (NIHSS)-arm score (elevate arm to 90 degrees: levels 0 = no drift, 1 = drift, 2 = arm cannot resist gravity, 3 = no effort against gravity, and 4 = no movement) was used to classify patients according to their degree of motor recovery from the acute to the chronic stage post-stroke. Substantial recovery was defined as NIHSS-arm improvement of one point or more from the acute to the chronic stage (15 patients). Of note, because the NIHSS-arm score is a rather coarse motor test, the absence of a change in the NIHSS-arm score should not be equated with no recovery, as the NIHSS cannot capture nuanced differences. In other words, a patient who is able to perform all NIHSS items flawlessly might still have difficulties performing more complex movements, as included in the ARAT. Therefore, patients without improvement in the NIHSS-arm score were summarized as the nonsubstantial recovery group (10 patients).

MRI Acquisition and Preprocessing

MRI data were recorded using a Siemens MAGNETOM Prisma 3 Tesla scanner (Siemens Medical Solutions, Erlangen, Germany). Preprocessing of diffusion data was performed using QSIPrep.[27] Maps of generalized fractional anisotropy (gFA) representing voxelwise microstructural integrity of WM tissue were generated in DSI Studio (https://dsi-studio.labsolver.org/; for a detailed description see Paul et al.[22]). Individual gFA-maps were normalized to Montreal Neurological Institute (MNI)-space using Advance Normalization Tools (ANTS).[28] Lesion masks were drawn in MRIcron (https://www.nitrc.org/projects/mricron) and verified by a certified neurologist. Images with lesions affecting the right hemisphere were flipped along the

TABLE 1. Demographic and clinical patient information

Patient	Sex	ARAT	MI-arm	NIHSS-arm acute	NIHSS-arm chronic	Substantial recovery	Months since stroke	Lesion side	Lesion location	Lesion volume (mm^3)	CST lesion volume (mm^3)
1	M	57	99	2	0	Yes	21	R	MCA (subcortical)	51,688	3,752
2	M	57	91	4	1	Yes	14	R	MCA (subcortical)	25,410	746
3	M	38	76	1	1	No	17	R	MCA (subcortical)	11,559	1,055
4	M	0	34	3	4	No	51	L	MCA (subcortical)	6,104	1,527
5	M	35	92	1	1	No	23	L	PCA (subcortical)	1,748	0.00
6	F	32	77	1	2	No	11	L	MCA (subcortical)	1,988	1,490
7	M	19	65	3	2	Yes	59	L	MCA (subcortical)	1,211	623
8	M	55	92	4	1	Yes	71	L	MCA (subcortical)	38,955	1,232
9	M	57	99	0	0	No	31	L	ACA/MCA (subcortical)	39,004	1,582
10	M	49	91	1	1	No	12	R	MCA (subcortical)	1,156	141
11	M	57	99	1	0	Yes	37	L	MCA (subcortical)	1,068	594
12	M	57	99	0	1	No	44	R	Brainstem	1,195	707
13	F	56	91	3	0	Yes	55	R	MCA (cortical)	34,402	4,736
14	M	57	99	4	0	Yes	32	R	MCA (cortical)	37,850	1,654
15	M	57	99	1	0	Yes	43	L	MCA (subcortical)	4,283	1,391
16	F	57	76	2	1	Yes	15	R	MCA (subcortical)	7,645	0.00
17	M	37	84	3	1	Yes	82	R	Brainstem	1,598	855
18	M	44	83	1	1	No	30	L	Brainstem	354	256
19	F	56	76	1	1	No	12	L	Brainstem	37	0.00
20	M	55	92	1	0	Yes	15	L	PCA (subcortical)	1,475	0.00
21	M	57	99	4	1	Yes	33	L	MCA (subcortical)	725	100
22	M	57	99	1	0	Yes	25	L	MCA (sub- and cortical)	12,102	1,838
23	M	53	99	1	0	Yes	35	R	MCA (subcortical)	4,242	2,152
24	F	57	83	1	1	No	20	R	Brainstem	582	539
25	M	57	99	4	0	Yes	23	R	MCA (subcortical)	1,072	703

Abbreviations: ACA = anterior cerebral artery; ARAT = Action Research Arm Test; F = female; L = left; M = male; MCA = middle cerebral artery; MI = Motricity Index; PCA = posterior cerebral artery; NIHSS = National Institutes of Health Stroke Scale; R = right.

mid-sagittal plane to facilitate group comparisons. To focus all subsequent analyses on WM voxels and exclude voxels located within the stroke lesion, gFA-maps were masked using both individual WM-masks derived from brain tissue segmentation and lesion masks.

Defining Regions of the Cortical Motor Network

As fMRI-based connectivity within a motor network comprising core motor areas have frequently been linked to motor impairment after stroke,[5–7,29] we accordingly included bilateral core motor areas, such as M1, dorsal premotor cortex (PMd), ventral premotor cortex (PMv), and supplementary motor area (SMA). To define the location of the aforementioned areas, automated term-based fMRI meta-analyses based on a large number of studies were performed using the neurosynth.org database (https://www.neurosynth.org/). The search terms "motor cortex", "dorsal premotor", "ventral premotor", and "supplementary motor" were used to derive MNI coordinates for our

