

Integrated neuroimaging and robotic rehabilitation in chronic stroke: Neural correlates and predictors of motor recovery

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Abstract. Chronic stroke survivors are frequently afflicted with persistent motor impairments. Neural mechanisms underlying recovery and predictors of rehabilitation response remain poorly understood. Advances in MRI-compatible robotic devices have enabled the integration of neuroimaging with targeted therapy, allowing for the real-time assessment of brain plasticity. The present study aimed to identify neuroimaging biomarkers of motor performance and recovery in patients with chronic stroke using functional MRI (fMRI), diffusion tensor imaging and robotic-assisted therapy. In total, 14 patients with chronic stroke (8 women, 6 men; mean age, 55.2±12.2 years) with left middle cerebral artery infarcts from Massachusetts General Hospital (Boston, USA) underwent a 10-week home-based rehabilitation program using an MRI-compatible robotic hand device. Motor outcomes were assessed using the Fugl-Meyer assessment for upper extremity (FMA-UE), Box and Block Test (BBT) and grip strength. Imaging data from 210 sessions were then analyzed to evaluate the degree of task-related brain activation and white matter integrity. Generalized linear mixed models revealed that focused activation in the ipsilesional primary motor cortex (M1) was positively associated with BBT ($B=7.57$; $P<0.001$)

and grip strength ($B=8.65$; $P<0.001$). By contrast, activation in the contralesional ventral premotor cortex was found to be negatively associated with motor outcomes ($B=-2.89$; $P<0.001$). Higher fractional anisotropy (FA) in the corticospinal tract and posterior limb of the internal capsule was positively associated with motor performance (FMA-UE, $B=133.10$; $P<0.001$), whilst higher FA in the posterior corona radiata was negatively associated with motor performance (BBT: $B=-1,409.10$; $P<0.001$). Rehabilitation-induced improvements were also associated with increased ipsilesional M1 activation ($B=0.67$; $P=0.002$) and recruitment of the contralesional dorsal premotor cortex ($B=3.43$; $P<0.001$). In conclusion, these data suggest that recovery from chronic stroke is supported by lateralized motor network engagement and preserved white matter integrity. Therefore, neuroimaging biomarkers may be exploited for guiding personalized rehabilitation strategies and predicting the patients' response to rehabilitation.

Introduction

Stroke is a devastating neurological condition that is one of the leading causes of long-term disability worldwide, imposing substantial physical, emotional, and socioeconomic burdens on survivors and their families (1). Despite significant advancements in acute stroke care, which have contributed to reducing mortality rates, the management of chronic stroke remains a critical and unresolved challenge in clinical practice (1-3). Historically, the prevailing assumption that functional recovery plateaus within the first few months post-stroke has limited the focus on rehabilitation efforts to the acute and subacute phases (4). However, emerging evidence challenges this notion by demonstrating that targeted rehabilitation interventions can yield meaningful improvements in functional outcomes even during the chronic phase of stroke recovery (5,6). This potential paradigm shift underscores the need for a deeper understanding of the mechanisms underlying chronic stroke recovery and the development of innovative therapeutic strategies to address the persistent unmet needs of this patient population (7).

The triage process in stroke rehabilitation is crucial for balancing patient outcomes and cost control (5). It involves screening patients, establishing assessment criteria and considering stroke severity to determine appropriate care settings (8).

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Abbreviations: DTI, diffusion tensor imaging; fMRI, functional MRI; MR_CHIROD, Magnetic Resonance Compatible Hand-Induced RObotic Device; FMA-UE, Fugl-Meyer assessment for upper extremity; ARAT, Action Research Arm Test; BBT, Box and Blocks Test; FOV, field of view; M1, primary motor cortex; PMv, ventral premotor cortex; PMd, dorsal premotor cortex; S1, primary somatosensory cortex; SMA, supplementary motor area; FA, fractional anisotropy; MD, mean diffusivity, GLMM, generalized linear mixed model; -2LL, -2 log-likelihood

Key words: stroke, MRI, hand, motor, rehabilitation, robotics

Although significant progress has been made in acute stroke care, disparities remain during the later phases of recovery (9). It has been suggested that severely affected patients with stroke can have the potential for benefiting from rehabilitation, albeit at a slower pace (10). Healthcare professionals however frequently lack awareness of the improvement potential of patients during the chronic recovery phases (9). To address these challenges, there is a need for improved outcome measures and carefully focused interventions for patients with chronic stroke (10).

Neuroimaging serves a crucial role in predicting outcomes and guiding rehabilitation strategies for patients with stroke (11). MRI techniques, including diffusion tensor imaging (DTI) and functional neuroimaging, have shown promise in providing prognostic information for individual patients during the early stages of recovery (12). These advanced imaging methods, when combined with clinical and neurophysiological assessments, can be applied to tailor rehabilitation approaches based on a patient's capacity for neural reorganization (12,13). MRI techniques have the potential to provide comprehensive assessments in chronic stroke, guiding treatment decisions for optimal clinical outcomes. As neuroimaging technology continues to advance, it is expected to serve an increasingly important role in stroke recovery prediction and personalized rehabilitation planning (14).

Advancements in MRI-compatible robotic devices have enabled simultaneous neuroimaging and rehabilitation for patients with stroke over the past decade. These devices, including soft wearable gloves (15) and hand-induced robotic systems (16-18), allow for the monitoring of brain activity during rehabilitation exercises. Previous studies have shown that training with such devices can increase sensorimotor cortical activation, indicating functional plasticity in patients with chronic stroke (19-21). The combination of MRI and robotic-assisted therapy demonstrates the potential of enhancing the understanding of brain plasticity and improving stroke recovery outcomes (20-22).

Despite the promising advancements in neuroimaging and robotic-assisted rehabilitation for patients with chronic stroke, to the best of our knowledge, a comprehensive assessment integrating functional MRI (fMRI) and DTI for triaging and predicting motor improvement potential in this patient population remains lacking. Current approaches are frequently ineffective at systematically evaluating neural mechanisms underlying recovery or identifying which patients are most likely to benefit from robotic rehabilitation interventions. This knowledge gap limits the ability to personalize rehabilitation strategies and optimize outcomes for chronic stroke survivors.

Therefore, the present study aims to address this need by leveraging a combined functional and structural brain assessment to triage patients with chronic stroke and evaluate their potential for motor improvement following robotic device training. By integrating advanced neuroimaging with robotic rehabilitation, the present study seeks to provide a deeper understanding of brain plasticity during chronic stroke and establish a framework for tailored, evidence-based therapeutic interventions.

