# Structural and functional representations of motor network reorganization after stroke

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# Abstract

Motor control deficits are among the most debilitating consequences of ischemic stroke and pose a significant challenge for rehabilitation and long-term functional independence. Although neuroplastic changes within the brain's motor network can partially restore motor abilities, the precise mechanisms of reorganization that drive individual differences in recovery remain elusive. This thesis aimed to advance mechanistic insights into how structural network constraints, such as the structural reserve—the premorbid level of structural integrity of pathways unaffected by the lesion—govern functional network reorganization after stroke. To this end, the two studies presented here examined how differences in preserved cortico-cortical structural connectivity (1) relate to basal and complex aspects of upper-limb motor control and (2) guide the adaptive rerouting of motor commands following network reorganization in a population of chronic stroke patients.

Study I investigated cortico-cortical structural connectivity as a marker of cortical structural reserve supporting distinct aspects of motor control after stroke. By combining diffusion spectrum imaging with a compartmentwise analytical approach and normative tract templates created from Human Connectome Project data, we quantified tractwise anisotropy between cortical motor regions in chronic stroke patients. Results revealed that basal motor control—defined as simple muscle recruitment—was strongly associated with interhemispheric M1–M1 connectivity, independent of ipsilesional corticospinal tract integrity. In contrast, complex motor control, involving coordinated motor synergies, critically relied on ipsilesional corticospinal fibers and intrahemispheric structural connectivity between ipsilesional M1 and bilateral premotor areas. Therefore, while complex motor control of the paretic upper-limb depended on preserved ipsilesional corticospinal output, basal motor control might be compensated via alternative pathways involving the rerouting of motor commands via contralesional M1 to access intact descending fibers.

Extending these findings, Study II examined how individual differences in cortical structural reserve constrain functional network reorganization after stroke. By incorporating dynamic causal modeling of task-related effective connectivity acquired during finger tapping movements alongside the previous structural analyses, this multimodal study assessed structure-function relationships to investigate how cortico-cortical structural connectivity relates to changes in intra- and interhemispheric effective connectivity. When the interhemispheric structural reserve was limited but ipsilesional corticospinal fibers were relatively preserved, motor commands seemed to be preferentially rerouted

intrahemispherically via premotor areas, supporting better hand motor control and recovery. Conversely, in patients with low corticospinal integrity and limited intrahemispheric structural reserve, interhemispheric rerouting via contralesional M1 was likely, a pattern associated with poor basal arm motor control and recovery. These results emphasize distinct, structural reserve-dependent rerouting mechanisms underlying motor recovery after stroke.

Together, the findings presented in this thesis elucidate the motor task-specific mechanisms of cortical network reorganization after stroke and highlight the pivotal role of individual structural motor network reserve in shaping functional plasticity. Clinically, assessing both CST integrity and broader cortico-cortical connectivity may markedly improve the prediction of motor recovery trajectories and inform personalized rehabilitation strategies, including targeted neuromodulation. Overall, this multimodal framework offers a novel perspective on post-stroke motor recovery and provides crucial insights toward biomarker-driven, individualized therapeutic interventions.

# List of abbreviations

| | |
|---|---|
| ANTs | Advanced Normalization Tools |
| ARAT | Action Research Arm Test |
| BIC | Bayesian Information Criterion |
| BOLD | blood oxygenation level-dependent |
| cl | contralesional |
| CST | corticospinal tract |
| DCM | dynamic causal modelling |
| dMRI | diffusion magnetic resonance imaging |
| DSI | diffusion spectrum imaging |
| DTI | diffusion tensor imaging |
| EEG | electroencephalography |
| EPI | echo-planar imaging |
| FA | fractional anisotropy |
| FDR | false discovery rate |
| FM-UE | Fugl-Meyer assessment for upper extremity |
| fMRI | functional magnetic resonance imaging |
| FoV | field of view |
| gFA | generalized fractional anisotropy |
| GQI | generalized *q*-sampling imaging |
| HARDI | high angular resolution diffusion imaging |
| HCP | Human Connectome Project |
| IHI | interhemispheric inhibition |
| il | ipsilesional |
| M1 | primary motor cortex |
| MEP | motor evoked potential |
| MI | Motricity Index |
| MNI | Montreal Neurological Institute |
| MRI | magnetic resonance imaging |
| NIHSS | National Institutes of Health Stroke Scale |
| ODF | orientation distribution function |
| PLIC | posterior limb of the internal capsule |
| PMd | dorsal premotor cortex |

| | |
|---|---|
| PMv | ventral premotor cortex |
| ROI | region of interest |
| RSA | representational similarity analysis |
| rTMS | repetitive transcranial magnetic stimulation |
| SMA | supplementary motor area |
| SPM | Statistical Parametric Mapping |
| TE | time to echo |
| TMS | transcranial magnetic stimulation |
| TR | repetition time |
| WM | white matter |

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# 1. Introduction

## 1.1 Investigation of motor recovery after stroke

Stroke represents one of the leading causes of death and long-term disability worldwide, with its prevalence steadily increasing despite major developments in acute treatment options (Feigin et al., 2021, 2025; Grefkes & Fink, 2020; Katan & Luft, 2018; Virani et al., 2020). Advances in interventional recanalization therapies, such as thrombectomy and thrombolysis have considerably improved survival rates (Goyal et al., 2016; Thomalla et al., 2018), yet many survivors are left with lasting neurological impairments (Dobkin, 2005). Among the most common sequelae are deficits in motor control, such as upper-limb hemiparesis (Dalton et al., 2024; Kolmos et al., 2025; Langhorne et al., 2009; Nakayama et al., 1994), with profound impact on patients' independence and quality of life (Nichols-Larsen et al., 2005; Veerbeek et al., 2011). Even with intensive rehabilitation aiming to improve outcomes, recovery is highly variable across individuals and often remains incomplete (Figure 1; van der Vliet et al., 2020), with residual impairment persisting over time (Bonita & Beaglehole, 1988; Kwakkel et al., 2003). Understanding the neurobiological processes that follow a stroke and govern recovery of motor functions is therefore crucial for improving treatment outcomes.

The vast majority of strokes—over 65%—are *ischemic* in nature, while intracranial and subarachnoid hemorrhages account for the remaining percentage (Feigin et al., 2025). An ischemic stroke is caused by the occlusion of a cerebral artery due to an atherosclerotic buildup or embolus, resulting in a sudden interruption of blood supply and subsequent brain lesion (Kuriakose & Xiao, 2020). During this local reduction of blood flow, the affected neural tissue is deprived of oxygen and nutrients, which leads to irreversible cell damage in the infarct core within the first hours after stroke (Broughton et al., 2009; Moskowitz et al., 2010). Although the infarcted brain tissue itself cannot be structurally restored, some patients still experience substantial functional recovery in the weeks and months following stroke (Krakauer, 2015).

Today, recovery is no longer understood solely as spontaneous restitution, but as a result of *neuroplasticity*—the brain's capacity to reorganize its specialized neural tissue after injury in order to compensate for lost functions (Cassidy & Cramer, 2017; Cramer, 2008; Krakauer, 2015). Critically, functional impairments following stroke are not confined to the damaged brain tissue alone; they often impact remote regions that are not directly affected yet are closely connected to the lesion site. This subsequent disruption or dysfunction in remote regions is

referred to as *diaschisis*. As diaschisis eases during the early recovery phase, the adverse symptoms caused by it may partially diminish, contributing to early functional improvement (Carrera & Tononi, 2014; von Monakow, 1914). Concurrently, the infarct triggers neuronal processes that foster plastic changes extending from molecular domains to large-scale neural systems. Such processes of *cortical reorganization* may occur locally in perilesional areas or more broadly through the engagement of remote brain regions that are not directly affected by the lesion (Nudo, 2006). These endogenous plasticity mechanisms, such as upregulation of genes or axonal sprouting, emerge independently of behavioral training and are often referred to as *spontaneous recovery*. However, they can be significantly amplified by rehabilitation interventions to enhance functional outcomes (Bernhardt et al., 2017; Cassidy & Cramer, 2017).

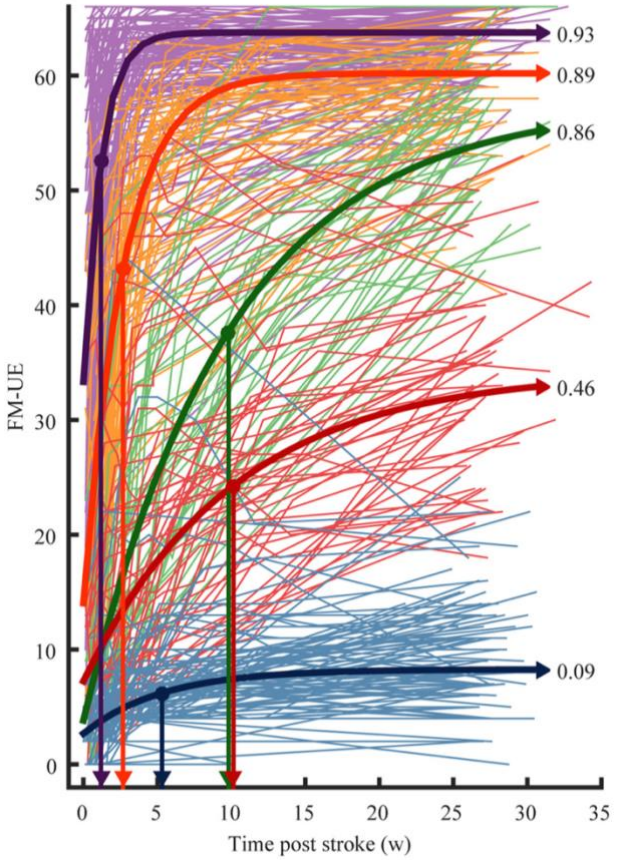


**Figure 1 | Longitudinal variability in motor recovery based on the Fugl–Meyer assessment for upper extremity (FM-UE) after ischemic stroke.** Individual FM-UE recovery trajectories from 412 patients highlight the remarkable heterogeneity in post-stroke motor recovery. Colored curves represent subgroups identified by a data-driven mixture model, distinguishing patients with mild, moderate, or severe initial impairment, indicated by their respective proportional recovery coefficient shown next to each curve. Distinct patterns emerge from minimal to complete recovery, illustrating how recovery potential and time course differ among patients–underscoring the high degree of variability in motor outcomes. Adapted from van der Vliet et al. (2020), *Annals of Neurology*, Volume 87, Issue 3, Pages 383-393.

Importantly, the recovery process proceeds in distinct temporal phases. To better describe and standardize the terminology of these discrete recovery stages, a conceptual framework was provided by the *Stroke Recovery and Rehabilitation Roundtable* (Bernhardt et al., 2017). This framework divides the time course of motor recovery into the *hyperacute* phase (first 24 hours), the *acute* phase (day 1 to 7), the *early subacute* phase (7 days to 3 months), the *late subacute* phase (4 to 6 months), and the *chronic* phase (from 6 months onward). The greatest potential for improvement occurs during the early stages of recovery. As patients enter the chronic phase, progress gradually declines and eventually reaches a plateau (Figure 2). Recognizing these temporal phases is crucial for both optimizing the timing of rehabilitation interventions and identifying appropriate windows to study functional reorganization.

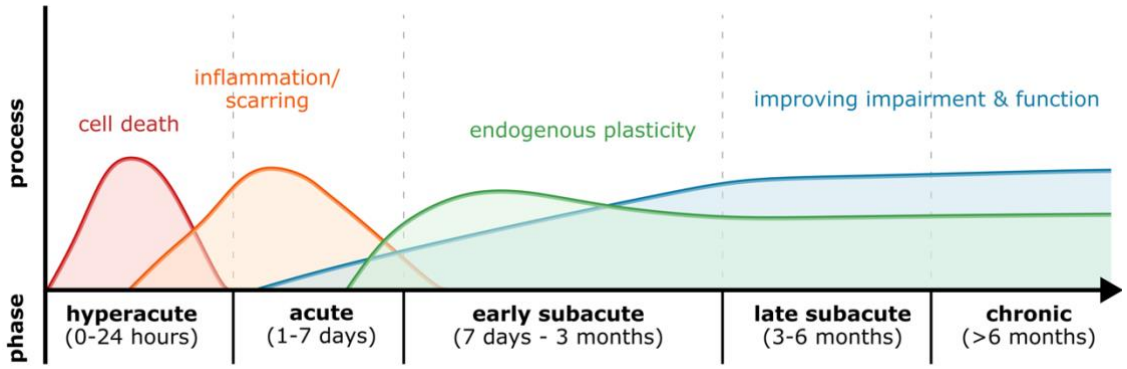


**Figure 2 | Reference framework for the temporal course of motor recovery after ischemic stroke.** Adapted with modifications from Bernhardt et al. (2017), *International Journal of Stroke*, Volume 12, Issue 5, Pages 444-450.

While behavioral assessments provide valuable measures of motor function, they offer no insight into the underlying neural mechanisms of motor recovery. Understanding how recovery emerges from dynamic changes in the human brain required tools capable of capturing neural activity and connectivity in vivo. The advent of modern neuroimaging techniques has therefore been crucial for identifying how structural and functional networks reorganize to support post-stroke motor recovery.

### 1.1.1 Functional magnetic resonance imaging

One major technical advancement was the introduction of functional magnetic resonance imaging (fMRI). This method can indirectly measure regional neural activation in vivo by detecting changes in the blood oxygenation level-dependent (BOLD) signal, which depends on the distinct magnetic properties of hemoglobin (Ogawa et al., 1990): oxygenated hemoglobin

is diamagnetic, while deoxygenated hemoglobin is paramagnetic (Pauling & Coryell, 1936). The concentration ratio of these two forms creates local magnetic field inhomogeneities that are detectable by MRI sequences (Ogawa et al., 1990). When a brain region becomes active, a dynamic cascade of physiological changes unfolds—neuronal firing increases local metabolic demand for oxygen, triggering a neurovascular response in which cerebral blood flow rises disproportionately to oxygen consumption (Fox & Raichle, 1986). This hemodynamic response causes an initial, transient increase in deoxygenated hemoglobin, followed by an oversupply of oxygenated blood that reduces the relative concentration of deoxyhemoglobin and thereby increases the local MRI signal intensity over baseline. This resulting BOLD signal evolves over several seconds, reflecting the characteristic temporal profile described by the hemodynamic response function (Boynton et al., 1996).

Based on these physiological mechanisms, early applications of fMRI successfully demonstrated that this non-invasive recording of neural activity could reliably identify brain regions that responded to specific stimuli (Ogawa et al., 1992) or that were active during the execution of tasks (Bandettini et al., 1992). After stroke, altered activation patterns within the motor network are observed, including changes in activation intensity of undamaged regions that may compensate for lost functions (Cramer et al., 2006; Grefkes, Nowak, et al., 2008; Jaillard et al., 2005; Saur, 2006; Ward et al., 2003). Moreover, *remapping* of cortical representations has been described, whereby adjacent or homologous cortical areas are thought to take over functions of lesioned regions (Campos et al., 2023; Murphy & Corbett, 2009).

Beyond activation mapping, *resting-state functional connectivity* and *task-related effective connectivity* analyses significantly expanded the applications of fMRI, which have been fundamental in advancing our understanding of reorganization processes associated with motor recovery after stroke (see 1.3.2; Grefkes & Fink, 2011). Resting-state functional connectivity, defined as the correlation of BOLD signal fluctuations between spatially distant brain regions over time, provided new insights into intrinsic activity patterns during rest (Biswal et al., 1995). In contrast, effective connectivity approaches were developed to infer the directional influence one brain region exerts over another, often studied during the execution of a task using dynamic causal modelling (DCM; Friston et al., 2003).

Notably, functional and effective connectivity analyses suggest that recovery depends less on changes in isolated regions and more on alterations in interregional interactions at the network level (Grefkes & Fink, 2011). In particular, intact pathways may modify their connectivity, either by strengthening existing connections or by reorganizing intra- and

interhemispheric communication patterns (Carter et al., 2010; Grefkes, Nowak, et al., 2008; Paul et al., 2021; Rehme, Eickhoff, et al., 2011). Eventually, the motor system appears to undertake larger-scale reconfiguration at the network level, engaging distributed cortical and subcortical circuits rather than relying on individual pathways (Adhikari et al., 2017; Bonkhoff et al., 2021; Siegel et al., 2016).

Importantly, not all observed alterations in neural activity and connectivity necessarily support motor recovery. While some changes are considered adaptive, supporting functional improvements, others are thought to be maladaptive and may interfere with the recovery of motor functions (Di Pino et al., 2014; Grefkes & Fink, 2020). A central question in this regard is the role of the contralesional hemisphere, particularly the contralesional primary motor cortex (M1). Changes in contralesional M1 activity and connectivity are frequently associated with motor reorganization (Grefkes, Nowak, et al., 2008; Hensel et al., 2021; Volz et al., 2017; Ward et al., 2003), yet it remains a subject of ongoing debate whether these alterations rather reflect maladaptive interference or compensatory support for motor recovery (see 1.3.3; Suputtitada et al., 2025). To better interpret such functional alterations, research increasingly considers them in the context of the underlying structural network, using structural neuroimaging techniques such as diffusion MRI (dMRI).

### 1.1.2 Diffusion magnetic resonance imaging

Because changes in neural activity and connectivity presumably unfold within a pre-existing structural network, dMRI provides a powerful tool to study the structural architecture that supports motor recovery after stroke (Koch et al., 2016; Umarova et al., 2024). dMRI enables in vivo characterization of microstructural properties of white matter (WM) fiber pathways by measuring the diffusion of water molecules in brain tissue (Basser, 1995; Beaulieu, 2002). This approach is based on the principle that diffusion occurs equally in all directions (isotropic) in free water, but becomes highly anisotropic in the WM of the brain, where water molecules preferentially diffuse along the length of axonal fibers. This directional property of water diffusion allows the reconstruction of major WM pathways and provides inferences about the orientation, density, and integrity of fiber tracts (Le Bihan et al., 2006).

The most common dMRI approach, diffusion tensor imaging (DTI), models voxelwise diffusion using a single ellipsoid-shaped tensor assuming Gaussian diffusion (Basser et al., 1994). This ellipsoidal representation captures both the principal direction and magnitude of water diffusion, where the longest axis of this ellipsoid aligns with the primary fiber orientation,

while the shorter axes reflect diffusion perpendicular to it. From this model, scalar indices such as fractional anisotropy (FA) can be derived, providing an indirect marker of WM *microstructural integrity*. To capture the three-dimensional diffusion profile, DTI requires repeated measurements along multiple—at least six—non-collinear gradient directions, represented by b-vectors. The degree of diffusion weighting applied during acquisition is quantified by the b-value, a parameter determined by the amplitude, duration, and timing of diffusion-sensitizing gradients (Stejskal & Tanner, 1965).

Despite its utility, the single-tensor model in DTI inherently assumes only one dominant fiber orientation per voxel, which fails in regions with complex fiber architectures, where multiple fiber directions coexist within a single voxel. In other words, the underlying model is limited by its inability to resolve complex fiber geometries such as crossing, kissing, or branching fiber tracts (Figure 3; Tournier et al., 2011). Thus, diffusion in these complex multi-directional voxels cannot be accurately represented by the tensor's elliptical model, often leading to systematic errors in fiber orientation estimates and microstructural metrics.

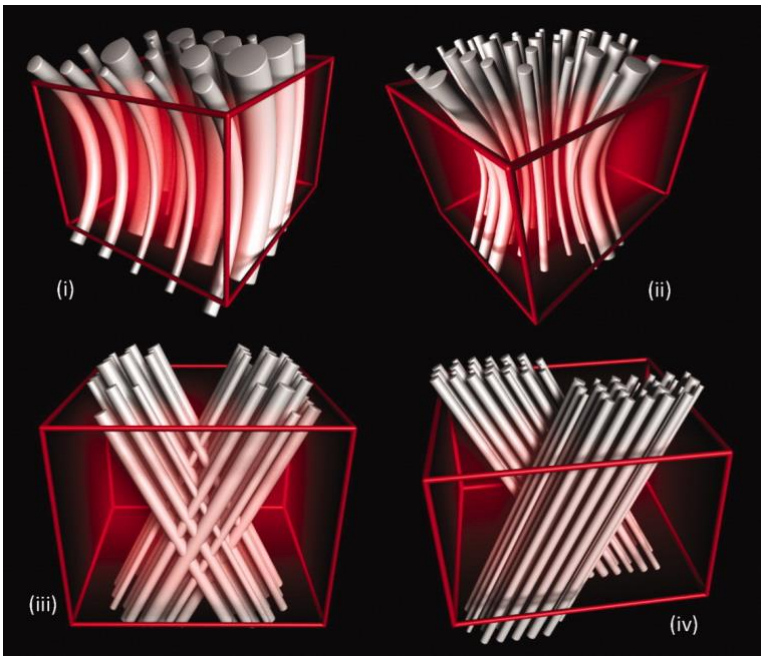


**Figure 3 | Representation of complex fiber architectures.** Simulations of different fiber configurations illustrating (**i**) bending, (**ii**) fanning, (**iii**) crossing and (**iv**) adjacent fiber bundles within a single voxel. Reproduced from*Tournier et al. (2011)*, *Magnetic Resonance in Medicine*, Volume 65, Issue 6, Pages 1532-1556, with permission from John Wiley and Sons.

Advanced diffusion imaging methods such as high angular resolution diffusion imaging (HARDI) and diffusion spectrum imaging (DSI) try to overcome these limitations by sampling the diffusion signal with higher angular and spatial resolution across numerous gradient directions and b-values. DSI, for example, uses Cartesian grid sampling (Wedeen et al., 2005),

thereby enabling the reconstruction of multiple fiber orientations within a voxel by estimating an orientation distribution function (ODF) using generalized *q*-sampling imaging (GQI; Yeh et al., 2010). Such an approach can therefore overcome single-tensor limitations and improve the characterization of complex white matter architecture.

By analyzing structural metrics of microstructural integrity—derived from voxelwise anisotropy estimates such as tensor-based FA or generalized fractional anisotropy (gFA), which quantifies anisotropy from ODFs (Basser, 1995; Tuch, 2004)—numerous studies have linked damage to motor output pathways, such as the corticospinal tract (CST), to impaired motor control and recovery after stroke (Koch et al., 2016). Of note, projecting or descending fiber bundles like the CST often contain voxels with multiple fiber directions beyond the primary descending fibers, complicating the interpretation of stroke-induced anisotropy changes. Although gFA computed from ODFs can account for multiple fiber directions, it cannot fully overcome methodological challenges associated with such kissing or crossing fibers (Volz et al., 2018). In these multi-directional voxels, damage to one fiber population can have paradoxical effects on overall anisotropy: it may decrease, stay stable, or even spuriously increase, depending on the relative proportions and orientations of the surviving fibers, resulting in unreliable microstructural integrity estimations.

To overcome this limitation, a novel compartmentwise analytical approach was introduced to differentiate brain voxels based on the number of intra-voxel fiber directions (Figure 4; Volz et al., 2018). This method uses deterministic directionality templates generated from large multi-shell HARDI datasets, allowing the compartmentalization of data to isolate direction-specific voxels—with one, two, or three fiber directions—and thereby reducing the biases in anisotropy estimation from multi-directional voxels (see 2.6). Building on this approach, Paul and colleagues (2023) applied the compartmentalization masks to individual gFA maps of patients to isolate unidirectional CST voxels, clarifying the contribution of the full length of descending CST fibers to motor control and recovery after stroke.

Importantly, adopting a compartmentwise approach becomes even more relevant when examining *structural connectivity* between cortical brain regions. Cortico-cortical structural pathways—such as those connecting M1 and premotor areas—traverse regions rich in multi-directional voxels near the cortical gray-white matter boundary (Reveley et al., 2015; Schilling et al., 2019). To assess the structural connectivity between these cortical motor regions, studies frequently used streamline counts derived from fiber tractography. However, several limitations constrain the reliability of such tractography-based methods. First, individual

tractography becomes increasingly unreliable in brains with substantial white matter atrophy, as often observed in elderly stroke cohorts, where altered tissue geometry distorts microstructural estimates (Salat et al., 2005). Second, the anatomical accuracy of tractography-derived connections is inherently limited by a sensitivity-specificity trade-off: higher sensitivity typically comes at the cost of reduced specificity, and optimal tracking parameters—such as angular thresholds, curvature constraints, and termination criteria—vary substantially across different pathways and brain regions (Maier-Hein et al., 2017; Thomas et al., 2014). Third, this results in a systematic overestimation of streamline counts due to an abundance of false-positive connections (Zalesky et al., 2016), rendering it nearly impossible to differentiate spurious connections from genuine anatomical pathways in the absence of histological ground truth (Grisot et al., 2021; Schilling et al., 2020).

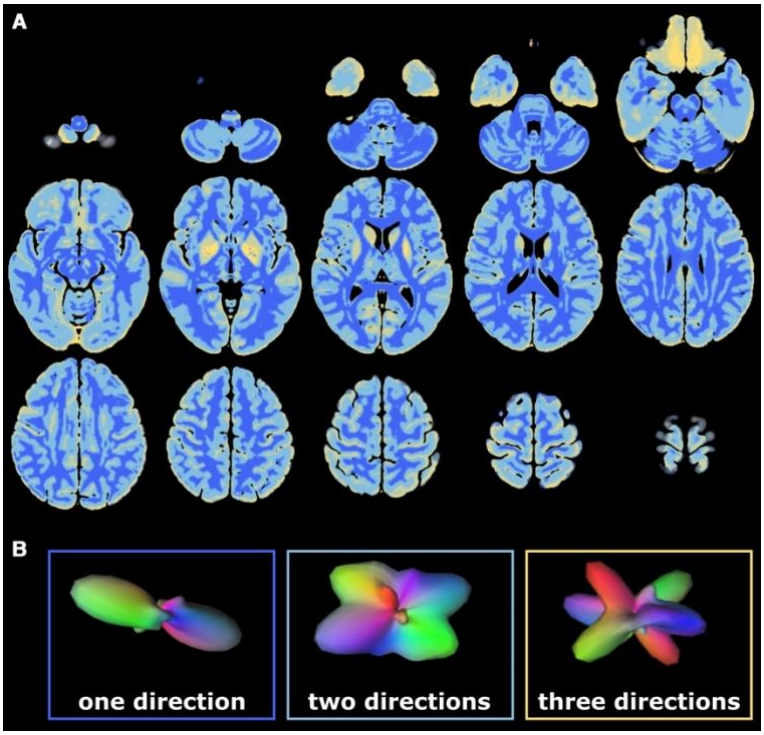


**Figure 4 | Deterministic directionality mask for whole-brain compartmentalization.** (**A**) Compartmentalization mask generated by Volz et al. (2018) from 630 HCP participants. Color-coded compartments indicate voxels classified by the number of trackable fiber orientations: dark blue (one direction), light blue (two directions), yellow (three or more directions). Visualizations in panel (**A**) are derived from the published nifti-file by Volz et al. (2018). (**B**) Trackable fiber direction count per voxel was established by analysis of the orientation distribution function (ODF), which can capture multiple diffusion orientations within individual voxels. Voxels were allocated to specific compartments based on the number of ODF peaks surpassing a defined threshold, representing intravoxel directional complexity. Representative ODFs displaying varying peak numbers are illustrated in panel (**B**). Reproduced from*Paul, Cieslak, et al. (2023)*, *Brain Communications*, Volume 5, Issue 1.