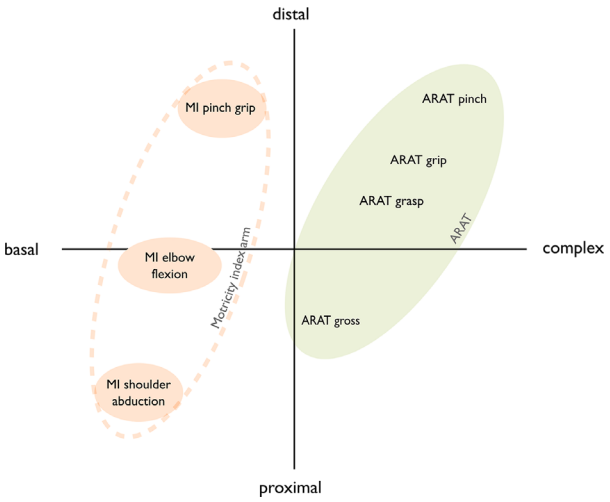

Figure 1: Schematic illustration of motor assessments via the ARAT and MI-arm score. The MI-arm score (orange) reflects basal motor control of simple movements involving specific muscle synergies with a precise delineation of the reliance on required muscle groups for proximal to distal movements. Conversely, the ARAT (green) quantifies more complex motor control of the affected arm that requires the interplay of different motor control policies, closely reflecting activities of daily living. ARAT = Action Research Arm Test; MI = Motricity Index. [Color figure can be viewed at www.annalsofneurology.org]

regions of interest (ROIs): M1 (MNI coordinates left = −38/−22/60, right = 38/−22/60), PMd (left = −24/−6/62, right = 24/−6/62), PMv (left = −54/−1/22, right = 54/−1/22), and SMA (left = −4/−4/54 and right = 4/−4/54).

Generation of Tract Templates

Fiber bundles connecting cortical motor regions were defined via deterministic fiber tracking, as implemented in DSI Studio[30] using the Human Connectome Project (HCP)-1,065 template based on diffusion data of 1,065 healthy subjects.[31] Deterministic fiber tracking was used to identify (1) intrahemispheric cortico-cortical fiber tracts between ipsilesional (il) M1 and ipsilesional premotor areas (ilPMd-ilM1, ilPMv-ilM1, and ilSMA-ilM1), (2) interhemispheric cortico-cortical fiber tracts between ipsilesional M1 and contralesional (cl) premotor areas (clPMd-ilM1, clPMv-ilM1, and clSMA-ilM1), as well as (3) the interhemispheric tract between bilateral M1 (clM1-ilM1; Fig 2). Fiber tracking was performed using the generated cortical ROIs, exclusion ROIs, and an angular threshold of 50 to 90 degrees. Resulting tracts were manually trimmed and validated by a certified neurologist. To address whether potential associations between structural motor network connectivity and motor impairment were independent of CST integrity, we generated an additional CST mask originating from M1, PMd, PMv, and SMA. Importantly, the CST is known to be slightly asymmetrical for the left and right hemispheres in healthy subjects.[32] Considering that right-hemispheric lesions were flipped to the left hemisphere, left- and right-hemispheric CST tracts were created and combined into a single mask after flipping the right-hemispheric tract along the mid-sagittal plane. Thereby we ensured that all relevant voxels were captured (see Fig 2).

Tractwise Anisotropy

To quantify structural connectivity, diffusion data was compartmentalized using a DSI-based compartment-wise approach.[32] A deterministic mask was applied to whole-brain diffusion images, that is, gFA-maps, in order to differentiate voxels according to the number of trackable fiber directions (for methodological details, see Volz et al.[32]). This approach has been shown to facilitate the analyses of anisotropy in stroke patients.[22] Importantly, tractwise gFA-values reflecting structural connectivity were determined based on voxels with only one dominant fiber direction. Focusing the analyses on one-directional voxels helped us to overcome the methodological limitations of biased anisotropy estimations in voxels with multiple fiber directions (for a detailed discussion regarding the impact of compartmentalization on analyses of anisotropy, see Paul et al. and Volz et al.[22,32]). To confirm that this approach helped to improve the signal-to-noise ratio and to rule out the possibility that sensitivity was lost, we repeated the analyses after extracting tractwise anisotropy from all voxels and two-directional voxels for each tract. Using one-directional voxels yielded by far the strongest statistical relationships with motor control compared to using all voxels or two-directional voxels, highlighting the utility of our compartment-wise analysis approach.

Structural Connectivity and Motor Control after Stroke

A potential relationship between anisotropy of cortico-cortical motor connections and different aspects of motor control after stroke was tested via Pearson correlations. To probe for relationships with basal motor control, correlations were computed between the MI-arm score and tractwise anisotropy. All p values were false discovery rate (FDR)-corrected for multiple comparisons.[33] To test for relationships with complex motor control, the analyses were repeated using the ARAT score.

To address the question whether the associations between cortico-cortical connectivity and motor control depended on CST damage, partial correlations were computed controlling for ipsilesional CST integrity. Importantly, CST integrity has also been related to the degree of motor recovery after stroke.[1] However, recovery is multifaceted, with good outcomes potentially deriving from distinct reorganization processes. For example, a small lesion may lead to mild initial impairment which yields a good outcome (almost) independent of the degree of recovery. On the other hand, patients with lesions involving a large amount of brain tissue suffering from severe initial impairment may recover substantially during rehabilitation, also resulting in a good outcome at the chronic stage. Therefore, we assessed the relationship between cortico-cortical motor network connectivity and motor outcome in a recovery-dependent manner. To this end, we divided the patient cohort into two subgroups featuring substantial or nonsubstantial upper limb recovery, as reflected by improvements in the NIHSS-arm score between the acute and chronic phases. Correlation analyses with basal motor outcome scores were repeated for both subgroups.