Materials and methods

Patients. Patients with chronic stroke were identified only by using the Massachusetts General Hospital (Boston, USA) stroke

survivor registries. The patients had been admitted between July 2006 and May 2019, and the registries were accessed by the authors between January 2019 and December 2023 for this study. Eligible participants were right-handed [per the revised Edinburgh Handedness Inventory EIH-8 (23)] adults who had sustained a first-ever left middle cerebral artery ischemic stroke ≥ 6 months prior to enrollment and those who exhibited persistent right-hand weakness [Medical Research Council scale (24) < 4 for ≥ 48 h]. To minimize heterogeneity and ensure reliable task performance during fMRI and robotic training, individuals with significant cognitive or sensory impairments were excluded. These impairments were defined as the inability to understand and comply with the fMRI task instructions. Additional exclusion criteria comprised any contraindications to MRI (such as metallic implants and severe claustrophobia), a history of other neurological (for example multiple sclerosis and Parkinson's disease) or major psychiatric disorders (for example schizophrenia and bipolar disorder), and any orthopedic or systemic conditions affecting motor function of the stroke-affected hand (for example, severe arthritis and peripheral neuropathy). All participants provided informed consent in writing, to a study that was approved by the Central Institutional review board serving Massachusetts General Hospital and Brigham and Women's Hospital Institutional review board (Partners Human Research Committee, approval no. 2005P000570).

Rehabilitation protocol. Patients underwent a supervised home-based rehabilitation program using the third-generation Magnetic Resonance Compatible Hand-Induced Robotic Device (MR_CHIROD), an in-house-developed system, paired with an interactive game (25). The training regime consisted of 45-min sessions conducted three times per week for 10 weeks. Motor performance assessments were conducted at the following time points: i) Before training (baseline); ii) monthly during training; and iii) 1-month post-training. Evaluations applied included the Fugl-Meyer assessment for upper extremity (FMA-UE) scale for sensorimotor impairment that are comprised of subscales for wrist, hand, coordination, sensation, passive joint motion, joint pain and total motor function. These subscales enable the comprehensive evaluation of upper extremity impairment (26). Functional hand use was assessed using the Action Research Arm Test (ARAT) (27), with subcategories for grasp, grip, pinch, gross movement and total performance. Spasticity severity was quantified using the modified Ashworth scale for the elbow, wrist, fingers and thumb (28). Hand grip strength (Force) was measured using a dynamometer (Jamar Hydraulic Hand Dynamometer 12-0600; Fabrication Enterprises, Inc.), whereas manual dexterity was evaluated using the Box and Blocks Test (BBT) (29). These assessments were selected to capture multiple dimensions of motor impairment, functional recovery and spasticity, offering a detailed understanding of the progress of each patient.

Imaging protocol. All imaging was performed using a 3T Siemens Skyra scanner equipped with a 32-channel phased-array coil (Siemens Healthineers). The imaging protocol included several sequences. T1-weighted anatomical imaging was conducted using a sagittal magnetization-prepared rapid gradient-echo sequence [repetition time (TR)/echo time

(TE)/inversion time (TI), 2,300/2.53/900 msec; field of view (FOV), 256 mm; resolution, $1 \times 1 \times 1 \text{ mm}^3$; parallel acquisition technique (PAT) factor, 2; acquisition time, 5.5 min]. Field mapping utilized a double-echo fast gradient-echo sequence (TR, 650 msec; TE1/TE2, 4.92/7.38 msec; FOV, 220 mm; resolution, $2 \times 2 \times 2 \text{ mm}^3$). fMRI data were acquired using echo-planar imaging (TR/TE, 3,000/30 msec; FOV, 220 mm; resolution, $2 \times 2 \times 2 \text{ mm}^3$; PAT factor, 2; 100 dynamics). DTI was performed with an axial spin-echo echo-planar imaging sequence (b-values 0/1,000 sec/mm²; TR/TE, 12,200/104 msec; 30 directions; resolution, $2 \times 2 \times 2 \text{ mm}^3$). Additionally, a 3D fluid-attenuated inversion recovery sequence was included for clinical evaluation (TR/TE/TI, 5,000/386/1,800 msec; resolution, $0.5 \times 0.5 \times 0.9 \text{ mm}^3$).

Motor paradigm. During fMRI, participants performed a motor task using the MR_CHIROD device with their right hand in a ‘boxcar’ paradigm (30), alternating between 21-sec rest and action blocks. During action blocks, participants synchronized grip compression and release with a visual metronome set at 0.52 Hz. During rest blocks, participants fixated on a stationary cross at the center of the screen, serving as a low-level baseline condition. In total, three fMRI scans were conducted per imaging session, each with a resistive force (resistive level) adjusted to 60, 40 or 20% of the pre-scanned maximum grip strength. To minimize motion artifacts, foam padding and straps were used, where mirror movements in the non-active hand were closely monitored.

Image processing. fMRI data were preprocessed and analyzed using ‘SPM12’ (30) in MATLAB 9.10 (MathWorks, Inc.). Preprocessing procedures included slice timing correction, realignment to correct head motion, co-registration of functional to T1-weighted anatomical images, normalization to the Montreal Neurological Institute template (30) ($2 \times 2 \times 2 \text{ mm}^3$ resolution) and smoothing with an 8-mm FWHM Gaussian kernel. Intra-subject analysis used a general linear model, with the motor task modeled as a boxcar function convolved with the canonical hemodynamic response function, including action/rest regressors and motion parameters as nuisance variables. Contrasts compared action with rest, using statistical maps thresholded at $P < 0.05$ (family-wise error-corrected). A region of interest analysis was conducted on the thresholded SPM_T maps using the Human Motor Area Template Atlas (31). For each defined region of interest, statistical measures, including maximum activation (max), cluster size (size) and mean activation (mean), were calculated separately for the left (L) and right (R) hemispheres. The analysis focused on key motor-related regions, such as the cerebellum (Cer), primary motor cortex (M1), ventral premotor cortex (PMv), dorsal premotor cortex (PMd), primary somatosensory cortex (S1) and supplementary motor area (SMA).

DTI data were processed using FMRIB Software Library, version 6.0 (Centre for Integrative Neuroimaging, University of Oxford). Pre-processing included correction for eddy currents and head motion, followed by brain extraction. Diffusion tensors were fitted to generate maps of fractional anisotropy (FA) and mean diffusivity (MD). For region-of-interest analysis, the JHU white matter tract atlas (32) was used to define motor-related tracts in the stroke-affected hemisphere. Mean

FA and MD values were extracted for the following motor related tracts of the lesioned left hemisphere: Corticospinal tract, cerebral peduncle, posterior limb of the internal capsule and posterior corona radiata.

Statistical analysis. Generalized linear mixed models (GLMM) were employed to analyze the repeated measures data structure arising from five experimental sessions and three resistive levels. This modeling approach is suited for datasets involving multiple observations from the same participants under different conditions, since it accounts for the non-independence of repeated measurements (33). Both fixed effects and random effects were included in the models. Fixed effects consisted of session (ordinal variable with values 1,2,3,4,5), Resistive level, sex, age and relevant clinical measures, providing estimates of the overall influence of these variables across the entire sample. Random intercepts were incorporated to account for individual differences and to accurately model within-subject variability, thereby improving the precision of effect estimates. To address potential violations of standard model assumptions, such as non-normality and heteroscedasticity, robust covariance estimates (sandwich estimators) were applied using SPSS. This method adjusts the estimated standard errors of fixed effects to provide valid statistical inference despite deviations from standard assumptions (34). Maximum likelihood estimation was used to accommodate missing data and to handle outcome variables that did not follow a normal distribution, ensuring that the hierarchical structure of the dataset was appropriately modeled and that all available data were utilized.