These methodological constraints can therefore compromise tractography outcomes and complicate structural connectivity analyses, likely contributing to the paucity of studies

examining cortico-cortical pathways such as M1-premotor connections—where reliable tract-specific quantification of their role in post-stroke motor reorganization has remained elusive. To overcome these challenges, this thesis introduces an innovative combination of compartmentwise analysis and the use of normative tract templates for individual tractwise anisotropy estimation in stroke patients. In this novel approach, normative tract templates were first generated through fiber tracking in a normative Human Connectome Project (HCP) dataset (see 2.5), allowing the robust extraction of tractwise anisotropy from cortical pathways by overlaying resulting binary tract masks with individual patients' gFA maps. This template-guided, compartmentwise approach circumvents subject-specific tractography limitations and biases from multi-directional voxels, yielding reliable metrics of cortico-cortical structural connectivity in stroke patients. Consequently, it enables investigation of these pathways' compensatory contributions to post-stroke motor network reorganization and recovery—previously only partially accessible due to dMRI's methodological constraints.

Together, both methodological advances, fMRI and dMRI, have profoundly enhanced our understanding of post-stroke reorganization processes. Nonetheless, more detailed mechanistic insights into these processes are essential for developing reliable biomarkers that can better predict variable recovery trajectories and guide individualized therapies to optimize motor rehabilitation outcomes. Since voluntary motor function ultimately depends on the integrity of descending motor pathways (Lemon, 2008), previous research has primarily focused on the CST as a key determinant of motor recovery after stroke (Koch et al., 2016).

## 1.2 The classical predictor: the ipsilesional CST

The CST is the principal descending motor output pathway responsible for voluntary motor control (Lemon, 2008). It primarily originates from pyramidal neurons in the precentral gyrus, descending through the corona radiata, the posterior limb of the internal capsule (PLIC), and cerebral peduncles, continuing down through the pons (Figure 5). CST fibers terminate on lower motor neurons in the spinal cord, where they mediate motor control and fine-skilled movements via peripheral muscles. Most CST fibers decussate in the pyramidal decussation to innervate distal contralateral limb muscles, while a smaller portion of fibers remain ipsilateral for proximal muscles (Kuypers, 1981; Lemon, 2008). Importantly, a substantial part of the corticospinal system consists of additional descending fibers emerging from premotor regions, creating a direct connection to the spinal cord independent from M1 (Dum & Strick, 1991).

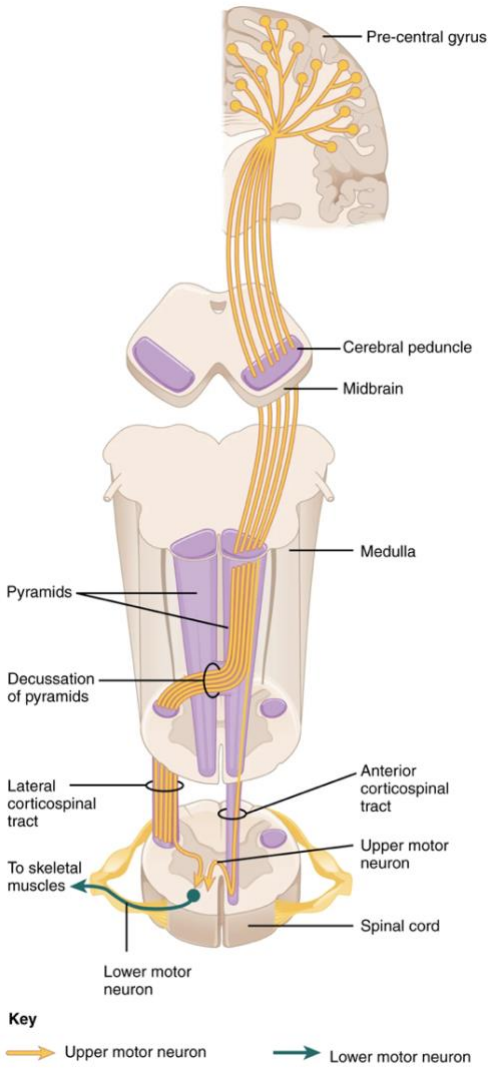


**Figure 5 | Corticospinal tract.** As the major descending motor output pathway, the CST is responsible for voluntary motor control. Upper motor neurons originate from cortical motor and sensory areas and descend through the brainstem to synapse onto lower motor neurons in the spinal cord, which innervate skeletal muscles. Reproduced from Betts et al. (2022), *Anatomy and Physiology 2e*, OpenStax, https://openstax.org/books/anatomy-and-physiology-2e/pages/14-3-motor-responses, CC BY 4.0.

As the primary descending pathway for motor output, preservation of the CST's structural integrity is crucial for motor control, making it a reliable biomarker for post-stroke motor impairment and recovery (Koch et al., 2016). Different measures of ipsilesional CST damage—including lesion overlap with normative CST templates or microstructural metrics like FA (see 1.1.2)—serve as strong predictors of motor outcome (Boyd et al., 2017). Notably, prediction models including CST lesion load significantly improve prognoses of motor control three months post-stroke beyond those based solely on baseline behavioral assessments, patient age, or lesion volume alone (Feng et al., 2015). Moreover, reduced microstructural integrity of the CST is robustly associated with greater motor impairment (Koch et al., 2016; Lindenberg et al., 2010; Paul, Cieslak, et al., 2023; Puig et al., 2011; Schaechter et al., 2009).

While most research predominantly focused on CST fibers descending directly from M1, attention has turned to the importance of additional CST projections from sensory and premotor areas (Archer et al., 2016; Boccuni et al., 2019; Schulz et al., 2012). Recent work indicates that, although output from M1-CST fibers seems crucial for upper-limb motor control in general, premotor-CST output appears essential for more complex motor control, such as dexterous hand or finger movements, and may also provide alternative routes for more basal motor functions in patients with persistent impairment, including proximal arm movements (Paul et al., 2024). Such task-specific findings are further underscored by a recent connectome-based lesion-symptom mapping study, demonstrating that distinct disconnection patterns can predict both initial impairment and recovery outcomes (Esser et al., 2025): complex reach-to-grasp movements involved overlapping disconnection profiles predictive of both impairment and recovery, while reorganization of basal motor functions like grip strength and gross arm movement was linked to distinct network disconnections. Moreover, the study highlighted a time- and task-dependent role of interhemispheric and contralesional network involvement in the recovery of basal motor control, emphasizing that motor recovery relies on the integrity of distributed structural networks beyond the classical ipsilesional CST.

Accordingly, although CST damage is recognized as a valid biomarker, increasing attention has been directed toward alternative descending pathways (McPherson et al., 2018; Paul, Cieslak, et al., 2023; Schulz et al., 2012) and cortico-cortical connections within the motor network (Peters et al., 2018; Schulz, Braass, et al., 2015; Schulz et al., 2017) as compensatory substrates for functional reorganization, perhaps better accounting for the considerable variability observed in motor recovery.

## 1.3 A motor network perspective

Motor control fundamentally relies not only on the CST but also on a distributed cortical network encompassing the primary motor cortex and several secondary (pre)motor regions (Figure 6), including the dorsal (PMd) and ventral premotor cortices (PMv), as well as the supplementary motor area (SMA; Strick et al., 2021). At the core of this network, located in the precentral gyrus, M1 serves as the principal generator of motor commands, translating cortical activity into descending corticospinal output. M1 is somatotopically organized in a homuncular arrangement, with body part representations arranged from the lower limb medially to the upper-limb and face laterally (Penfield & Boldrey, 1937). Notably, disproportionately large cortical representations are devoted to body parts involved in skilled,

precise voluntary movements, particularly the hands and face, reflecting the high density of motor innervation required for fine motor control (Schieber, 2001).

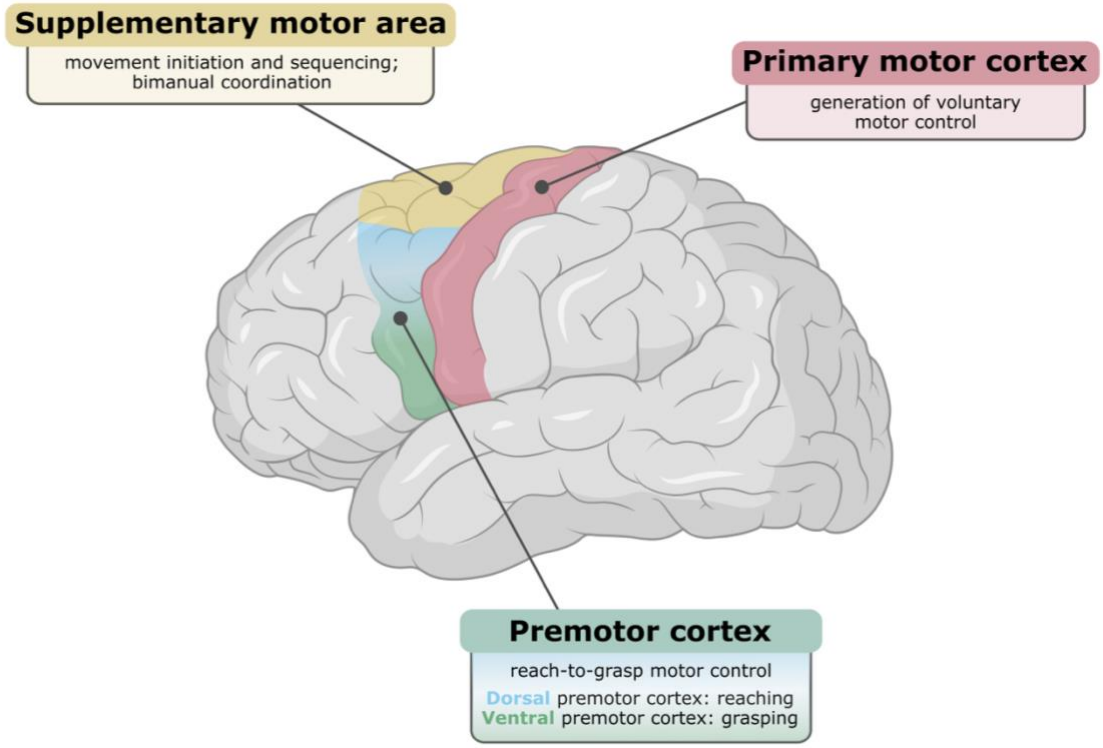


**Figure 6 | Schematic representation of cortical motor regions.** The areas illustrated here represent core motor regions for the generation and coordination of motor control. Brain image adapted and modified from BioRender.com.

Premotor regions in the frontal lobe further modulate and refine motor output through excitatory projections to M1 and additional descending pathways (Dum & Strick, 1991). Specifically, PMd and PMv play distinct but complementary roles in goal-directed reach-to-grasp movements. The PMd primarily contributes to planning and orchestrating reaching movements, specifying movement parameters such as direction, amplitude, and muscle coordination, whereas the PMv supports object-oriented grasping and controlling correct hand and finger positioning during visually guided manual actions (Davare et al., 2006; Kantak et al., 2012). In contrast, the SMA is particularly involved in movement initiation, sequencing, and temporal organization, supporting internally generated and bimanual actions (Gerloff et al., 1997; Nachev et al., 2008). Together, these regions form an integrated cortical network that enables the flexible, precise execution of voluntary movements. While M1 primarily generates the descending motor commands for movement execution, premotor areas contribute by selecting appropriate motor plans and adapting them according to current task demands.

Beyond their local interactions, these core motor areas are strongly interconnected to parietal regions that provide visuospatial and somatosensory information, constituting a frontoparietal network that supports the transformation of sensory inputs into goal-directed actions (Buneo et al., 2002; Grefkes & Fink, 2005; Rizzolatti et al., 1998). In addition, they are embedded in subcortical circuits involving the basal ganglia and cerebellum that form recurrent cortico-subcortical loops, such as the cerebellar-thalamo-cortical pathway, which are important for movement initiation, online control, and motor learning, thereby supporting flexible and context-dependent motor behavior (Bostan & Strick, 2018; Dacre et al., 2021; Henschke & Pakan, 2023; Horne & Butler, 1995; Mink, 1996).

### 1.3.1 Structural connectivity of the cortical motor network

When the core motor network or its primary output pathways become compromised by a stroke, the structural integrity of these interconnected cortical motor regions may act as a *structural reserve* for motor recovery (Di Pino et al., 2014; Umarova et al., 2024)—reflected by the premorbid level of spared structural fibers undamaged by the stroke lesion. This concept postulates that the residual structural capacity of cortico-cortical connections may provide a scaffold to support reorganization and functional recovery after stroke. In particular, both inter- and intrahemispheric connections, may provide alternative pathways for the rerouting of motor output essential for compensation when major descending output pathways are compromised: while intrahemispheric connections between M1 and premotor areas may sustain residual motor control when direct output pathways are severely disrupted (Paul et al., 2024; Schulz, Braass, et al., 2015; Schulz et al., 2017), interhemispheric connectivity might facilitate recruitment of contralesional regions to reroute motor control, thereby supporting the recovery of the affected limb (Buetefisch, 2015; Lotze et al., 2012; Schaechter et al., 2009).

Despite this notion, the role of the cortical structural reserve in post-stroke motor recovery remains less explored and results are often inconsistent—not least due to methodological limitations (see 1.1.2). Existing tractwise analytical approaches focusing on core motor connections have demonstrated that the structural connectivity of these pathways correlates with motor impairment and recovery after stroke (Koch et al., 2016). Particularly, interhemispheric M1-M1 structural connectivity, measured as anisotropy of the corpus callosum fibers between bilateral M1 regions, shows consistent associations with post-stroke motor control, whereby motor impairment can be reliably explained by reduced microstructural

integrity of these transcallosal fibers (Chen & Schlaug, 2013; Hayward et al., 2022; Li et al., 2015; Lindenberg et al., 2012; Peters et al., 2018; Wang et al., 2012).

In contrast, the specific contribution of interhemispheric premotor–M1 connections as structural reserve to motor recovery remains critically underexplored: although nominally included in whole-brain connectivity analyses, conventional atlas parcellations often fail to delineate functionally distinct premotor subregions (e.g., distinguishing dorsal vs. ventral premotor cortex), severely constraining the anatomical specificity and interpretability of these findings (Frontzkowski et al., 2025; Schlemm et al., 2020).

Evidence regarding intrahemispheric premotor–M1 structural pathways—especially in the ipsilesional hemisphere—is somewhat more substantive but remains sparse and distinctively heterogenous. While studies have linked ipsilesional premotor-M1 connectivity to residual motor function, the reported associations vary depending on patient heterogeneity, lesion location, or the type of motor assessment used (Koch et al., 2016). For instance, structural connectivity between ipsilesional PMv and M1 has shown significant associations with motor performance in the Fugl–Meyer assessment for upper extremity (FM-UE; Schulz, Koch, et al., 2015), which captures stroke-specific sensorimotor impairment of more basal arm functions (Fugl-Meyer et al., 1975). Conversely, structural connectivity between ipsilesional PMd–M1, but not between PMv or SMA and M1, has been linked to impaired motor function when assessed differently, namely using a composite motor score that integrates grip and pinch force with finger tapping speed (Schulz, Braass, et al., 2015). In turn, structural SMA–M1 connectivity has been reported to correlate with grip strength and dexterity, but not with the performance in the Motricity Index (MI; Peters et al., 2018), capturing more basal, isolated muscle synergies of the paretic upper-limb (Demeurisse et al., 1980). These variable associations highlight the complexity of premotor–M1 contributions and underscore the need for further targeted research to clarify tract-specific effects across different clinical measures and motor assessments.

Moreover, the functional relevance of premotor–M1 connections may scale with the severity of CST damage, highlighting these pathways as crucial substrates and structural reserve for alternative rerouting of motor output. Structural PMv–M1 connectivity, for instance, becomes increasingly predictive of outcome in patients with extensive CST damage, suggesting that compensatory recruitment of cortico-cortical routes intensifies in cases of profound CST disruption (Schulz et al., 2017). Thus, incorporating measures of cortical structural reserve—such as diffusion-based estimates of cortico-cortical connectivity—

alongside assessments of CST integrity significantly improve the prognostic value of motor recovery models (Di Pino et al., 2014; Koch et al., 2016). Adopting such a network-level perspective might be essential to capture the high complexity of post-stroke motor reorganization, moving beyond simple biomarkers toward individualized recovery predictions that account for the patient's unique structural network capacity for compensation. While structural connectivity provides important insights and represents a crucial facet of reorganization, a comprehensive understanding of post-stroke recovery also necessitates examining functional reorganization within the motor network.

### 1.3.2 Functional reorganization of cortical motor regions

Beyond structural changes, stroke causes widespread functional alterations within the cortical motor network that extend beyond the lesion. These changes can comprise alterations in regional BOLD activation and interregional coupling, reflecting functional network reorganization that can be sensitively captured using neuroimaging techniques such as fMRI (Grefkes & Fink, 2011; Ward et al., 2003).

In the healthy brain, unilateral hand movements predominantly evoke lateralized activation of contralateral motor areas, i.e., regions in the hemisphere opposite to the moving hand (Kim et al., 1993; Pool et al., 2013). After stroke, particularly in the acute stage, movement of the affected hand is often represented bilaterally in both hemispheres with overall elevated BOLD responses compared to healthy individuals (Figure 7; Hensel et al., 2021; Rehme, Fink, et al., 2011; Ward et al., 2003). This elevated activity involves the additional recruitment of premotor regions, including PMd and PMv, as well as SMA (Johansen-Berg et al., 2002; Pineiro et al., 2001; Ward et al., 2003), reflecting compensatory remapping processes that may facilitate residual motor output through alternative descending pathways. Alongside recovery, this bilateral activation pattern tends to progressively normalize toward the typical lateralized pattern observed in healthy subjects (Rehme et al., 2012; Ward et al., 2003), whereas persistent bihemispheric overactivation in the chronic phase is linked to poor outcome (Rehme et al., 2012).

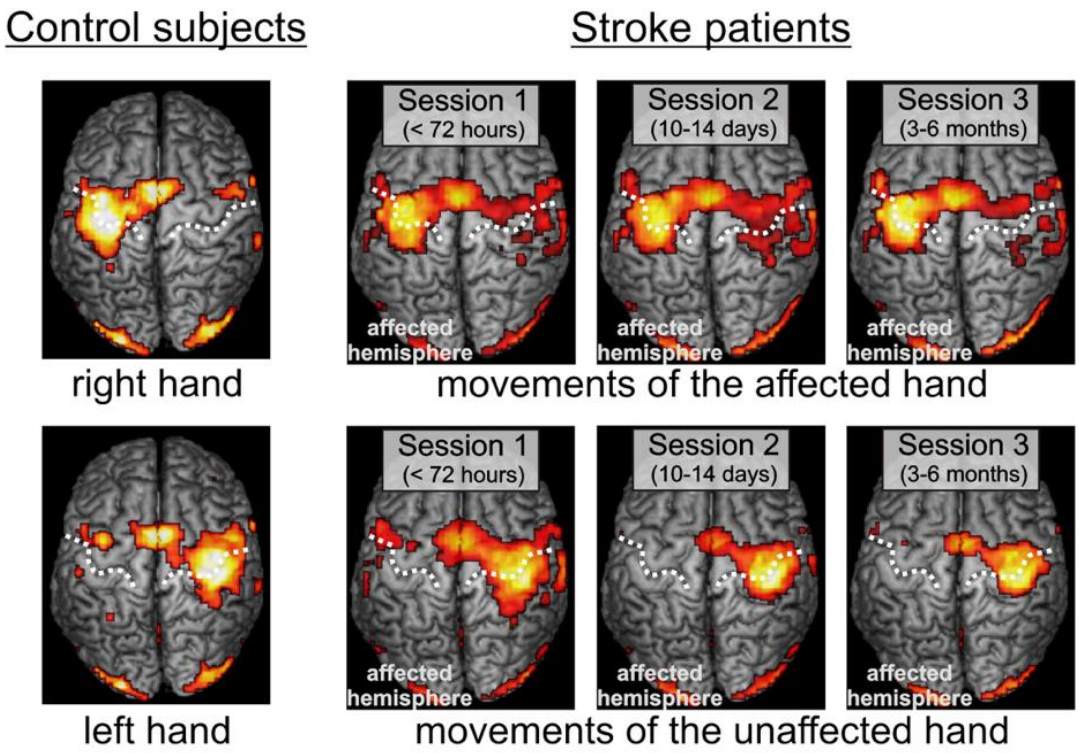


**Figure 7 | Activation shift of BOLD signal after stroke.** Comparison of BOLD signal in healthy participants during hand movements and BOLD signal changes in stroke patients during movements of the affected and unaffected hand across different recovery stages ($P_{FDR} < 0.05$). Adapted from Rehme, Eickhoff, et al., (2011), *Neuroimage*, Volume 55, Issue 3, Pages 1147-58, with permission from Elsevier.

Importantly, alterations in local BOLD activation alone do not provide insights into whether or how specific regions contribute to recovery, motivating the use of network-level methods such as resting-state functional connectivity or task-related effective connectivity. After stroke, time-course-specific alterations in resting-state connectivity are thought to reflect reorganization (Grefkes & Fink, 2014). In particular, changes in intrahemispheric resting-state connectivity between ipsilesional premotor regions and M1 (Bonkhoff et al., 2020; Hensel et al., 2025; Rehme et al., 2015; Wang et al., 2010), as well as interhemispheric connectivity between bilateral M1 (Bonkhoff et al., 2020; Carter et al., 2010; Hensel et al., 2025; Rehme et al., 2015), have been associated with motor impairment. Early subacute disruptions are characterized by state-independent interhemispheric alterations alongside task-dependent intrahemispheric changes (Paul et al., 2021). Interestingly, these altered patterns tend to normalize to levels observed in healthy individuals alongside recovery (Park et al., 2011; Volz et al., 2016).

Similar network alterations have been reported in effective connectivity during motor task execution. In healthy individuals, DCM analyses have revealed a robust connectivity

pattern between cortical regions of the motor system (Pool et al., 2013, 2014; Rehme, Eickhoff, et al., 2011; Volz et al., 2015). During unilateral hand movements, the active M1 (contralateral to the moving hand) receives excitatory inputs from premotor regions, while inhibitory influences are exerted both from premotor areas and from the active onto the inactive M1 (ipsilateral to the moving hand). This pattern reflects a finely tuned balance of interhemispheric and intrahemispheric interactions that ensures efficient and lateralized motor control.

In the early phases after stroke, DCM studies have described diminished excitatory coupling from the ipsilesional premotor cortex to ipsilesional M1 compared to control subjects (Grefkes, Nowak, et al., 2008; Rehme, Eickhoff, et al., 2011). Interestingly, as recovery progresses and patients improve, reinstatement of this excitatory modulation of M1 activity by premotor areas can be observed, potentially reflecting functional reorganization within the ipsilesional hemisphere. Moreover, initially stronger premotor–M1 coupling in the acute phase has been shown to predict better subsequent motor recovery, indicating an adaptive influence and beneficial role of intrahemispheric premotor–M1 connectivity in post-stroke motor reorganization (Rehme, Eickhoff, et al., 2011). Conversely, the functional significance of alterations in interhemispheric connectivity and contralesional activity, particularly involving contralesional M1, remains more controversial.

### 1.3.3 The contralesional hemisphere: beneficial versus maladaptive motor network reorganization

The role of the contralesional hemisphere in functional reorganization after stroke has been a focus of ongoing scientific debate (Suputtitada et al., 2025). While some studies suggest a compensatory contribution of altered contralesional activity to motor recovery, others have interpreted persistent overactivation and *interhemispheric imbalance* as maladaptive, interfering with ipsilesional motor control.

In the acute and early subacute phases, resting-state studies consistently report a decline in interhemispheric functional connectivity between bilateral (sensori)motor regions early after stroke (Bonkhoff et al., 2020; Rehme et al., 2015), followed by a gradual normalization alongside functional recovery (Park et al., 2011; Volz et al., 2016). Patients with better outcomes typically show a restoration of connectivity over time, whereas persistent disconnection or imbalance in the chronic phase are associated with poor motor outcome.

Previous DCM studies indicated that interhemispheric interactions between bilateral M1 can become transiently supportive after stroke. In a longitudinal study, Rehme and

colleagues (2011) observed initially reduced inhibition from the ipsilesional to the contralesional M1, followed by gradually increased excitation from the contralesional to the ipsilesional M1 in the subacute phase. These changes have been interpreted as adaptive mechanisms that may facilitate early functional recovery by engaging contralesional motor resources when ipsilesional output is compromised. During the course of recovery, however, interhemispheric dynamics can shift toward a maladaptive pattern. In the late subacute stage, patients showing pronounced inhibition of ipsilesional M1 activity by the contralesional M1 exhibit more severe impairment (Grefkes, Nowak, et al., 2008). Persistent interhemispheric imbalance into the chronic phase, manifested as excessive inhibition of ipsilesional M1 or attenuated physiological inhibition of contralesional M1 (Rehme, Eickhoff, et al., 2011; Volz et al., 2015), has been linked to poor outcomes, indicating a detrimental impact of such altered coupling on functional recovery.

Supporting this notion, neurophysiological studies using transcranial magnetic stimulation (TMS) demonstrated that this unphysiological inhibition of ipsilesional M1 by contralesional M1 may reflect maladaptive reorganization, with increased inhibitory drive impeding motor control (Grefkes et al., 2010; Murase et al., 2004). Interestingly, during online TMS, temporary disruption of contralesional M1 activity in acute stroke patients improved finger tapping performance, suggesting that excessive contralesional activation can interfere with distal motor execution early after stroke (Volz et al., 2017). However, the same intervention had no effect on grip strength or reaction time tasks. Therefore, the functional relevance of contralesional M1 in motor recovery may vary not only with regard to time post-stroke and stage of recovery but also depending on specific task demands. Consistent with this view, online TMS studies in chronic stroke patients have shown the opposing effect: for complex or sequential movements such as grasping speed (Hensel et al., 2023) and finger tapping sequences (Lotze et al., 2006), contralesional M1 activity appeared to be beneficial in a task-specific fashion.

The dichotomy between beneficial and maladaptive contralesional involvement may furthermore be explained by individual differences in structural reserve of the motor network (Di Pino et al., 2014). In particular, patients with substantial ipsilesional damage may more heavily rely on contralesional pathways for residual motor function, whereas those with preserved ipsilesional integrity benefit from engaging alternative ipsilesional pathways. Consequently, the available structural reserve might constrain the extent of functional reorganization, influencing whether contralesional M1 impacts recovery in a beneficial or

maladaptive way. This notion is nicely captured by the *bimodal balance-recovery model* proposed by Di Pino and colleagues (2014), which offers a unifying framework to explain the variable role of the contralesional hemisphere after stroke. This model conceptualizes recovery as a non-linear function of interhemispheric balance modulated critically by the amount of residual structural reserve. Accordingly, patients with preserved ipsilesional structural reserve and low corticospinal damage may potentially recover through *rebalancing* of unphysiological interhemispheric interactions, whereby excessive inhibition by the contralesional M1 can be reduced and interhemispheric balance restored. In contrast, patients with severe structural CST damage and limited structural reserve may rely on *vicariation* by recruiting distant motor areas to compensate for lost ipsilesional function. In this latter case, interhemispheric imbalance may persist but might serve a compensatory role supporting residual motor output. Thus, whether increased contralesional hemisphere activation and interhemispheric imbalance are adaptive or maladaptive may fundamentally depend on the extent of the patient's residual structural resources.

