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Structural reserve-dependent cortical rerouting of motor control after stroke

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Structural cortico-cortical connectivity is essential for motor recovery after stroke, with undamaged fibre tracts potentially serving as structural reserve for functional reorganization. Yet, the mechanisms by which the structural reserve contributes to changes in functional network configurations to improve post-stroke motor control remain unknown.

Here, we assessed structural (diffusion spectrum imaging) and effective (functional MRI-based dynamic causal modelling) connectivity to examine how the structural reserve may guide motor network reorganization of upper limb motor control.

Specific features of cortico-cortical structural reserve were associated with distinct patterns of functional network configurations: limited intrahemispheric structural reserve between ipsilesional primary motor cortex and premotor areas was linked to interhemispheric rerouting of motor commands via the contralesional primary motor cortex, particularly when ipsilesional corticospinal tract integrity was low. In contrast, limited interhemispheric structural reserve between ipsilesional primary motor cortex and contralesional premotor areas was related to intrahemispheric rerouting via the ipsilesional premotor cortex, especially in patients with high residual corticospinal tract integrity. Even though both alternative pathways may allow bypassing damaged corticospinal tract fibres originating from the ipsilesional primary motor cortex, we observed a clear behavioural dissociation: in patients who substantially recovered, enhanced intrahemispheric rerouting was indicative of better hand function, reflecting beneficial reorganization. Conversely, interhemispheric rerouting was associated with pronounced motor impairment of the paretic arm and primarily observed in non-substantially recovered patients, in line with task-specific maladaptive reorganization.

Our findings emphasize that the motor network's available structural reserve critically shapes functional network reorganization by predetermining whether motor commands are primarily rerouted intra- or interhemispherically with distinct implications for motor recovery. Besides helping to reconcile previous conflicting interpretations on the role of contralesional primary motor cortex, our results underscore that the individual level of structural motor network reserve should be considered for future therapeutic approaches aiming at amplifying motor recovery after stroke.

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Introduction

The structural reserve, denoting the level of premorbid structural connectivity of white matter pathways undamaged by the stroke lesion, has gained increasing attention regarding its role in motor recovery after stroke.[1-4] As damaged long-range white matter connections between remote brain regions are unlikely to be re-established in the adult brain,[5] functional network reorganization is assumed to primarily rely on pre-existing, undamaged structural connections.[1,4] In particular, higher levels of structural connectivity are thought to promote motor recovery after stroke.[2,3,6-8] For example, post-stroke motor control has been shown to be associated with higher structural connectivity between ipsilesional primary motor cortex (M1) and premotor areas,[3,7] as well as between bilateral M1.[3] However, it remains unknown how the available structural reserve of the motor network may facilitate changes in functional network configurations enabling upper limb recovery.

To address this question, we combined analyses of diffusion MRI (dMRI)-based structural and functional MRI (fMRI)-based effective connectivity within the cortico-cortical motor network in a cohort of chronic stroke patients. Specifically, inter-regional structural connectivity was quantified using diffusion spectrum imaging (DSI) and a compartmentwise analysis approach.[2,9] Task-related effective connectivity was estimated using dynamic causal modelling (DCM)[10] during simple affected hand movements, characterizing the influence that cortical motor regions exert on each other.

Conceptually, cortico-cortical connections may support post-stroke motor recovery by providing alternative routes when lesions compromise primary motor output pathways such as the corticospinal tract (CST). In other words, motor commands issued by the ipsilesional M1 might be relayed to other motor areas with access to intact descending fibres. Such rerouting of descending motor commands may occur: (i) intrahemispherically via preserved CST fibres originating from ipsilesional premotor areas[11,12]; or (ii) interhemispherically via non-crossing CST fibres originating from contralesional M1.[3,13] Building on recent evidence suggesting that premotor-CST fibres are likely to facilitate motor control post-stroke,[12] we hypothesized that intrahemispheric rerouting from the ipsilesional M1 via premotor areas might be advantageous for the recovery of upper limb motor control, including dextrous hand movements. Of note, we assumed that the propensity of the motor network to instantiate such beneficial intrahemispheric rerouting via premotor areas critically depends on sufficient residual CST integrity and the level of intrahemispheric structural reserve. Conversely, the role of the contralesional M1 in motor recovery remains a topic of ongoing scientific debate, rendering a prediction on the functional role of interhemispheric rerouting more challenging.[1,14-17] We hypothesized to observe interhemispheric rerouting particularly in patients suffering from severe CST damage and a high level of interhemispheric structural reserve. Of note, while interhemispheric rerouting was expected to be beneficial for more basal aspects of arm motor control, we assumed no beneficial impact on hand motor function.[3] Taken together, exploring the role of the structural reserve for motor recovery may not only expand our mechanistic understanding of post-stroke network reorganization but might also hold seminal implications for future therapeutic interventions.

Materials and methods

Participants

Twenty-five chronic stroke patients [mean age = 66.68 years, standard deviation (SD) = 11.25 years, 5 females], previously hospitalized at the University Hospital Cologne, Department of Neurology, were recruited for this study. Two patients had to be excluded from the final analyses due to insufficient fMRI data (for detailed demographic and clinical information, see Supplementary Table 1). Inclusion criteria were: (i) a first ischaemic stroke more than 6 months ago; (ii) initial unilateral upper limb motor deficits; and (iii) age between 40 and 90 years. Exclusion criteria were: (i) any contraindications to MRI; (ii) reinfarction or other neurological diseases; (iii) persistence of severe neglect or aphasia; (iv) bihemispheric stroke; and (v) cerebral haemorrhage. Moreover, 22 age-matched healthy participants were recruited (mean age = 67.05 years, SD = 6.59 years, 6 females). All subjects provided written 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. While diffusion MRI data of the patient cohort were reported in previous publications,[2,3,12] analyses of effective connectivity and the multimodal assessment of structural and effective connectivity represent novel aspects unique to the current study.

Behavioural motor assessments

We quantified motor impairment of patients with regard to different aspects of motor control.[3] Basal arm motor control of the paretic upper limb was assessed using the Motricity Index (MI)-arm score,[18] while impairment of hand motor control was measured via the relative frequency of finger tapping of the affected compared with the unaffected hand during the fMRI motor task. Patients were divided into substantially or non-substantially recovered subgroups to examine whether network-level differences were reflected by the degree of motor recovery. Improvement of one point or more in the National Institutes of Health Stroke Scale (NIHSS)-arm score from the acute (upon Stroke Unit admission) to the chronic phase (at the time of MRI scanning) post-stroke was classified as substantial recovery ($n = 13$), whereas non-substantial recovery ($n = 10$) was denoted by a lack of improvement in the NIHSS-arm score.[3] Of note, given the coarse nature of the NIHSS-arm scale, no change in this score from the acute to the

chronic stage does not signify a lack of motor recovery *per se*. In other words, patients without improvement in the NIHSS-arm score were categorized as patients with no substantial recovery rather than no recovery of motor function at all.