To ensure that results were not driven by the direct impact of lesions on cortico-cortical connections, all correlation analyses were repeated after excluding tracts that showed an overlap of

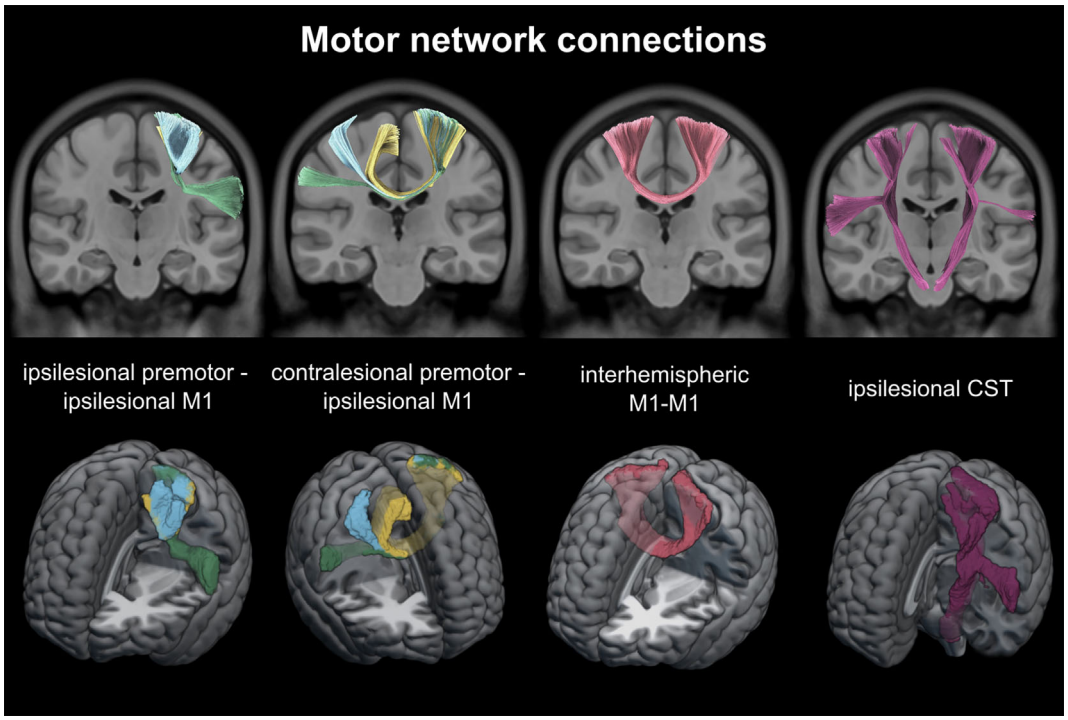

Figure 2: Cortico-cortical and descending motor network connections. Fiber tracts between core areas of the cortical motor network were created using deterministic fiber tracking based on the HCP1065-template[31] in DSI Studio (upper row). Motor tract templates used for anisotropy extraction are depicted as overlays in MRIcroGL (lower row). Note that for the ipsilesional CST, tracking was first performed in both hemispheres (upper row). Bilateral tracts were then combined into a single ipsilesional CST mask after flipping the right-hemispheric tract to the left (lower row). Blue = connections with PMd; green = connections with PMv; yellow = connections with SMA; red = interhemispheric M1 to M1 connection; purple = corticospinal tract; CST = corticospinal tract; M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; SMA = supplementary motor area. [Color figure can be viewed at www.annalsofneurology.org]

more than 10% between the subject's lesion and the tract's one-directional voxels (N = 3 subjects).

Stepwise Linear Backward Regressions

Stepwise linear backward regressions based on the Bayesian information criterion (BIC; k = log(N), N = 25) were computed to probe for the extent of explained variance in basal (MI-arm) and complex (ARAT) motor performance by the integrity of ipsilesional CST and cortico-cortical connectivity. For a better appraisal of the ratio of explained variance by the combined model, we separately assessed how much variance was accounted for by (i) cortico-cortical connectivity without the CST and (ii) CST integrity alone. As CST damage is considered a valid biomarker for motor impairment post-stroke,[2] the direct comparison is a good indicator for the suitability of cortico-cortical structural connectivity to potentially improve the prediction of behavior.

Results

Correlation Analyses

For both basal and complex upper limb motor control, positive correlations were observed with anisotropy of the homologous clM1 to ilM1 connection, all intra-hemispheric premotor-ilM1 connections and inter-hemispheric clPMv to ilM1 and clSMA to ilM1 connections (all $p < 0.05$, FDR-corrected; for details, see Table 2 and Fig 3A). Thus, higher levels of structural connectivity were found in patients featuring higher levels of basal and complex motor control of the stroke-affected arm. Of note, after excluding tracts which were considerably affected by stroke lesions, correlation analyses yielded highly similar results, corroborating the robustness of our findings (Table S1). Likewise, repeating correlation analyses after excluding patients suffering from brainstem (N = 5) or cortical infarctions (N = 3) yielded highly similar results, thus rendering a considerable bias introduced by varying infarct locations highly unlikely.

In general, correlations with tractwise anisotropy tended to be stronger for basal than for complex motor control. Our findings are in line with the notion that structural motor network connectivity between ipsilesional M1 and (i) bilateral premotor areas as well as (ii) contralesional M1 supports both basal and complex motor function of the paretic arm and hand in chronic stroke patients. Considering the prominent role of the CST in motor control, we next addressed the question whether the observed correlations were dependent on the level of CST integrity by means of partial correlations.