The statistical analysis consisted of two primary components. The first component (motor assessment) evaluated the association between clinical scale scores and neuroimaging measurements across all five sessions using GLMM, thereby assessing the relationship between brain plasticity and motor performance throughout the intervention period. The second component (motor prediction) focused on identifying early neuroimaging predictors of motor improvement using GLMM by examining whether imaging measurements from the first two sessions could predict changes in motor performance, as measured by the difference in clinical scale scores between the final session and the initial sessions.

Among the clinical outcome measures, particular emphasis was placed on the ARAT Grip scores, given their direct relevance to both the fMRI task and the rehabilitation exercises. Additional dependent variables included the FMA_UE scale, the BBT and Force. In all models, session, resistive level, sex and age were included as covariates to control for potential confounding effects. Model performance was assessed using the -2 log-likelihood (-2LL) criterion, facilitating comparison of model fit. All statistical analyses were conducted using SPSS version 26 (IBM Corp.). $P < 0.05$ was considered to indicate a significance for the estimated regression coefficients.

Results

Baseline data. In total, 14 chronic patients with left middle cerebral artery ischemic stroke (sex, 8 females, 6 males; age, 55.2 ± 12.2 years) completed 210 MRI sessions (5 timepoints $\times$ 3 resistive levels) during the present study. The Modified Ashworth Scale was assessed in all patients and found to be

0, indicating the absence of muscle spasticity, and thus spasticity was not included as a variable in the statistical analyses. Table I displays their clinical characteristics before rehabilitation, showing that according to the FMA-UE scale, six patients presented with severe disability in the range 0-28, and eight with moderate disability in the range 29-42 (35). A total of three patients achieved the >4-point motor improvement threshold for clinically important difference according to the FMA-UE scale (Fig. 1 and Table I) (36). Only two patients achieved the corresponding improvement threshold in the BBT and seven patients in Force scale (Table I) (37). ARAT-Grip was not analyzed, because no changes were detected during the training sessions. Fig. 2 depicts a comparison between baseline images of a patient (no. 14 in Table I) who failed to show significant motor improvement and a patient (no. 13 in Table I) who succeeded. FLAIR images reveal the site and extent of the stroke lesions. Colored brain activation maps superimposed on T1 anatomical images illustrate different activation patterns. Absence of progress is related to an abnormal activation pattern with focal intense activation posterior to the motor cortex. By contrast, normal left M1 and bilateral SMA activation was observed in the patient who achieved motor gains after rehabilitation. Coronal colored FA images indicate an intact corticospinal tract at the lesioned hemisphere in both cases.

Motor assessment. Analysis revealed distinct patterns linking neuroimaging markers to motor outcomes (Table II). In the ipsilesional hemisphere, activation in M1 and SMA showed robust positive associations with motor performance. The mean activation in left M1 is positively associated with both the BBT ($B=7.57$ and $P<0.001$) and Force ($B=8.65$ and $P<0.001$) measures, suggesting that stronger, more focused recruitment of the core motor areas supports superior motor performance. By contrast, activation in left premotor regions is characterized by negative associations. Specifically, increased activity in the left PMv ($\max_PMv_L$, $B=-0.91$ and $P=0.001$) and PMd (mean_PMd_L , $B=-1.70$ and $P=0.023$ for FMA-UE; $B=-11.84$ and $P<0.001$ for Force) appeared to associate with poorer motor outcomes, which indicate that diffuse or excessive recruitment in these secondary regions may reflect compensatory mechanisms that are less efficient. A similar trend is observed in the left S1 ($\max_S1_L$, $B=-0.54$ and $P=0.014$), where overactivation is negatively associated with motor performance.

In the contralesional hemisphere, the relationships were found to be more nuanced. Activation in right M1 ($\max_M1_R$, $B=-3.16$ and $P<0.001$ for BBT; $B=-5.64$ and $P<0.001$ for Force) and right PMv ($\max_PMv_R$, $B=-2.89$ and $P<0.001$ for BBT) exhibited negative associations with motor scales, implying that excessive recruitment in these regions may be maladaptive. However, right PMd showed a positive association ($\max_PMd_R$: $B=2.66$ and $P<0.001$ for BBT; $B=3.35$ and $P<0.001$ for Force), which may suggest that selective engagement of this region can serve a compensatory function when the ipsilesional network is compromised. In addition, right S1 activation is positively associated with motor performance (mean_S1_R , $B=3.38$ and $P=0.003$ for BBT; mean_S1_R , $B=3.28$ and $P=0.009$ for Force), indicating that contralesional sensory processing may serve a beneficial role. By contrast,

right SMA activation ($\max_SMA_R$, $B=-1.79$ and $P<0.001$ for FMA-UE) was negatively associated with motor function, further supporting the notion that not all contralesional recruitment contributes equally to recovery.

DTI metrics add a complementary perspective, by reflecting white matter integrity. Higher FA values in the corticospinal tract ($B=34.88$ and $P<0.001$ for FMA-UE) and posterior limb of the internal capsule ($B=133.10$ and $P<0.001$ for FMA-UE; $B=493.18$ and $P<0.001$ for BBT) associated positively with motor scales, supporting the importance of intact descending pathways for functional recovery. By contrast, increased FA in the posterior corona radiata ($B=-283.94$ and $P<0.001$ for FMA-UE; $B=-1,409.10$ and $P<0.001$ for BBT) was negatively associated with motor performance. MD measurements also aligned with this interpretation. Specifically, elevated MD in posterior corona radiata ($B=-567,911.91$ and $P<0.001$ for BBT; $B=-284,152.48$ and $P=0.001$ for Force) tended to associate with inferior motor outcomes, suggesting that tissue damage and subsequent structural disorganization adversely affect recovery.