MRI acquisition and preprocessing

MRI data were recorded using a Siemens MAGNETOM Prisma 3 Tesla scanner (Siemens Medical Solutions). Stroke lesion masks were drawn on individual T2-weighted images in MRIcron (https://www.nitrc.org/projects/mricron) and verified by a certified neurologist. All right-hemispheric lesions were flipped along the mid-sagittal plane so that all lesions were located in the left hemisphere (Supplementary Fig. 1).

DSI scans were collected with a spatial resolution of $1.8 \times 1.8 \times 1.8$ mm^3 using b-values ranging from 0 to 5000 s/mm^2 (b-values in s/mm²: 0, 300, 600, 900, 1200, 1250, 1500, 1800, 2400, 2450, 2700, 2750, 3000, 3050, 3300, 3350, 3600, 3900, 3950, 4200, 4250, 4850, 4900), 128 diffusion directions and 10 additional b0s for movement correction (repetition time = 4300 ms, echo time = 96 ms, field of view = 262 mm). Preprocessing of DSI data was performed using QSIPrep.[19] Generalized fractional anisotropy (gFA) maps were generated using DSI Studio (https://dsi-studio.labsolver.org/) to assess the microstructural integrity of the white matter connections between cortical motor regions. Please see our previous publications for a detailed description of dMRI acquisition and preprocessing.[2,3] Resulting individual gFA maps were normalized to the Montreal Neurological Institute (MNI) standard space using Advanced Normalization Tools (ANTs).[20] To facilitate group comparisons and ensure that all lesions were located in the left hemisphere, gFA maps with right-hemispheric lesions were flipped along the mid-sagittal plane.

Functional MRI data were recorded using a gradient echo planar imaging (EPI) multiband sequence with the following parameters: repetition time = 800 ms, echo time = 30 ms, 72 axial slices, 2.0 mm^3 isometric voxel size, flip angle = 52°. Participants performed a visually cued motor task in a block-design, consisting of repetitive index finger tapping movements.[21,22] During each block, repetitive tapping movements were performed with the paretic or the unaffected hand. Blocks were presented in a pseudorandomized order. fMRI data were preprocessed and analysed using Statistical Parametric Mapping (SPM12; The Wellcome Centre for Human Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk) in MATLAB version 2022a (The Mathworks Inc., MA, USA). The first 12 EPI scans were discarded as dummy images to prevent noise from potential magnetic field saturation. During preprocessing, EPI images were realigned, co-registered to the subject's T1-weighted image, spatially normalized to standard MNI template space with masked lesions and smoothed with a Gaussian kernel of 5 mm full-width at half-maximum (FWHM). Each preprocessing step was visually inspected to ensure successful co-registration and normalization. For the first level analysis, a general linear model (GLM) was applied to the three experimental conditions (movement of the affected hand, movement of the unaffected hand and visual instructions) and convolved with a canonical haemodynamic response function. The six head motion parameters as well as the white matter and cerebrospinal fluid confounds were used as covariates.

Estimation of structural connectivity

Deterministic fibre tracking, as implemented in DSI Studio,[23] was used to generate normative fibre tract templates connecting cortical motor areas based on the Human Connectome Project (HCP)-1065 template. Intrahemispheric fibre tracts were defined for connections between ipsilesional (il) premotor areas, i.e. dorsal/ventral premotor cortex (PMd; PMv) and supplementary motor area (SMA), and ipsilesional M1 (ilM1-ilPMd, ilM1-ilPMv and ilM1-SMA). Interhemispheric fibre tracts were characterized for connections between contralesional (cl) premotor areas and ipsilesional M1 (ilM1-clPMd, ilM1-clPMv and ilM1-clSMA), and between bilateral M1 (ilM1-clM1). Additionally, a CST mask with descending fibres originating from M1, PMd, PMv and SMA was generated to assess ipsilesional CST integrity. To determine the structural connectivity of the motor network, we quantified tractwise anisotropy for these normative tract templates—also referred to as tractwise mean gFA—using a compartmentwise approach.[2,3] In other words, after extraction of mean gFA values from voxels inside the defined fibre tracts, quantification of structural connectivity was restricted to voxels with only one dominant fibre direction to overcome methodological constraints of reliable anisotropy quantification in multidirectional voxels.[2,9]

Estimation of task-related effective connectivity

Task-related effective connectivity was analysed using DCM as implemented in SPM12. This model-based framework conceptualizes effective connectivity as a directed excitatory or inhibitory influence of one brain area over another, leading to changes in the system's neuronal state that are expressed by the following bilinear differential state equation:[24]

$$\frac{dz}{dt} = \left[A + \sum_{j=1}^{m} u_j B^{(j)} \right] z + Cu \quad (1)$$

Here, the neuronal state is defined by z and A, B and C represent matrices containing the coupling parameters that describe the rate of activity change induced by synaptic influences. u defines the experimental input. The endogenous connectivity, i.e. the connectivity of the system in the absence of external interference, is captured by matrix A. Instead, matrix B contains the connectivity changes due to external inputs like the experimental conditions, here finger tapping movements. Matrix C comprises respective extrinsic influences. We focused our analyses on the effective connectivity among the same cortical regions of interest (ROIs) as described above with respect to structural connectivity: bilateral M1, PMd, PMv and SMA. To determine the coordinates of the different ROIs, individual activation maps of the contrasts 'movement of the affected hand versus rest' and 'movement of the unaffected hand versus rest' were used. Anatomical constraints[25-27] and a voxel-level threshold of $P < 0.001$ were used to identify subject-specific activation peaks that served as ROI coordinates (Supplementary Tables 2 and 3). The first eigenvariate of the time series was extracted from each ROI in the affected and unaffected hemisphere, centred around the individual activation peaks within a 10 mm sphere and adjusted for effects of interest. Identifying individual activation peaks ensured that each ROI exhibited a task-relevant blood oxygenation level-dependent (BOLD) signal and precluded relevant biases introduced by potential partial volume effects with lesioned tissue. We estimated a total of 10 DCMs varying in their complexity ranging from sparsely (i.e. connections only with ipsilesional M1) to fully connected models (Supplementary Figs 2–4). Bilateral premotor ROIs (six premotor areas) were defined as driving input regions (DCM-C matrix). Bayesian model selection

based on a random effects approach[28] identified the fully connected model as the winning model given our empirical data (Supplementary Fig. 5). Coupling parameters of the fully connected model estimated during finger tapping movements of the affected hand (DCM-B_{aff}) were tested for statistical significance at the group level using one-sample *t*-tests against zero [false discovery rate (FDR)-corrected for multiple comparisons]. Significantly modulated coupling parameters were used for subsequent analyses.