In summary, the contralesional hemisphere may play a dynamic and time-dependent role in motor recovery after stroke. In the early phase, contralesional M1 may provide compensatory support for impaired ipsilesional output, aiding initial recovery. Over time, however, persistent interhemispheric imbalance can become maladaptive, limiting further improvement. Importantly, the functional contribution of the contralesional hemisphere is not inherently beneficial or maladaptive but may depend on several factors, such as specific task demands and the underlying structural reserve of the motor network. A closer look at this dynamic balance between beneficial and maladaptive processes requires integrating structural and functional network measures—an essential step toward developing a comprehensive framework for individualized neuromodulation strategies. Neither structural damage patterns nor functional connectivity alterations alone can fully predict individual recovery trajectories or guide optimal therapeutic interventions. Ultimately, a multimodal integration of structural and functional network markers of network reorganization will be essential for understanding variable recovery outcomes and optimizing rehabilitation after stroke.

## 1.4 Integrating structure and function: toward a mechanistic framework of recovery

In recent years, awareness has grown that recovery after stroke depends not solely on which pathways are damaged by the lesion but also on how the brain can leverage its individual structural reserve to restore efficient network connectivity and motor control (Di Pino et al., 2014). Consequently, a comprehensive understanding of motor recovery after stroke demands an integrated view that combines structural and functional markers within a unified analytical framework. Structural metrics such as CST integrity, lesion load, and structural connectivity serve as indicators of the brain's structural reserve, which constrains the potential for functional reorganization (Di Pino et al., 2014; Umarova et al., 2024). In contrast, functional connectivity measures may capture the dynamic reorganization of interregional interactions that accompany recovery-related plasticity (Grefkes & Fink, 2011). Complementing these imaging-based markers, neurophysiological approaches such as TMS provide a functional readout of corticospinal excitability and interhemispheric balance, offering direct physiological measures of motor pathway integrity (Spampinato et al., 2023).

Previous multimodal studies demonstrated the value of integrating these markers. Foundational work by Stinear and colleagues (2012) represents a pioneering study integrating structural measures of CST integrity, based on dMRI, with TMS-derived excitability measures, enabling early and accurate prediction of upper-limb motor recovery. Extending this work, Guggisberg and colleagues (2017) conducted a longitudinal study combining dMRI and electroencephalography (EEG), that linked CST integrity to recovery outcome while concurrent changes in EEG-based motor network connectivity provided complementary insight into heterogeneous recovery trajectories. Similarly, Nazarova and colleagues (2021) demonstrated that combining CST integrity with TMS-derived cortical excitability improves classification of distinct recovery profiles, emphasizing the predictive advantage of multimodal integration.

Considering the interplay between structural and functional markers, understanding their direct relationship is key to establishing a mechanistic framework of recovery. Graph-theoretical approaches have provided powerful analytical tools to characterize such patterns of *structure-function relationships* or *coupling* (Honey et al., 2010). Structure-function coupling reflects how well functional connectivity patterns align with the underlying anatomical connectome, serving as a measure of the efficiency of neural signaling constrained by the

brain's structural architecture (Honey et al., 2010; Park & Friston, 2013). For instance, Honey and colleagues (2009) demonstrated that diffusion-derived structural connectivity can predict resting-state functional connectivity in healthy individuals, establishing that anatomical pathways constrain the capacity of functional network configurations. Rubinov and Sporns (2010) extended this view by characterizing how structural topology shapes information integration and segregation across brain networks, providing a framework that supports the understanding of flexible structure-function relationships.

Following stroke, these structure-function relationships undergo significant alterations due to lesion-induced disconnections, often associated with behavioral impairments. Siegel and colleagues (2016) demonstrated that structural disconnections can predict functional network dysfunction across multiple behavioral domains. Griffis and colleagues (2019) further revealed that structural disconnections not only directly impair functional connectivity but also trigger cascading effects throughout the broader network, with greater disruption in structure-function coupling correlating with worse clinical outcomes. Conversely, patients with preserved or restored coupling tend to show better motor control and recovery, as also demonstrated by Liu and colleagues (2023), underscoring the importance of maintaining or re-establishing coordinated structure-function relationships for successful rehabilitation.

Despite growing recognition that structure-function coupling is crucial for recovery, which specific structural pathways underpin functional reorganization within the motor network remains incompletely understood. In particular, insights into how cortico-cortical structural connections contribute to recovery-related functional reorganization are surprisingly scarce. Previous multimodal findings suggest that cortical pathways may constitute alternative routes to support motor function after stroke, thereby representing important substrates of structural reserve. However, these studies have typically focused either on single tracts, such as transcallosal motor fibers, or on large-scale networks, rather than disentangling the roles of distinct cortico-cortical motor pathways within the motor network.

For example, Chen and Schlaug (2013) demonstrated that both functional interhemispheric M1–M1 connectivity during rest and WM integrity of transcallosal motor fibers correlated with upper-limb motor impairment in chronic stroke patients, highlighting complementary contributions of structural and functional domains. Furthermore, computational models integrating structural diffusion metrics—including cortical pathways—with lesion information and resting-state functional connectivity outperformed unimodal or clinical approaches in predicting upper-limb recovery (Lee et al., 2022). More recently, Mustin

and colleagues (2024) examined how contralesional motor areas functionally influence motor performance early after stroke depending on the level of ipsilesional structural reserve. By integrating connectome-based lesion-symptom mapping, CST lesion quantification, and online TMS, they showed that perturbation of contralesional M1 and anterior intraparietal sulcus differentially impacted early motor performance, with effects depending on the extent of ipsilesional structural network damage.

Taken together, integrating multimodal neuroimaging techniques not only enhances predictive accuracy but also paves the way toward a mechanistic framework of post-stroke recovery that explicitly links structural constraints, functional network dynamics, and behavioral outcome measures. While previous work has established the central role of the CST, far less is known about how the cortical structural reserve shapes functional reorganization within the motor network and influences recovery. Critically, no study to date has systematically investigated whether specific cortico-cortical connections within the motor system may operate as alternative pathways for the rerouting of motor commands to support recovery. Elucidating the distinct contributions of cortico-cortical connections to motor network reorganization is therefore essential for developing comprehensive, network-level models of stroke recovery.

## 1.5 Thesis objectives

This thesis aims to advance the current understanding of the structural and functional representations underlying motor network reorganization and recovery after stroke, with a particular emphasis on the role of the cortical structural reserve. This concept reflects the premorbid level of undamaged structural connectivity within the motor network, which is assumed to constrain the capacity for functional reorganization and thereby affect recovery outcomes (Di Pino et al., 2014; Umarova et al., 2024). Given that long-range WM pathways disrupted by a lesion are unlikely to regenerate in the adult brain (Makin & Krakauer, 2023), remaining cortico-cortical connections might constitute a critical substrate for post-stroke network reorganization. In light of the strong structure-function relationships observed in the healthy brain (Rubinov & Sporns, 2010), structural connectivity is proposed to play a pivotal role in supporting motor control after stroke. Furthermore, as previous studies have reported divergent findings depending on the level of behavioral assessment, this thesis explicitly differentiates between distinct aspects of motor control.

Despite extensive research using different approaches to study functional reorganization and motor recovery, a critical gap remains: the systematic characterization of cortico-cortical structural connectivity within the motor network as a structural reserve for motor control and functional reorganization after stroke. While previous studies have predominantly focused on the CST or whole-brain analyses, the specific role of individual cortico-cortical connections as compensatory pathways for the rerouting of motor control has not been investigated.

Accordingly, this thesis addresses this gap by elucidating how the integrity of cortico-cortical structural connections within the motor system (1) contributes to distinct aspects of motor control and (2) underlies functional reorganization processes by providing alternative routes to support motor recovery after stroke. To address these research questions, the thesis employs a novel two-stage neuroimaging approach conducted in a well-characterized cohort of chronic stroke patients and healthy controls.

**Study I:**

The first study investigated the contribution of cortico-cortical structural connectivity as a marker of cortical structural reserve for basal and complex aspects of motor control after stroke. Here, basal motor control was defined based on simple, isolated muscle recruitment of the upper-limb, while complex motor control was conceptualized as movements involving coordination of fine motor synergies (see 2.2). Using DSI data in chronic stroke patients, this study applied a compartmentwise analytical approach to quantify tractwise structural connectivity within the cortical motor system, thereby overcoming previous limitations inherent to conventional anisotropy estimation in regions with complex fiber architectures and subject-specific tractography (Paul, Cieslak, et al., 2023; Volz et al., 2018). Based on previous fMRI findings, we hypothesized structural connectivity between bilateral premotor–M1 and interhemispheric M1–M1 to be associated with both basal and complex motor control after stroke (Paul et al., 2021; Rehme, Eickhoff, et al., 2011). However, since recovery of complex and basal motor control demonstrates differential responsiveness to rehabilitation interventions (George et al., 2017), we hypothesized that improvements in these domains emerge from distinctive mechanisms. Therefore, the study investigated whether these structural connections serve as alternative pathways that support motor control independently of residual ipsilesional CST integrity. Considering that basal motor impairment might be compensated via contralesional pathways, including non-crossing CST fibers (Schaechter et al., 2009), we

hypothesized that the relationship between cortico-cortical connectivity and basal motor control is less dependent on ipsilesional CST integrity than the relationship with complex motor control. Finally, we addressed how the contribution of individual connections relates to different recovery trajectories following stroke, aiming to identify specific features of cortico-cortical structural connectivity linked to motor recovery.

Please note that Study I presented here is based on the following original publication:

> Paul, T.*, **Wiemer, V. M.***, Hensel, L., Cieslak, M., Tscherpel, C., Grefkes, C., Grafton, S. T., Fink, G. R. & Volz, L. J. (2023). Interhemispheric structural connectivity underlies motor recovery after stroke. *Annals of Neurology*, Volume 94, Issue 4, Pages 785-797.
>
> * These authors contributed equally to this work.

**Study II:**

Building on the structural findings of the first study, Study II used a multimodal neuroimaging approach to explore the relationship between the cortical structural reserve and functional network reorganization underlying motor recovery after stroke. Specifically, we addressed whether the cortical pathways identified as important for post-stroke motor control and recovery are functionally engaged, indicating motor network reorganization. To examine these potential structure-function relationships, Study II related cortico-cortical structural connectivity derived from DSI to task-related effective connectivity estimated with DCM during finger tapping of the affected hand. This approach allowed us to investigate how individual levels of structural reserve constrain or guide functional reorganization within the motor network, with particular emphasis on the rerouting of motor commands within and between hemispheres. Building on previous evidence that premotor-CST pathways support complex motor control after stroke (Paul et al., 2024), we hypothesized that *intrahemispheric rerouting* from the ipsilesional M1 via premotor areas support upper-limb recovery, including dexterous hand movements such as distal finger tapping, provided sufficient CST integrity and intrahemispheric structural reserve. In contrast, *interhemispheric rerouting* via the contralesional M1 was expected to occur predominantly in patients with severe CST damage and high interhemispheric structural reserve (Di Pino et al., 2014). However, considering the findings from Study I, this compensatory pathway was assumed to primarily benefit more basal aspects of upper-limb motor control rather than complex hand function (Paul, Wiemer, et al., 2023). By integrating structural and functional connectivity measures, this study aimed to

evaluate the behavioral relevance of these distinct rerouting mechanisms and to reconcile conflicting interpretations of interhemispheric reorganization by accounting for individual differences in structural network reserve.

Please note that Study II presented here is based on the following original publication:

> **Wiemer, V. M.**, Paul, T., Hensel, L., Cieslak, M., Tscherpel, C., Grefkes, C., Grafton, S. T., Fink, G. R. & Volz, L. J. (2025). Structural reserve-dependent cortical rerouting of motor control after stroke. *Brain,* awaf434.

Together, these two studies address the primary aim of this thesis: to provide a deeper understanding of the interplay between cortical structural reserve, functional network alterations, and motor impairment in functional reorganization after stroke. To achieve this, the thesis implements a novel methodological approach combining normative tract templates with compartmentwise anisotropy analysis, enabling—for the first time—robust tractwise quantification of cortico-cortical structural connectivity in stroke patients while circumventing conventional tractography limitations. By systematically linking the integrity of cortical structural pathways to both distinct levels of motor behavior and task-specific effective connectivity patterns, this work advances stroke research by providing a network-level characterization of how preserved cortical connections constitute a critical structural reserve. The insights gained offer a foundation for identifying structure–function relationships with potential for novel biomarkers, ultimately improving the prediction of recovery outcomes and guiding the development of individualized therapeutic interventions.

# 2. Methods

Please note that the following methods and results presented in this thesis are based on the original publications mentioned above.

## 2.1 Participants

In this thesis, data of twenty-five chronic stroke patients (mean age: 66.68 ± 11.25 years; 5 women) who had previously undergone treatment at the Department of Neurology, University Hospital Cologne, were analyzed. Comprehensive demographic and clinical details are presented in Supplementary Table 1. Participants were eligible if they were aged between 40 and 90 years, had sustained a first-ever ischemic stroke more than six months prior to enrollment, and initially exhibited unilateral motor impairment of the upper-limb. Exclusion criteria were recurrent stroke, bilateral infarctions, intracerebral hemorrhage, other neurological conditions, severe persistent aphasia or neglect, or any contraindications for MRI. For Study II, two patients were excluded from the final analyses because their fMRI data did not meet quality criteria and additional data of twenty-two age-matched healthy controls (mean age: 67.05 ± 6.59 years; 6 female) were analyzed. All individuals provided written informed consent before participation. Ethical approval was obtained from the Medical Faculty of the University of Cologne, and the study was conducted in accordance with the Declaration of Helsinki.

## 2.2 Clinical and behavioral motor assessment

To characterize motor impairment across distinct levels of upper-limb motor control, different standardized behavioral assessments were employed reflecting both basal and complex motor functions. Complex motor control, involving goal-directed movements requiring coordination of the hand and arm, was measured using the Action Research Arm Test (ARAT; Lyle, 1981). This test evaluates performance in everyday manual tasks such as grasping, moving, and releasing objects, thereby focusing on visuomotor integration, coordination of fine motor synergies and the status of distal control mechanisms (Figure 8).

In contrast, the Motricity Index (MI)-arm subscore was used to determine the capacity of basal arm motor control, primarily reflecting proximal upper-limb control with some distal movements (Demeurisse et al., 1980). This measure predominantly assesses isolated muscle movements based on the strength necessary to, for example, hold the arm against gravity or

resist examiner-applied force. The combination of these complementary measures enabled a more nuanced behavioral characterization of the variable motor impairments across the patient cohort.

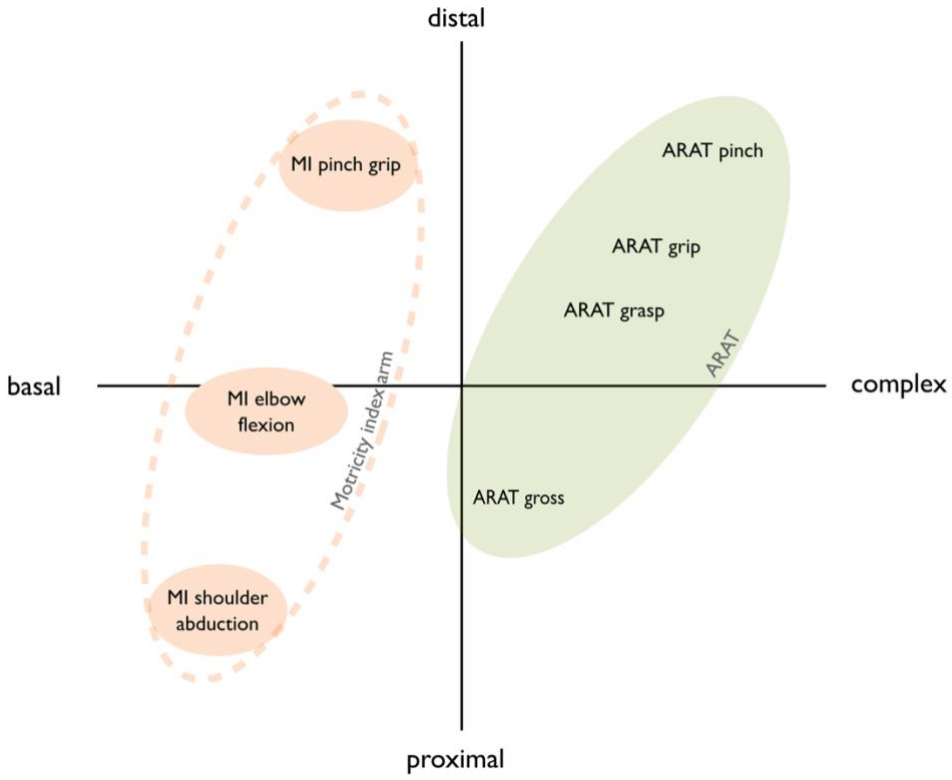


**Figure 8 | Conceptual overview of motor control assessment using the ARAT and MI-arm score.** The MI-arm score assesses basal motor functions by testing discrete movements that innervate specific muscle synergies, systematically identifying the contribution of individual muscle groups across the proximal-to-distal axis (orange). The ARAT, however, evaluates complex motor control demands that necessitate integration of diverse motor control mechanisms, thereby capturing performance relevant to everyday functional tasks (green). ARAT = Action Research Arm Test; MI = Motricity Index. Reproduced from Paul, Wiemer, et al. (2023), *Annals of Neurology*, Volume 94, Issue 4, Pages 785-797.

Additionally, in Study II, a task-specific metric for hand motor control was operationalized during the fMRI session. This score was defined as the ratio of finger tapping frequency between the affected and unaffected hand during the fMRI scan, providing an index of residual distal hand motor function associated with the recorded fMRI task.

Finally, to capture longitudinal motor recovery, the arm item of the National Institutes of Health Stroke Scale (NIHSS) was used to compare motor impairment between the acute (measured at Stroke Unit admission) and the chronic phase (time point of recorded MRI data during the study) after stroke. This subscore of the widely-used clinical bedside test evaluates gross motor function by assessing items such as lifting and holding the arm against gravity (Brott et al., 1989). The severity of symptoms was rated on an ordinal scale from 0 (normal)

up to 4 (no movement) points. An improvement of at least one point on the NIHSS-arm score was considered indicative of *substantial* motor recovery (Supplementary Table 1). Patients who did not meet this criterion were classified as having experienced *non-substantial* recovery. Importantly, due to the relatively coarse granularity and limited sensitivity of the NIHSS, a lack of improvement does not imply the absence of any recovery, as subtle gains in motor control may be detected only with more fine-graded assessments like the ARAT assessing more complex movements.

## 2.3 MRI acquisition and preprocessing

MRI data were acquired using a Siemens MAGNETOM Prisma 3 Tesla scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a 64-channel head coil. Structural scans included T1-weighted images (TR = 2500 ms, TE = 2.22 ms, FoV = 241 mm, 208 axial slices, voxel size = 0.94 × 0.94 × 0.94 mm³) and T2-weighted images with identical spatial parameters. Lesion masks were manually delineated on T2-weighted images using MRIcron (https://www.nitrc.org/projects/mricron) and confirmed by a certified neurologist (Figure 9).

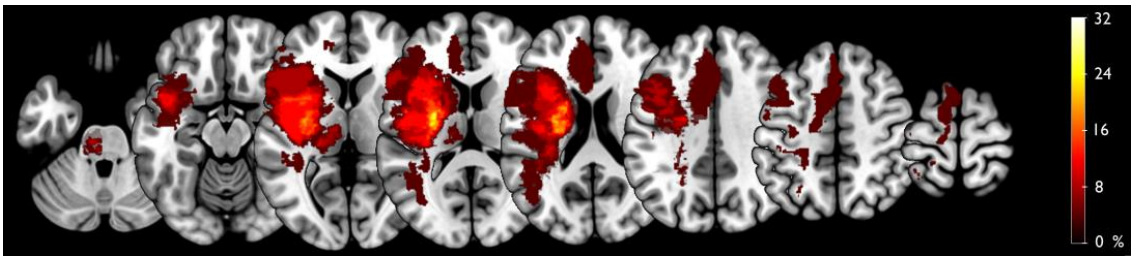


**Figure 9 | Lesion overlay of stroke patients.** Lesion maps showing the overlap of individual lesions as the percentage of patients featuring a lesion in a given voxel across all patients ($n$ = 25). The highest overlap was found in the internal capsule, which was affected in more than 30% of patients. Please note that all right-hemispheric lesions were flipped to the left hemisphere.

### 2.3.1 Diffusion MRI data

Diffusion MRI data were acquired via DSI at an isotropic voxel resolution of 1.8 × 1.8 × 1.8 mm³, and sampled with multiple b-values ranging from 0 up to 5000 s/mm² across 128 diffusion directions and 10 non-diffusion-weighted (b0) volumes for motion correction (TR = 4300 ms, TE = 96 ms, FoV = 262 mm).

Preprocessing of the DSI data was conducted using QSIPrep (Cieslak et al., 2021) and is described in detail in the study by Paul and colleagues (2023). T1-weighted images were used as reference and corrected for intensity non-uniformity using *N4BiasFieldCorrection* (Tustison et al., 2010) based on Advanced Normalization Tools (ANTs 2.3.1; Avants et al.,

2009), skull-stripped using *antsBrainExtraction*, and spatially normalized to the Montreal Neurological Institute (MNI) template via nonlinear registration with *antsRegistration* (Avants et al., 2008). Brain tissue segmentation into cerebrospinal fluid, WM, and gray matter was performed on brain-extracted T1 images using FSL's *FAST* (Zhang et al., 2001). All diffusion images with b-values below 100 s/mm² were treated as b0 images. MP-PCA denoising (*dwidenoise*) from MRtrix3 (Veraart et al., 2016) was applied with a 5-voxel sliding window, followed by B1 field inhomogeneity correction (*dwibiascorrect*) using the N4 algorithm (Tustison et al., 2010). Intensity normalization ensured consistent mean b0 intensities across each diffusion-weighted scanning sequence. Motion correction was based on the 3dSHORE algorithm (Merlet & Deriche, 2013) integrated within QSIPrep. The diffusion time series were resampled into AC-PC space with 1.8 mm isotropic voxels.

Orientation distribution functions were reconstructed using GQI with a diffusion distance ratio of 1.25 (Yeh et al., 2010). Afterwards, gFA maps were generated with DSI Studio (https://dsi-studio.labsolver.org/) and normalized into MNI standard space using ANTs. To ensure that subsequent analyses focused on intact, non-lesioned WM voxels, gFA maps were masked with individual WM segmentations and lesion masks. Finally, individual gFA maps with lesions located in the right hemisphere were flipped along the midsagittal plane to standardize lesion lateralization to the left hemisphere, facilitating group analyses.

### 2.3.2 Functional MRI data

Functional MRI data were acquired using a gradient echo-planar imaging (EPI) multiband sequence (TR = 800 ms, TE = 30 ms, 72 axial slices, voxel size = 2.0 × 2.0 × 2.0 mm³, flip angle 52°). During scanning, participants performed a visually-cued motor task involving repetitive index finger tapping with either the affected or unaffected hand in pseudorandomized blocks (Grefkes, Nowak, et al., 2008; Hensel et al., 2021).

Preprocessing of fMRI data was conducted using the Statistical Parametric Mapping software (SPM12; The Wellcome Centre for Human Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk) within MATLAB version 2022a (The Mathworks Inc., MA, USA). The first 12 EPI volumes were discarded to allow for magnetic field saturation. Preprocessing steps included realignment of EPIs to the mean image of the time series, co-registration of EPIs to the individual's T1-weighted image, spatial normalization to MNI template space with lesion masking, and spatial smoothing with a 5 mm full-width at half-maximum Gaussian kernel (Ashby, 2019; Di & Biswal, 2023; Poldrack et al., 2011). Quality

control involved visual inspection of each preprocessing step to ensure co-registration and normalization accuracy.

First-level statistical analysis was based on a general linear model incorporating three experimental conditions (*affected* hand movement, *unaffected* hand movement, and visual instruction), convolved with the canonical hemodynamic response function. Motion parameters, along with WM and cerebrospinal fluid signals, were entered as nuisance regressors to control for residual confounds.

## 2.4 Identification of cortical motor regions

Given the well-documented association between motor impairment and altered functional connectivity within the cortical motor network after stroke (Grefkes & Fink, 2014; Larsen et al., 2018; Schulz et al., 2016; Ward et al., 2003), bilateral core motor regions were selected for further analysis, including M1, PMd, PMv, and SMA. The precise anatomical locations of these areas were identified through automated term-based meta-analyses of fMRI studies using the Neurosynth platform (https://www.neurosynth.org/). The search terms "motor cortex," "dorsal premotor," "ventral premotor," and "supplementary motor" were queried to extract specific MNI coordinates corresponding to each region of interest (ROI). The resulting coordinates can be found in Table 1 and were subsequently used to define the cortical motor ROIs and generate fiber tract templates for structural connectivity analyses.

**Table 1 | MNI coordinates of motor regions of interest.** This table presents the MNI coordinates for bilateral motor regions selected based on automated meta-analyses of fMRI studies using the Neurosynth platform. Coordinates correspond to the primary motor cortex (M1), dorsal premotor cortex (PMd), ventral premotor cortex (PMv), and supplementary motor area (SMA).

| Region | Left (x, y, z) | Right (x, y, z) |
|---|---|---|
| M1 | -38, -22, 60 | 38, -22, 60 |
| PMd | -24, -6, 62 | 24, -6, 62 |
| PMv | -54, -1, 22 | 54, -1, 22 |
| SMA | -4, -4, 54 | 4, -4, 54 |

## 2.5 Deterministic fiber tracking

Normative fiber tract templates between cortical core motor regions were generated using deterministic fiber tracking as implemented in DSI Studio to overcome limitations of subject-specific tractography (see 1.1.2). Fiber tracking between the predefined motor ROIs was performed in the HCP-1,065 template of healthy subjects (Yeh et al., 2018), applying an

angular threshold ranging from 50° to 90° along with exclusion ROIs to improve specificity. Resulting streamlines were manually refined and validated by a certified neurologist to ensure anatomical plausibility. Thereby, deterministic tractography enabled the definition of specific WM tracts including (1) intrahemispheric cortico-cortical connections between ipsilesional M1 and premotor areas (i.e., ilPMd–ilM1, ilPMv–ilM1, ilSMA–ilM1), (2) interhemispheric connections linking ipsilesional M1 with contralesional premotor areas (clPMd–ilM1, clPMv–ilM1, clSMA–ilM1), as well as (3) direct interhemispheric fibers between bilateral M1 (clM1–ilM1; Figure 10).

Moreover, to assess CST integrity, an additional CST mask was created from fibers descending from M1, PMd, PMv, and SMA. Considering the documented hemispheric asymmetry of the CST in healthy subjects (Volz et al., 2018), two CST tracts descending from both hemispheres were merged after flipping the right-hemispheric tract to the left hemisphere, ensuring comprehensive coverage of relevant voxels.