Motor prediction. Changes in the ipsilesional cortex (left hemisphere) demonstrate a mixed pattern of positive and negative associations between peak or mean activation and rehabilitation-induced motor gains (Table III). Maximum activation in left M1 ($\max_M1_L$, $B=0.67$ and $P=0.002$) and cluster size in left M1 (size_M1_L , $B=2.81 \times 10^{-3}$ and $P=0.001$) both show positive relationships with $\Delta(\text{FMA-UE})$, whilst mean activation in left M1 (mean_M1_L , $B=-3.44$ and $P=0.001$) is negatively associated with $\Delta(\text{FMA-UE})$. Similarly, left PMv exhibited a positive association with $\Delta(\text{FMA-UE})$ (mean_PMv_L , $B=2.95$ and $P=0.012$), whereas left PMd associated negatively (mean_PMd_L , $B=-2.18$ and $P=0.010$). In the left somatosensory cortex, activation cluster size showed an inverse relationship with $\Delta(\text{FMA-UE})$ (size_S1_L : $B=-2.32 \times 10^{-3}$ and $P=0.029$) but a positive one with $\Delta(\text{BBT})$ (size_S1_L : $B=0.02$ and $P=0.002$), whereas mean activation is positively associated with $\Delta(\text{FMA-UE})$ (mean_S1_L , $B=2.27$ and $P=0.021$). Finally, negative associations in left SMA maximum ($\max_SMA_L$, $B=-1.46$ and $P=0.044$) and mean activations (mean_SMA_L , $B=-2.84$ and $P=0.004$) suggest that heightened activation in this region may not necessarily translate into improved upper-limb function.

In the contralesional hemisphere, fewer significant patterns emerged for motor improvement. Maximum activation in right Cer showed a positive association with $\Delta(\text{FMA-UE})$ ($\max_Cer_R$, $B=0.85$ and $P=0.016$), whereas maximum activation in right PMv yielded a negative association for the same outcome ($\max_PMv_R$, $B=-0.81$ and $P=0.019$). Right PMd is positively associated with $\Delta(\text{FMA-UE})$ (mean_PMd_R , $B=3.43$ and $P<0.001$), whilst its cluster size exhibited a negative association with $\Delta(\text{FMA-UE})$ (size_PMd_R , $B=-1.37 \times 10^{-3}$ and $P=0.032$) and a positive association for the other two scales [$\Delta(\text{BBT})$: Size_PMd_R , $B=4.39 \times 10^{-3}$ and $P=0.019$; $\Delta(\text{Force})$: Size_PMd_R , $B=0.01$ and $P=0.014$]. Right somatosensory cortex yielded a positive association with changes in BBT ($\max_S1_R$, $B=1.96$ and $P=0.001$), whereas right SMA shows consistent positive association with $\Delta(\text{FMA-UE})$ (mean_SMA_R , $B=5.27$ and $P<0.001$).

Table I. Clinical characteristics of patients with chronic stroke, motor scores at baseline and differences with the last session.

Patients no.	Sex	Age, years	FMA-UE	Δ (FMA_UE)	BBT	Δ (BBT)	Force, pound-force	Δ (Force), pound-force
1	F	39.1	27	5	43	4	56.4	15.3
2	M	64.2	36	0	54	3	105.7	-20
3	M	50.2	36	0	69	23	103.8	12.9
4	F	47.3	36	0	61	2	72.7	-11.7
5	F	60.5	18	3	0	2	51.5	4.8
6	F	46.5	28	0	13	1	45.8	-3.5
7	M	41.0	32	0	46	3	81.1	9.3
8	F	34.0	32	0	51	7	39.9	5
9	F	70.0	32	0	42	3	30.8	7.4
10	M	58.5	12	10	0	0	71.5	-1.9
11	M	71.4	36	0	27	3	53.7	10.9
12	M	67.9	36	0	15	-4	52.3	10.8
13	F	64.5	6	8	0	0	41.9	13.8
14	F	57.1	28	1	0	5	64.8	4.1

F, female; M, male; FMA, Fugl-Meyer Assessment; UE, upper extremity; BBT, Box and Block Test; Δ , difference between last and first session.

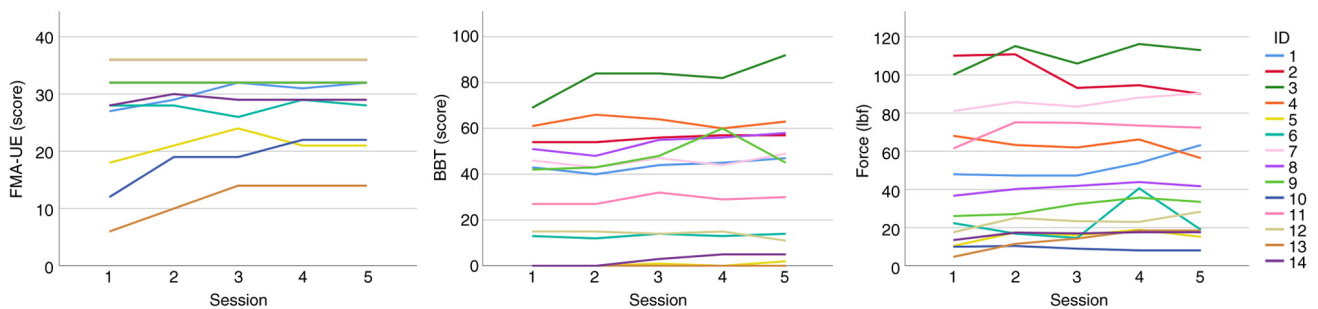


Figure 1. Evolution of FMA-UE, BBT and grip strength (Force) in lbf across imaging sessions for all patients (ID). Session 1 was conducted before the start of rehabilitation (baseline), sessions 2, 3, and 4 occurred during rehabilitation (1 month apart), and session 5 was 1-month post-rehabilitation. Note that in some cases, ID lines overlap completely and are obscured. FMA-UE, Fugl-Meyer assessment upper extremity; BBT, Box and Blocks Test. Lbf, pound-force.

Diffusion metrics revealed additional insights. Negative associations between FA in the cerebral peduncle (FA Cerebral peduncle, $B=-57.84$ and $P=0.001$) or posterior limb of the internal capsule (FA Posterior limb of internal capsule, $B=-102.86$ and $P<0.001$) and Δ (FMA-UE), coupled with positive associations for BBT (FA Cerebral peduncle, $B=230.56$ and $P<0.001$; FA Posterior limb of internal capsule, $B=137.27$ and $P=0.037$), suggest that microstructural changes in specific descending pathways may differentially influence upper-limb function compared with gross dexterity. FA in the posterior corona radiata exhibited an opposite pattern [positive for Δ (FMA-UE), $B=164.28$ and $P=0.001$; negative for Δ (BBT), $B=-556.04$ and $P<0.001$], indicating that microstructural integrity in more diffuse white matter regions may favor certain motor outcomes but not others. MD metrics reinforced this distinction, with some regions (such as the corticospinal tract) associating positively with Δ (BBT) (MD Corticospinal tract, $B=145,126.61$ and $P<0.001$), whereas others (such as the cerebral peduncle) appear to associate negatively to BBT (MD Cerebral peduncle, $B=-494,726.62$ and $P<0.001$).

Taken together, these patterns reflect a complex interplay among focal ipsilesional reactivation, contralesional compensatory mechanisms and white matter tract integrity in determining changes in motor outcomes.