Statistical analyses

To determine whether structural connectivity (tractwise mean gFA) or effective connectivity (DCM-B_{aff}) obtained from stroke patients differed from those of healthy subjects, group comparisons were performed via independent *t*-tests. Similarly, group comparisons of effective connectivity between patients featuring substantial versus non-substantial recovery were conducted using independent *t*-tests. All group comparisons and correlation analyses reported below were FDR-corrected for intra- and interhemispheric connections to account for multiple comparisons.

Moreover, we explored structure–function relationships to determine whether the available structural reserve was associated with effective connectivity reflecting intra- or interhemispheric rerouting of motor commands. To do so, Pearson correlation analyses were computed including structural and effective connectivity for connections from ipsilesional M1 to intra- and interhemispheric premotor areas as well as contralesional M1. To further investigate the impact of residual CST integrity on structure–function relationships, we stratified patients into high and low CST integrity groups (Supplementary Table 1) using a median split of individual ipsilesional CST mean gFA values and repeated the correlation analyses within each subgroup.

To address the question whether multimodal connectivity of specific motor network connections was associated with upper limb motor control after stroke, Pearson correlation analyses were performed between patients' structural or effective connectivity and estimates of arm or hand motor control. In order to determine recovery-related differences, correlation analyses between effective connectivity and motor control were repeated for both recovery subgroups.

Finally, to ensure that our results were not biased by a potential overlap between lesions and ROIs used for BOLD signal extraction, we repeated group comparisons and correlation analyses after excluding subjects whose lesions overlapped with any of their individual ROIs ($n = 3$ subjects).

Results

Motor network connectivity

Comparison of structural cortico-cortical connectivity between control subjects and stroke patients revealed that patients demonstrated lower interhemispheric M1-M1 [$t(43) = 2.63$, $P_{FDR} = 0.047$] as well as lower intrahemispheric premotor-M1 connectivity compared with healthy subjects [$t(43) > 2.23$, $P_{FDR} < 0.046$; Fig. 1].

Movements of the affected hand significantly modulated various connections of the bilateral motor network (Fig. 2A). In particular, excitatory coupling from ipsilesional premotor areas to ipsilesional M1 was observed alongside an inhibitory coupling from ipsilesional M1 onto bilateral premotor areas. Unlike healthy subjects, patients exhibited a significant decrease in the excitatory influences exerted on ipsilesional M1 by premotor areas [$t(43) > 2.68$, $P_{FDR} < 0.024$]. Most importantly, the inhibitory coupling from the active (ipsilesional) M1 to the inactive (contralesional) M1 observed in healthy subjects turned into a non-physiological excitatory coupling in stroke patients [$t(43) = -4.48$, $P_{FDR} < 0.001$; Fig. 2C].

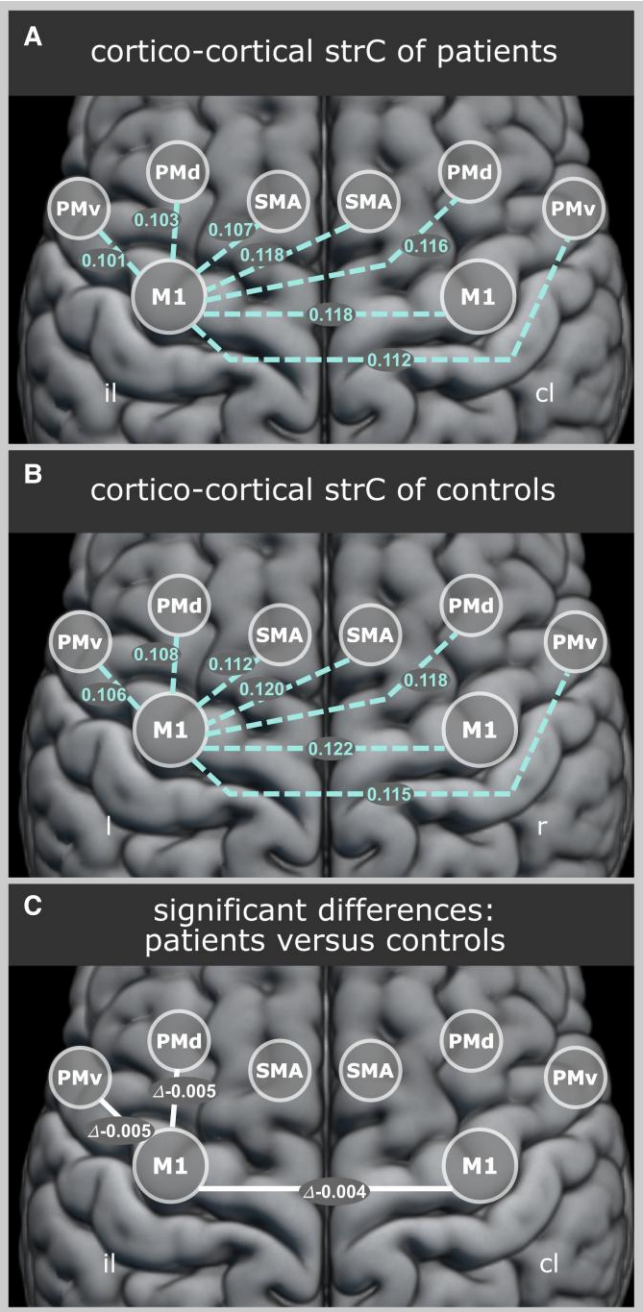

Figure 1 Structural motor network connectivity in patients and control subjects. (**A**) Cortico-cortical structural connectivity (dashed blue lines) defined by tractwise mean generalized fractional anisotropy in chronic stroke patients and (**B**) healthy participants. (**C**) Group differences revealed significantly lower levels of interhemispheric M1-M1 and intrahemispheric premotor-M1 structural connectivity in patients compared with controls ($P_{FDR} < 0.05$). cl = contralesional; FDR = false discovery rate; il = ipsilesional; l = left; M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; r = right; SMA = supplementary motor area; strC = structural connectivity.