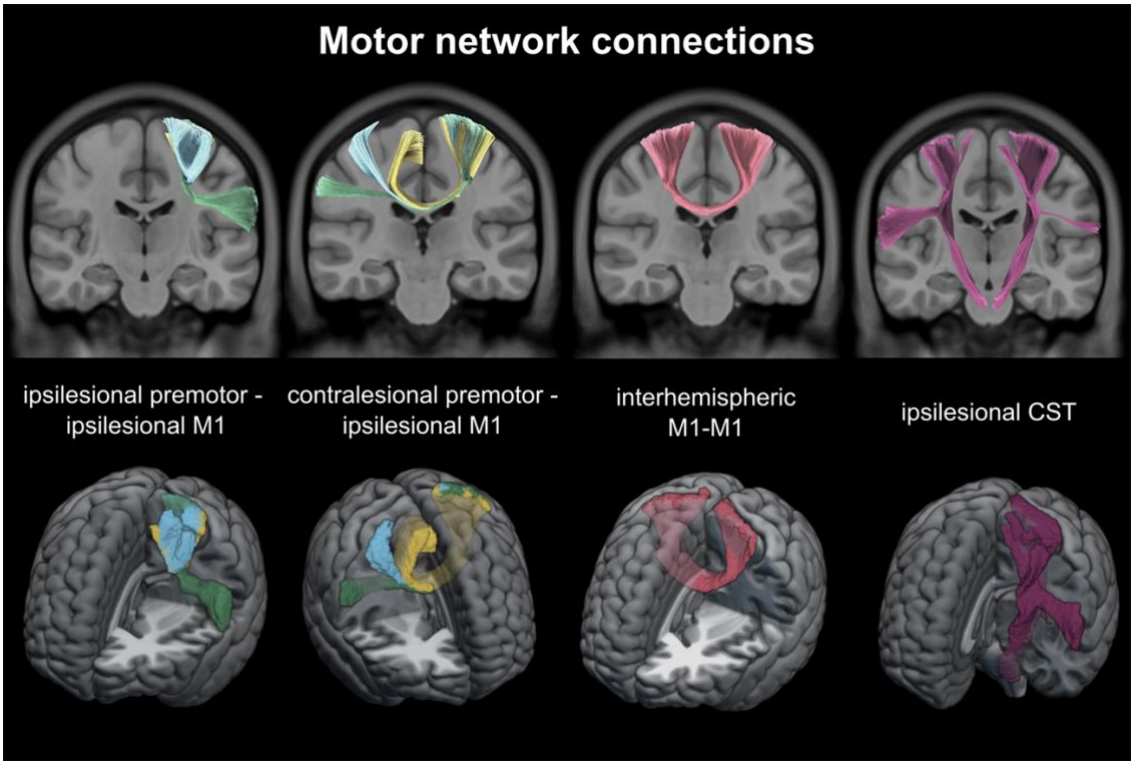


**Figure 10 | Visualization of structural white matter connections within the motor network**. Deterministic tractography reconstructions of fiber tracts between cortical motor regions were generated using the HCP1065-template in DSI Studio (top panel). Resulting tract templates for anisotropy extraction are displayed as three-dimensional overlays in MRIcroGL (bottom panel). The ipsilesional CST was constructed by first generating bilateral descending tracts (upper panel), then combining them into a single left-hemisphere template after horizontal flipping of the right-hemispheric tract (lower panel). Color coding: blue = dorsal premotor cortex connections; green = ventral premotor cortex connections; yellow = supplementary motor area connections; red = interhemispheric connection between bilateral primary motor cortices; purple = corticospinal tract. Reproduced from Paul, Wiemer, et al. (2023), *Annals of Neurology*, Volume 94, Issue 4, Pages 785-797.

## 2.6 Analysis of structural connectivity

Structural connectivity within the motor network was quantified as tractwise mean gFA-values for each generated normative tract template. To obtain estimates of WM anisotropy, a whole-brain compartmentwise approach was applied (Volz et al., 2018). Individual gFA maps were segmented into compartments according to the number of resolvable fiber orientations present within each voxel—specifically, voxels with one, two, or three fiber directions—using a deterministic directionality mask (see 1.1.2; cf. Figure 4). This compartmentalization allowed the selective extraction of tractwise mean gFA-values from voxels predominantly containing a single dominant fiber direction, thereby reducing biases inherent to voxels with multiple fiber directions and enhancing the robustness of structural connectivity analyses in stroke patients (Paul, Cieslak, et al., 2023). By focusing on one-directional voxels within each tract of interest, tract-specific mean gFA-values were derived, providing measures of microstructural integrity that reflect structural connectivity of the underlying WM pathways.

To further confirm the specificity and sensitivity of this approach, complementary analyses were performed using multi-directional voxel compartments. The most robust associations with motor control consistently emerged when analyses were restricted to one-directional voxels, emphasizing the methodological benefit of the compartmentwise approach for structural connectivity assessment in clinical stroke research.

## 2.7 Analysis of task-related effective connectivity

Task-related effective connectivity during finger tapping movements was investigated by DCM (as implemented in SPM12). This computational framework models effective connectivity as directional influences—either excitatory or inhibitory—exerted by one brain region over another, resulting in modulations of neuronal activity states. These changes can be described by the bilinear differential state equation (Friston et al., 2003; Stephan et al., 2010):

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

In this model, the neural state vector $z$ is influenced by three connectivity matrices: $A$, $B$, and $C$. The matrix $A$ captures the connectivity pattern in the absence of external stimuli, reflecting endogenous or intrinsic connectivity. Matrix $B$ encodes modulatory changes in connectivity driven by the experimental conditions, such as repetitive finger tapping movements, represented by the external input vector $u$. Matrix $C$ reflects the direct influences of extrinsic or driving inputs.

The analysis described in the following focused on the effective connectivity between the same cortical regions used for structural connectivity analysis (bilateral M1, PMd, PMv, and SMA). Subject-specific peak activation coordinates for each ROI were individually identified from first-level contrasts comparing '*affected* hand movement versus rest' and '*unaffected* hand movement versus rest' using anatomical constraints (Rehme et al., 2012) and a voxel-level threshold of $P < 0.001$ (Supplementary Table 2 & 3). For each ROI, the primary temporal component of the BOLD signal was extracted by computing the first eigenvariate from voxel time series centered on the individually determined activation peaks within a 10 mm sphere. This individualized approach ensured that the selected signal predominantly reflected task-induced neural activity while minimizing confounding influences from partial volume effects caused by the lesion.

A set of 10 DCM models with varying complexity was constructed, ranging from sparse models including only connections with the ipsilesional M1 to fully-connected architectures (Supplementary Figure 1-3). The six premotor areas were designated as driving input regions (DCM-C matrix). The fully-connected model was identified by Bayesian model selection using a random effects approach (Stephan et al., 2009) as the best fit given the empirical data (Supplementary Figure 4). The coupling parameters from the fully-connected model during finger tapping of the affected hand (DCM-$B_{aff}$ matrix) were statistically tested at the group level via one-sample *t*-tests against zero, applying false discovery rate (FDR) correction to account for multiple comparisons. Parameters found to be significantly modulated were included in subsequent analyses.

## 2.8 Statistical analyses – Study I

### 2.8.1 Association between structural connectivity and motor control

To investigate associations between the structural connectivity—reflecting microstructural integrity—of cortico-cortical motor pathways and distinct aspects of motor control post-stroke, Pearson correlation analyses were conducted. Potential relationships with complex motor control were evaluated by correlating tractwise mean gFA-values with the ARAT score, while associations with basal motor control were assessed using the MI-arm score. All resulting *P*-values were FDR-corrected to account for multiple comparisons.

Furthermore, partial correlation analyses controlling for ipsilesional CST damage were performed to determine whether the relationships between cortico-cortical structural

connectivity and motor control were influenced by the residual integrity of the ipsilesional CST. If previously observed significant correlations disappeared, this would suggest a dependence on CST integrity; in contrast, persistence of correlations would point toward independence from CST integrity. Given that CST integrity is a well-established predictor of motor recovery after stroke (Koch et al., 2016), we acknowledged that recovery trajectories are versatile: patients with small lesions and mild initial impairments may achieve favorable outcomes in the chronic stage with minimal recovery, whereas those with extensive lesions and severe deficits may demonstrate substantial recovery during rehabilitative processes, ultimately achieving good outcomes as well. Accordingly, the patient cohort was stratified into subgroups exhibiting *substantial* ($n$ = 15) or *non-substantial* ($n$ = 10) upper-limb recovery, as defined by an improvement in the NIHSS-arm score from the acute to the chronic stage. Repeating correlation analyses of basal motor control within these subgroups aimed to uncover recovery-dependent associations.

To mitigate confounding effects of lesions on structural connectivity analyses, all correlation analyses were repeated after excluding tracts demonstrating over 10% overlap between the lesion mask and the tract's one-directional voxels in individual subjects ($n$ = 3). This step ensured that the associations reflected genuine microstructural pathway integrity rather than direct lesion effects.

### 2.8.2 Explanation of variance

Stepwise backward linear regression models were conducted guided by the Bayesian Information Criterion (*BIC*; with $k = \log(n)$ where $n = 25$). These analyses aimed to evaluate the proportion of variance explained in basal (measured by the MI-arm score) and complex motor control (assessed by the ARAT score) by combining contributions from both the integrity of the ipsilesional CST and cortico-cortical structural connectivity.

To better delineate the relative contributions of these predictors, we separately estimated the variance accounted for by (i) CST integrity alone and (ii) cortico-cortical connectivity without CST integrity. This direct comparison serves as a valuable benchmark for evaluating whether cortico-cortical structural connectivity adds predictive value for motor outcomes beyond CST integrity, considering its established role as a biomarker for post-stroke motor impairment (Boyd et al., 2017).

## 2.9 Statistical analyses – Study II

### 2.9.1 Group-specific differences in network connectivity

To compare structural connectivity (measured as tractwise mean gFA) and effective connectivity (derived from DCM-$B_{aff}$ matrix) between stroke patients ($n$ = 23) and healthy controls ($n$ = 22), independent sample $t$-tests were conducted. Similarly, independent $t$-tests were utilized to examine differences in effective connectivity between patient subgroups categorized by *substantial* ($n$ = 13) or *non-substantial* ($n$ = 10) motor recovery. All statistical group comparisons and correlation analyses described below were corrected for multiple testing across intra- and interhemispheric connections using FDR correction.

### 2.9.2 Structure-function relationships

Furthermore, structure-function relationships were investigated to assess whether tractwise structural connectivity—indicative of the cortical structural reserve—was associated with task-related effective connectivity reflecting *intra-* and *interhemispheric rerouting* of motor commands. Specifically, Pearson correlations were performed, examining the association between structural and effective connectivity from the ipsilesional M1 to bilateral premotor regions, and to contralesional M1. To evaluate how residual integrity of the CST influences these structure-function relationships, patients were categorized into *high* or *low* CST integrity subgroups via a median split based on individual ipsilesional CST mean gFA-values (Supplementary Table 1). Correlation analyses were then repeated within each subgroup.

### 2.9.3 Association with post-stroke motor control

To examine whether multimodal connectivity within specific cortical motor network connections was related to upper-limb motor function following stroke, we conducted Pearson correlation analyses between patients' structural or effective connectivity measures and estimates of basal arm (assessed by the MI-arm score) or distal hand motor performance (measured by relative finger tapping frequency during the fMRI task). To explore differences related to the degree of recovery, correlation analyses between effective connectivity and motor control were conducted separately for the recovery subgroups.

Notably, to rule out potential confounding effects due to lesion overlap with ROIs used for extracting BOLD signals, we repeated group comparisons and correlation analyses after excluding individuals ($n$ = 3) whose lesions intersected with any of their respective ROIs.

# 3. Results – Study I

## 3.1 Association between structural connectivity and motor control

Significant positive associations were observed between both basal and complex motor control with tractwise anisotropy, including the interhemispheric connection between contralesional to ipsilesional M1, all intrahemispheric premotor–M1 connections, and the interhemispheric connections between contralesional PMv and SMA to ipsilesional M1 (all $P_{FDR} < 0.05$; Table 2; Figure 11A). Accordingly, patients with higher cortico-cortical structural connectivity within these motor pathways exhibited better motor control after stroke. Overall, correlations were generally stronger for basal than for complex motor control.

**Table 2 | Correlation analyses between structural connectivity and different aspects of motor control.** 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. Adapted from Paul, Wiemer, et al. (2023), *Annals of Neurology*, Volume 94, Issue 4, Pages 785-797.

| | 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 | 0.16 |

Abbreviations: cl = contralesional; CST = corticospinal tract; il = ipsilesional; M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; SMA = supplementary motor area. Asterisks signify the following significance thresholds: ***$P_{FDR} < 0.001$, **$P_{FDR} < 0.01$, *$P_{FDR} < 0.05$.

Importantly, when fiber tracts with substantial lesion overlap were excluded from analysis, the observed correlations persisted, confirming the robustness of these results (Supplementary Table 4). Similarly, excluding subjects with brainstem ($n$ = 5) or cortical ($n$ = 3) infarctions led to highly similar findings, indicating that differences in lesion site did not substantially bias the findings.

In summary, these observations support our hypothesis that preserved structural connectivity between ipsilesional M1 and (i) bilateral premotor areas as well as (ii) contralesional M1 underlies both basal and complex motor functions of the paretic upper-limb in chronic stroke patients. Given the crucial role of the CST in voluntary motor control, subsequent analyses assessed whether the identified associations were dependent on residual ipsilesional CST integrity using partial correlation analyses.

## 3.2 Ipsilesional CST-dependency

Partial correlation analyses were conducted to account for the influence of ipsilesional CST integrity on the observed associations between tractwise anisotropy and motor control. For basal motor control, partial correlations remained consistent with the initial correlation findings (Table 2; Figure 11). Specifically, higher anisotropy within all intrahemispheric premotor–M1 connections (all $r > 0.59$, $P_{FDR} < 0.006$) remained associated with basal motor control (Figure 11B). Likewise, interhemispheric connectivity between the contralesional PMv and ipsilesional M1 ($r$ = 0.53, $P_{FDR}$ = 0.013) as well as between bilateral M1 ($r$ = 0.45, $P_{FDR}$ = 0.040) remained significant after controlling for CST integrity. Taken together, these results indicate that basal motor control was related to structural connectivity linking ipsilesional M1 with (i) ipsilesional premotor areas, (ii) contralesional PMv, and (iii) contralesional M1, independent of CST integrity

In contrast, the relationships between cortico-cortical connectivity and complex motor control strongly depended on residual CST integrity (Table 2; Figure 11B). After multiple comparison correction, no partial correlation remained significant. Notably, these findings were specific to CST integrity rather than to general lesion parameters such as overall infarct size or the lesion load within the CST, which showed no significant association with impaired motor control.

In conclusion, these results underscore the pivotal role of ipsilesional CST integrity for complex motor control following stroke, suggesting that cortical connections alone cannot fully compensate for motor impairment when CST damage is pronounced.

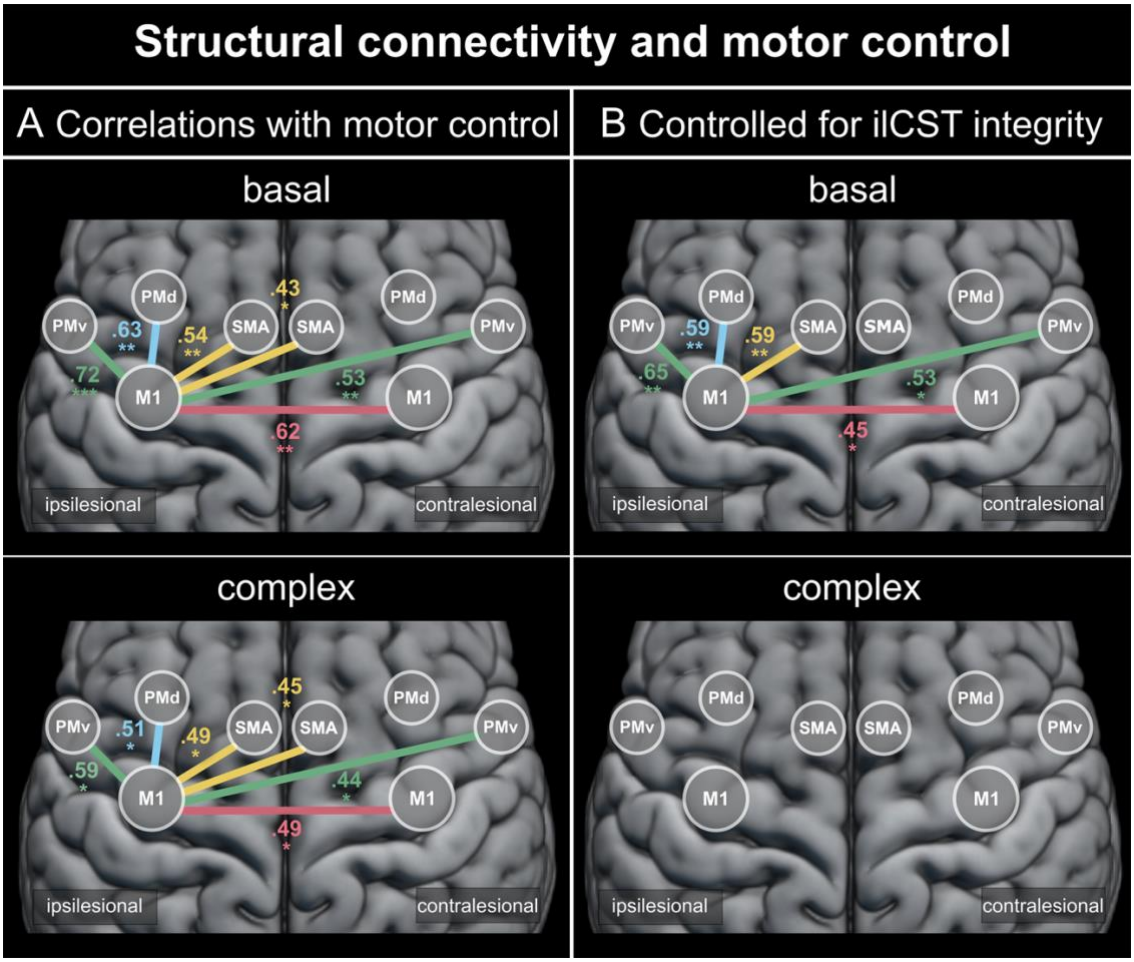


**Figure 11 | Association between cortico-cortical structural connectivity and distinct aspects of motor control.** (**A**) Tractwise anisotropy values of various cortico-cortical connections revealed significant correlations with both basal and complex motor control after stroke (Pearson correlation coefficients are displayed for significant associations). (**B**) Partial correlations demonstrating associations between cortico-cortical connectivity and motor control independent of ipsilesional CST integrity. Connections shown withstood FDR-corrected multiple comparison testing ($P_{FDR} < 0.05$). Significance levels: $^{***}P_{FDR} < 0.001$, $^{**}P_{FDR} < 0.01$, $^{*}P_{FDR} < 0.05$. *ilCST = ipsilesional corticospinal tract; M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; SMA = supplementary motor area.* Reproduced from Paul, Wiemer, et al. (2023), *Annals of Neurology*, Volume 94, Issue 4, Pages 785-797.

## 3.3 Structural connectivity and motor recovery

To explore whether the level of motor recovery impacted the relationship between structural connectivity and motor control, patients were categorized into two recovery subgroups: those who experienced *substantial* recovery of arm motor function ($n$ = 15) and those who featured *non-substantial* recovery ($n$ = 10). In patients with substantial recovery, interhemispheric connectivity between contralesional and ipsilesional M1 showed a strong positive association with basal motor control ($r$ = 0.79, $P_{FDR}$ = 0.003; Table 3; Figure 12A), whereas no significant relationships were found with premotor–M1 tracts. This association remained robust even after statistically adjusting for CST integrity ($r$ = 0.75, $P_{FDR}$ = 0.016; Figure 12B).

**Table 3 | Recovery-specific subgroup analysis: Correlation analyses between structural connectivity and basal motor control.** Analyses were carried out separately for patients exhibiting (i) substantial or (ii) non-substantial recovery. Partial correlations assessed the relationship between basal motor control and tractwise anisotropy while controlling for ipsilesional CST integrity. Adapted from Paul, Wiemer, et al. (2023), *Annals of Neurology*, Volume 94, Issue 4, Pages 785-797.

| | 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 | 0.3 | 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 | 0.5 | 0.139 | 0.42 | 0.325 |
| | | | | |
| | | **Non-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 | 0.06 |
| ilSMA–ilM1 | 0.9 | 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 | 0.3 | 0.392 | 0.21 | 0.657 |

Abbreviations: cl = contralesional; CST = corticospinal tract; il = ipsilesional; M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; SMA = supplementary motor area. Asterisks signify the following significance thresholds: ***$P_{FDR}$ < 0.001, **$P_{FDR}$ < 0.01, *$P_{FDR}$ < 0.05.

In contrast, among patients without substantial recovery, basal motor control was significantly related to both the interhemispheric connection from contralesional PMv to ipsilesional M1 ($r$ = 0.71, $P_{FDR}$ = 0.036) and intrahemispheric premotor–M1 connections (all $r$ > 0.81, $P_{FDR}$ < 0.011; Table 3; Figure 12A). By comparison, the interhemispheric M1–M1 connection showed no significant relation to motor control in this group ($r$ = 0.44, $P_{FDR}$ = 0.279). When controlling for CST integrity, only the ipsilesional SMA–M1 connection retained statistical significance ($r$ = 0.87, $P_{FDR}$ = 0.015; Figure 12B). Furthermore, exclusion of connections directly overlapping with the lesion produced nearly identical results (Supplementary Table 5), supporting the robustness of these recovery-dependent findings.

Overall, these results indicate that the functional significance of the interhemispheric connection between contralesional and ipsilesional M1 is linked to the level of post-stroke motor recovery. Specifically, patients who showed substantial recovery relied strongly on interhemispheric M1–M1 connectivity to maintain basal motor control, whereas this association was absent in those with non-substantial recovery. Thus, recruitment of the contralesional motor network via preserved interhemispheric M1–M1 motor fibers may constitute a crucial compensatory pathway supporting residual arm function after stroke when direct corticospinal output is compromised.

## 3.4 Explanation of clinical variability

We first examined the contribution of ipsilesional CST integrity to upper-limb motor control impairment. For basal motor control, ipsilesional CST accounted for approximately 28% of the behavioral variance ($R^2$ = 27.71%, *adjusted* $R^2$ = 24.57%, $P$ = 0.007, $BIC$ = 132.46). Comparable proportions of explained variance were observed for complex motor function ($R^2$ = 27.77%, *adjusted* $R^2$ = 24.63%, $P$ = 0.007, $BIC$ = 130.88).

Subsequent stepwise backward regression analyses incorporating both cortico-cortical connectivity and CST integrity substantially increased the amount of explained variance by the model. This combined model explained 71% of the variance in basal motor control ($R^2$ = 71.01%, *adjusted* $R^2$ = 65.22%, $P$ < 0.001, $BIC$ = 119.27) and 60% in complex motor control ($R^2$ = 60.17%, *adjusted* $R^2$ = 46.90%, $P$ = 0.006, $BIC$ = 132.09). When the CST was excluded from the model, cortico-cortical pathways alone still accounted for a remarkable portion of the variance in basal motor control ($R^2$ = 63.26%, *adjusted* $R^2$ = 58.01%, $P$ < 0.001, $BIC$ = 121.98). In contrast, for complex motor control, the explanatory power of this model

was notably reduced after excluding ipsilesional CST, though the model remained statistically significant ($R^2 = 35.02\%$, *adjusted* $R^2 = 32.19\%$, $P = 0.002$, $BIC = 128.24$).

In summary, regression analyses demonstrate that the integrity of the cortical motor network provides strong predictive information on post-stroke motor control. Basal upper-limb function can largely be accounted for by cortico-cortical connectivity alone, whereas complex motor function critically depends on the structural integrity of the ipsilesional CST.

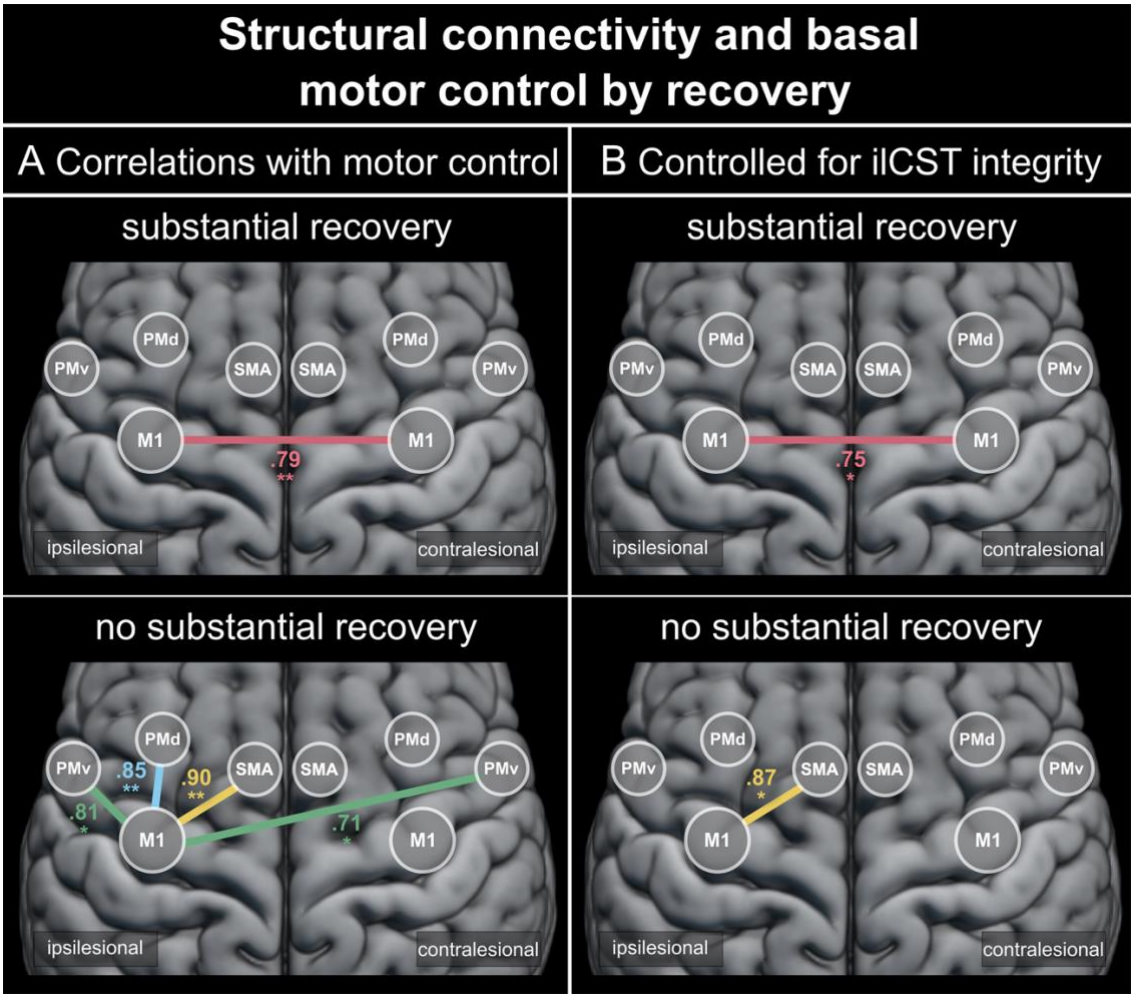


**Figure 12 | Recovery-specific subgroup analysis: Association between cortico-cortical structural connectivity and basal motor control.** (**A**) Tractwise anisotropy values of various cortico-cortical connections revealed significant correlations with basal motor control in patients with substantial versus non-substantial recovery (Pearson correlation coefficients are displayed for significant associations). (**B**) Partial correlations demonstrating associations between cortico-cortical connectivity and basal motor control independent of ipsilesional CST integrity for both recovery subgroups. Notably, the association between interhemispheric M1–M1 connectivity and basal motor control was observed exclusively in patients with substantial recovery, suggesting a compensatory mechanism involving transcallosal pathways. Connections shown withstood FDR-corrected multiple comparison testing ($P_{FDR} < 0.05$). Significance levels: ***$P_{FDR} < 0.001$, **$P_{FDR} < 0.01$, *$P_{FDR} < 0.05$. *ilCST = ipsilesional corticospinal tract; M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; SMA = supplementary motor area.* Reproduced from Paul, Wiemer, et al. (2023), *Annals of Neurology*, Volume 94, Issue 4, Pages 785-797.