Model comparison. Model fit comparisons for the three motor assessments are presented in Table IV. For prediction models, the -2LL values were substantially lower overall because they used a smaller dataset. Within each model type (assessment vs. prediction), the FMA-UE consistently outperformed the BBT and Force, suggesting the greater sensitivity of neuroimaging data to FMA-UE changes. Fig. 3 illustrates the performance of GLMM in predicting FMA-UE and its change [Δ (FMA-UE)] using circular scatter plots displaying observed vs. predicted values, where circle color indicates frequency. The clustering of the majority of circles along the diagonal line of perfect prediction (observed value=predicted value) in both plots indicates a strong agreement between the model's estimates and the actual observed data. This close alignment, observed for both absolute and change scores, suggests that the FMA-UE is a reliable score for the assessment and prediction of motor

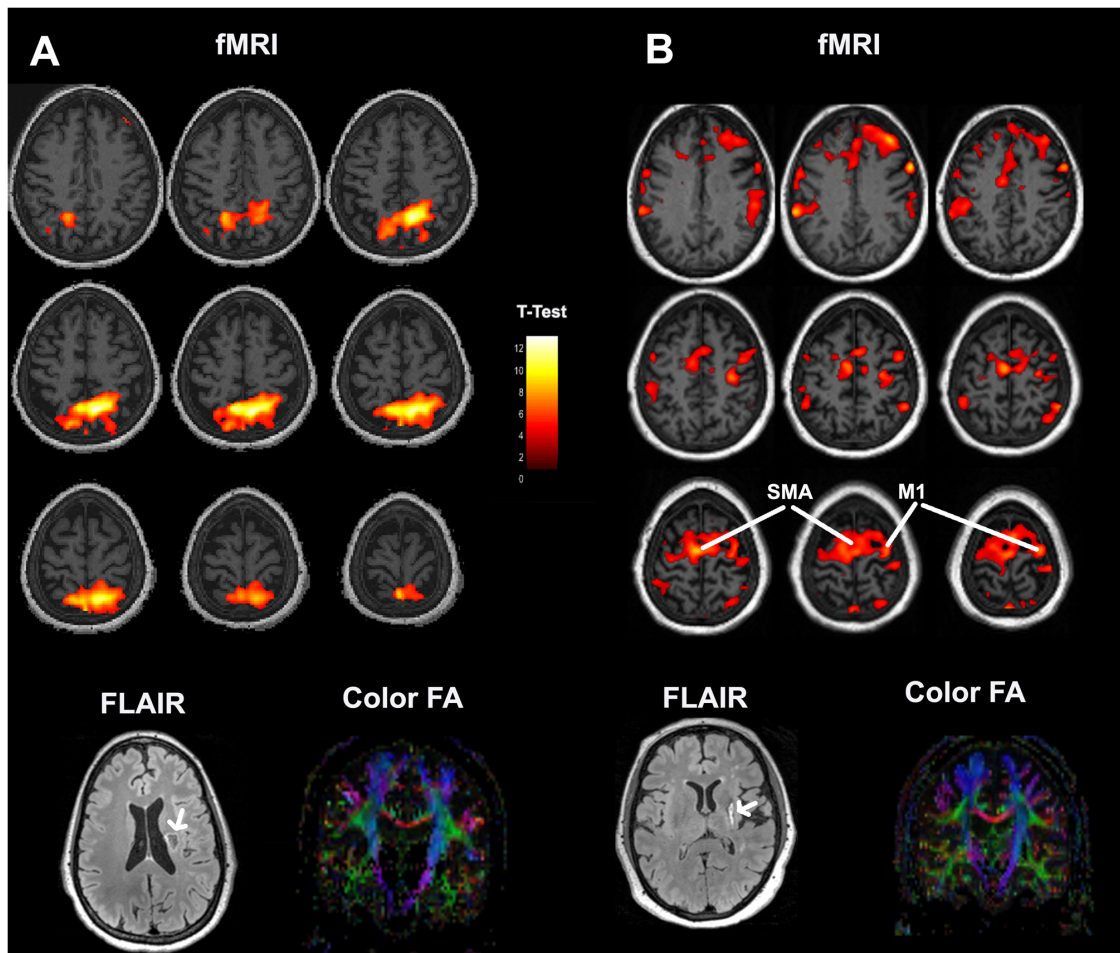


Figure 2. Representative baseline imaging findings in (A) patient no. 14 of Table I without post-rehabilitation motor improvement and (B) patient no 13 with post-rehabilitation motor improvement. FLAIR images reveal the site and extent of the stroke lesions (white arrow). Axial T1-weighted imaging have superimposed fMRI statistical parametric SPM(T) color maps depicting brain activation. Note the difference between the focal bilateral hyper activation posterior to the M1 (A) and the dispersed mild activation pattern including normal activation of the SMA and M1 in (B). In both cases, FA mapping reveals preserved corticospinal tract integrity at the left lesioned hemisphere, though the measured mean FA value of 0.44 in (A) lies at the lower end of the normal reference range (0.44-0.64) compared to the FA of 0.53 in (B). fMRI, functional MRI; FA, Fractional Anisotropy; FLAIR, fluid attenuation inversion recovery; SMA, supplementary motor area; M1, primary motor cortex.

recovery, as evidenced by the model's ability to accurately estimate both static and dynamic aspects of upper extremity function.

Discussion

The present study demonstrated that although motor performance improvement is feasible in patients with chronic stroke, it is not universally achievable. Among the 14 participants, only three attained clinically meaningful gains in the FMA-UE scale, whilst two showed improvements in gross dexterity (BBT) and seven in grip strength (Force). This variability in outcomes aligns with prior evidence suggesting that chronic stroke recovery is contingent on the interplay among residual brain plasticity, lesion characteristics, and rehabilitation intensity (4,38,39).

The motor scales used capture distinct facets of recovery, each associated with specific neural parameters. The FMA-UE, which evaluates sensorimotor coordination and selective movement, primarily reflects the integrity of the ipsilesional corticospinal tract and functional reorganization within the

primary motor and premotor cortices (40-42). These regions are critical for precision and voluntary control. By contrast, the BBT, assessing gross manual dexterity and speed, mainly engages cerebellar-thalamocortical circuits and bilateral premotor areas, which support rhythmic, goal-directed movements (43). Finally, grip strength (Force), a measure of maximal voluntary contraction, relies heavily on corticospinal tract integrity and motor unit recruitment, which is primarily modulated by the M1 and spinal cord pathways (41,44). These theoretical distinctions highlight why the detected recovery trajectories diverged across scales, since each metric taps into unique neuroanatomical and functional systems.

The observed lateralization patterns in motor assessment analysis suggest the task-specific recruitment of motor networks during the chronic stroke phase. The preservation of ipsilesional left M1 and cerebellar activation in FMA-UE aligns with functional reorganization within the spared peri-lesional circuits, a hallmark of successful motor recovery (45,46). Conversely, the negative relationship between contralesional PMv/M1 activation and BBT or Force may reflect inefficient recruitment of non-primary motor regions, consistent

Table II. Generalized linear mixed model results for motor function outcomes: Associations with age, sex, session progression (ordinal variable with values 1-5) and imaging measurements.