TABLE 2. Correlation analyses between different aspects of motor control and cortico-cortical connections

	Pearson correlations		Partial correlations	
Connection	**r**	***p* (FDR)**	**r**	***p* (FDR)**
		Basal motor control		
Homologous				
clM1-ilM1	**0.62**	**0.002****	**0.45**	**0.040***
Intrahemispheric				
ilPMd-ilM1	**0.63**	**0.002****	**0.59**	**0.006****
ilPMv-ilM1	**0.72**	**< 0.001*****	**0.65**	**0.004****
ilSMA-ilM1	**0.54**	**0.009****	**0.59**	**0.006****
Interhemispheric				
clPMd-ilM1	0.31	0.134	0.25	0.246
clPMv-ilM1	**0.53**	**0.009****	**0.53**	**0.013***
clSMA-ilM1	**0.43**	**0.036***	0.31	0.172
		Complex motor control		
Homologous				
clM1-ilM1	**0.49**	**0.023***	0.26	0.246
Intrahemispheric				
ilPMd-ilM1	**0.51**	**0.023***	0.44	0.068
ilPMv-ilM1	**0.59**	**0.013***	0.49	0.057
ilSMA-ilM1	**0.49**	**0.023***	0.53	0.052
Interhemispheric				
clPMd-ilM1	0.28	0.183	0.21	0.332
clPMv-ilM1	**0.44**	**0.033***	0.42	0.068
clSMA-ilM1	**0.45**	**0.032***	0.33	0.160

Note: Analyses were carried out separately for (i) basal and (ii) complex motor control. Partial correlations assessed the relationship between motor control and tractwise anisotropy while controlling for ipsilesional CST integrity. Bold font indicates significance after FDR-correction ($p < 0.05$). Asterisks signify the following significance thresholds: ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$. Results are visualized in Figure 3.

Abbreviations: clM1 = contralesional primary motor cortex; clPMd = contralesional dorsal premotor cortex; clPMv = contralesional ventral premotor cortex; clSMA = contralesional supplementary motor area; CST = corticospinal tract; FDR = false discovery rate; ilM1 = ipsilesional primary motor cortex; ilPMd = ipsilesional dorsal premotor cortex; ilPMv = ipsilesional ventral premotor cortex; ilSMA = ipsilesional supplementary motor area; r = correlation coefficient.

Partial Correlation Analyses

Partial correlation analyses were performed to control for the effect of ipsilesional CST integrity on tractwise correlations with motor behavior. Here, a lack of previously significant correlations would indicate a strong dependence on ipsilesional CST integrity, whereas a preservation of significance would imply independence of CST integrity. For basal motor control, results of correlation analyses and partial correlations were highly similar (see Table 2, Fig 3). In particular, anisotropy of all intrahemispheric premotor-ilM1 connections (all r > 0.59, $p < 0.006$, FDR-corrected) were associated with basal motor control (see Fig 3B). Regarding interhemispheric connectivity, clPMv to ilM1 (r = 0.53, $p = 0.013$, FDR-corrected) as well as M1 to M1 connectivity (r = 0.45, $p = 0.040$, FDR-corrected) also remained significant when controlling for CST integrity. In summary, structural connectivity between the ipsilesional M1 and (i) all ipsilesional