Interestingly, we observed recovery-specific network differences: non-substantially recovered patients showed more pronounced inhibitory coupling from ipsilesional M1 onto contralesional SMA [$t(21) = 2.51$, $P_{FDR} = 0.031$] and featured significantly greater excitatory

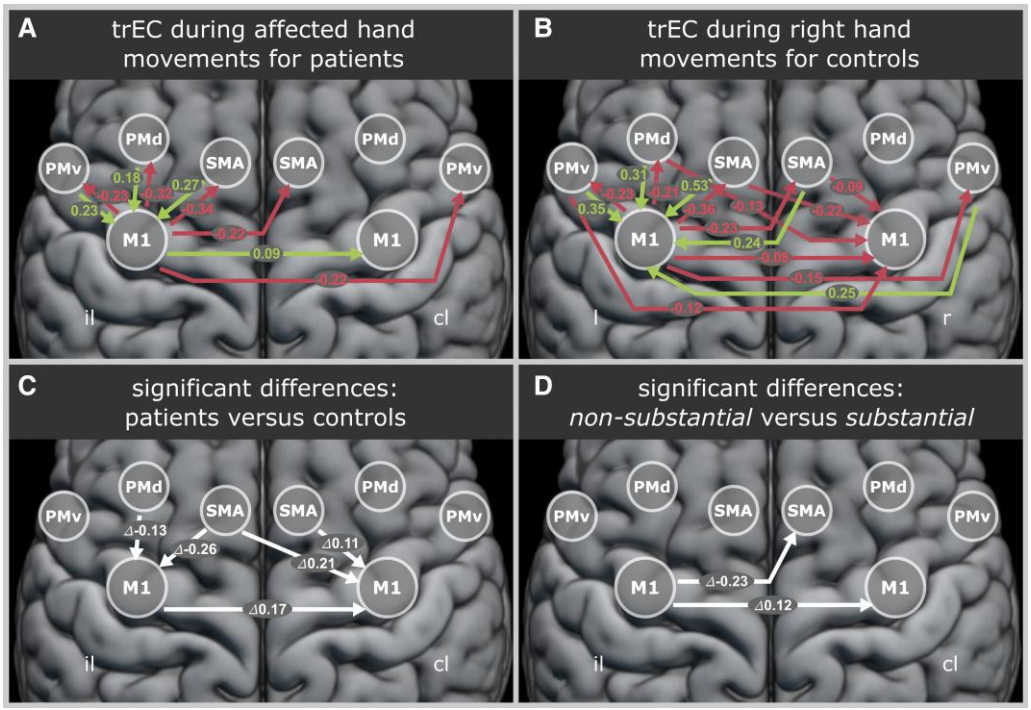

Figure 2 Task-related effective motor network connectivity during repetitive hand movements. (**A**) Connections significantly modulated during affected hand movements in chronic stroke patients at the group level (DCM-B_{aff}). Results revealed a strong excitatory coupling from ipsilesional premotor areas onto ipsilesional M1 along with inhibitory influences from ipsilesional M1 onto bilateral premotor areas. Of note, an excitatory coupling from ipsilesional M1 onto contralesional M1 was observed. (**B**) Conversely, control subjects exhibited the physiologically expected inhibition from ipsilesional M1 onto contralesional M1. Green arrows indicate excitatory, red arrows indicate inhibitory coupling between regions. Presented values represent significant group-level averages across the respective groups ($P_{FDR} < 0.05$). (**C**) Group differences in effective connectivity indicated that patients featured increased excitatory drive onto contralesional M1 and decreased facilitatory influences targeting ipsilesional M1 compared with healthy controls ($P_{FDR} < 0.05$). (**D**) Of note, pronounced excitatory coupling from ipsilesional M1 onto contralesional M1 [$t(21) = -2.59$, $P_{FDR} = 0.031$] and stronger inhibition issued by ipsilesional M1 onto contralesional SMA [$t(21) = 2.51$, $P_{FDR} = 0.031$] were observed in non-substantially compared with substantially recovered patients. cl = contralesional; FDR = false discovery rate; il = ipsilesional; l = left; M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; r = right; SMA = supplementary motor area; trEC = task-related effective connectivity.

coupling from ipsilesional to contralesional M1 compared with substantially recovered patients [$t(21) = -2.59$, $P_{FDR} = 0.031$; Fig. 2D]. In other words, increased interhemispheric rerouting was recovery-specific, with patients featuring non-substantial motor recovery demonstrating higher interhemispheric rerouting from ipsilesional M1 to the contralesional M1.

Of note, highly similar effective connectivity patterns were observed when comparing patients suffering from left- or right-hemispheric lesions (Supplementary Fig. 6). Furthermore, after excluding subjects with lesion-ROI overlap ($n = 3$), group comparisons yielded highly similar results. Thus, these findings render a bias introduced by lesion lateralization or lesions directly affecting cortical motor regions unlikely.

Structural reserve and effective motor network connectivity

No significant correlation was observed between structural and effective connectivity for any single connection. In other words, the underlying structural connectivity of a connection was not indicative of the modulation of effective connectivity of this respective connection observed during affected hand movements. However, we observed that the pathophysiologically enhanced interhemispheric effective connectivity from ipsilesional M1 onto contralesional M1 significantly correlated with intrahemispheric structural connectivity between ipsilesional M1 and all premotor areas (Fig. 3A). Specifically, patients featuring low levels of ipsilesional premotor-M1 structural connectivity showed high interhemispheric connectivity from ipsilesional M1 onto contralesional M1 (all $r < -0.46$, $P_{FDR} < 0.027$; Fig. 3B). This finding is in line with the notion that limited intrahemispheric structural reserve might prompt interhemispheric rerouting via the contralesional hemisphere, while this is not observed in patients with higher levels of intrahemispheric structural reserve. Moreover, patients with lower interhemispheric structural connectivity showed stronger intrahemispheric rerouting from ipsilesional M1 to PMv (all $r > 0.47$, $P_{FDR} < 0.05$; Fig. 3C). Importantly, these structure–function relationships were related to the level of CST integrity. Patients featuring low CST integrity only exhibited increased interhemispheric rerouting when intrahemispheric structural reserve was limited (all $r < -0.61$, $P_{FDR} < 0.024$; Fig. 3D). Conversely, patients with high levels of residual CST integrity exclusively showed pronounced intrahemispheric rerouting of motor control ($r = 0.70$, $P_{FDR} = 0.043$; Fig. 3E). These structure–function relationships were only observed for connections that also featured altered structural connectivity compared with healthy controls (cf. Fig. 1).