A, Fugl-Meyer assessment for upper extremity			
Parameter	B	SE	P-value
Session=1	49.85	35.69	0.166
Session=2	49.90	35.89	0.168
Session=3	51.55	35.79	0.153
Session=4	51.42	35.76	0.154
Session=5	50.89	35.67	0.157
Resistive level=60%	-0.26	0.29	0.370
Resistive level=20%	-0.40	0.24	0.102
Sex=Female	8.54	1.11	<0.001
Age, years	0.09	0.12	0.452
Max_Cer_L	-0.41	0.24	0.090
Size_Cer_L	-3.32x10 ⁻⁴	9.35x10 ⁻⁵	0.001
Mean_Cer_L	4.03	0.84	<0.001
Max_M1_L	1.19	0.16	<0.001
Size_M1_L, (8 mm ³)	-1.61x10 ⁻³	8.47x10 ⁻⁴	0.061
Mean_M1_L	-1.32	0.77	0.089
Max_PMv_L	-0.91	0.26	0.001
Size_PMv_L, (8 mm ³)	9.76x10 ⁻⁵	3.13x10 ⁻⁴	0.756
Mean_PMv_L	0.28	0.29	0.339
Max_PMd_L	0.07	0.17	0.670
Size_PMd_L, (8 mm ³)	8.06x10 ⁻⁴	4.24x10 ⁻⁴	0.060
Mean_PMd_L	-1.70	0.74	0.023
Max_S1_L	-0.54	0.21	0.014
Size_S1_L, (8 mm ³)	2.65x10 ⁻³	9.14x10 ⁻⁴	0.005
Mean_S1_L	-0.76	0.47	0.108
Max_SMA_L	0.86	0.31	0.006
Size_SMA_L, (8 mm ³)	-3.38x10 ⁻³	7.32x10 ⁻⁴	<0.001
Mean_SMA_L	3.38	0.91	<0.001
Max_Cer_R	0.27	0.26	0.298
Size_Cer_R, (8 mm ³)	2.75x10 ⁻⁴	1.20x10 ⁻⁴	0.024
Mean_Cer_R	-2.13	1.06	0.046
Max_M1_R	-0.06	0.28	0.826
Size_M1_R, (8 mm ³)	-3.82x10 ⁻⁴	3.02x10 ⁻⁴	0.208
Mean_M1_R	1.35	0.67	0.046
Max_PMv_R	0.75	0.39	0.062
Size_PMv_R, (8 mm ³)	-8.89x10 ⁻⁶	4.90x10 ⁻⁴	0.986
Mean_PMv_R	-3.27	1.19	0.007
Max_PMd_R	0.23	0.30	0.432
Size_PMd_R, (8 mm ³)	-8.43x10 ⁻⁴	4.94x10 ⁻⁴	0.091
Mean_PMd_R	1.50	1.01	0.141
Max_S1_R	0.32	0.23	0.169
Size_S1_R, (8 mm ³)	5.63x10 ⁻⁴	4.34x10 ⁻⁴	0.198
Mean_S1_R	-0.30	0.45	0.503
Max_SMA_R	-1.79	0.33	<0.001
Size_SMA_R, (8 mm ³)	2.50x10 ⁻³	6.12x10 ⁻⁴	<0.001
Mean_SMA_R	0.06	0.52	0.907
FA Corticospinal tract	34.88	5.50	<0.001
FA Cerebral peduncle	0.68	9.15	0.941
FA Posterior limb of internal capsule	133.10	13.05	<0.001

Table II. Continued.

A, Fugl-Meyer assessment for upper extremity			
Parameter	B	SE	P-value
FA Posterior corona radiata	-283.94	37.85	<0.001
MD Corticospinal tract (10 ⁻⁶ mm ² /s)	-57,624.69	8909.14	<0.001
MD Cerebral peduncle (10 ⁻⁶ mm ² /s)	1,850.91	20582.64	0.929
MD Posterior limb of internal capsule (10 ⁻⁶ mm ² /s)	89,988.54	21056.94	<0.001
MD Posterior corona radiata (10 ⁻⁶ mm ² /s)	-52,670.76	26162.98	0.047
B, Box and block test			
Parameter	B	SE	P-value
Session=1	665.00	73.44	<0.001
Session=2	665.97	74.01	<0.001
Session=3	669.93	73.86	<0.001
Session=4	669.98	73.86	<0.001
Session=5	672.63	73.79	<0.001
Force=60%	0.22	0.50	0.665
Force=20%	0.54	0.51	0.290
Sex=Female	29.01	2.26	<0.001
Age, years	-1.98	0.25	<0.001
Max_Cer_L	-1.17	0.50	0.021
Size_Cer_L, (8 mm ³)	3.3x10 ⁻⁵	2.04x10 ⁻⁶	0.872
Mean_Cer_L	2.46	1.91	0.200
Max_M1_L	0.06	0.35	0.857
Size_M1_L, (8 mm ³)	-2.15x10 ⁻³	1.60x10 ⁻³	0.183
Mean_M1_L	7.57	1.93	<0.001
Max_PMv_L	-0.29	0.53	0.580
Size_PMv_L, (8 mm ³)	-9.77x10 ⁻⁴	8.26x10 ⁻⁴	0.240
Mean_PMv_L	0.11	0.73	0.875
Max_PMd_L	0.60	0.36	0.103
Size_PMd_L, (8 mm ³)	1.04x10 ⁻³	1.13x10 ⁻³	0.358
Mean_PMd_L	-8.52	1.48	<0.001
Max_S1_L	-0.69	0.46	0.133
Size_S1_L, (8 mm ³)	2.97x10 ⁻³	1.89x10 ⁻³	0.120
Mean_S1_L	-2.52	0.95	0.009
Max_SMA_L	-0.51	0.66	0.447
Size_SMA_L, (8 mm ³)	-4.60x10 ⁻³	1.69x10 ⁻³	0.008
Mean_SMA_L	7.16	1.88	<0.001
Max_Cer_R	-0.23	0.57	0.692
Size_Cer_R, (8 mm ³)	-1.10x10 ⁻⁴	2.76x10 ⁻⁴	0.692
Mean_Cer_R	1.65	2.45	0.503
Max_M1_R	-3.16	0.54	<0.001
Size_M1_R, (8 mm ³)	5.41x10 ⁻⁴	8.65x10 ⁻⁴	0.533
Mean_M1_R	-2.07	1.72	0.232
Max_PMv_R	-2.89	0.72	<0.001
Size_PMv_R, (8 mm ³)	-4.97x10 ⁻⁴	9.98x10 ⁻⁴	0.619
Mean_PMv_R	-0.76	2.63	0.774

Table II. Continued.