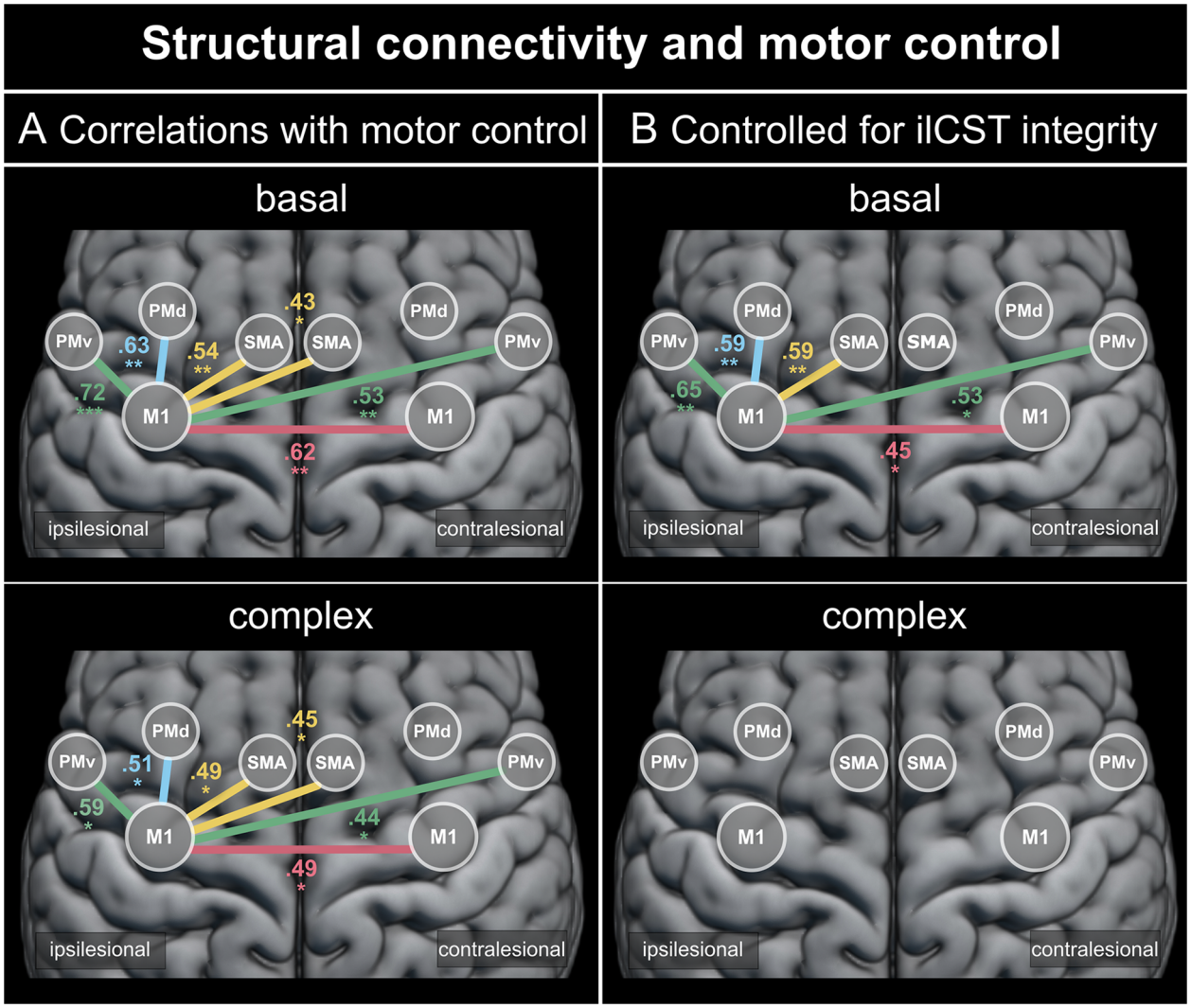

Figure 3: Association between structural motor network connectivity and motor control after stroke. Tractwise anisotropy of several cortico-cortical connections showed a significant association with basal or complex motor control. (A) Correlation coefficients of significant Pearson correlations. (B) Significant partial correlations of cortico-cortical connections with motor behavior when controlling for ilCST damage. All depicted connections were significant after FDR-correction for multiple comparisons ($p < 0.05$). Significance thresholds: ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$. ilCST = ipsilesional corticospinal tract; M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; SMA = supplementary motor area. [Color figure can be viewed at www.annalsofneurology.org]

premotor areas, (ii) contralesional PMv, as well as (iii) contralesional M1 was associated with basal motor control independent of ipsilesional CST integrity.

In contrast, correlations between cortico-cortical connections and complex motor control were not independent of ipsilesional CST integrity (see Table 2, Fig 3B). No significant partial correlations were observed after correction for multiple comparisons, with some premotor-M1 connections showing a trend toward significance (see Table 2). Of note, these effects were specific to CST integrity reflected by anisotropy across the entire CST, whereas more simple lesion characteristics, such as lesion size or CST lesion volume, did not feature any significant associations with motor impairment.

In summary, our findings outline the crucial role of ipsilesional CST integrity for complex motor control after stroke, as compensatory effects at the cortical level seem to be limited in case of substantial ipsilesional CST damage.

Motor Network Connectivity and Motor Recovery

Patients were divided into subgroups with (N = 15) and without (N = 10) substantial recovery of arm motor function to assess whether the degree of recovery impacted the association between structural connectivity and motor control. For patients featuring substantial recovery, basal motor control was strongly associated with structural connectivity of the homologous clM1 to ilM1 tract

TABLE 3. Recovery-dependent subgroup analysis: Correlations analyses between basal motor control and cortico-cortical connections

	Pearson correlations		Partial correlations	
Connection	**r**	***p* (FDR)**	**r**	***p* (FDR)**
		Substantial recovery		
Homologous				
clM1-ilM1	**0.79**	**0.003****	**0.75**	**0.016***
Intrahemispheric				
ilPMd-ilM1	0.25	0.492	0.30	0.427
ilPMv-ilM1	0.58	0.081	0.55	0.153
ilSMA-ilM1	0.05	0.862	0.19	0.549
Interhemispheric				
clPMd-ilM1	0.22	0.492	0.18	0.549
clPMv-ilM1	0.31	0.467	0.34	0.416
clSMA-ilM1	0.50	0.139	0.42	0.325
		No substantial recovery		
Homologous				
clM1-ilM1	0.44	0.279	0.17	0.657
Intrahemispheric				
ilPMd-ilM1	**0.85**	**0.007****	0.77	0.053
ilPMv-ilM1	**0.81**	**0.010***	0.73	0.060
ilSMA-ilM1	**0.90**	**0.003****	**0.87**	**0.015***
Interhemispheric				
clPMd-ilM1	0.33	0.392	0.34	0.521
clPMv-ilM1	**0.71**	**0.036***	0.68	0.076
clSMA-ilM1	0.30	0.392	0.21	0.657

Note: Analyses were carried out separately for patients featuring (i) substantial or (ii) no substantial recovery as assessed by the difference in NIHSS-arm score in the acute and chronic stage. Partial correlations assessed the relationship between basal motor control and tractwise anisotropy while controlling for ipsilesional CST integrity. Bold font indicates significance after FDR-correction ($p < 0.05$). Asterisks signify the following significance thresholds: ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$. Results are visualized in Figure 4.

Abbreviations: clM1 = contralesional primary motor cortex; clPMd = contralesional dorsal premotor cortex; clPMv = contralesional ventral premotor cortex; clSMA = contralesional supplementary motor area; CST = corticospinal tract; FDR = false discovery rate; ilM1 = ipsilesional primary motor cortex; ilPMd = ipsilesional dorsal premotor cortex; ilPMv = ipsilesional ventral premotor cortex; ilSMA = ipsilesional supplementary motor area; NIHSS = National Institutes of Health Stroke Scale; r = correlation coefficient.