Connectivity and motor control after stroke

Higher levels of structural cortico-cortical connectivity between all ipsilesional premotor areas and M1 as well as between bilateral M1 were significantly associated with better arm motor control, as

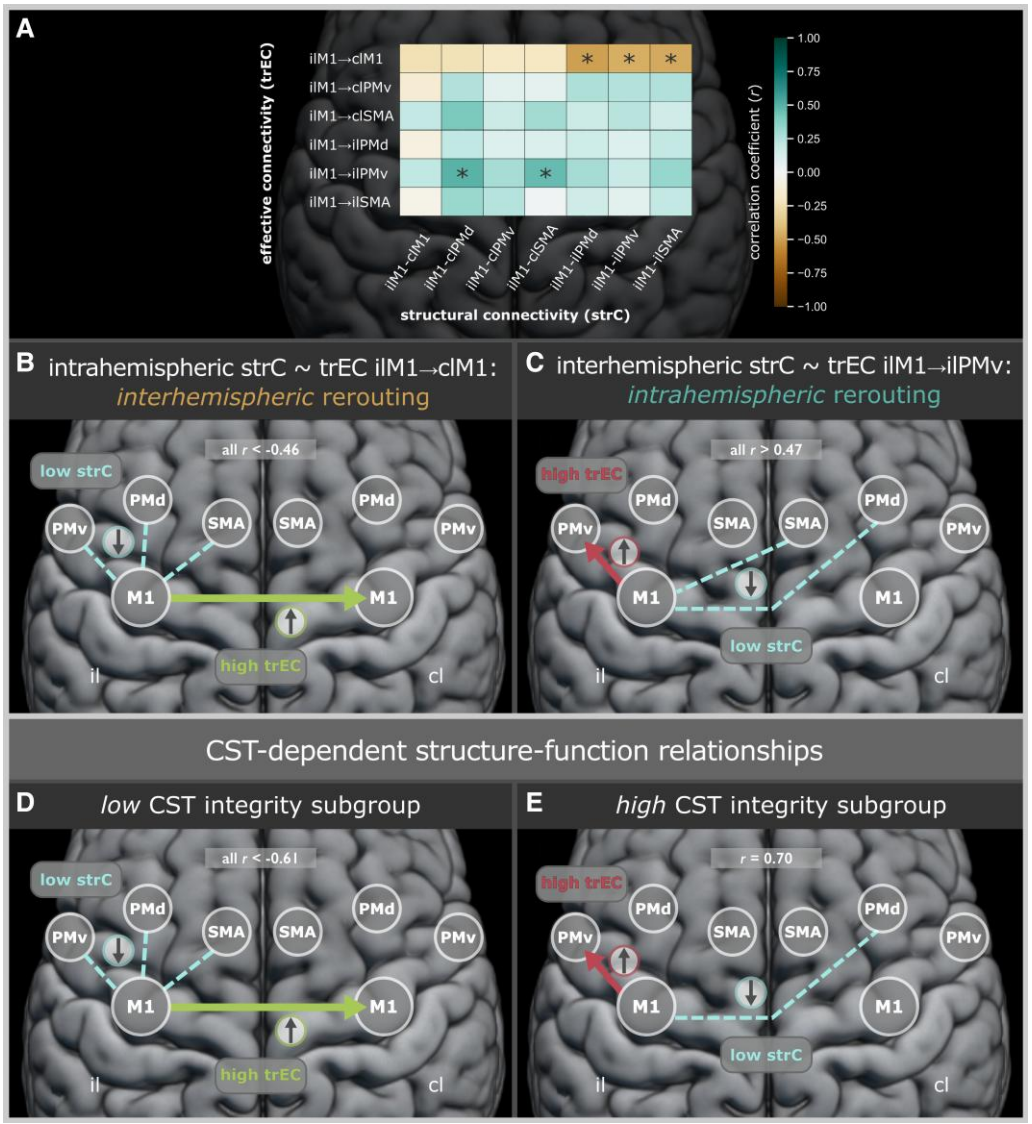

Figure 3 Structure–function relationships after stroke. (**A**) Associations between structural and effective connectivity reflecting intra- or interhemispheric rerouting of motor commands during affected hand movements across patients (*$P_{FDR} < 0.05$). Colours indicate Pearson correlation coefficients (*r*), ranging from −1 (orange) to +1 (blue) as represented by the colour bar. (**B**) Patients with lower intrahemispheric structural connectivity between ipsilateral M1 and premotor areas (blue dashed lines) exhibited higher excitatory coupling (green arrow) from ipsilesional to contralesional M1 (all $r < -0.46$, $P_{FDR} < 0.027$), reflecting enhanced interhemispheric rerouting. (**C**) Conversely, patients with lower interhemispheric structural connectivity (blue dashed lines) exhibited stronger inhibition (red arrow) from ipsilesional M1 to PMv (all $r > 0.47$, $P_{FDR} < 0.05$), in line with intrahemispheric rerouting of motor commands via premotor areas. Interestingly, these distinct structure–function relationships were CST dependent. (**D**) Patients with low CST integrity only showed the structural reserve-dependent increase in interhemispheric rerouting via the contralesional M1 (all $r < -0.61$, $P_{FDR} < 0.024$). (**E**) In contrast, patients featuring high CST integrity after stroke exclusively exhibited increased intrahemispheric rerouting from ipsilesional M1 to PMv with lower interhemispheric network structural reserve ($r = 0.70$, $P_{FDR} = 0.043$). Of note, opposing structure-function correlation coefficients resulted from excitatory (positive) and inhibitory (negative) trEC coupling parameters. cl = contralesional; CST = corticospinal tract; FDR = false discovery rate; il = ipsilesional; M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; SMA = supplementary motor area; strC = structural connectivity; trEC = task-related effective connectivity.

reflected by the MI-arm score (all $r > 0.44$, $P_{FDR} < 0.045$), in line with previous reports.[3] Moreover, significant correlations were observed between structural connectivity of these connections and hand motor control, as assessed via the relative finger tapping frequency (all $r > 0.49$, $P_{FDR} < 0.037$; Fig. 4A). Of note, all connections that showed a significant association between structural connectivity and motor control were also significantly modulated during affected hand movements (cf. Fig. 2A).