# 4. Results – Study II

## 4.1 Connectivity of the cortical motor network

Relative to healthy participants, chronic stroke patients exhibited reduced interhemispheric structural connectivity between the primary motor cortices ($t(43) = 2.63$, $P_{FDR} = 0.047$) and diminished intrahemispheric connectivity between ipsilesional M1 and premotor regions ($t(43) > 2.23$, $P_{FDR} < 0.046$; Figure 13).

During movements of the affected hand, connectivity within the bilateral motor network was substantially modulated (Figure 14A). Specifically, excitatory influences from ipsilesional premotor regions onto ipsilesional M1 were accompanied by inhibitory coupling from ipsilesional M1 toward bilateral premotor regions. In contrast to healthy participants, stroke patients showed a significant reduction in the excitatory drive exerted by premotor areas onto ipsilesional M1 ($t(43) > 2.68$, $P_{FDR} < 0.024$). Notably, while healthy subjects exhibited an inhibitory influence from active (ipsilesional) M1 to the inactive (contralesional) M1, stroke patients demonstrated a non-physiological reversal of this pattern—manifesting as a pronounced excitatory coupling from ipsilesional to contralesional M1 ($t(43) = -4.48$, $P_{FDR} < 0.001$; Figure 14C).

Further network-level differences were observed for distinct levels of recovery. Patients with non-substantial recovery displayed stronger inhibitory coupling from ipsilesional M1 to contralesional SMA ($t(21) = 2.51$, $P_{FDR} = 0.031$) and greater excitatory connectivity from ipsilesional to contralesional M1 compared to those with substantial recovery ($t(21) = -2.59$, $P_{FDR} = 0.031$; Figure 14C). Thus, enhanced *interhemispheric rerouting* was characteristic of patients with non-substantial recovery, indicating a recovery-dependent reorganization of transcallosal interactions between bilateral M1.

Importantly, similar effective connectivity patterns were found regardless of whether the lesion was located in the left or right hemisphere (Supplementary Figure 5). Excluding individuals with any overlap between the lesion and predefined ROIs ($n = 3$) yielded nearly identical results. Taken together, these findings argue against potential confounds related to lesion laterality or direct effects of the lesion on cortical regions, underscoring the robustness of the observed connectivity patterns.

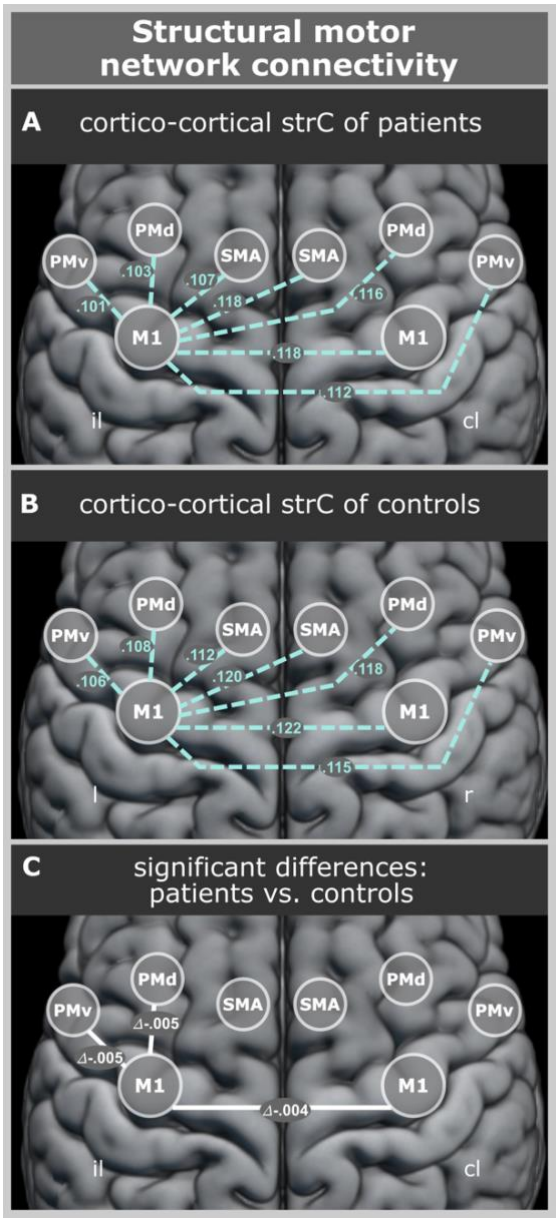


**Figure 13 | Structural motor network connectivity in patients and healthy subjects.** (**A**) Cortico-cortical structural connectivity (blue dashed lines) quantified by tractwise anisotropy in chronic stroke patients and (**B**) control subjects. (**C**) Between-group comparisons demonstrated reduced interhemispheric M1–M1 and intrahemispheric premotor–M1 connectivity in the patient cohort relative to controls ($P_{FDR} < 0.05$). *cl = contralesional; 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.* Adapted from Wiemer et al., 2025), *Brain*.

## 4.2 Identification of structure-function relationships

No direct association emerged between structural and effective connectivity metrics when assessed on a connection-by-connection basis. In essence, the underlying structural connectivity of a single connection was not related to the dynamic modulation of effective connectivity in the same connection during movements of the affected hand.

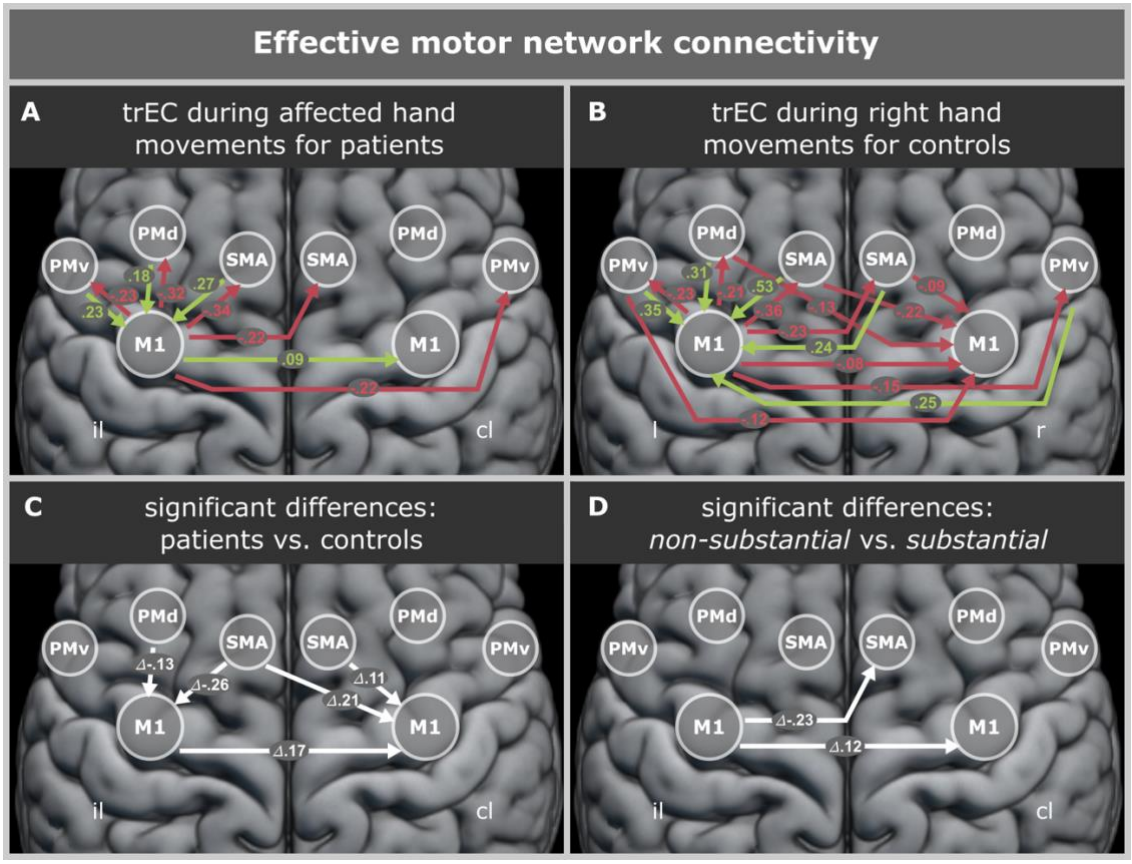


**Figure 14 | Task-related effective connectivity within the motor network during repetitive hand movements.** (**A**) Connections exhibiting significant modulation during paretic hand movements in chronic stroke patients at the group level (DCM-$B_{aff}$). Findings demonstrated robust excitatory coupling from ipsilesional premotor regions to ipsilesional M1 alongside inhibitory coupling from ipsilesional M1 to bilateral premotor areas. Notably, excitatory coupling from ipsilesional M1 to contralesional M1 was evident. (**B**) In contrast, healthy subjects showed the expected physiological inhibition from ipsilesional M1 to contralesional M1. Green arrows denote excitatory coupling; red arrows denote inhibitory coupling. Values represent significant group-level means ($P_{FDR} < 0.05$). (**C**) Between-group comparisons revealed that patients exhibited heightened excitatory input to contralesional M1 and diminished facilitatory influences on ipsilesional M1 relative to controls ($P_{FDR} < 0.05$). (**D**) Notably, patients with non-substantial recovery demonstrated stronger excitatory coupling from ipsilesional M1 to contralesional M1 ($t(21) = -2.59$, $P_{FDR} = 0.031$) and enhanced inhibition from ipsilesional M1 to contralesional SMA ($t(21) = 2.51$, $P_{FDR} = 0.031$) compared to patients with substantial recovery. *cl = contralesional; 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.* Adapted from Wiemer et al. (2025), *Brain*.

However, a notable pattern of structure-function associations appeared for the increased excitatory interhemispheric coupling from ipsilesional to contralesional M1. This pathophysiological effective coupling was related to the structural connectivity between intrahemispheric ipsilesional M1 and premotor areas (Figure 15A). Specifically, patients exhibiting lower structural connectivity within the ipsilesional motor network displayed stronger interhemispheric excitation from ipsilesional to contralesional M1 (all $r < -0.46$, $P_{FDR} < 0.027$; Figure 15B). This observation supports the notion that insufficient levels of intrahemispheric structural reserve might promote compensatory *interhemispheric*

*rerouting* of motor signals via the contralesional hemisphere. Conversely, reduced *interhemispheric* structural connectivity was accompanied by enhanced *intrahemispheric rerouting* from ipsilesional M1 toward PMv (all $r > 0.47$, $P_{FDR} < 0.05$; Figure 15C).

These relationships between structural and effective connectivity appeared to depend on the individual level of CST integrity. In particular, patients featuring low CST integrity displayed increased *interhemispheric rerouting* when the intrahemispheric structural reserve was limited (all $r < -0.61$, $P_{FDR} < 0.024$; Figure 15D). Conversely, patients with higher CST integrity showed pronounced *intrahemispheric rerouting* of motor commands within the ipsilesional hemisphere ($r = 0.70$, $P_{FDR} = 0.043$; Figure 15E). Importantly, these structure–function relationships were confined to connections that also exhibited significant structural alterations in comparison to healthy controls (cf. Figure 13), underscoring their relevance to network reorganization after stroke.

## 4.3 Multimodal connectivity and motor control

Higher structural connectivity across the cortical motor network—specifically between ipsilesional premotor areas and M1 as well as between bilateral M1—was linked to better basal upper-limb control of stroke patients, as indicated by the MI-arm score (all $r > 0.44$, $P_{FDR} < 0.045$), in accordance with the findings reported in Study I. Additionally, robust positive correlations were identified between the structural connectivity of these pathways and distal hand motor control measured as relative finger tapping frequency (all $r > 0.49$, $P_{FDR} < 0.037$; Figure 16A). Notably, each of these structurally relevant connections also exhibited significant functional modulation during movements of the affected hand (cf. Figure 14).

When exploring the association between effective connectivity and motor functions, we observed that patients displaying elevated excitatory coupling from ipsilesional M1 to contralesional M1 exhibited poor basal motor control of the paretic arm ($r = -0.64$, $P_{FDR} = 0.003$; Figure 16B). This aberrant *interhemispheric rerouting* was therefore indicative of impaired basal upper-limb motor control. Importantly, the relationship was contingent on the level of recovery: excitatory *interhemispheric rerouting* via contralesional M1 was correlated with greater basal arm impairment only in non-substantially recovered patients ($r = -0.80$, $P_{FDR} = 0.016$; Figure 16D).

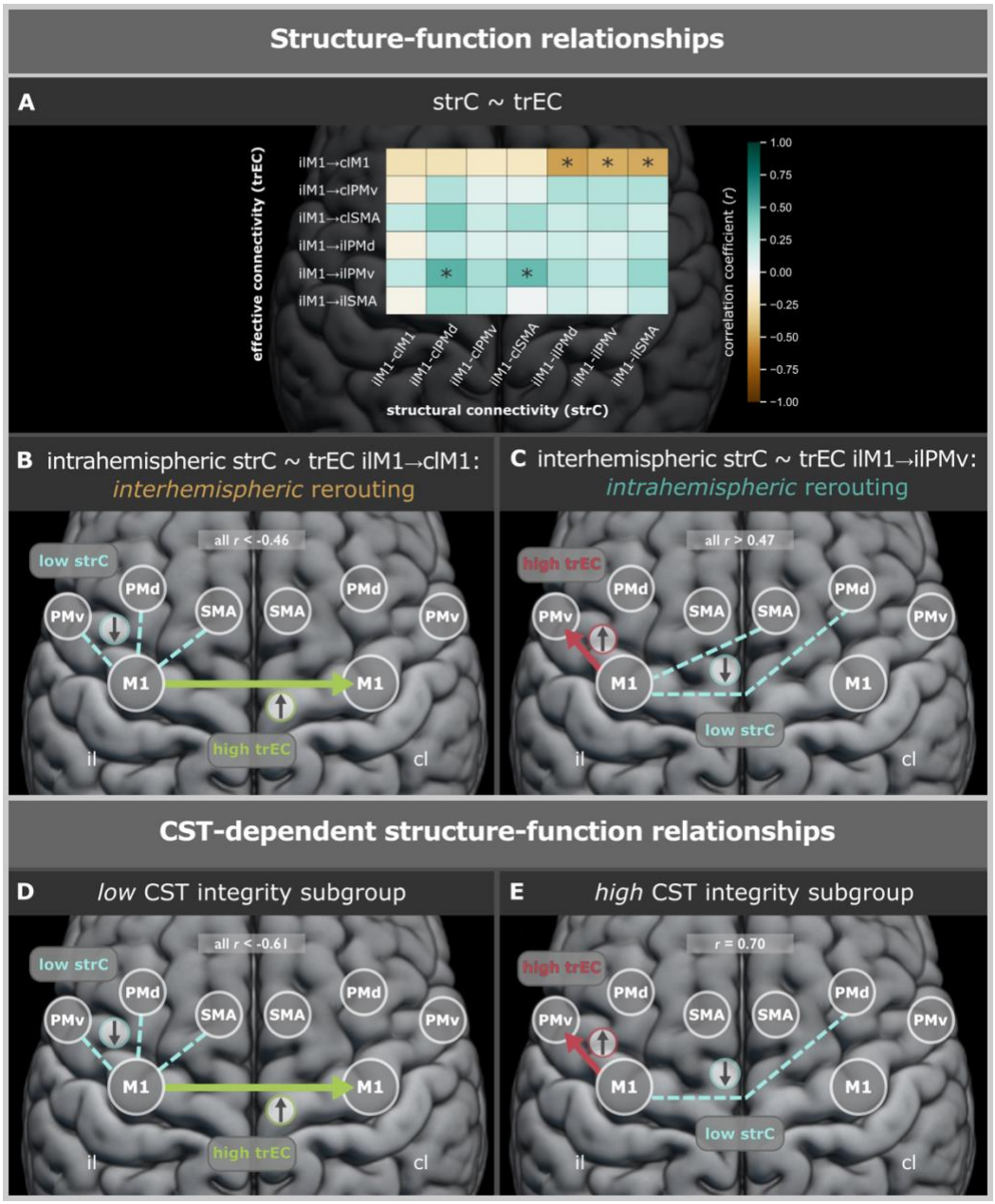


**Figure 15 | Structure-function relationships in the post-stroke motor network.** (**A**) Relationships between structural and effective connectivity reflecting *intra-* and *interhemispheric rerouting* of motor commands during paretic hand movements (*$P_{FDR}$ < 0.05). Color scale represents Pearson correlation coefficients (*r*) from -1 (orange) to +1 (blue). (**B**) Patients with reduced intrahemispheric structural connectivity between ipsilateral M1 and premotor regions (blue dashed lines) demonstrated greater excitatory coupling (green arrow) from ipsilesional to contralesional M1 (all $r < -0.46$, $P_{FDR} < 0.027$), consistent with enhanced *interhemispheric rerouting*. (**C**) Conversely, patients with diminished interhemispheric structural connectivity (blue dashed lines) showed increased inhibition (red arrow) from ipsilesional M1 to PMv (all $r > 0.47$, $P_{FDR} < 0.05$), supporting *intrahemispheric rerouting* through premotor pathways. These distinct structure-function patterns were CST-dependent: (**D**) patients with low CST integrity exclusively displayed structural reserve-dependent increases in *interhemispheric rerouting* via contralesional M1 (all $r < -0.61$, $P_{FDR} < 0.024$). (**E**) By contrast, patients with preserved CST integrity showed enhanced *intrahemispheric rerouting* from ipsilesional M1 to PMv when interhemispheric structural reserve was lower ($r = 0.70$, $P_{FDR} = 0.043$). Note that opposing correlation coefficients reflect the directionality of trEC coupling (excitatory: positive; inhibitory: negative). *cl = contralesional; CST = corticospinal tract; 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.* Adapted from Wiemer et al. (2025), *Brain*.

In contrast, no significant correlation was identified for substantially recovered patients after correction for multiple comparisons. At an uncorrected level, however, stronger *intrahemispheric rerouting* from ipsilesional M1 to SMA was associated with improved hand motor control ($r = -0.60$, $P_{uncorr} = 0.029$, $P_{FDR} = 0.173$; Figure 16C). Importantly, highly similar relationships were obtained when excluding individuals whose lesions overlapped with any ROI ($n = 3$), supporting the robustness of these findings.

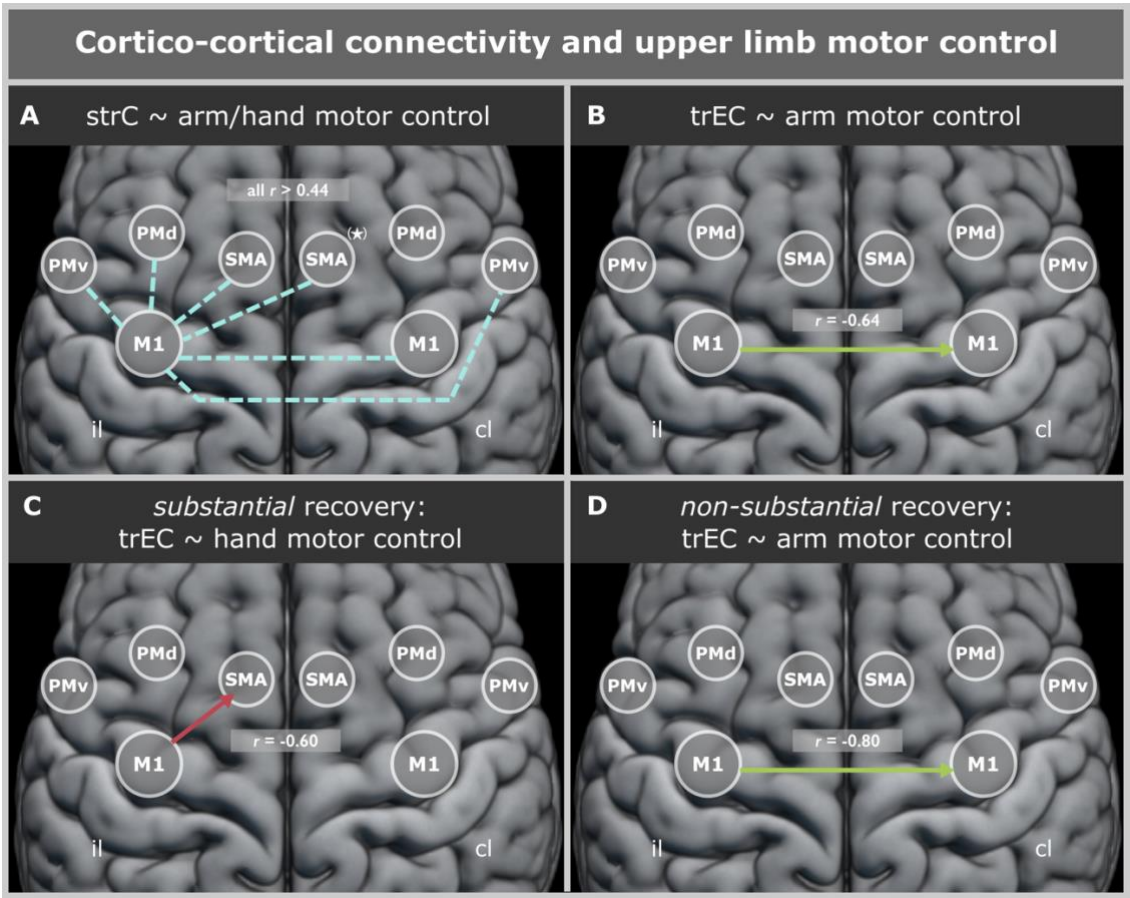


**Figure 16 | Multimodal network connectivity is associated with upper-limb motor control after stroke.** (**A**) Structural connectivity (blue dashed lines) showed significant positive correlations with paretic basal arm motor control ($r > 0.44$, $P_{FDR} < 0.045$) and distal hand motor control ($r > 0.49$, $P_{FDR} < 0.037$). Notably, all ipsilesional structural M1 connections associated with upper-limb motor control were also modulated during affected hand movements in the fMRI task (Figure 14; (★) denotes significant association with basal arm but not distal hand motor control). (**B**) Task-related excitatory effective connectivity (green arrow) from ipsilesional M1 to contralesional M1 during paretic hand movements was negatively correlated with basal motor control of the arm ($r = -0.64$, $P_{FDR} = 0.003$). Recovery-specific patterns emerged: (**C**) in patients with substantial recovery, greater inhibitory effective connectivity (red arrow) from ipsilesional M1 to ipsilesional SMA was associated with better hand motor control ($r = -0.60$, $P_{uncorr} = 0.029$, $P_{FDR} = 0.173$). (**D**) In contrast, excitatory *interhemispheric rerouting* via contralesional M1 correlated with poor basal arm motor control in patients with non-substantial recovery ($r = -0.80$, $P_{FDR} = 0.016$). *cl = contralesional; 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.* Adapted from Wiemer et al. (2025), *Brain*.

# 5. Discussion

The overarching aim of this thesis was to advance our understanding of motor recovery after stroke by elucidating the role of the cortical structural reserve in constraining or guiding functional motor network reorganization. Although numerous studies have characterized functional reorganization patterns after stroke, a critical gap remained: whether the structural connectivity of specific cortico-cortical connections support motor control and how these connections underlie functional reorganization patterns associated with recovery. This thesis fills this gap via a neuroimaging framework that quantifies tractwise cortico-cortical structural connectivity using a template-based, compartmentwise approach and integrates these structural measures with task-specific effective connectivity modeling. Together, this framework allowed the first systematic investigation of direct structure–function relationships within individual cortical pathways and provided a network-level characterization of how the cortical structural reserve supports distinct aspects of motor control and functional reorganization after stroke.

Motor recovery after stroke fundamentally depends on the motor system's capacity to reorganize its functional architecture following disruption of its primary output route, the CST (Grefkes & Fink, 2011; Lemon, 2008). Within the distributed motor network, cortico-cortical interactions between premotor regions and M1 constitute a critical architectural foundation for generating and adapting motor commands (Strick et al., 2021). When a lesion damages the CST and disrupts the primary output route from M1, the motor system faces the challenge of maintaining effective communication across its remaining pathways to sustain function and support recovery. In other words, the motor system must redirect motor commands through alternative routes. Importantly, functional patterns of motor network connectivity have been shown to reorganize in distinct but sometimes opposing ways, potentially reflecting both adaptive and maladaptive plasticity (Grefkes et al., 2008; Rehme et al., 2011; Volz et al., 2015). Variability in these changes has been attributed to several factors, including lesion extent, CST integrity, time since stroke, degree of recovery, and the specific behavioral demands of the motor task (Carter et al., 2012; Paul et al., 2021; Schaechter et al., 2008; Volz et al., 2017; Ward et al., 2006). Yet, how these functional changes relate to the underlying structural reserve of the motor network has remained largely unresolved.

Specifically, intrahemispheric connections between ipsilesional M1 and premotor areas, as well as interhemispheric pathways between bilateral M1, may serve as a scaffold for functional reorganization and critically determine the system’s capacity for compensation

(Paul, Cieslak, et al., 2023; Schulz, Braass, et al., 2015; Schulz et al., 2017). On the one hand, higher cortico-cortical structural connectivity may provide a substrate for more efficient intra- and interhemispheric communication, promoting modulatory influences from premotor regions on M1 (Rehme et al., 2011), thereby facilitating use of residual CST output. On the other hand, recovery may rely on the recruitment of alternative pathways and descending projections. Motor commands that can no longer be conveyed through damaged ipsilesional CST fibers might instead be rerouted intrahemispherically via preserved CST fibers emerging from ipsilesional premotor areas (Boccuni et al., 2019; Paul et al., 2024) or interhemispherically via non-crossing CST fibers descending from contralesional M1 (Schaechter et al., 2009). However, the relative contribution of these distinct routes to functional recovery remains uncertain, partly explaining divergent interpretations in the literature.

Study I established the structural foundation by characterizing how structural connectivity of preserved cortico-cortical motor pathways relates to distinct aspects of motor control after stroke. By applying a compartmentwise anisotropy approach to diffusion MRI data, we overcame limitations of conventional subject-specific fiber tractography and quantified the microstructural integrity of tract-specific cortico-cortical connections as a marker of structural reserve. Critically, we determined how these connections differentially support basal and complex motor control and whether they operate independently of residual CST integrity. In light of the structural findings, Study II investigated whether and how these structural cortico-cortical connections are functionally recruited during affected-hand finger tapping by estimating task-related effective connectivity to characterize potential structure-function relationships. This multimodal approach directly linked specific levels of structural reserve to task-specific functional reorganization, delineating how preserved cortical connections constrain or enable motor recovery after stroke.

In the following sections, I synthesize the key findings from both studies and discuss how they resolve prior interpretive conflicts by accounting for variation in structural network reserve. I then highlight the strengths of the applied multimodal approach and address the clinical relevance of our findings before outlining methodological limitations and future directions in stroke research.