(r = 0.79, $p = 0.003$, FDR-corrected; Table 3, Fig 4A) but showed no significant association with premotor-M1 connectivity. Importantly, this association persisted when controlling for CST integrity (r = 0.75, $p = 0.016$, FDR-corrected; Fig 4B). Conversely, for patients showing no substantial recovery of arm motor function, the interhemispheric clPMv to ilM1 connection (r = 0.71, $p = 0.036$, FDR-corrected) as well as intrahemispheric premotor to ilM1 connectivity was significantly correlated with basal motor control (all r > 0.81, $p < 0.011$, FDR-corrected; see Table 3, Fig 4A). Of note, no significant association was observed for the clM1 to ilM1 connection in patients without substantial recovery (r = 0.44, $p = 0.279$, FDR-corrected). When controlling for CST

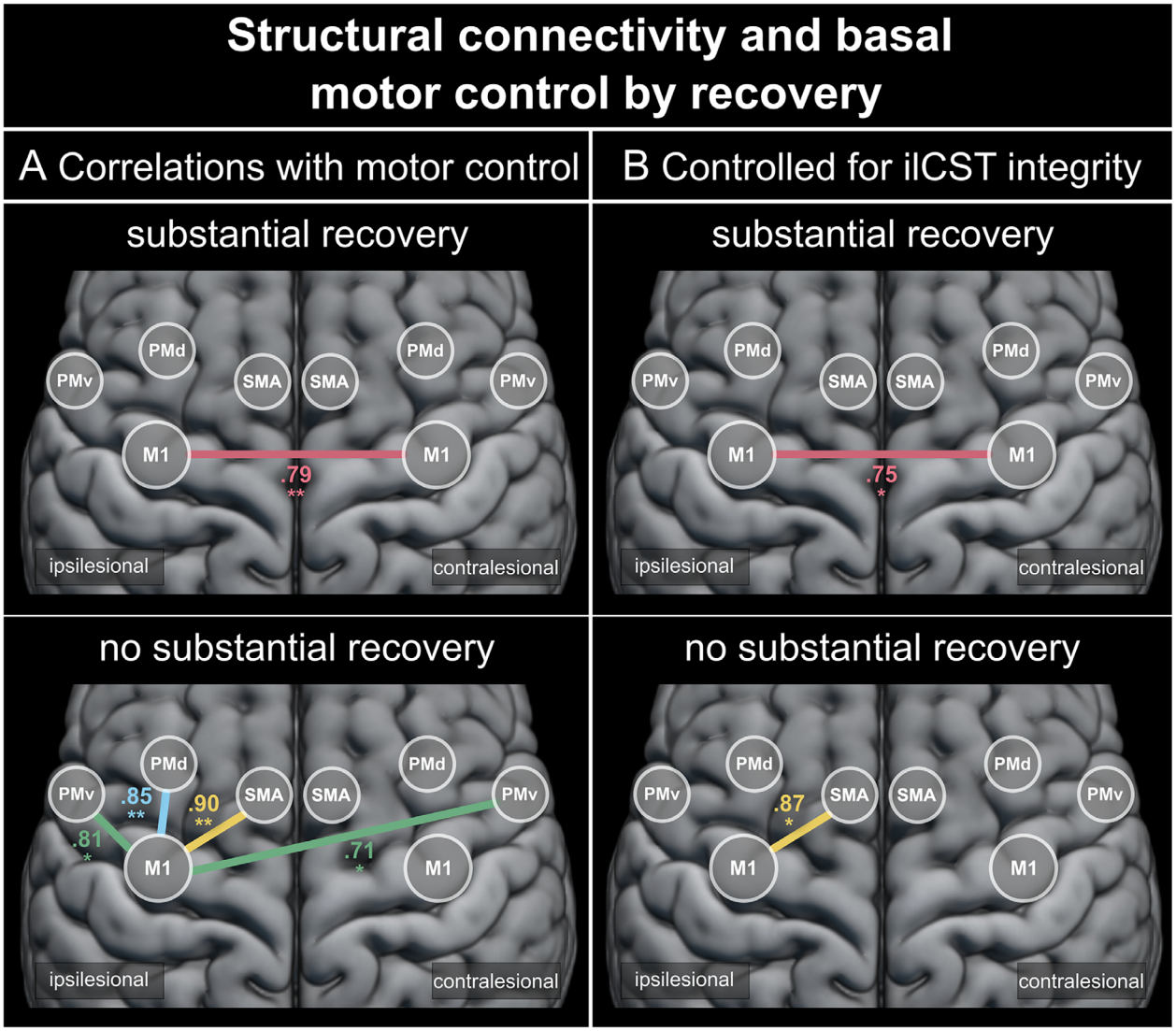

Figure 4: Recovery-dependent subgroup analysis: associations between structural motor network connectivity and basal motor control after stroke. (A) Significant Pearson correlations between tractwise anisotropy and basal control for patients showing (i) substantial or (ii) no substantial recovery. (B) Significant partial correlations between tractwise anisotropy and basal motor control when controlling for ilCST integrity in patients featuring (i) substantial or (ii) no substantial recovery. Of note, only subjects featuring substantial recovery of arm motor function showed an association of interhemispheric M1 to M1 connectivity with basal motor control, highlighting a compensatory role of callosal fibers. All depicted connections were significant after FDR-correction for multiple comparisons ($p < 0.05$). Significance thresholds: ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$. FDR = false discovery rate; ilCST = ipsilesional corticospinal tract; M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; SMA = supplementary motor area. [Color figure can be viewed at www.annalsofneurology.org]

integrity, only the ilSMA to ilM1 connection yielded a significant correlation ($r = 0.87$, $p = 0.015$, FDR-corrected; see Fig 4B). Again, excluding cortico-cortical connections directly affected by the lesion yielded highly similar results (Table S2). Thus, these findings corroborate a recovery-dependent association between structural M1 to M1 connectivity and basal motor control.