Examining the relationship between effective connectivity and upper limb function, we found that patients with higher excitatory coupling from ipsilesional M1 onto contralesional M1 demonstrated more severe impairment of arm motor control ($r = -0.64$, $P_{FDR} = 0.003$; Fig. 4B). In other words, the non-physiological interhemispheric rerouting via the contralesional M1 was associated with severe arm motor impairment. Notably, this negative association was recovery-specific: interhemispheric rerouting was linked to poor arm motor control only in patients featuring non-substantial recovery from the acute to the chronic phase after stroke ($r = -0.80$, $P_{FDR} = 0.016$; Fig. 4D). In contrast, in substantially recovered patients, no significant correlation was found after correcting for multiple

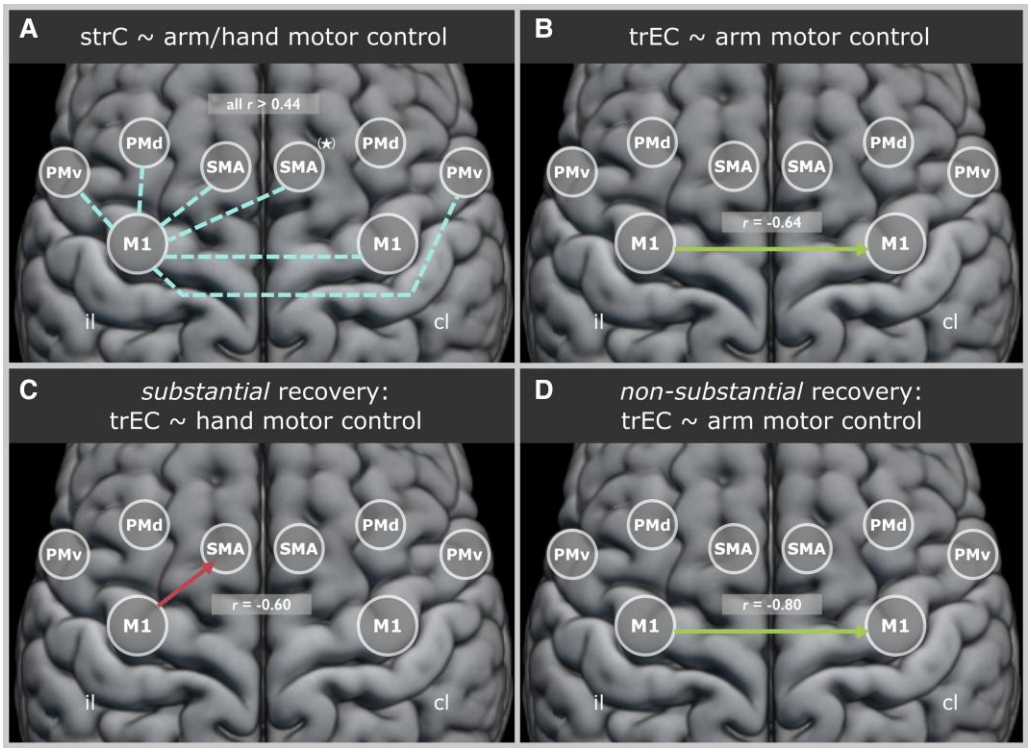

Figure 4 Multimodal network connectivity and association with upper limb motor control after stroke. (**A**) Significant positive associations were observed between structural connectivity (blue dashed lines) and paretic arm motor control ($r > 0.44$, $P_{FDR} < 0.045$) as well as hand motor control ($r > 0.49$, $P_{FDR} < 0.037$). Of note, all ipsilesional structural M1 connections featuring a significant association with upper limb motor control were also significantly modulated during affected hand movements in the functional MRI task (Fig. 2A; (★)significant association with arm but not hand motor control). Correlation plots are further illustrated in Supplementary Figs 7–8. (**B**) Task-related excitatory effective connectivity (green arrow) from ipsilesional M1 onto contralesional M1 during affected hand movements was negatively associated with arm motor control ($r = -0.64$, $P_{FDR} = 0.003$). Of note, recovery-specific associations were observed: (**C**) in substantially recovered patients, stronger inhibitory effective connectivity (red arrow) from ipsilesional M1 onto ipsilesional SMA was linked to better hand motor control ($r = -0.60$, $P_{uncorr} = 0.029$, $P_{FDR} = 0.173$). (**D**) Conversely, the excitatory interhemispheric rerouting via contralesional M1 was associated with poor arm motor control in non-substantially recovered stroke patients ($r = -0.80$, $P_{FDR} = 0.016$). Subgroup correlation plots are further illustrated in Supplementary Fig. 9. cl = contralesional; FDR = false discovery rate; il = ipsilesional; M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; SMA = supplementary motor area; strC = structural connectivity; trEC = task-related effective connectivity.

comparisons. However, on an uncorrected level, intrahemispheric rerouting from ipsilesional M1 to ipsilesional SMA was associated with better hand motor control ($r = -0.60$, $P_{uncorr} = 0.029$, $P_{FDR} = 0.173$; Fig. 4C). Of note, highly similar results were obtained after excluding subjects with any lesion-ROI overlap ($n = 3$).

Discussion

The structural reserve of the cortical motor network is increasingly recognized to play a crucial role in motor control and recovery after stroke. In particular, structural connectivity between ipsilesional premotor areas and M1,[3,6,7] as well as interhemispheric connectivity between bilateral M1[3] have been reported to contribute to upper limb motor function after stroke. From a functional perspective, physiological patterns of effective motor network connectivity have been shown to change in distinct ways with beneficial and sometimes maladaptive effects on motor control.[22,25,26,29-31] Such changes in functional network configurations have been interpreted to depend on several factors, including the extent of ipsilesional CST damage, time after stroke, degree of motor recovery and the specific task used in a given study.[16,22,25,26,32-36] However, it remains unknown how the structural reserve of the cortical motor network may predetermine changes in functional network configurations facilitating motor recovery.

Intrahemispheric rerouting of motor control

From a mechanistic perspective, premotor-M1 connectivity may support post-stroke motor control in at least two ways. On the one hand, white matter connections between premotor areas and ipsilesional M1 might promote modulation of M1 activity by premotor areas, as observed in healthy subjects[29-31] and stroke patients.[25,26,32,37] While excitatory premotor-M1 connectivity in stroke patients was indeed altered compared with healthy controls (Fig. 2C) in line with previous findings,[25] no association with upper limb motor control was evident, hindering a conclusive interpretation regarding the functional significance of this observation.