B, Box and block test			
Parameter	B	SE	P-value
Max_PMd_R	2.66	0.49	<0.001
Size_PMd_R, (8 mm ³)	5.97x10 ⁻⁴	1.25x10 ⁻³	0.634
Mean_PMd_R	-3.37	2.32	0.149
Max_S1_R	0.79	0.50	0.113
Size_S1_R, (8 mm ³)	-5.65x10 ⁻⁴	1.04x10 ⁻³	0.589
Mean_S1_R	3.38	1.12	0.003
Max_SMA_R	-0.15	0.68	0.827
Size_SMA_R, (8 mm ³)	3.16x10 ⁻³	1.45x10 ⁻³	0.031
Mean_SMA_R	0.64	1.34	0.636
FA Corticospinal tract	-20.01	11.20	0.077
FA Cerebral peduncle	203.93	19.31	<0.001
FA Posterior limb of internal capsule	493.18	26.26	<0.001
FA Posterior corona radiata	-1,409.10	76.95	<0.001
MD Corticospinal tract (10 ⁻⁶ mm ² /s)	-25,075.34	18,703.06	0.183
MD Cerebral peduncle (10 ⁻⁶ mm ² /s)	-322,732.16	42,539.39	<0.001
MD Posterior limb of internal capsule (10 ⁻⁶ mm ² /s)	551,343.22	41,706.80	<0.001
MD Posterior corona radiata (10 ⁻⁶ mm ² /s)	-567,911.91	52,335.33	<0.001
C, Force			
Parameter	B	SE	P-value
Session=1	400.67	110.93	<0.001
Session=2	405.02	111.68	<0.001
Session=3	403.23	111.31	<0.001
Session=4	407.88	111.42	<0.001
Session=5	407.23	111.39	<0.001
Force=60%	0.51	0.54	0.348
Force=20%	0.42	0.60	0.484
Sex=Female	-26.43	3.81	<0.001
Age, years	-0.88	0.40	0.031
Max_Cer_L	0.39	0.47	0.412
Size_Cer_L, (8 mm ³)	-4.16x10 ⁻⁴	2.43x10 ⁻⁴	0.090
Mean_Cer_L	-6.50	2.02	0.002
Max_M1_L	-0.91	0.48	0.060
Size_M1_L, (8 mm ³)	-4.93x10 ⁻³	1.73x10 ⁻³	0.005
Mean_M1_L	8.65	2.04	<0.001
Max_PMv_L	-1.14	0.62	0.068
Size_PMv_L, (8 mm ³)	3.15x10 ⁻³	1.50x10 ⁻³	0.039
Mean_PMv_L	1.59	1.32	0.229
Max_PMd_L	1.93	0.48	<0.001
Size_PMd_L, (8 mm ³)	-3.42x10 ⁻³	1.58x10 ⁻³	0.033
Mean_PMd_L	-11.84	2.18	<0.001
Max_S1_L	-1.64	0.61	0.009
Size_S1_L, (8 mm ³)	3.16x10 ⁻³	2.30x10 ⁻³	0.172

Table II. Continued.

C, Force			
Parameter	B	SE	P-value
Mean_S1_L	-0.05	1.16	0.967
Max_SMA_L	0.36	0.97	0.710
Size_SMA_L, (8 mm ³)	1.10x10 ⁻³	2.51x10 ⁻³	0.663
Mean_SMA_L	10.73	1.88	<0.001
Max_Cer_R	0.45	0.85	0.596
Size_Cer_R, (8 mm ³)	3.19x10 ⁻⁴	3.14x10 ⁻⁴	0.312
Mean_Cer_R	6.85	3.11	0.030
Max_M1_R	-5.64	0.74	<0.001
Size_M1_R, (8 mm ³)	2.79x10 ⁻⁴	9.01x10 ⁻⁴	0.757
Mean_M1_R	-0.40	2.06	0.848
Max_PMv_R	-3.05	0.84	<0.001
Size_PMv_R, (8 mm ³)	-2.90x10 ⁻³	1.20x10 ⁻³	0.018
Mean_PMv_R	1.99	3.20	0.536
Max_PMd_R	3.35	0.70	<0.001
Size_PMd_R, (8 mm ³)	1.26x10 ⁻³	1.49x10 ⁻³	0.397
Mean_PMd_R	-3.81	3.18	0.234
Max_S1_R	1.79	0.75	0.018
Size_S1_R, (8 mm ³)	-1.33x10 ⁻³	1.10x10 ⁻³	0.233
Mean_S1_R	3.28	1.23	0.009
Max_SMA_R	-2.22	0.88	0.013
Size_SMA_R, (8 mm ³)	0.01	1.73x10 ⁻³	0.004
Mean_SMA_R	-0.46	1.10	0.677
FA Corticospinal tract	-55.34	17.05	0.002
FA Cerebral peduncle	-97.80	36.37	0.008
FA Posterior limb of internal capsule	172.38	34.05	<0.001
FA Posterior corona radiata	-256.99	122.14	0.038
MD Corticospinal tract (10 ⁻⁶ mm ² /s)	21,981.23	28,434.79	0.441
MD Cerebral peduncle (10 ⁻⁶ mm ² /s)	63,281.49	72,490.82	0.385
MD Posterior limb of internal capsule (10 ⁻⁶ mm ² /s)	-24,991.11	74,130.48	0.737
MD Posterior corona radiata (10 ⁻⁶ mm ² /s)	-284,152.48	81,310.86	0.001

L, left; R, right; Cer_L/R, cerebellar left/right hemisphere; M1_L/R, primary motor cortex left/right hemisphere; PMv_L/R, ventral premotor cortex left/right hemisphere; PMd_L/R, dorsal premotor cortex left/right hemisphere; S1_L/R, primary sensory cortex left/right hemisphere; SMA_L/R, supplementary motor area left/right hemisphere; max, maximum activation; size, cluster size; mean, average activation; B, regression coefficient; SE, standard error; FA, fractional anisotropy; MD, mean diffusivity.

with previous studies finding maladaptive overactivation in contralesional areas during simple motor tasks (47-49). The divergent positive association of PMd with both BBT and Force may point to a region that, when appropriately engaged, supports motor function. These results emphasize that not all

Table III. Results of generalized linear mixed model analysis: Rehabilitation induced motor scores' changes predicted by demographics and imaging measurements from the first two sessions (session values 1 and 2).