In summary, whereas patients with substantial motor recovery heavily relied on interhemispheric M1 to M1 connectivity to ensure basal motor control, patients without substantial recovery of arm function featured no such association. Hence, our findings highlight an essential role of interhemispheric M1 to M1 connectivity in motor recovery, which may serve as a critical route to recruit the intact contralesional motor network and its descending pathways to compensate for the lesion-induced motor impairment after stroke.

Stepwise Linear Backward Regressions

First, we assessed the propensity of CST integrity to explain behavioral impairment. For basal motor control, 28% of variance ($R^2 = 27.71\%$, adjusted $R^2 = 24.57\%$, $p = 0.007$, BIC = 132.46) was explained by the

ipsilesional CST. A highly similar result was obtained for complex motor control ($R^2 = 27.77\%$, adjusted $R^2 = 24.63\%$, $p = 0.007$, BIC = 130.88). Stepwise backward regression models including cortico-cortical connections and ipsilesional CST integrity explained a high amount of variance for both basal and complex motor control. Specifically, 71% of variance in basal motor control ($R^2 = 71.01\%$, adjusted $R^2 = 65.22\%$, $p < 0.001$, BIC = 119.27) and 60% of variance in complex motor control ($R^2 = 60.17\%$, adjusted $R^2 = 46.90\%$, $p = 0.006$, BIC = 132.09) were captured. When excluding the ipsilesional CST and only using cortico-cortical connections in the analysis, the resulting model still explained a substantial amount of variance in basal motor control ($R^2 = 63.26\%$, adjusted $R^2 = 58.01\%$, $p < 0.001$, BIC = 121.98). Conversely, although complex motor control was still explained significantly ($R^2 = 35.02\%$, adjusted $R^2 = 32.19\%$, $p = 0.002$, BIC = 128.24), the ratio of explained variance in complex motor control considerably decreased after ipsilesional CST exclusion. Thus, the stepwise linear backward regression analyses showed that structural motor network connectivity holds valuable information on motor control across subjects. Whereas basal motor control is readily explained by cortico-cortical connectivity, complex motor control crucially relies on ipsilesional CST integrity.

Discussion

Motor control is assumed to rely on a distributed network of cortical and subcortical motor areas, as well as its descending pathways, such as the CST.[34] At the cortical level, premotor areas are crucially involved in shaping motor commands in M1 via dense cortico-cortical connections.[35] After stroke-inflicted CST damage, the question arises how the motor network can reorganize its functional architecture to recover motor control. From a mechanistic perspective, stronger structural cortico-cortical connectivity may allow for more flexible and efficient signal transmission, thereby enabling increased influences of bilateral premotor areas onto ipsilesional M1.[5] Alternatively, ipsilesional M1 output signals that can no longer be transmitted through damaged CST fibers might be relayed either via CST fibers descending from ipsilesional premotor areas or via non-crossing CST fibers originating from contralesional M1.[24,36]

Of note, the functional significance of these proposed mechanisms remains largely unknown and has resulted in conflicting interpretations of previous findings. Given that recovery of basal and complex movements has been shown to differentially benefit from rehabilitation,[37] we hypothesized that both derive from distinct mechanisms.

Complex Motor Control

After stroke, intact structural connections are thought to enable the functional reorganization of motor network dynamics to facilitate recovery. For complex motor skills, such as reaching and grasping movements, we here observed significant correlations with structural connectivity between ipsilesional M1 and contralesional M1 as well as bilateral premotor areas (see Fig 3A). An explanation for this observation may derive from previous fMRI studies indicating that motor performance post-stroke critically relies on ipsilesional premotor-M1 connectivity.[5,7] In general, two possible mechanisms could explain the importance of these connections. First, premotor areas may use intact structural cortico-cortical connections to enhance recruitment of ipsilesional M1. Alternatively, motor signals might be relayed from the ipsilesional M1 to premotor regions and transmitted via their descending CST fibers. However, when controlling for ipsilesional CST integrity, no significant correlations were observed between cortico-cortical connectivity and complex motor control (see Fig 3B). Thus, the potential to adapt hand motor output signals on the cortical level – regardless of their directionality – may be critically limited in case of extensive CST damage, which is well in line with earlier studies.[2,18,38–41] Therefore, our findings emphasize that complex motor commands rely on both cortico-cortical connectivity and ipsilesional CST output signals.