On the other hand, ipsilesional premotor-M1 structural connectivity may enable intrahemispheric rerouting of motor commands. More specifically, after damage to CST fibres originating from M1, motor commands computed in M1 may be relayed to premotor areas that offer access to intact premotor-CST fibres as alternative descending pathways.[12] Importantly, our findings underscore that the motor network's propensity for intrahemispheric rerouting of motor commands might critically depend on the network's structural reserve. Higher levels of intrahemispheric structural reserve between

ipsilesional M1 and premotor areas were associated with decreased interhemispheric rerouting. In contrast, lower interhemispheric structural reserve was linked to enhanced intrahemispheric rerouting via ipsilesional PMv, particularly when residual CST integrity was high (Fig. 5A). In other words, given sufficient CST integrity, intrahemispheric rerouting may allow the recruitment of ipsilesional premotor areas to generate descending motor commands in order to facilitate motor control.[6,11,12,36,38] Support for this interpretation derives from work in macaques showing that the ventral premotor area projects to spinal segments that innervate hand muscles, representing essential projections for the recovery of hand function.[39] Consistent with this notion, enhanced intrahemispheric rerouting from ipsilesional M1 to SMA seemed to support hand motor control in substantially recovered patients (Fig. 4C), in line with the SMA's central role in self-initiated and sequential hand movements.[40,41] Moreover, recent work in humans reported stroke-related changes in functional connectivity between premotor areas, particularly SMA and PMv, and the spinal cord, which were linked to residual motor impairment.[42] The authors proposed that premotor areas are functionally connected to spinal cord segments which contribute to hand function after stroke.

Together, these findings suggest that intrahemispheric rerouting via premotor areas may represent an essential aspect of successful reorganization, supporting hand motor control by engaging descending fibre tracts that circumvent compromised primary motor pathways.

Interhemispheric rerouting of motor control

An alternative route to bypass damaged motor output pathways may involve an interhemispheric rerouting of motor commands via the corpus callosum, providing access to non-crossing CST fibres originating from contralesional M1.[3,13] In contrast to the physiological inhibition of the inactive (contralesional) M1 by the active (ipsilesional) M1 observed in healthy subjects,[22,25,26,31] chronic stroke patients showed an excitatory coupling from the ipsilesional to the contralesional M1 (Fig. 2). Of note, this finding provides empirical evidence for a pathophysiological rerouting from the ipsilesional onto the contralesional M1, as speculated in our previous work.[3]

Contrary to our hypothesis, interhemispheric rerouting did not depend on the level of structural connectivity between bilateral M1. Instead, it was particularly pronounced when structural connectivity between ipsilesional M1 and premotor areas was low. Especially in cases of compromised CST integrity, limited intrahemispheric structural reserve seemed to prompt interhemispheric rerouting of motor commands to the contralesional hemisphere (Fig. 5B). This finding nicely aligns with previous research highlighting that the recruitment of the contralesional hemisphere and alterations of interhemispheric connectivity may be pronounced after severe CST damage.[8,33-35,43,44] Mechanistically, more extensive CST damage along with limited intrahemispheric structural reserve may necessitate rerouting of motor commands via the corpus callosum to access intact descending motor output pathways of the contralesional hemisphere.[3,13]

Notably, interhemispheric rerouting was associated with pronounced arm motor impairment and most prominent in non-substantially recovered patients (Fig. 4). At first glance, this finding contradicts our initial assumption of a beneficial impact of interhemispheric rerouting after stroke,[3] a view supported by several previous studies.[43,45-47] For example, Peng et al.[45] reported that enhanced interhemispheric connectivity targeting contralesional M1 during grasping movements facilitated motor control in well-recovered stroke patients. A potential explanation for the negative association with arm motor control observed here might derive from the well-documented task-specific nature of changes in motor network connectivity.[16,32,48] In particular, we here assessed effective connectivity during finger tapping, which constitutes a distal motor task. Since interhemispheric rerouting likely accesses non-crossing contralesional CST fibres[3,13] that primarily innervate proximal muscles of the arm but do not project to distal hand muscles,[49] an fMRI task involving more proximal arm movements might reveal different functional network configurations. More specifically, during proximal arm movements contributing to reaching and grasping, interhemispheric rerouting might benefit upper limb motor control after stroke. To resolve this caveat and prevent a generalized interpretation of our current findings, future studies that include both distal and proximal fMRI tasks are warranted.

An alternative explanation for the maladaptive implications of interhemispheric rerouting could lie in the structural reserve dependency of effective connectivity patterns observed here. Support for this notion derives from recent evidence linking greater intrahemispheric structural disconnections of ipsilesional M1 to maladaptive influences exerted by the contralesional M1.[50] Together, these findings suggest a network-level perspective of structural reserve-dependent rerouting: rather than being driven by connection-specific structure–function relationships, changes of functional network configurations seem to depend on the structural reserve of the motor network.

This interpretation is well in line with recent bimodal balance recovery models, which propose that the level of ipsilesional structural reserve influences whether reorganization preferentially engages intrahemispheric or interhemispheric pathways.[1,51] Specifically, a lower reserve might favour a greater reliance on interhemispheric connections to the contralesional hemisphere, which is discussed to play a task-specific vicarious or maladaptive role.[8,16,21,34,50,52] Finally, this network view nicely aligns with whole-brain studies, suggesting that brain-wide functional networks become more integrated or segregated depending on the underlying network's structural properties after stroke.[53,54]

In summary, our results shed new light on the crucial yet controversial role of the contralesional M1 for motor recovery.[1,14,15,17,21,55] In particular, previous opposing findings may be explained in the context of structural network constraints—a novel insight that complements the well-established role of the CST in motor reorganization after stroke. Specifically, pronounced interhemispheric rerouting was mainly observed in patients with low intrahemispheric structural network reserve. Given that previous studies investigating the role of the contralesional M1 after stroke typically did not account for the level of structural reserve, mixed results may be partly explained by sampling biases based on patients' varying levels of structural network connectivity. Shifting from a one-size-fits-all approach toward a personalized framework that incorporates CST integrity as well as the individual level of cortical structural reserve will be of utmost importance for future work in order to develop personalized therapies.