## 5.1 Study-specific key findings

Study I demonstrated that both basal and complex motor control after stroke were closely linked to structural connectivity between the ipsilesional M1 and bilateral premotor regions, as

well as interhemispheric M1–M1 connectivity. Notably, complex motor control depended on the integrity of the ipsilesional CST, whereas basal motor control was associated with cortico-cortical structural connectivity largely independently of CST damage. In particular, patients who substantially recovered appeared to rely on interhemispheric M1–M1 connectivity for basal motor control. This pathway may therefore serve as a critical structural reserve that supports basal motor function through alternative routes, potentially by recruiting contralesional M1 and its descending CST fibers. Together, these findings highlight the importance of cortico-cortical structural connectivity as a structural reserve for task-specific motor recovery after stroke.

Based on this, the findings of Study II suggested that the structural reserve of the cortical motor network critically influences functional motor network reorganization after stroke. Specifically, the individual level of structural reserve was linked to distinct patterns of functional rerouting that appeared to depend on residual CST integrity. When ipsilesional CST integrity was markedly reduced and intrahemispheric structural reserve between ipsilesional M1 and premotor areas was limited, motor commands were likely rerouted interhemispherically via the contralesional M1, a pattern associated with poor arm motor control and recovery. Conversely, when CST integrity was relatively preserved and interhemispheric structural reserve was limited, motor commands seemed to be rerouted intrahemispherically via ipsilesional premotor areas, which was linked to better hand function and recovery. In summary, these findings support the notion that individual differences in structural motor network reserve shape distinct functional reorganization pathways, underscoring the need for personalized rehabilitation strategies that target these mechanisms to optimize stroke recovery.

## 5.2 Structural connectivity supports task-specific motor control

### 5.2.1 Complex motor control

Following stroke, the recovery of complex motor functions, such as grasping and reaching, is thought to critically depend on intact structural connections that facilitate functional reorganization within the cortical motor network. Complex motor control in particular requires fine inter-joint coordination, visuomotor integration, and precise timing of distal muscle synergies (d'Avella et al., 2006; Gentner & Classen, 2006; Ting & McKay, 2007), placing high demands on both cortico-cortical connectivity and corticospinal output. In line with this view,

our present findings reveal robust associations between complex motor control and structural connectivity, including connectivity between ipsilesional M1 and bilateral premotor areas as well as contralesional M1 (Figure 11A). This aligns with previous functional MRI studies demonstrating that post-stroke motor performance heavily depends on ipsilesional premotor−M1 connectivity (Paul et al., 2021; Rehme, Eickhoff, et al., 2011).

Two complementary mechanisms may help explain these observations. First, premotor regions may leverage intact cortico-cortical structural pathways to enhance the recruitment of ipsilesional M1 by modulating its excitability, thereby shaping complex motor control that involves inter-joint coordination and visuomotor integration. Through this route, premotor areas can integrate sensory, cognitive, and visuomotor information and project this integrated signal onto M1 to optimize the selection and refinement of complex motor synergies. Second, motor commands might be partially rerouted within the ipsilesional hemisphere—from ipsilesional M1 to premotor areas. Thereby, premotor areas do not merely modulate M1 activity but contribute task-specific descending output via their respective corticospinal projections, supporting residual complex motor control when M1-associated projections are compromised.

Of note, when controlling for the integrity of the ipsilesional CST, the significant correlations between cortico-cortical connectivity and complex motor control were no longer evident (Figure 11B). This indicates that the capacity to modulate complex hand motor output at the cortical level—whether expressed as enhanced premotor–M1 interaction or increased reliance on corticospinal premotor output—ultimately remains constrained by the residual capacity of the ipsilesional CST to convey motor signals to the spinal cord. This interpretation is consistent with converging evidence that CST damage is a principal limiting factor for more elaborate upper-limb recovery (Boyd et al., 2017; Lindenberg et al., 2010; Peters et al., 2021; Puig et al., 2013; Schulz et al., 2017; Stinear et al., 2007).

Recent work has refined this view by demonstrating that, while integrity of the M1-CST projections appeared necessary to permit any movement of the upper-limb, complex motor control relied primarily on corticospinal premotor “subtracts” originating from PMd, PMv, and SMA (Paul et al., 2024). These premotor “subtracts” seemed particularly relevant for coordinating multi-joint and distal hand actions, suggesting that structural reserve within these pathways is a key determinant of complex motor recovery. This dual dependency—on both cortico-cortical and corticospinal premotor pathways—may explain why cortico-cortical connectivity alone cannot compensate for CST damage in the context of complex motor control. Thus, complex motor control appears to rely predominantly on motor commands

conveyed through the ipsilesional CST, leaving only limited scope for effective compensation by alternative pathways. Anatomical evidence reinforces this notion, indicating that ipsilateral, non-crossing corticospinal fibers predominantly target proximal arm muscles and provide only limited innervation of distal hand and finger muscles (Lemon, 2008). Consequently, compensating complex motor deficits via alternative pathways, such as the contralesional CST, appears improbable.

In summary, our results suggest that ipsilesional premotor areas may contribute to complex motor control both through their descending CST fibers and via cortico-cortical interactions with M1, underscoring their pivotal role in post-stroke motor recovery. This integrated perspective highlights that successful recovery of complex motor control may not simply be a matter of alternative rerouting but requires preservation of CST integrity combined with intact cortico-cortical communication, particularly involving premotor−M1 interactions.

### 5.2.2 Basal motor control

Recovery of basal motor control—encompassing simple movements such as lifting the arm against gravity that involve basic control of muscle synergies—appeared less dependent on residual CST integrity than complex motor functions. In earlier diffusion imaging studies that generally did not distinguish between distinct aspects of motor control, more basal functions have been variably linked to structural premotor−M1 connectivity (Peters et al., 2018; Schulz, Braass, et al., 2015; Schulz et al., 2017) as well as interhemispheric M1−M1 connectivity (Chen & Schlaug, 2013; Hayward et al., 2022; Peters et al., 2018; Stewart et al., 2017), thereby yielding a somewhat ambiguous picture.

Our findings partially clarify this ambiguity by demonstrating robust associations between basal motor control and structural connectivity involving ipsilesional M1, bilateral premotor areas, and contralesional M1 (Figure 11A). Unlike complex motor function, these cortico-cortical relationships with basal motor control remained significant even after accounting for ipsilesional CST damage (Figure 11B), indicating that alternative routes may support compensation of basal function when principal descending pathways are compromised.

Among these alternative routes, interhemispheric structural connectivity between bilateral M1 emerged as particularly relevant for basal motor control, pointing to the contralesional hemisphere's capacity to support motor recovery. Higher structural integrity of transcallosal fibers might enable the contralesional M1 either to exert modulatory influences on the ipsilesional M1 (Rehme, Eickhoff, et al., 2011) or to facilitate a relay of motor signals

from the ipsi- to the contralesional hemisphere, thereby providing an alternative pathway for transmitting motor commands via the contralesional CST (Schaechter et al., 2009). Anatomical evidence supports the latter assumption, as the contralesional CST predominantly innervates proximal muscle groups—such as those controlling the shoulder and upper arm—making it ideally suited to partially restore gross, basal movements of the paretic upper-limb after stroke (Lemon, 2008).

This notion is further corroborated by our recovery-dependent findings. While patients with non-substantial recovery from acute to chronic stage seemed to rely on ipsilesional premotor–M1 connectivity and ipsilesional CST integrity, those exhibiting substantial motor recovery demonstrated a stronger dependence on the interhemispheric M1−M1 connectivity for basal motor control (Figure 12). This finding aligns with prior reports linking higher callosal anisotropy to better motor functions in patients with favorable chronic outcomes (Stewart et al., 2017). Functional neuroimaging studies provide complementary evidence by showing enhanced activation and connectivity of contralesional M1 during affected hand movements that correlated with motor outcomes and microstructural integrity of the corpus callosum (Peng et al., 2019; Wang et al., 2012). These converging findings underscore that the interhemispheric M1–M1 structural connection might provide a critical structural reserve, potentially facilitating compensatory motor output to proximal arm muscles through effective recruitment of the contralesional M1, thereby supporting the reorganization and recovery of basal motor control after stroke.

Moreover, our observations shed light on the longstanding debate regarding the contralesional M1's functional relevance after stroke. While some studies suggest a vicarious, supportive role of the contralesional hemisphere (Grefkes, Nowak, et al., 2008; Murase et al., 2004; Takeuchi & Izumi, 2012), others report maladaptive effects (Biernaskie et al., 2005; Johansen-Berg et al., 2002; Lotze et al., 2006; Rehme, Fink, et al., 2011). The findings discussed here support the notion that such divergent results may partly be explained by a task-specific dichotomy: recovery of basal motor control might be compensated by interhemispheric M1–M1 connectivity and the contralesional CST, while preservation of ipsilesional CST integrity remains crucial for the recovery of complex motor skills. This notion is complemented by recent work by Esser and colleagues (2025), who demonstrated that distinct structural disconnection patterns underlie task-specific motor impairments and outcomes after stroke. They reported substantial overlap in disconnections related to impairment and recovery for complex reach-to-grasp movements, whereas basal motor functions showed markedly different

disconnection profiles across timepoints, suggesting that recovery of basal motor control may involve recruitment of alternative pathways not typically engaged under physiological conditions. This time- and task-dependent involvement of structural networks aligns with our observations on the critical role of ipsilesional CST integrity for complex skills and the compensatory recruitment of interhemispheric M1–M1 connectivity and contralesional CST for basal motor recovery. Their data further underline the nuanced and dynamic role of the contralesional hemisphere in supporting motor recovery, extending our understanding of network-level mechanisms in task-specific motor control after stroke.

In summary, recovery of basal motor function seemed to capitalize on cortico-cortical structural reserve, especially through interhemispheric M1–M1 connectivity. This alternative route might facilitate basal motor control independently of ipsilesional CST integrity, in contrast to the pronounced CST-dependence observed in complex motor control. Recognizing these distinct mechanisms is essential for tailoring rehabilitation strategies that target specific motor deficits after stroke.

## 5.3 Structural reserve-dependent rerouting

In light of the insights gained from Study I, Study II aimed to determine whether and how these alternative routes are functionally engaged during motor network reorganization and recovery. Specifically, while Study I established that cortico-cortical structural connectivity reflects the anatomical capacity to recruit alternative motor pathways, it remained unclear whether motor commands are functionally rerouted *intrahemispherically* or *interhemispherically* via these pathways and how this reorganization depends on the individual level of structural reserve. By linking measures of effective connectivity with underlying structural network integrity, Study II addressed this gap by investigating the interplay between structural reserve and functional network reorganization patterns after stroke.

### 5.3.1 Intrahemispheric cortical rerouting

Structural connectivity between premotor areas and ipsilesional M1 may contribute to post-stroke motor control in two major ways. First, structural premotor−M1 connections might allow premotor areas to exert top-down modulation of M1 activity, a pattern observed both in healthy individuals (Bönstrup et al., 2016; Grefkes, Eickhoff, et al., 2008; Pool et al., 2013) and stroke patients (Diekhoff-Krebs et al., 2017; Paul et al., 2021; Rehme, Eickhoff, et al., 2011; Volz et al., 2015). Although excitatory connectivity from premotor areas to M1 was

altered in stroke patients relative to healthy controls (Figure 14C), its precise relationship with motor impairment remains unclear, as no associations with post-stroke motor control were observed.

Second, structural premotor–M1 connectivity within the ipsilesional hemisphere may provide a substrate for *intrahemispheric rerouting* of motor commands when direct corticospinal output fibers originating from M1 are damaged. Specifically, motor commands generated in M1 might be relayed to ipsilesional premotor regions that allow access to intact corticospinal fibers, thereby serving as alternative descending pathways (Paul et al., 2024). Our findings suggest that the capacity for such *intrahemispheric rerouting* critically depends on the individual level of structural reserve within the motor network. Notably, when interhemispheric structural reserve was limited, *intrahemispheric rerouting* via ipsilesional PMv was increased, especially when ipsilesional CST integrity was largely preserved (Figure 17A). In other words, with sufficient integrity of corticospinal output fibers, *intrahemispheric rerouting* might facilitate the recruitment of ipsilesional premotor regions, highlighting their adaptive role in sustaining descending motor commands to support residual motor function (Boccuni et al., 2019; Guggisberg et al., 2017; Paul et al., 2024; Schulz, Braass, et al., 2015; Schulz et al., 2012, 2017).

Consistent with this notion, studies in macaques have demonstrated that ventral premotor cortex projections reach spinal segments responsible for hand muscle control, underscoring their importance for hand motor recovery (Borra et al., 2010). Supporting this, our findings revealed that enhanced *intrahemispheric rerouting* from ipsilesional M1 to SMA was indicative of better hand function in patients with substantial recovery (Figure 16C), aligning with SMA's established role in self-initiated and sequential movements (Gerloff et al., 1997; Halsband et al., 1993). Furthermore, recent research demonstrated that stroke-related changes in functional connectivity between the spinal cord and premotor areas, especially SMA and PMv, correlate with residual motor control (Braaß et al., 2025). These findings indicate that premotor regions may exert direct influence on lower spinal circuits contributing to hand function following stroke.

Taken together, these insights into *intrahemispheric rerouting* complement our prior results on structural connectivity underlying task-specific motor control, emphasizing the pivotal role of ipsilesional premotor−M1 connections especially when CST integrity is preserved. *Intrahemispheric rerouting* may indeed constitute a crucial alternative pathway for

successful motor network reorganization, facilitating motor control by effectively circumventing damaged primary motor pathways.

### 5.3.2 Interhemispheric cortical rerouting

An alternative pathway to bypass compromised motor output pathways lies in *interhemispheric rerouting* of motor commands via the corpus callosum, potentially granting access to non-crossing CST fibers originating from the contralesional M1 (Schaechter et al., 2009). While healthy individuals typically exhibit physiological inhibition of the inactive (contralesional) M1 by the active (ipsilesional) M1 (Grefkes, Nowak, et al., 2008; Pool et al., 2013; Rehme, Eickhoff, et al., 2011; Volz et al., 2015), chronic stroke patients showed a shift towards excitatory coupling from ipsilesional to contralesional M1 (Figure 14). This observation provides direct empirical evidence for pathophysiological rerouting of motor commands via the contralesional hemisphere, as speculated in light of the findings in Study I.

However, in contrast to our hypothesis, the occurrence of *interhemispheric rerouting* was not directly linked to the level of structural connectivity between bilateral M1. Instead, it was most prominent when structural connectivity between ipsilesional premotor areas and M1 was reduced. Particularly with low CST integrity, limited intrahemispheric structural reserve appeared to promote *interhemispheric rerouting* of motor commands to the contralesional hemisphere (Figure 17B). This finding nicely aligns with prior studies reporting increased contralesional hemisphere involvement and altered interhemispheric connectivity following severe CST damage (Carter et al., 2012; Domin et al., 2023; Liu et al., 2015; Murase et al., 2004; Schaechter et al., 2008; Ward et al., 2006). Thus, significant CST disruption combined with low intrahemispheric structural reserve may force motor commands to be rerouted via the corpus callosum in order to exploit intact descending pathways in the contralesional hemisphere.

Interestingly, this *interhemispheric rerouting* was associated with poor arm motor control and was mostly evident in patients with non-substantial recovery (Figure 16). In other words, these results seemingly contradict our earlier suggestions and previous reports outlining a beneficial role of *interhemispheric rerouting* (Liu et al., 2015; Lotze et al., 2006; Peng et al., 2019; Rehme, Fink, et al., 2011). For example, results by Peng and colleagues (2019) emphasized that increased interhemispheric connectivity involving the contralesional M1 during grasping movements was linked to improved motor control in well-recovered patients.

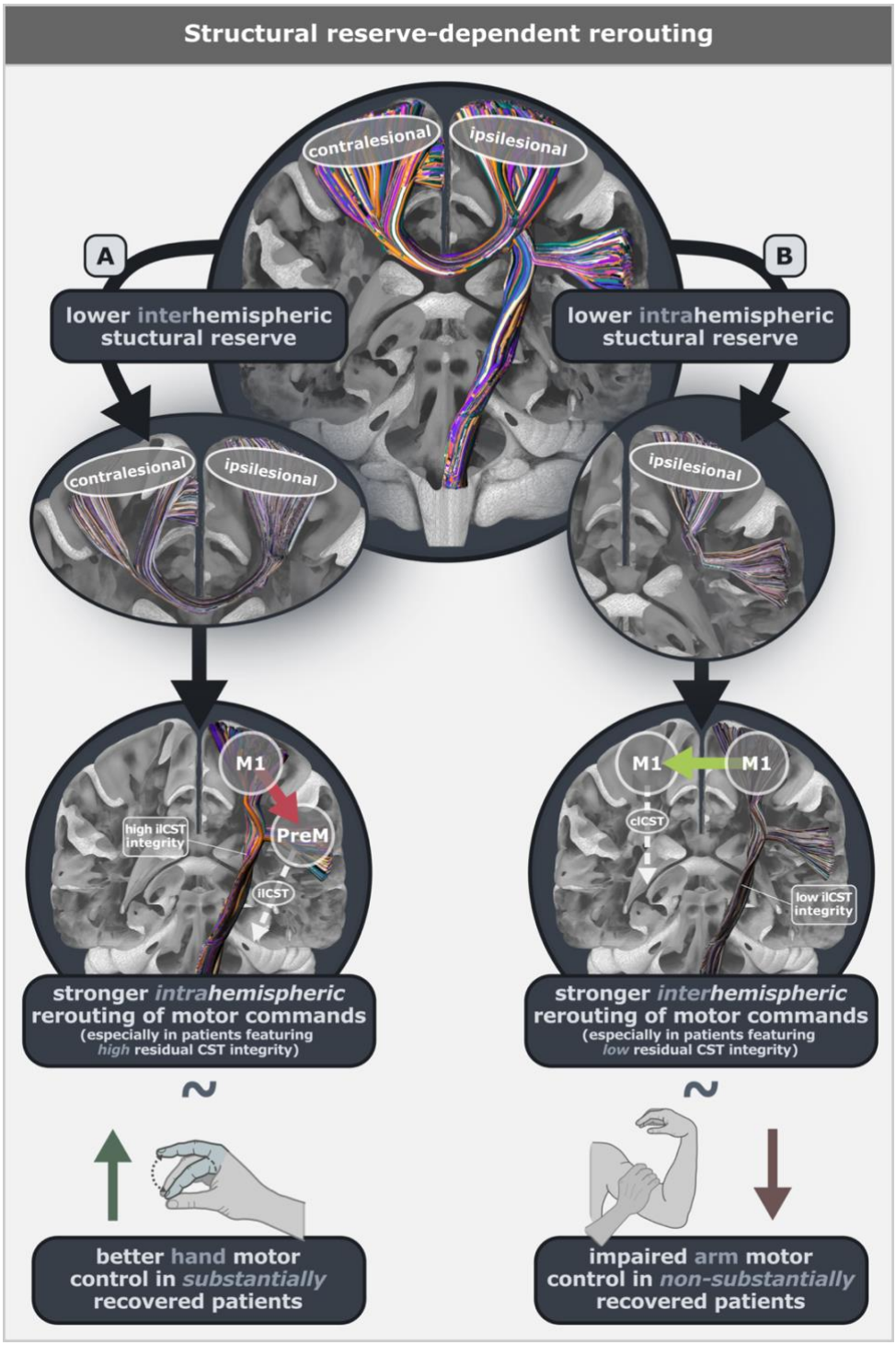


**Figure 17 | Summary of structural reserve-dependent motor command rerouting mechanisms.** (**A**) Reduced interhemispheric structural reserve along with preserved CST integrity may facilitate *intrahemispheric rerouting* through ipsilesional premotor regions. Mechanistically, *intrahemispheric rerouting* may enable recruitment of intact premotor-CST pathways to support hand motor control and recovery. (**B**) Conversely, diminished intrahemispheric structural reserve was linked to enhanced *interhemispheric rerouting* via contralesional M1, particularly when CST integrity was compromised. This heightened *interhemispheric rerouting* correlated with impaired basal arm motor control and was predominantly observed in patients demonstrating non-substantial motor recovery from the acute to chronic stage post-stroke. Notably, effective connectivity was measured during paretic hand movements, suggesting that *interhemispheric rerouting* may represent a task-specific maladaptive pattern in this context. *cl = contralesional; CST = corticospinal tract; il = ipsilesional; M1 = primary motor cortex; PreM = premotor areas.* Adapted from Wiemer et al. (2025), *Brain*.

One explanation for these divergent findings could lie in the task-specific nature of motor network reorganization (Paul et al., 2021; Suputtitada et al., 2025; Vinehout et al., 2022; Volz et al., 2015). To assess effective connectivity, our study used a distal finger tapping task. Given that *interhemispheric rerouting* likely recruits contralesional CST fibers predominantly innervating proximal arm muscles rather than distal muscles of the hand (Lemon, 2008), this task may not optimally capture the compensatory role of contralesional pathways for basal arm motor control. It is plausible that *interhemispheric rerouting* may even play a beneficial role during proximal arm movements contributing to grasping and reaching. In other words, an alternative fMRI task encompassing more proximal movements might potentially reveal different patterns of functional network configurations. Thus, future studies employing both distal and proximal motor tasks are necessary to clarify this issue.

Another explanation for the maladaptive impact of *interhemispheric rerouting* observed here relates to the dependence of effective connectivity patterns on the level of structural reserve. Recent evidence demonstrated that extensive intrahemispheric structural disconnections in ipsilesional M1 were linked to maladaptive contralesional M1 influences (Mustin et al., 2024). Complementing these findings, whole-brain network studies emphasize that functional connectivity shifts between states of greater integration or segregation depending on the residual structural properties after stroke (Frontzkowski et al., 2025; Griffis et al., 2019; Siegel et al., 2016). Specifically, more severely affected patients tend to exhibit heightened network segregation characterized by strongly interconnected but functionally isolated modules, whereas patients with better outcomes maintain more integrated connectivity patterns facilitating global communication. Moreover, Bonkhoff and colleagues (2020) further demonstrated that stroke alters the brain's temporal preference for distinct dynamic connectivity states, with severely impaired patients spending more time in weakly connected, segregated states, indicating reduced network flexibility and integration. These dynamic changes seem to have direct implication for differences in recovery trajectories after stroke (Bonkhoff et al., 2021). Building on this, Hensel and colleagues (2025) recently combined dynamic connectivity analyses with repetitive TMS (rTMS) interference to show that contralesional regions contribute to movements in a state- and network-dependent manner, reinforcing the view that contralesional influences may become maladaptive particularly when embedded in segregated, structurally constrained network configurations.

Together with our results, these findings suggest a network-level framework for structural reserve-dependent cortical rerouting: changes in functional network configurations

after stroke seem to be constrained by the structural reserve of the motor network—specifically, the integrity and availability of intrahemispheric premotor–M1 connections, interhemispheric M1–M1 pathways, and residual CST fibers—rather than by discrete structure–function relationships of individual tracts.

### 5.3.3 Bimodal balance-recovery hypothesis

This perspective nicely complements the bimodal balance-recovery model, which proposes that the level of ipsilesional structural reserve determines whether recovery primarily relies on intrahemispheric or interhemispheric pathways for reorganization (Di Pino et al., 2014; Plow et al., 2016). Specifically, when ipsilesional CST integrity is relatively preserved, recovery predominantly depends on the recruitment of intrahemispheric motor pathways, fostering adaptive plasticity within the affected hemisphere. Conversely, severe damage to the ipsilesional motor system is thought to shift reliance of recovery toward compensatory interhemispheric mechanisms involving the contralesional hemisphere. Our findings align well with this framework and further refine it: while patients with reduced interhemispheric (and preserved ipsilesional) structural reserve preferentially engaged intrahemispheric premotor–M1 pathways, those with marked CST disruption and reduced intrahemispheric reserve seemed to rely more on *interhemispheric rerouting* via the contralesional M1.

Plow and colleagues (2016) further elaborated that the role of contralesional hemisphere involvement is dynamic and context-dependent, varying with lesion characteristics and the phase of recovery. Not all contralesional contributions may be beneficial; some may be maladaptive depending on individual neuroanatomical and functional profiles. Consistent with this notion, Sankarasubramanian and colleagues (2017) provided neurophysiological evidence that the balance between ipsilesional and contralesional motor cortex excitability influences recovery potential and motor outcomes, reinforcing the idea that interhemispheric imbalance must be interpreted in light of each patient's lesion pattern, residual network architecture, and recovery stage. In line with this view, our data suggest that *interhemispheric rerouting* via contralesional M1 was particularly tied to poor basal arm motor control and recovery in patients with limited intrahemispheric structural reserve, whereas *intrahemispheric rerouting* via ipsilesional premotor areas was indicative of better hand function and motor recovery when sufficient structural reserve was preserved.

Lin and colleagues (2020) offered an important empirical extension of this framework by quantifying contralesional influence via interhemispheric inhibition (IHI) assessed with

TMS, relating it to ipsilesional structural reserve in chronic stroke patients. They identified a nonlinear relationship between IHI and FM-UE scores with a critical impairment threshold that separated patients into two distinct subgroups: less-impaired patients exhibited stronger IHI with increasing impairment, whereas more-impaired patients showed reduced IHI, with improvements during rehabilitation alongside IHI reduction. Complementing these findings, Mirdamadi and colleagues (2023) demonstrated that IHI is strongly state-dependent, with abnormal modulation of interhemispheric inhibition during movement preparation and execution relating to individual differences in motor control in chronic stroke. Together, these studies operationalize the bimodal balance-recovery hypothesis by demonstrating that contralesional influences and their evolution during rehabilitation systematically depend on the level of structural reserve, thereby offering concrete criteria for patient stratification. Consistent with this stratified view, our results indicate that patients falling into a "high-reserve" configuration predominantly recruit ipsilesional premotor–M1 pathways, whereas those in a "low-reserve" configuration exhibit stronger contralesional engagement, again underscoring the potential of structural reserve-specific prognosis and treatment advancement.

In light of this, Di Pino and Di Lazzaro (2020) revisited the bimodal balance-recovery model, emphasizing its use a heuristic framework rather than a deterministic rule. They note that although several studies support the central tenet that contralesional influences change depending on the ipsilesional reserve, substantial inter-individual variability and important methodological differences across studies limit further interpretations. Consistently, Fokas and colleagues (2025) showed that contralesional transcallosal inhibition in the subacute phase was not detrimental to upper-limb recovery, calling into question neuromodulatory strategies that aim to broadly suppress contralesional inhibition without considering structural reserve and impairment level. This highlights the need to integrate structural and functional markers when applying the bimodal balance-recovery model to guide treatment decisions. By combining compartmentwise structural connectivity with task-related effective connectivity, the present thesis addresses this need and illustrates how incorporating cortical structural reserve alongside CST integrity helps to reconcile some of the apparently conflicting findings regarding contralesional M1 involvement.

Consistent with this framework, our findings position the ipsilesional premotor cortex as a particularly promising neuromodulatory target given its dense cortico-cortical connectivity and additional descending projections that might constitute alternative compensatory pathways. Facilitatory stimulation, for example excitatory rTMS protocols such as intermittent

theta-burst stimulation, may enhance the use of these alternative intrahemispheric pathways and promote adaptive plasticity in patients who fall into the “high-reserve” end of the bimodal spectrum. In contrast, lower intrahemispheric structural reserve appeared to favor increased dependence on interhemispheric connections, which may serve either supportive or maladaptive roles depending on task demands and recovery stage (Domin et al., 2023; Fokas et al., 2025; Hensel et al., 2021; Lotze et al., 2012; Mustin et al., 2024; Volz et al., 2017; Ward et al., 2006). Neuromodulatory strategies in this “low-reserve” configuration might thus involve mitigating chronic interhemispheric imbalance or abnormal excitability by inhibiting either ipsi- or contralesional M1 (via low-frequency rTMS) or facilitating contralesional regions to bolster compensatory mechanisms. This nuanced integration of the bimodal balance-recovery hypothesis with our structural-reserve findings highlights the critical need for future studies and therapeutic approaches to explicitly account for each patient’s structural network reserve when designing individualized rehabilitation strategies.