Basal Motor Control

Previous diffusion imaging studies have not typically differentiated basal and complex motor control. Studies focusing on more basal aspects of motor functions have reported varying associations with ipsilesional premotor-M1[11,17,18] as well as interhemispheric M1 to M1[11–14] structural connectivity, painting a rather inconclusive picture. We conceptualized basal motor control as simple movements that require only basic control of specific muscle synergies, such as lifting the arm against gravity. Basal motor control was associated with structural connectivity between ipsilesional M1 and ipsilesional premotor areas, contralesional premotor areas, and contralesional M1 (see Fig 3A). In contrast to complex motor control, partial correlation analyses keeping the influence of ipsilesional CST integrity constant revealed that associations between cortico-cortical connections and basal motor control were largely independent of CST damage (see Fig 3B). In other words, basal motor performance showed less reliance on CST integrity than complex motor control and may thus be compensated via alternative routes. In particular, the fact that structural connectivity between bilateral M1 was significantly associated with basal but not complex motor

control indicates that basal skills may be compensated via recruitment of the contralesional M1.[24] Contralesional M1 may facilitate basal motor control of the paretic arm by either (i) exerting facilitatory influences on the ipsilesional M1[5] or (ii) offering an alternative route for descending motor commands via the contralesional CST.[24] As non-crossing CST fibers predominantly innervate proximal arm and shoulder muscles,[34] this pathway is ideally situated to support proximal movements of the paretic upper limb to facilitate basal movements. Indeed, our recovery-dependent results emphasize that interhemispheric M1 to M1 connectivity constitutes a structural reserve for the reorganization of basal motor control. Patients featuring substantial recovery of motor function showed strong correlations between interhemispheric M1 to M1 connectivity and basal motor control independent of ipsilesional CST integrity (see Fig 4). Further support for this notion stems from Stewart and colleagues who reported callosal anisotropy to be linked to (basal) motor control in patients with favorable motor outcomes at the chronic stage.[14] Hence, recovery of basal motor function seems to depend on a patient's structural reserve enabling the recruitment of contralesional M1 via interhemispheric callosal fibers.

Clinical Relevance

Our current findings highlight the potential of structural cortico-cortical motor network connectivity as a future biomarker to predict specific aspects of motor impairment following stroke. Structural scans can be easily integrated into the clinical routine as they only require little patient compliance.[42,43] For example, the DSI scanning protocol used in the present study offers a fast acquisition time of only 11 minutes. However, the reliable assessment of cortico–cortical connectivity via anisotropy is hindered by voxels with multiple fiber directions. To overcome this problem, we used a compartment-wise approach that differentiates voxels according to the number of trackable fiber directions.[32] Importantly, stepwise backward regression analyses yielded a high ratio of explained variance for both basal and complex motor skills, by far exceeding the ratio of explained variance achieved by CST integrity alone. Moreover, adding CST integrity to the stepwise backward regression drastically increased the percentage of explained variance only for complex motor control. Thus, a potential biomarker should ideally be task-specific: Although it should focus on cortico-cortical connectivity for basal motor control, complex motor control is best explained when considering cortico-cortical connectivity and CST integrity in concert.

Limitations

A major limitation pertains to the limited sample size of 25 chronic stroke patients. Although this sample size is not unusual for hypothesis-driven imaging studies in patient cohorts, a larger sample size would allow for additional analyses. Furthermore, whereas behavioral data were acquired longitudinally, imaging data were acquired cross-sectionally. Thus, to probe the applicability of cortico-cortical connectivity as a clinical biomarker, future research should ideally assess structural connectivity early after stroke.

In addition, the interpretation of our current findings suggesting that basal motor function appears to depend on a patient's ability to recruit non-crossing fibers of the contralesional CST emerging from contralesional M1 via interhemispheric callosal fibers remains speculative. Functional or effective connectivity studies in conjunction with structural analyses are necessary to empirically address the directionality of interhemispheric M1 interactions underlying distinct aspects of motor control. Moreover, one might argue that our results may have been biased by lesions affecting cortico-cortical connections. However, repeating the analyses without considerably lesion-affected cortico-cortical connections yielded highly similar results corroborating the robustness of our findings. Finally, the heterogeneity of lesion locations across patients may have biased our current results. However, stroke is a very heterogeneous disease with motor deficit resulting from different lesion locations.[44] To investigate the compensatory potential of the cortico-cortical motor network we included patients with varying lesion locations. Importantly, repeating our analyses excluding subjects with cortical or brainstem lesions yielded highly similar results, corroborating the robustness of our findings.

Conclusion

Our current findings highlight the seminal importance of structural cortico-cortical motor network connectivity, which serves as a structural reserve for distinct aspects of motor control post-stroke. Our data emphasize that complex motor control depends on an interplay of cortico-cortical motor commands and descending motor output via the ipsilesional CST. Thus, severe CST damage seems to preclude the control of complex motor functions of the paretic hand. Conversely, basal motor control can be successfully compensated via alternative routes. Interhemispheric pathways between bilateral M1 seem to play a crucial role in relaying motor commands to the contralesional motor cortex. This

might help to access intact descending pathways, such as non-crossing fibers of the contralesional CST.[24] Especially patients who underwent substantial recovery from the acute to the chronic stage post-stroke, seemed to heavily rely on this route emphasizing its seminal role in functional reorganization of basal motor control. Our findings thus highlight a differential role of interhemispheric M1 to M1 structural connectivity for basal and complex motor control. This dichotomy may help to explain why different studies have argued that contralesional M1 plays a supportive[45–48] or maladaptive role[23,49,50] for motor control of the paretic hand depending on the used motor tasks. Finally, our results suggest that future studies should consider a combination of cortico-cortical structural connectivity and CST integrity as a possible biomarker for basal and complex motor functions after stroke.

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Author Contributions

T.P., C.G., S.T.G., G.R.F., and L.J.V. contributed to the conception and design of the study. T.P., V.M.W., L.H., M.C., C.T., and L.J.V. contributed to the acquisition and analysis of data. T.P., V.M.W., S.T.G., and L.J.V. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

The authors report no competing interests.

Data Availability Statement

Data are available from the corresponding author upon reasonable request. Tract templates used for the extraction of tractwise anisotropy can be downloaded from the following link: https://tinyurl.com/4ttnnzsr.

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