Limitations

A significant limitation of our current study is the limited sample size of 23 stroke patients. While this number is comparable to other neuroimaging studies in stroke patients, future studies including larger patient cohorts will enhance generalizability and increase sensitivity to detect additional mechanisms of motor reorganization with smaller effect sizes. Moreover, larger cohorts will allow

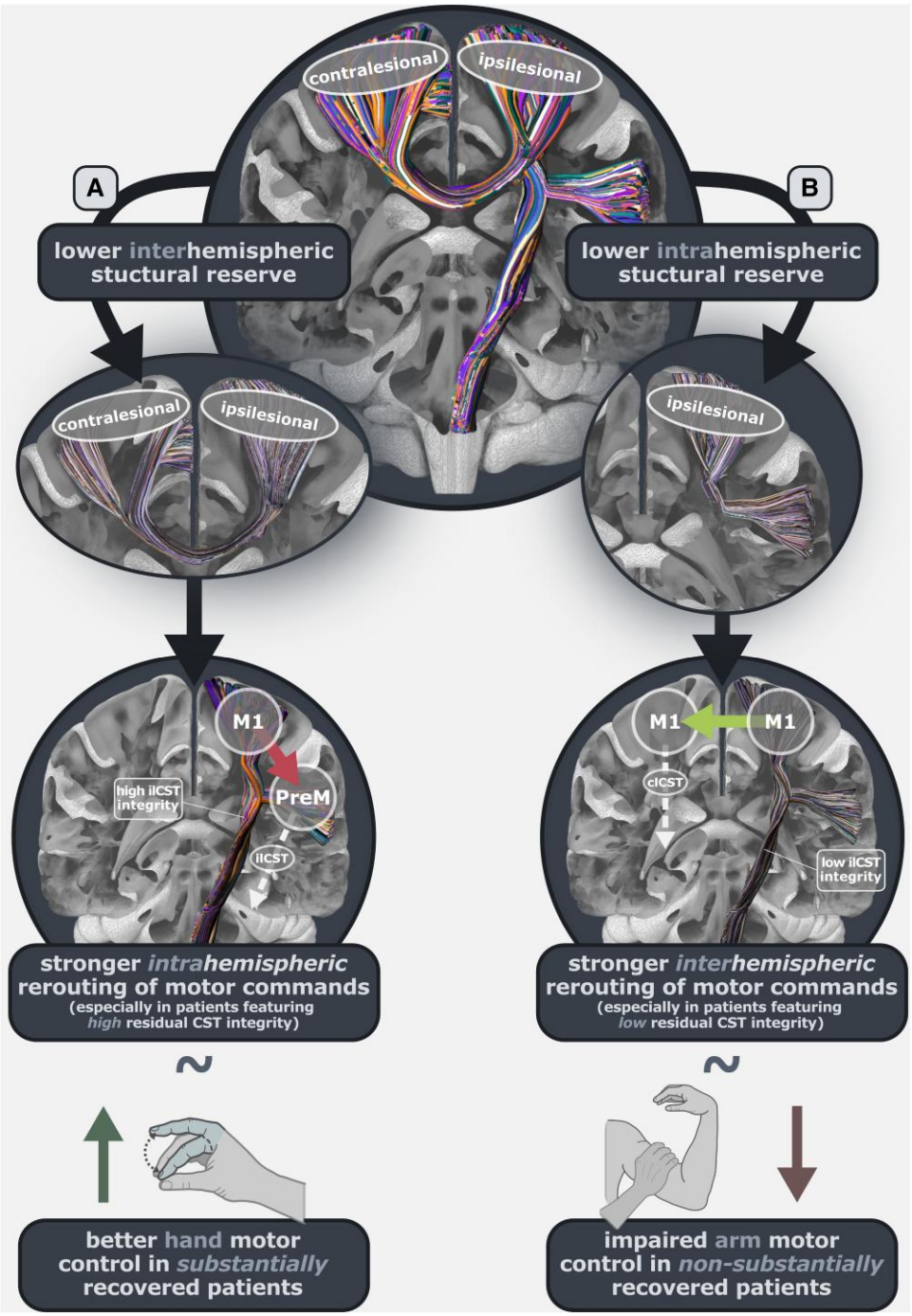

Figure 5 Synopsis of structural reserve-dependent rerouting of motor commands. (**A**) Low interhemispheric structural reserve of the motor network in concert with sufficient residual CST integrity may enhance intrahemispheric rerouting of motor commands via ipsilesional premotor areas. Mechanistically, intrahemispheric rerouting might allow access to spared premotor-CST fibres to support hand motor control and recovery. (**B**) In contrast, reduced intrahemispheric structural reserve was associated with pronounced interhemispheric rerouting to the contralesional M1, in particular when residual CST integrity was low. This increased interhemispheric rerouting was related to poor arm motor control and primarily observed in patients featuring non-substantial motor recovery from the acute to the chronic phase after stroke. Of note, effective connectivity was assessed during affected hand movements for which interhemispheric rerouting might thus be interpreted as task-specifically maladaptive. cl = contralesional; CST = corticospinal tract; il = ipsilesional; M1 = primary motor cortex; PreM = premotor areas.

to further differentiate and stratify individual recovery trajectories,[56] expanding our mechanistic understanding of motor recovery.

The analysis of effective connectivity during finger tapping movements allows for a comparison of our current results with previous work using similar repetitive hand movements.[22,25,31,32,57,58] However, given the task-specific nature of effective connectivity, future studies should estimate effective connectivity for a range of proximal to distal motor tasks to allow for a more comprehensive understanding of the task-specific role of cortico-cortical connectivity in upper limb motor control and recovery after stroke.

Moreover, while we focused our analyses on a specific set of bilateral motor regions (M1, PMd, PMv and SMA), future research should address the role of the primary somatosensory cortex and subcortical motor regions such as the basal ganglia or cerebellum. Finally, although our study benefits from the combination of structural and functional data, MRI data were collected cross-sectionally, limiting our ability to infer dynamic reorganization processes evolving over time. Future longitudinal MRI studies are needed to validate and extend our interpretations in order to advance our mechanistic understanding of motor network reorganization and recovery after stroke.

Conclusion

We provide novel insights into the critical role of the structural reserve in determining the motor network's ability to reroute motor commands and thereby shape functional reorganization after stroke. Low levels of CST integrity and limited intrahemispheric structural reserve of the ipsilesional hemisphere were associated with pronounced interhemispheric rerouting of motor commands to the contralesional M1, which was tied to poor arm motor control and recovery. Conversely, when the ipsilesional CST remained sufficiently intact, structural reserve-dependent intrahemispheric rerouting via spared ipsilesional premotor-CST fibres seemed to support hand motor control and recovery. Future therapeutic interventions, particularly personalized non-invasive brain stimulation protocols, should strategically consider individual levels of structural network reserve to derive the greatest benefit by targeting such rerouting mechanisms and thereby maximize the potential for recovery.

Data availability

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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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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