Importantly, prior work has mainly operationalized the bimodal balance-recovery hypothesis using neurophysiological measures such as IHI, which only capture contralesional-to-ipsilesional influences through consecutive contralesional stimulation. In contrast, the effective-connectivity approach employed here quantified directional coupling during actual movement execution, which revealed increased excitatory drive from ipsi- to contralesional M1—or a strong reduction of the physiological inhibition—associated with impairment in the chronic phase. These complementary perspectives suggest that different methodological approaches tap into related but distinct aspects of interhemispheric balance and underlying neurophysiological mechanisms, which may partly explain divergent or even conflicting findings throughout the literature.

Integrating our data with the bimodal balance-recovery hypothesis sheds new light on the important but controversial role of contralesional M1 in motor recovery. Variability in previous results regarding contralesional involvement may be better understood within the framework of structural network constraints, providing a novel perspective that complements the well-established role of the CST in post-stroke motor reorganization. Whether interhemispheric interactions are beneficial or maladaptive seemed potentially to depend on the residual structural network reserve of intra- and interhemispheric pathways, rather than on contralesional activity per se. Since earlier studies did not account for individual differences in structural connectivity, inconsistent findings may partly reflect sample heterogeneity related to varying levels of structural network reserve. Moving beyond a one-size-fits-all approach, future

research and therapeutic strategies should adopt a personalized framework that stratify patients according to CST integrity and cortical structural reserve to tailor neuromodulation and rehabilitation protocols to their position along the bimodal spectrum.

## 5.4 The value of a multimodal approach

By leveraging DSI to quantify cortico-cortical structural reserve and DCM to assess task-related effective connectivity, this thesis bridges the gap between anatomical constraints and functional network dynamics. While previous studies have often focused on either structural connectivity or functional connectivity in isolation, the present work demonstrates how combining these modalities provides a more comprehensive understanding of the complex mechanisms underlying motor recovery.

This multimodal approach had several advantages. First, it allowed the identification of specific structural cortical pathways that serve as potential substrates for post-stroke motor control, clarifying how preserved cortico-cortical connections may facilitate compensatory mechanisms after stroke. Second, it revealed how individual differences in structural reserve constrain or enable distinct patterns of functional reorganization, such as *intrahemispheric* versus *interhemispheric rerouting*, depending on the integrity of the corticospinal tract and motor task demands. Third, the integration of structural and functional data provided a more nuanced framework for interpreting conflicting findings in the literature, such as the variable role of the contralesional hemisphere in motor recovery, by accounting for both structural and functional network characteristics and their representations.

Methodologically, an additional strength lies in the compartmentwise diffusion analysis, which addresses limitations of conventional anisotropy metrics in voxels with multiple fiber orientations by stratifying voxels according to the number of distinct fiber directions (Volz et al., 2018). Combined with the tractwise anisotropy extraction, this approach improves the specificity and reliability of cortico-cortical connectivity estimates and thereby sharpens inferences about the cortical structural reserve and its relationship to effective connectivity.

Together, these methodological advances demonstrate that a multimodal, tract-specific characterization of cortico-cortical and corticospinal pathways can uncover task- and pathway-specific mechanisms of motor network reorganization that would have likely remained obscured when modalities are considered in isolation.

## 5.5 Clinical implications

Building on these mechanistic insights, the present findings underscore the clinical potential of structural cortico-cortical connectivity as a biomarker to predict the recovery of motor impairment following stroke. In contrast to traditional biomarkers that focus narrowly on ipsilesional CST integrity, assessing the structural reserve of the broader cortical motor network—including premotor–M1 pathways and interhemispheric M1–M1 connections—substantially improved the explanation of distinct facets of motor function after stroke. These structural connectivity metrics can be obtained from relatively brief diffusion imaging protocols, such as the fast 11-minute DSI protocol used here, which could be integrated into clinical routines with relatively low patient burden (Bonkhoff & Grefkes, 2022; Horn et al., 2016), thereby facilitating wider application of such network-level biomarkers.

Our regression analyses further reinforced the notion of task-specific network reorganization by elucidating a marked distinction between basal and complex motor control. Cortico-cortical structural connectivity explained variance in both domains, but adding ipsilesional CST integrity markedly increased the explained variance only for complex, but not basal, motor control. This suggests that complex motor abilities, such as skilled grasping and reaching, depend on an intact CST in combination with preserved ipsilesional premotor–M1 connectivity, whereas more basal motor functions may rely more strongly on alternative routes, including interhemispheric M1–M1 connections and contralesional pathways. Consequently, future prognostic models should adopt task-specific biomarkers: cortico-cortical structural connectivity may indicate compensation potential for basal motor impairments, while a combined assessment of network connectivity and CST integrity seemed necessary to explain complex hand function after stroke. Such task-specific biomarkers would enable more precise stratification of patients according to their unique structural network reserve profiles.

Therapeutically, these insights argue for a shift from uniform treatment paradigms toward personalized rehabilitation strategies that incorporate both CST integrity and cortical structural reserve. Our findings provide a rationale for tailoring neuromodulatory interventions such as rTMS to individual network profiles, which are suited to enhance and modulate reorganization in the post-stroke motor network (Di Lazzaro et al., 2008; Di Pino et al., 2014; Hensel et al., 2019; Volz et al., 2016). Severely impaired patients with basal motor deficits and limited ipsilesional structural reserve may benefit from targeting contralesional M1 to increase residual motor output via alternative pathways for gross motor control, while those with

preserved CST integrity but deficits in complex or distal hand functions might respond better to stimulation of ipsilesional premotor areas, which offer alternative corticospinal routes. Moreover, selecting stimulation targets based on lesion pattern, residual structural reserve, and functional connectivity—potentially informed by multimodal approaches—may optimize treatment efficacy by aligning interventions with each patient's specific motor network architecture.

Collectively, the findings presented in this thesis encourage integrating multimodal imaging biomarkers, encompassing both structural and functional connectivity markers, into personalized rehabilitation frameworks. This is in line with consensus recommendations advocating for biomarker-driven, individualized interventions to maximize motor recovery (Boyd et al., 2017). This combined perspective is essential for future personalized rehabilitation strategies, as it enables stratification of patients according to their structural network reserve profiles and may improve the prediction of recovery trajectories. Expanding this framework through longitudinal imaging, complemented by detailed neurophysiological and behavioral assessments, holds promise for clarifying the task-specific dynamics underpinning motor recovery over time. Moving forward, future clinical protocols should prioritize the development and rigorous validation of such nuanced biomarkers and systematically investigate their value for guiding targeted, reserve-informed therapies, with the ultimate aim of improving functional outcomes across diverse stroke populations.

## 5.6 Limitations and future directions

The presented studies entail several conceptual and methodological limitations that warrant consideration and provide important directions for future research. The most evident limitation lies in the relatively small sample size of up to 25 chronic stroke patients. Although such sample sizes are common in hypothesis-driven approaches and comparable to other neuroimaging studies in clinical populations (Puig et al., 2011; Schulz, Koch, et al., 2015; Volz et al., 2016), larger cohorts help to further increase statistical power and generalizability of findings. Nonetheless, it remains demanding to find adequately sized cohorts of chronic stroke patients who meet strict inclusion criteria, particularly for MRI acquisition. Larger samples would not only increase sensitivity but also enable more fine-grained analyses that better account for lesion heterogeneity and varying degrees of CST damage, thereby facilitating the delineation of distinct patient subgroups and more precise stratification of individual recovery trajectories (van der Vliet et al., 2020).

Another limitation pertains to the cross-sectional design of our imaging data, which restricts inferences about the underlying dynamic plasticity processes enabling recovery. Although the clinical data used for the classification of different degrees of motor recovery were acquired in a longitudinal manner and allow partial characterization of recovery trajectories, causal links between evolving network changes over time and behavioral improvements cannot be established. To determine the clinical utility of cortico-cortical structural or effective connectivity and their structure-function relationships as a potential biomarker for motor outcome, future research should incorporate longitudinal imaging starting early after stroke. Such designs will help to characterize temporal shifts in intra- versus interhemispheric network connectivity and clarify how these changes relate to evolving recovery patterns.

At the methodological level, structural connectivity analyses relied on a compartmentwise approach, which improves specificity over conventional tensor-based methods by differentiating voxels according to underlying fiber complexity (Paul, Cieslak, et al., 2023; Volz et al., 2018). However, this approach combined with the applied template-based strategy is inherently constrained to "known" anatomical pathways and cannot capture novel or reorganized cortico-cortical connections that may emerge post-stroke, as suggested by mechanisms of short-distance axonal sprouting observed in animal models (Carmichael et al., 2017; Dancause et al., 2005). In principle, patient-specific tractography could be used to detect such structural network changes, but streamline reconstructions in individual brains are strongly influenced by tracking parameters, susceptible to false-positive connections, and complicated by age-related atrophy and lesion-induced signal distortions (Salat et al., 2005; Schilling et al., 2020; Zalesky et al., 2016). These inherent limitations of fiber tractography motivated the implementation of the template-guided, compartmentwise analysis in the present work, yet also highlight the need for improved tracking algorithms and multimodal validation approaches to reliably map patient-specific network reorganization in future studies. Nevertheless, using our novel approach allowed the robust estimation of cortico-cortical structural connectivity in stroke patients, circumventing conventional tractography constraints.

Concerning the analysis of motor network dynamics, our investigation of effective connectivity during finger tapping movements allowed a direct comparison with previous fMRI work employing similar repetitive hand movements (Binder et al., 2021; Grefkes, Nowak, et al., 2008; Hensel et al., 2023; Paul et al., 2021; Pool et al., 2013; Rehme, Eickhoff, et al., 2011). Yet, given the task-specific nature of effective connectivity, such findings cannot

be easily generalized across distinct motor functions involving different sensorimotor demands. Future studies should systematically assess effective connectivity across a spectrum of diverse motor tasks to reveal how network dynamics reorganize and alternative pathways are engaged for the recovery of different aspects of motor control.

From a behavioral perspective, while our motor assessments distinguished between basal and complex motor functions, they remain limited in dissecting specific subcomponents of motor control attributable to distinct premotor areas. Future work should employ refined behavioral assessments that selectively probe proximal versus distal control, or compare specific reach-to-grasp actions versus simpler repetitive movements, to better delineate the distinct contributions of individual premotor regions.

Moreover, the current analyses were restricted to a canonical set of bilateral cortical motor regions (M1, PMd, PMv, and SMA). Extending future analyses to include subcortical motor regions such as the basal ganglia and cerebellum or the primary somatosensory cortex will further expand our understanding of how sensory feedback and subcortical modulation contribute to motor network reorganization.

Finally, the work focused on regional activity and connectivity but did not examine how stroke alters the representational structure of motor actions associated with functional reorganization. Multimodal approaches that combine differentiated behavioral tasks with multivariate pattern analyses, such as representational similarity analysis (RSA; Kriegeskorte et al., 2008), could link changes in the underlying neuronal representational geometry to network-level reorganization. In contrast to conventional univariate activation analyses, RSA can capture the similarity structure of multivoxel activity patterns across different motor functions and thereby reveal whether representations of specific movements become more distinct or diffuse, thereby indicating reorganization over time. Applying RSA across multiple motor tasks varying in complexity and effector specificity may thus provide a fine-grained marker of cortical plasticity that complements connectivity measures and helps to explain how emerging functional differentiation relates to regained motor control after stroke.

## 5.7 Conclusion

The present thesis intended to advance our understanding of the neuronal mechanisms supporting motor recovery after stroke by elucidating the interplay between structural and functional representations of network reorganization within the cortical motor system. The two studies presented here provide converging evidence that the integrity of cortico-cortical structural connectivity is critical for distinct aspects of motor function and may serve as structural reserve that guides how functional networks reorganize.

Study I established the foundational role of cortico-cortical structural connectivity as a relevant marker of the cortical structural reserve that appeared to differentially support basal and complex motor control after stroke. Specifically, complex motor functions seemed dependent on the interplay between cortico-cortical pathways and the ipsilesional CST, highlighting that severe CST damage may limit the recovery of more complex hand movements. In contrast, basal motor control may be sustained via alternative cortico-cortical routes, with interhemispheric M1–M1 connectivity playing a pivotal compensatory role by potentially facilitating access to non-crossing contralesional CST fibers.

Expanding upon these results, Study II elucidated how individual differences in structural reserve may govern the functional reorganization of the motor network, revealing that alternative pathways are likely recruited intra- or interhemispherically to support motor recovery after stroke. When CST integrity was preserved and interhemispheric structural reserve limited, *intrahemispheric rerouting* via ipsilesional premotor areas seemed to benefit hand motor control and recovery. Conversely, compromised CST integrity combined with limited intrahemispheric reserve resulted in increased *interhemispheric rerouting* to contralesional M1, which was associated with poor arm motor control and recovery. Crucially, this maladaptive *interhemispheric rerouting* has to be interpreted in a task-specific context, as it was observed during a distal hand motor task in which contralesional pathways may be less effective in compensating motor impairment.

Together, these studies emphasize a multimodal framework wherein the structural motor network reserve provides the anatomical scaffold for post-stroke motor control while simultaneously constraining the capacity for functional reorganization, with the efficacy of rerouting mechanisms likely depending on task-specific demands and individual network architecture. The integration of these findings reinforces the need to consider both CST integrity and broader cortico-cortical connectivity in identifying biomarkers of motor recovery,

aligning with the bimodal balance-recovery hypothesis. Such a dual perspective not only elucidates the controversial role of contralesional M1 but may also account for heterogeneity in recovery trajectories and help provide mechanistic guidance for optimizing personalized rehabilitation strategies. Therapeutic interventions, particularly targeted neuromodulation protocols, should thus be tailored to each patient's structural network profile to strategically harness adaptive rerouting mechanisms and suppress maladaptive reorganization patterns. By establishing the critical role of the structural reserve in shaping functional reorganization, this thesis offers novel mechanistic insights that can advance personalized, biomarker-guided rehabilitation strategies to optimize motor recovery after stroke.

# 6. Zusammenfassung

Diese Dissertation hatte zum Ziel, unser Verständnis der neuronalen Mechanismen der motorischen Erholung nach einem Schlaganfall zu vertiefen. Hierzu wurde das Zusammenspiel zwischen struktureller Reserve und funktioneller Netzwerkreorganisation im kortikalen Motorsystem untersucht. Die beiden hier vorgestellten Studien liefern übereinstimmende Evidenz dafür, dass die Integrität der kortiko-kortikalen strukturellen Konnektivität unterschiedliche Aspekte motorischer Funktionen beeinflusst und vermutlich prädeterminiert, wie sich funktionelle Netzwerke reorganisieren können, um die Schädigung kortikospinaler Bahnen zu kompensieren.

Studie I etablierte die zentrale Bedeutung der kortiko-kortikalen strukturellen Konnektivität als Maß der strukturellen Reserve, die basale und komplexe motorische Kontrolle nach einem Schlaganfall in unterschiedlicher Weise unterstützt. Komplexe Handfunktionen schienen dabei vom Zusammenspiel zwischen kortiko-kortikalen Bahnen und dem ipsiläsionalen CST abzuhängen, was verdeutlicht, dass eine ausgeprägte CST-Schädigung die Wiedererlangung komplexerer Handbewegungen begrenzt. Basale motorische Kontrolle konnte hingegen über alternative kortiko-kortikale Wege aufrechterhalten werden, wobei die interhemisphärische M1–M1-Konnektivität eine zentrale kompensatorische Rolle spielte, indem sie möglicherweise den Zugang zu nicht-kreuzenden kontraläsionalen CST-Fasern erleichterte.

Aufbauend auf diesen Ergebnissen zeigte Studie II, dass individuelle Unterschiede in der strukturellen Reserve die funktionelle Reorganisation des motorischen Netzwerks wesentlich mitbestimmen und dadurch potentiell beeinflussen, ob alternative Bahnen eher intra- oder interhemisphärisch rekrutiert werden, um die motorische Erholung nach einem Schlaganfall zu unterstützen. Wenn die CST-Integrität erhalten und die interhemisphärische strukturelle Reserve begrenzt war, schien intrahemisphärisches Rerouting über ipsiläsionale prämotorische Areale mit besserer Handmotorik und günstigeren Erholungsverläufen einherzugehen. Umgekehrt war eine Kombination aus eingeschränkter CST-Integrität und geringer intrahemisphärischer Reserve mit verstärktem interhemisphärischem Rerouting zum kontraläsionalen M1 verbunden, was wiederum mit schlechterer Armfunktion und Erholung assoziiert war. Entscheidend ist, dass dieses scheinbar maladaptive interhemisphärische Rerouting im Kontext der untersuchten motorischen Aufgabe interpretiert werden muss, da es

während einer distalen Handaufgabe beobachtet wurde, bei der kontraläsionale Pfade weniger effektiv zur Kompensation motorischer Beeinträchtigungen beitragen können.

Zusammen etablieren diese Studien ein multimodales Konzept, in dem die strukturelle Netzwerkreserve die anatomische Grundlage für motorische Kontrolle nach einem Schlaganfall bildet und zugleich die Möglichkeiten funktioneller Reorganisation prädeterminiert. Die Wirksamkeit von Rerouting-Mechanismen hängt dabei vermutlich von aufgabenspezifischen Anforderungen und der individuellen Netzwerkarchitektur ab. Die Integration dieser Ergebnisse unterstreicht die Relevanz einer gleichzeitigen Betrachtung von CST-Integrität und kortiko-kortikaler Konnektivität für die Identifizierung neuer Biomarker der motorischen Erholung und steht im Einklang mit der "bimodal balance-recovery" Hypothese. Eine solche duale Perspektive beleuchtet nicht nur die kontrovers diskutierte Rolle des kontraläsionalen M1, sondern kann auch zur Erklärung der Heterogenität individueller Erholungsverläufe beitragen und Ansatzpunkte für die Optimierung personalisierter Rehabilitationsstrategien liefern. Therapeutische Interventionen, insbesondere gezielte Neuromodulationsprotokolle, sollten daher an das strukturelle Netzwerkprofil der Patient:innen angepasst werden, um adaptive Reorganisation gezielt zu fördern und maladaptive Muster zu vermeiden. Durch die Hervorhebung der strukturellen Reserve als Schlüsselfaktor für funktionelle Reorganisation liefert diese Dissertation neue mechanistische Erkenntnisse, die die Entwicklung personalisierter Rehabilitationsstrategien zur Optimierung der motorischen Erholung nach Schlaganfall voranbringen könnten.

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# 8. Appendix

## 8.1 Supplementary material

**Supplementary Table 1 | Clinical and demographic patient information**

| ID | sex | age | ARAT | MI-arm | relative tapping frequency | NIHSS-arm acute | NIHSS-arm chronic | substantial recovery | months since stroke | lesion side | lesion location | lesion volume ($mm^3$) | CST lesion volume ($mm^3$) | CST integrity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | m | 59 | 57 | 99 | 0.98 | 2 | 0 | yes | 21 | r | MCA (subcortical) | 51,688 | 3,752 | low |
| 2 | m | 55 | 57 | 91 | 0.92 | 4 | 1 | yes | 14 | r | MCA (subcortical) | 25,410 | 746 | low |
| 3 | m | 66 | 38 | 76 | 0.72 | 1 | 1 | no | 17 | r | MCA (subcortical) | 11,559 | 1,055 | low |
| 4 | m | 65 | 0 | 34 | 0.00 | 3 | 4 | no | 51 | l | MCA (subcortical) | 6,104 | 1,527 | low |
| 5 | m | 60 | 35 | 92 | 0.51 | 1 | 1 | no | 23 | l | PCA (subcortical) | 1,748 | 0 | low |
| 6 | f | 80 | 32 | 77 | 0.95 | 1 | 2 | no | 11 | l | MCA (subcortical) | 1,988 | 1,490 | high |
| 7 | m | 70 | 19 | 65 | 0.52 | 3 | 2 | yes | 59 | l | MCA (subcortical) | 1,211 | 623 | low |
| 8* | m | n.a. | 55 | 92 | n.a. | 4 | 1 | yes | 71 | l | MCA (subcortical) | 38,955 | 1,232 | n.a. |
| 9 | m | 64 | 57 | 99 | 0.99 | 0 | 0 | no | 31 | l | ACA/MCA (subcortical) | 39,004 | 1,582 | high |
| 10 | m | 64 | 49 | 91 | 0.88 | 1 | 1 | no | 12 | r | MCA (subcortical) | 1,156 | 141 | high |
| 11 | m | 58 | 57 | 99 | 0.96 | 1 | 0 | yes | 37 | l | MCA (subcortical) | 1,068 | 594 | high |
| 12 | m | 54 | 57 | 99 | 0.82 | 0 | 1 | no | 44 | r | Brainstem | 1,195 | 707 | low |
| 13 | f | 74 | 56 | 91 | 0.80 | 3 | 0 | yes | 55 | r | MCA (cortical) | 34,402 | 4,736 | high |
| 14 | m | 82 | 57 | 99 | 0.84 | 4 | 0 | yes | 32 | r | MCA (cortical) | 37,850 | 1,654 | high |
| 15* | m | n.a. | 57 | 99 | n.a. | 1 | 0 | yes | 43 | l | MCA (subcortical) | 4,283 | 1,391 | n.a. |
| 16 | f | 50 | 57 | 76 | 0.65 | 2 | 1 | yes | 15 | r | MCA (subcortical) | 7,645 | 0 | low |
| 17 | m | 83 | 37 | 84 | 0.55 | 3 | 1 | yes | 82 | r | Brainstem | 1,598 | 855 | high |
| 18 | m | 82 | 44 | 83 | 0.89 | 1 | 1 | no | 30 | l | Brainstem | 354 | 256 | high |
| 19 | f | 81 | 56 | 76 | 0.77 | 1 | 1 | no | 12 | l | Brainstem | 37 | 0 | low |
| 20 | m | 81 | 55 | 92 | 1.06 | 1 | 0 | yes | 15 | l | PCA (subcortical) | 1,475 | 0 | high |
| 21 | m | 62 | 57 | 99 | 0.50 | 4 | 1 | yes | 33 | l | MCA (subcortical) | 725 | 100 | high |
| 22 | m | 68 | 57 | 99 | 0.92 | 1 | 0 | yes | 25 | l | MCA (sub- & cortical) | 12,102 | 1,838 | high |
| 23 | m | 55 | 53 | 99 | 0.71 | 1 | 0 | yes | 35 | r | MCA (subcortical) | 4,242 | 2,152 | low |
| 24 | f | 84 | 57 | 83 | 0.91 | 1 | 1 | no | 20 | r | Brainstem | 582 | 539 | high |
| 25 | m | 46 | 57 | 99 | 0.93 | 4 | 0 | yes | 23 | r | MCA (subcortical) | 1,072 | 703 | low |

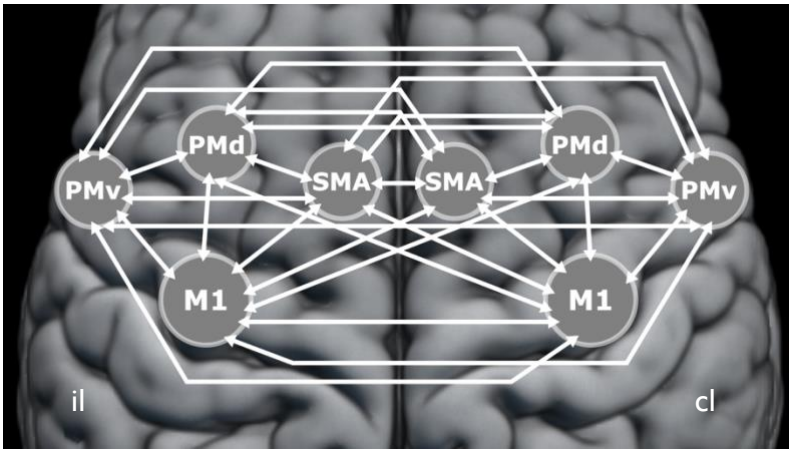
Abbreviations: ACA = anterior cerebral artery; ARAT = Action Research Arm Test; CST = corticospinal tract; f = female; l = left; m = male; MCA = middle cerebral artery; MI-arm = Motricity-Index-arm; NIHSS = National Institutes of Health Stroke Scale; PCA = posterior cerebral artery; r = right. Asterisk (*) indicates patients who were excluded from the analyses in Study II due to insufficient quality of functional MRI data.

**Supplementary Table 2 | Coordinates of regions of interest used for DCM analyses of patients.** Subject-specific local activation maximum within region-specific anatomical constraints were identified to define the coordinates. *M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; SMA = supplementary motor area.* Adapted from Wiemer et al. (2025), *Brain*.

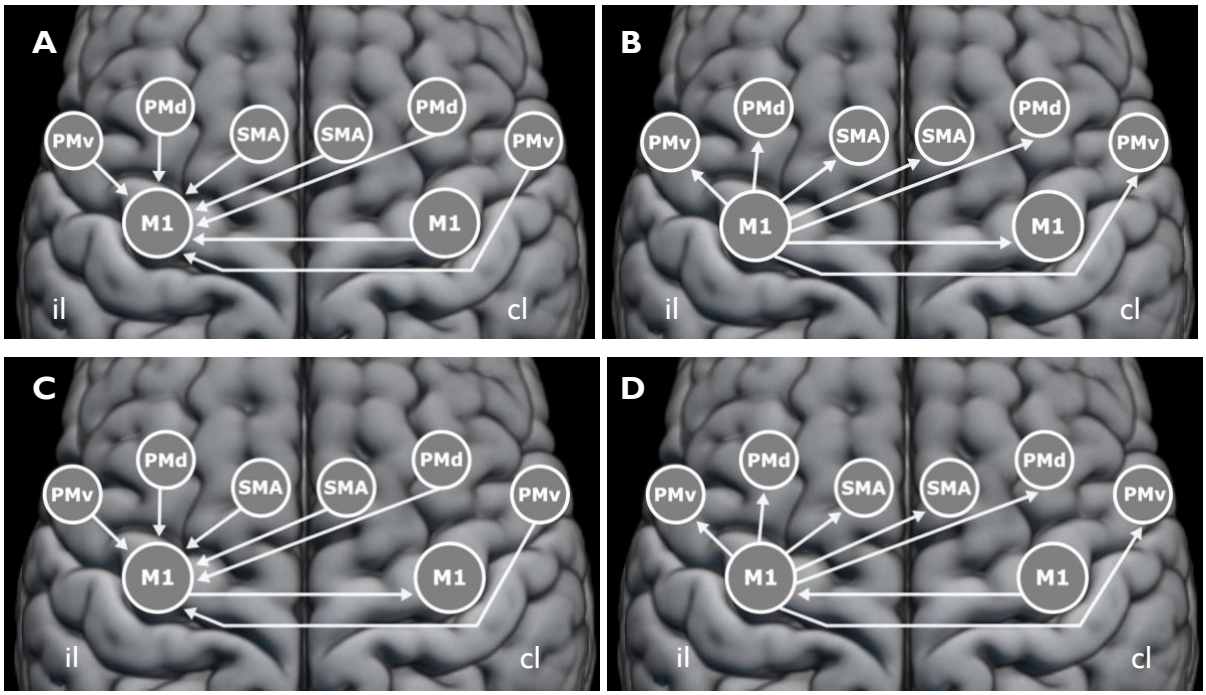
| | Contralesional hemisphere | | | | | | | | | | | | Ipsilesional hemisphere | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ID** | **M1** | | | **PMd** | | | **PMv** | | | **SMA** | | | **M1** | | | **PMd** | | | **PMv** | | | **SMA** | | |
| **1** | -34 | -22 | 58 | -24 | -14 | 56 | -56 | -2 | 42 | -6 | 0 | 54 | 32 | -28 | 52 | 30 | -10 | 52 | 52 | 8 | 48 | 6 | -2 | 54 |
| **2** | -40 | -24 | 58 | -34 | -16 | 54 | -56 | 8 | 34 | -6 | -10 | 62 | 40 | -24 | 58 | 40 | -14 | 54 | 60 | 12 | 34 | 6 | -8 | 56 |
| **3** | -36 | -26 | 56 | -26 | -14 | 56 | -48 | 0 | 40 | -6 | -6 | 64 | 30 | -28 | 56 | 28 | -12 | 60 | 60 | 0 | 40 | 6 | -8 | 56 |
| **4** | 38 | -22 | 64 | 28 | -20 | 66 | 58 | 6 | 32 | 6 | -12 | 64 | -30 | -24 | 58 | -38 | -16 | 60 | -56 | 2 | 34 | -6 | -10 | 62 |
| **5** | 38 | -22 | 58 | 34 | -16 | 58 | 50 | 4 | 46 | 6 | -8 | 64 | -32 | -30 | 56 | -36 | -18 | 58 | -54 | 0 | 42 | -6 | -10 | 64 |
| **6** | 36 | -28 | 58 | 24 | -22 | 60 | 52 | 4 | 40 | 6 | -6 | 62 | -40 | -22 | 56 | -26 | -14 | 66 | -54 | -6 | 40 | -6 | -12 | 60 |
| **7** | 38 | -24 | 52 | 26 | -20 | 66 | 54 | 4 | 40 | 6 | -4 | 56 | -40 | -26 | 54 | -18 | -18 | 66 | -54 | -4 | 44 | -6 | -6 | 54 |
| **9** | 40 | -20 | 62 | 32 | -8 | 60 | 58 | 12 | 34 | 6 | -10 | 52 | -42 | -22 | 60 | -32 | -10 | 56 | -56 | 10 | 32 | -8 | -10 | 54 |
| **10** | -28 | -28 | 60 | -26 | -16 | 64 | -52 | 6 | 40 | -6 | -12 | 66 | 38 | -18 | 52 | 18 | -14 | 64 | 56 | 8 | 34 | 6 | -10 | 66 |
| **11** | 30 | -30 | 60 | 26 | -16 | 60 | 58 | 2 | 36 | 6 | -12 | 58 | -38 | -24 | 60 | -32 | -14 | 62 | -54 | 4 | 44 | -6 | -14 | 60 |
| **12** | -32 | -28 | 58 | -28 | -12 | 60 | -52 | 4 | 44 | -6 | -2 | 54 | 38 | -16 | 58 | 38 | -2 | 56 | 56 | 8 | 46 | 6 | -4 | 56 |
| **13** | -42 | -18 | 58 | -28 | -18 | 60 | -60 | 4 | 30 | -6 | -14 | 56 | 42 | -20 | 52 | 22 | -22 | 64 | 50 | 10 | 30 | 6 | -14 | 64 |
| **14** | -30 | -30 | 64 | -22 | -20 | 64 | -56 | -18 | 42 | -8 | -8 | 58 | 40 | -24 | 60 | 26 | -24 | 62 | 52 | -14 | 42 | 6 | -6 | 60 |
| **16** | -40 | -20 | 54 | -34 | -22 | 60 | -50 | 0 | 46 | -6 | -14 | 54 | 40 | -22 | 54 | 26 | -14 | 60 | 56 | 6 | 40 | 6 | -14 | 58 |
| **17** | -34 | -32 | 62 | -20 | -14 | 60 | -54 | 2 | 28 | -6 | -10 | 60 | 34 | -34 | 62 | 28 | -12 | 60 | 56 | 0 | 30 | 6 | -6 | 64 |
| **18** | 34 | -28 | 64 | 20 | -14 | 64 | 56 | 4 | 34 | 6 | -10 | 64 | -30 | -28 | 60 | -30 | -16 | 64 | -50 | 0 | 30 | -6 | -14 | 64 |
| **19** | 40 | -20 | 56 | 28 | -12 | 62 | 44 | 0 | 42 | 6 | -10 | 64 | -40 | -24 | 58 | -32 | -8 | 56 | -48 | -6 | 42 | -6 | -12 | 64 |
| **20** | 28 | -26 | 64 | 20 | -16 | 66 | 60 | 8 | 28 | 6 | -12 | 58 | -36 | -22 | 62 | -22 | -14 | 64 | -58 | 4 | 32 | -6 | -10 | 56 |
| **21** | 36 | -22 | 66 | 26 | -14 | 64 | 60 | 10 | 24 | 6 | -6 | 60 | -30 | -30 | 66 | -26 | -12 | 62 | -58 | 8 | 28 | -6 | -16 | 60 |
| **22** | 34 | -28 | 60 | 28 | -18 | 64 | 56 | 8 | 32 | 6 | -8 | 54 | -36 | -24 | 58 | -20 | -16 | 60 | -54 | 6 | 38 | -6 | -4 | 54 |
| **23** | -36 | -30 | 54 | -40 | -18 | 52 | -52 | -6 | 50 | -6 | -6 | 60 | 32 | -28 | 56 | 40 | -16 | 56 | 54 | -6 | 48 | 6 | -2 | 58 |
| **24** | -42 | -24 | 64 | -24 | -12 | 58 | -54 | 4 | 40 | -6 | -8 | 58 | 40 | -26 | 62 | 30 | -12 | 66 | 54 | -2 | 44 | 6 | -14 | 60 |
| **25** | -30 | -24 | 58 | -38 | -14 | 56 | -58 | 8 | 30 | -6 | -2 | 56 | 32 | -28 | 58 | 38 | -12 | 60 | 60 | 14 | 24 | 6 | -4 | 56 |

**Supplementary Table 3 | Coordinates of regions of interest used for DCM analyses of control subjects.** Subject-specific local activation maximum within region-specific anatomical constraints were identified to define the coordinates. *M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; SMA = supplementary motor area.* Adapted from Wiemer et al. (2025), *Brain*.

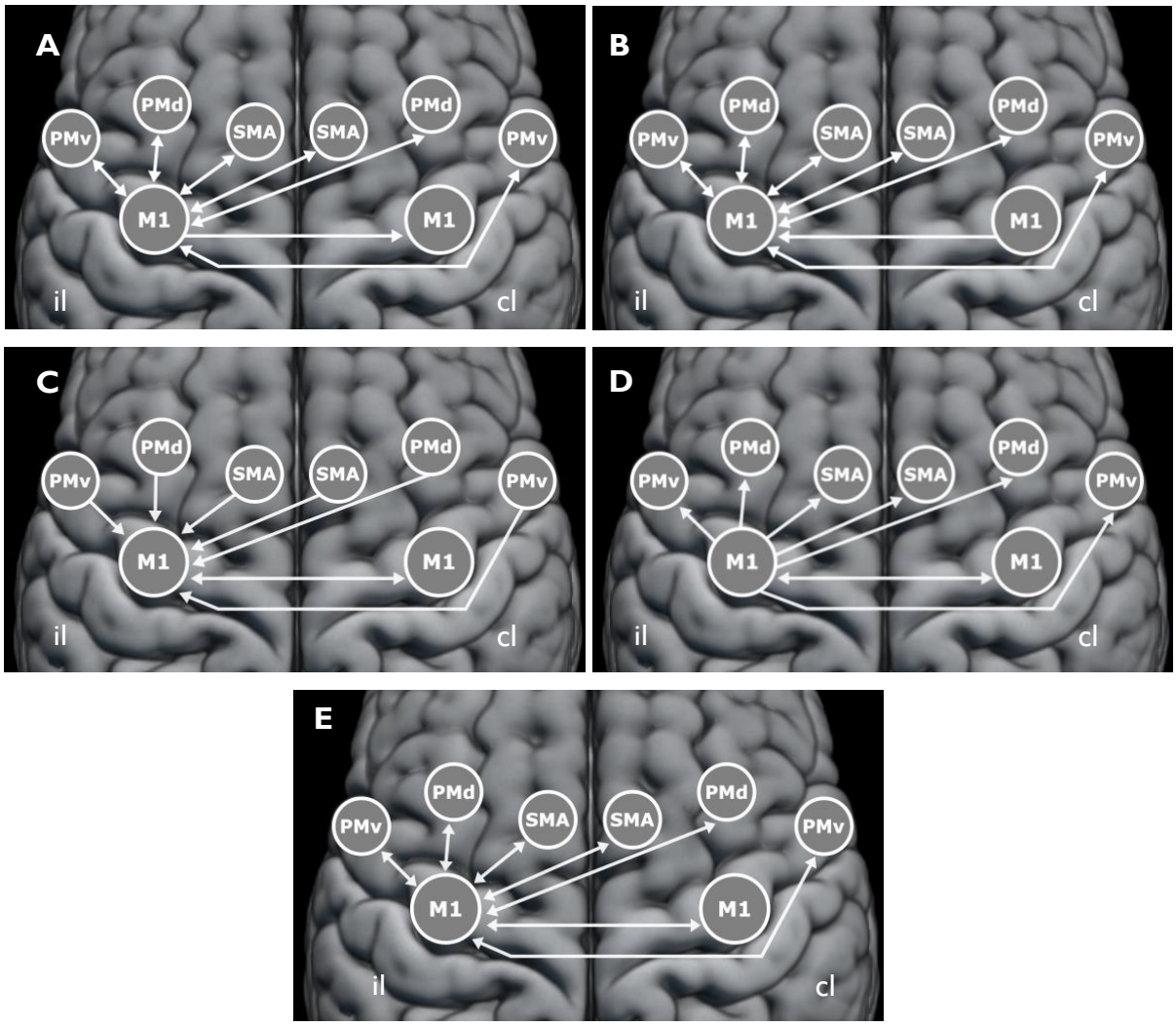
| | Right hemisphere | | | | | | | | | | | | Left hemisphere | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ID** | **M1** | | | **PMd** | | | **PMv** | | | **SMA** | | | **M1** | | | **PMd** | | | **PMv** | | | **SMA** | | |
| **1** | 40 | -28 | 58 | 38 | -8 | 50 | 52 | 0 | 40 | 6 | -14 | 60 | -36 | -34 | 58 | -28 | -22 | 56 | -50 | -4 | 44 | -6 | -14 | 58 |
| **2** | 36 | -24 | 56 | 26 | -12 | 58 | 56 | 2 | 38 | 10 | -4 | 56 | -40 | -24 | 52 | -28 | -14 | 56 | -50 | -4 | 38 | -6 | -2 | 56 |
| **3** | 34 | -26 | 62 | 36 | -2 | 56 | 56 | 6 | 40 | 6 | -4 | 62 | -30 | -28 | 54 | -30 | -16 | 60 | -50 | 2 | 34 | -6 | -8 | 58 |
| **4** | 42 | -22 | 52 | 34 | -12 | 60 | 54 | 0 | 46 | 6 | -6 | 58 | -40 | -22 | 56 | -32 | -12 | 62 | -52 | 6 | 42 | 6 | -8 | 58 |
| **5** | 36 | -28 | 60 | 30 | -14 | 62 | 54 | 2 | 46 | 6 | -14 | 62 | -36 | -26 | 60 | -28 | -12 | 56 | -52 | 2 | 46 | -6 | -10 | 64 |
| **6** | 28 | -28 | 58 | 28 | -10 | 60 | 54 | 4 | 42 | 6 | -12 | 58 | -34 | -28 | 64 | -30 | -10 | 62 | -56 | 6 | 38 | -6 | -6 | 58 |
| **7** | 30 | -24 | 62 | 24 | -14 | 62 | 56 | 8 | 32 | 6 | -8 | 56 | -30 | -20 | 66 | -28 | -16 | 58 | -56 | 2 | 34 | -6 | -16 | 58 |
| **8** | 40 | -18 | 60 | 24 | -12 | 58 | 54 | 10 | 42 | 6 | -2 | 62 | -40 | -18 | 60 | -28 | -16 | 56 | -56 | 6 | 36 | -6 | -2 | 60 |
| **9** | 34 | -26 | 62 | 32 | -14 | 60 | 62 | 8 | 24 | 6 | -10 | 64 | -34 | -30 | 62 | -28 | -16 | 60 | -60 | 10 | 24 | -6 | -10 | 62 |
| **10** | 36 | -20 | 56 | 26 | -10 | 56 | 52 | -2 | 46 | 6 | -6 | 62 | -32 | -20 | 58 | -34 | -10 | 58 | -56 | 0 | 40 | -6 | -6 | 56 |
| **11** | 34 | -18 | 54 | 26 | -14 | 62 | 52 | 8 | 32 | 6 | -10 | 64 | -34 | -22 | 56 | -24 | -16 | 58 | -58 | 12 | 26 | -6 | -14 | 58 |
| **12** | 40 | -20 | 56 | 36 | -6 | 58 | 56 | 12 | 30 | 6 | 0 | 58 | -40 | -26 | 56 | -22 | -8 | 58 | -58 | 10 | 30 | -6 | 0 | 60 |
| **13** | 38 | -26 | 64 | 38 | -18 | 56 | 56 | 8 | 34 | 6 | -16 | 64 | -36 | -30 | 62 | -30 | -12 | 58 | -58 | 4 | 40 | -6 | -12 | 60 |
| **14** | 38 | -26 | 54 | 22 | -14 | 62 | 56 | -2 | 44 | 6 | -14 | 56 | -32 | -30 | 60 | -24 | -18 | 64 | -56 | 0 | 38 | -6 | -8 | 56 |
| **15** | 32 | -26 | 60 | 40 | -10 | 56 | 56 | 8 | 36 | 6 | -2 | 60 | -32 | -28 | 58 | -36 | -8 | 58 | -56 | 8 | 38 | -6 | -2 | 58 |
| **16** | 46 | -20 | 56 | 24 | -16 | 62 | 58 | 8 | 36 | 6 | -10 | 56 | -38 | -22 | 56 | -22 | -16 | 60 | -54 | 6 | 46 | -6 | -8 | 58 |
| **17** | 40 | -30 | 64 | 30 | -14 | 64 | 58 | 8 | 36 | 6 | -14 | 58 | -34 | -30 | 60 | -20 | -14 | 62 | -54 | 8 | 38 | -6 | -12 | 60 |
| **18** | 30 | -28 | 62 | 44 | -18 | 58 | 54 | 4 | 42 | 6 | -4 | 60 | -28 | -26 | 56 | -36 | -16 | 52 | -56 | 4 | 42 | -6 | -6 | 60 |
| **19** | 36 | -28 | 54 | 38 | -14 | 54 | 50 | 4 | 36 | 6 | -4 | 54 | -42 | -28 | 60 | -36 | -14 | 56 | -60 | -2 | 38 | -6 | -2 | 58 |
| **20** | 30 | -30 | 58 | 34 | -18 | 60 | 56 | 8 | 34 | 6 | -12 | 58 | -34 | -32 | 58 | -30 | -14 | 58 | -56 | 0 | 32 | -6 | -12 | 60 |
| **21** | 36 | -24 | 60 | 26 | -12 | 60 | 54 | 6 | 28 | 6 | -2 | 54 | -34 | -28 | 60 | -24 | -14 | 58 | -56 | 0 | 34 | -6 | -2 | 54 |
| **22** | 40 | -26 | 54 | 34 | -6 | 58 | 56 | 10 | 34 | 6 | -10 | 60 | -36 | -26 | 56 | -26 | -6 | 56 | -58 | 6 | 32 | -6 | -10 | 58 |



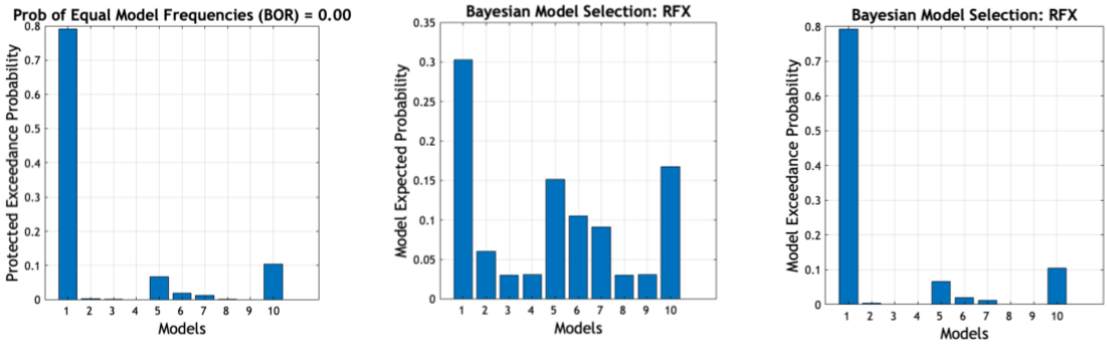

**Supplementary Figure 1 | Fully-connected model.** Bidirectional model including all possible connections between all bilateral motor areas in the DCM-B matrix (Model 1). *cl = contralesional; il = ipsilesional. M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; SMA = supplementary motor area.* Reproduced from Wiemer et al. (2025), *Brain*.




**Supplementary Figure 2 | Unidirectional DCM-models featuring distinct connection patterns.** In these models, the B-matrix included different connections. (**A**) Connections from contra- and ipsilesional motor areas to ipsilesional M1 (Model 2). (**B**) Connections from ipsilesional M1 to contra- and ipsilesional motor areas (Model 3). (**C**) Connections from bilateral premotor areas to ipsilesional M1 and from ipsilesional M1 to contralesional M1 (Model 4). (**D**) Connections from ipsilesional M1 to bilateral premotor areas and from contralesional to ipsilesional M1 (Model 5). *cl = contralesional; il = ipsilesional. M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; SMA = supplementary motor area.* Reproduced from Wiemer et al. (2025), *Brain.*




**Supplementary Figure 3 | Bidirectional DCM-models featuring distinct connection patterns.** In these models, the B-matrix included different connections. (**A**) Connections between bilateral premotor areas and ipsilesional M1 and from ipsilesional to contralesional M1 (Model 6). (**B**) Connections bilateral premotor areas and ipsilesional M1 and from contralesional to ipsilesional M1 (Model 7). (**C**) Connections from bilateral premotor areas to ipsilesional M1 and between ipsilesional and contralesional M1 (Model 8). (**D**) Connections from ipsilesional M1 to bilateral premotor areas and between ipsilesional and contralesional M1 (Model 9). (**E**) Connections between bilateral premotor areas and ipsilesional M1 and between ipsilesional and contralesional M1 (Model 10). *cl = contralesional; il = ipsilesional. M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; SMA = supplementary motor area.* Reproduced from Wiemer et al. (2025), Brain.




**Supplementary Figure 4 | Bayesian model selection results.** Bayesian model selection based on a random effects approach was performed to compare the above-described DCM-models. This approach identified the fully-connected model (Model 1) as the winning model given the empirical data. Reproduced from Wiemer et al. (2025), *Brain*.

**Supplementary Table 4 | Correlation analyses between structural connectivity and different aspects of motor control after tract-specific subject exclusion.** Specific cortico-cortical tracts were excluded for three subjects who showed considerable overlap (> 10%) of the tract's one-directional voxels with the lesion. 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. Adapted from Paul, Wiemer, et al. (2023), *Annals of Neurology*, Volume 94, Issue 4, Pages 785-797.

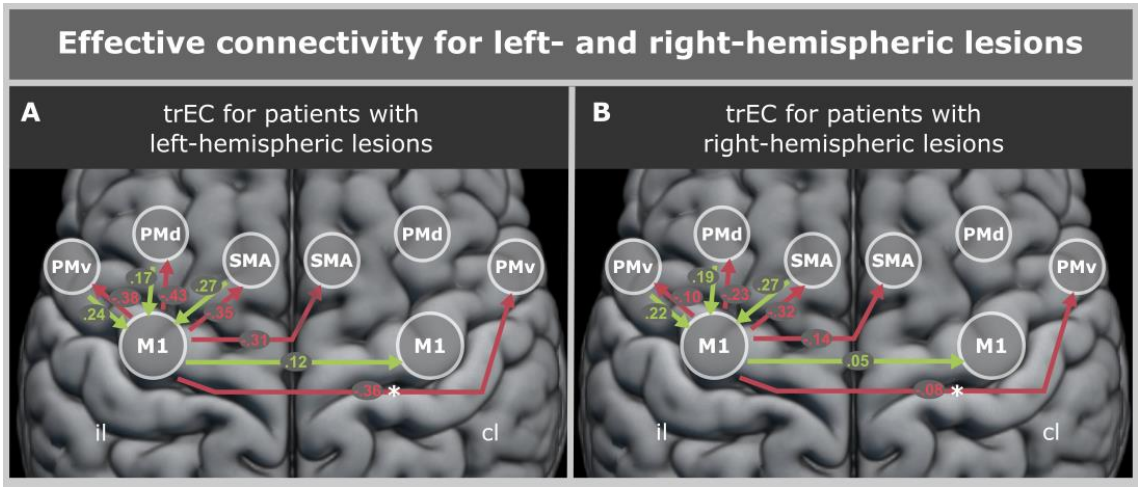
| | Pearson correlations | | Partial correlations | |
|---|---|---|---|---|
| **Connection** | ***r*** | ***P*$_{FDR}$** | ***r*** | ***P*$_{FDR}$** |
| | | **Basal motor control** | | |
| *Homologous* | | | | |
| clM1–ilM1 | 0.62 | 0.002** | 0.45 | 0.040* |
| *Intrahemispheric* | | | | |
| ilPMd–ilM1 | 0.66 | 0.002** | 0.61 | 0.005** |
| ilPMv–ilM1 | 0.74 | <0.001*** | 0.67 | 0.003** |
| ilSMA–ilM1 | 0.63 | 0.002** | 0.65 | 0.003** |
| *Interhemispheric* | | | | |
| clPMd–ilM1 | 0.31 | 0.134 | 0.25 | 0.246 |
| clPMv–ilM1 | 0.56 | 0.007** | 0.54 | 0.013* |
| clSMA–ilM1 | 0.43 | 0.036* | 0.31 | 0.172 |
| | | | | |
| | | **Complex motor control** | | |
| *Homologous* | | | | |
| clM1–ilM1 | 0.49 | 0.022* | 0.26 | 0.246 |
| *Intrahemispheric* | | | | |
| ilPMd–ilM1 | 0.53 | 0.018* | 0.45 | 0.073 |
| ilPMv–ilM1 | 0.6 | 0.015* | 0.49 | 0.073 |
| ilSMA–ilM1 | 0.56 | 0.015* | 0.56 | 0.035* |
| *Interhemispheric* | | | | |
| clPMd–ilM1 | 0.28 | 0.183 | 0.21 | 0.332 |
| clPMv–ilM1 | 0.46 | 0.029* | 0.43 | 0.073 |
| clSMA–ilM1 | 0.45 | 0.029* | 0.33 | 0.16 |

Abbreviations: cl = contralesional; CST = corticospinal tract; il = ipsilesional; M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; SMA = supplementary motor area. Asterisks signify the following significance thresholds: ***$P_{FDR} < 0.001$, **$P_{FDR} < 0.01$, *$P_{FDR} < 0.05$.

**Supplementary Table 5 | Recovery-specific subgroup analysis: Correlation analyses between structural connectivity and basal motor control after tract-specific subject exclusion.** Specific cortico-cortical tracts were excluded for three subjects who showed considerable overlap (> 10%) of the tract's one-directional voxels with the lesion. Analyses were carried out separately for patients exhibiting (i) substantial or (ii) non-substantial recovery. Partial correlations assessed the relationship between basal motor control and tractwise anisotropy while controlling for ipsilesional CST integrity. Adapted from Paul, Wiemer, et al. (2023), *Annals of Neurology*, Volume 94, Issue 4, Pages 785-797.

| | 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 | 0.31 | 0.397 | 0.33 | 0.387 |
| ilPMv–ilM1 | 0.62 | 0.079 | 0.58 | 0.166 |
| ilSMA–ilM1 | 0.16 | 0.582 | 0.26 | 0.467 |
| *Interhemispheric* | | | | |
| clPMd–ilM1 | 0.22 | 0.492 | 0.18 | 0.549 |
| clPMv–ilM1 | 0.35 | 0.39 | 0.36 | 0.387 |
| clSMA–ilM1 | 0.5 | 0.139 | 0.42 | 0.325 |
| | | | | |
| | | **Non-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 | 0.06 |
| ilSMA–ilM1 | 0.9 | 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 | 0.3 | 0.392 | 0.21 | 0.657 |

Abbreviations: cl = contralesional; CST = corticospinal tract; il = ipsilesional; M1 = primary motor cortex; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; SMA = supplementary motor area. Asterisks signify the following significance thresholds: ***$P_{FDR} < 0.001$, **$P_{FDR} < 0.01$, *$P_{FDR} < 0.05$.




**Supplementary Figure 5 |** Task-related effective connectivity within the motor network for patients with (**A**) left-hemispheric lesions compared to patients with (**B**) right-hemispheric lesions at group level (DCM-$B_{aff}$). Notably, patients with left-hemispheric lesions exhibited enhanced inhibition from ipsilesional M1 to contralesional PMv ($t(21) = 3.09$, $P_{FDR} = 0.017$), whereas effective connectivity across all other connections remained comparable ($P_{FDR} > 0.05$), indicating no substantial influence of lesion laterality on the present results. *cl = contralesional; 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.* Reproduced from Wiemer et al. (2025), *Brain*.

# 9. Erklärung

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertationsschrift selbstständig und ohne die Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Alle Stellen—einschließlich Tabellen, Karten und Abbildungen —, die wörtlich oder sinngemäß aus veröffentlichten und nicht veröffentlichten anderen Werken im Wortlaut oder dem Sinn nach entnommen sind, sind in jedem Einzelfall als Entlehnung kenntlich gemacht. Ich versichere an Eides statt, dass diese Dissertationsschrift noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie—abgesehen von unten angegebenen Teilpublikationen—noch nicht veröffentlicht worden ist sowie, dass ich eine solche Veröffentlichung vor Abschluss der Promotion nicht ohne Genehmigung der / des Vorsitzenden des IPHS-Promotionsausschusses vornehmen werde. Die Bestimmungen dieser Ordnung sind mir bekannt. Die von mir vorgelegte Dissertation ist von Prof. Dr. Lukas J. Volz betreut worden.

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Übersicht der Publikationen:

1. Paul, T.*, **Wiemer, V. M.***, Hensel, L., Cieslak, M., Tscherpel, C., Grefkes, C., Grafton, S. T., Fink, G. R. & Volz, L. J. (2023). Interhemispheric structural connectivity underlies motor recovery after stroke. *Annals of Neurology*, *94*(4), 785-797.
   * geteilte Erstautorenschaft
2. **Wiemer, V. M.**, Paul, T., Hensel, L., Cieslak, M., Tscherpel, C., Grefkes, C., Grefkes, C., Grafton, S. T., Fink, G. R. & Volz, L. J. (2025). Structural reserve-dependent cortical rerouting of motor control after stroke. *Brain,* awaf434.

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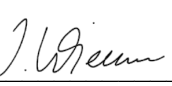
Köln, 16.07.2026, 

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