A, Δ (Fugl-Meyer assessment for upper extremity)			
Parameter	B	SE	P-value
Session=1	-8.34	28.98	0.777
Session=2	-9.18	28.84	0.754
Resistive level=60%	-0.11	0.33	0.753
Resistive level=40%	0.16	0.15	0.281
Sex=Female	-9.71	2.24	<0.001
Age, years	0.26	0.11	0.026
Max_Cer_L	-0.87	0.3	0.009
Size_Cer_L, (8 mm ³)	1.31x10 ⁻⁴	2.41x10 ⁻⁴	0.595
Mean_Cer_L	-0.3	1.24	0.812
Max_M1_L	0.67	0.19	0.002
Size_M1_L, (8 mm ³)	2.81x10 ⁻³	6.62x10 ⁻⁴	0.001
Mean_M1_L	-3.44	0.84	0.001
Max_PMv_L	0.14	0.38	0.721
Size_PMv_L, (8 mm ³)	2.89x10 ⁻⁴	3.84x10 ⁻⁴	0.462
Mean_PMv_L	2.95	1.05	0.012
Max_PMd_L	-0.13	0.36	0.724
Size_PMd_L, (8 mm ³)	-1.04x10 ⁻⁴	5.27x10 ⁻⁴	0.846
Mean_PMd_L	-2.18	0.76	0.01
Max_S1_L	-0.15	0.32	0.644
Size_S1_L, (8 mm ³)	-2.32x10 ⁻³	9.75x10 ⁻⁴	0.029
Mean_S1_L	2.27	0.89	0.021
Max_SMA_L	-1.46	0.67	0.044
Size_SMA_L, (8 mm ³)	-1.02x10 ⁻³	5.59x10 ⁻⁴	0.086
Mean_SMA_L	-2.84	0.86	0.004
Max_Cer_R	0.85	0.31	0.016
Size_Cer_R, (8 mm ³)	-2.37x10 ⁻⁴	1.55x10 ⁻⁴	0.145
Mean_Cer_R	1.45	0.76	0.073
Max_M1_R	0.07	0.25	0.77
Size_M1_R, (8 mm ³)	1.59x10 ⁻⁴	4.84x10 ⁻⁴	0.747
Mean_M1_R	0.22	0.43	0.611
Max_PMv_R	-0.81	0.31	0.019
Size_PMv_R, (8 mm ³)	9.32x10 ⁻⁴	5.03x10 ⁻⁴	0.081
Mean_PMv_R	-0.66	1.16	0.579
Max_PMd_R	-0.78	0.4	0.066
Size_PMd_R, (8 mm ³)	-1.37x10 ⁻³	5.87x10 ⁻⁴	0.032
Mean_PMd_R	3.43	0.7	<0.001
Max_S1_R	0.18	0.2	0.383
Size_S1_R, (8 mm ³)	1.98x10 ⁻⁴	6.88x10 ⁻⁴	0.777
Mean_S1_R	-0.51	0.76	0.514
Max_SMA_R	0.77	0.27	0.011
Size_SMA_R, (8 mm ³)	-9.67x10 ⁻⁴	6.21x10 ⁻⁴	0.138
Mean_SMA_R	5.27	1.05	<0.001
FA Corticospinal tract	0.35	2.92	0.906
FA Cerebral peduncle	-57.84	13.54	0.001
FA Posterior limb of internal capsule	-102.86	24	<0.001
FA Posterior corona radiate	164.28	42.06	0.001

Table III. Continued.

A, Δ (Fugl-Meyer assessment for upper extremity)			
Parameter	B	SE	P-value
MD Corticospinal tract (10 ⁻⁶ mm ² /s)	5,347.84	6,443.77	0.418
MD Cerebral peduncle (10 ⁻⁶ mm ² /s)	83,833.91	21,245.93	0.001
MD Posterior limb of internal capsule (10 ⁻⁶ mm ² /s)	-132,136.83	26,796.45	<0.001
MD Posterior corona radiata (10 ⁻⁶ mm ² /s)	67,404.04	20,132.5	0.004
B, Δ (Box and block test)			
Parameter	B	SE	P-value
Session=1	548.91	132.81	0.001
Session=2	547.51	132.31	0.001
Force=60%	-0.2	1.32	0.879
Force=40%	0.29	0.96	0.766
Sex=female	15.45	6.66	0.033
Age, years	-3.07	0.57	<0.001
Max_Cer_L	0.66	0.81	0.43
Size_Cer_L, (8 mm ³)	-4.33x10 ⁻⁴	6.72x10 ⁻⁴	0.528
Mean_Cer_L	0.84	4.14	0.841
Max_M1_L	-1.24	0.71	0.1
Size_M1_L, (8 mm ³)	-1.54x10 ⁻³	2.38x10 ⁻³	0.526
Mean_M1_L	4.82	2.66	0.087
Max_PMv_L	2.58	1.31	0.066
Size_PMv_L, (8 mm ³)	-3.63x10 ⁻³	1.69x10 ⁻³	0.046
Mean_PMv_L	-3.85	3.17	0.242
Max_PMd_L	1.11	1.35	0.421
Size_PMd_L, (8 mm ³)	-1.53x10 ⁻³	1.67x10 ⁻³	0.373
Mean_PMd_L	0.77	2.43	0.754
Max_S1_L	0.12	0.92	0.899
Size_S1_L, (8 mm ³)	0.02	4.47x10 ⁻³	0.002
Mean_S1_L	-4.61	3.55	0.212
Max_SMA_L	-0.99	1.63	0.552
Size_SMA_L, (8 mm ³)	-9.01x10 ⁻⁴	2.14x10 ⁻³	0.679
Mean_SMA_L	0.81	4.1	0.846
Max_Cer_R	-0.36	1.29	0.787
Size_Cer_R, (8 mm ³)	3.71x10 ⁻⁴	4.98x10 ⁻⁴	0.466
Mean_Cer_R	-3.68	2.61	0.176
Max_M1_R	-0.17	0.89	0.849
Size_M1_R, (8 mm ³)	-1.84x10 ⁻⁴	1.26x10 ⁻³	0.885
Mean_M1_R	2.41	2.65	0.376
Max_PMv_R	0.99	1.12	0.387
Size_PMv_R, (8 mm ³)	3.96x10 ⁻³	1.93x10 ⁻³	0.056
Mean_PMv_R	2.03	2.61	0.448
Max_PMd_R	-0.42	1.33	0.754
Size_PMd_R, (8 mm ³)	4.39x10 ⁻³	1.70x10 ⁻³	0.019
Mean_PMd_R	-1.56	3.02	0.613
Max_S1_R	1.96	0.51	0.001

Table III. Continued.

B, Δ(Box and block test)			
Parameter	B	SE	P-value
Size_S1_R, (8 mm ³)	-3.98x10 ⁻³	1.95x10 ⁻³	0.057
Mean_S1_R	-4.82	2.95	0.121
Max_SMA_R	-0.76	1	0.456
Size_SMA_R, (8 mm ³)	-1.98x10 ⁻³	2.13x10 ⁻³	0.366
Mean_SMA_R	-2.68	3.71	0.48
FA Corticospinal tract	-73.6	16.25	<0.001
FA Cerebral peduncle	230.56	42.29	<0.001
FA Posterior limb of internal capsule	137.27	60.69	0.037
FA Posterior corona radiate	-556.04	126.08	<0.001
MD Corticospinal tract (10 ⁻⁶ mm ² /s)	145,126.61	32,423.39	<0.001
MD Cerebral peduncle (10 ⁻⁶ mm ² /s)	-494,726.62	87,353.51	<0.001
MD Posterior limb of internal capsule (10 ⁻⁶ mm ² /s)	485,377.99	89,218.61	<0.001
MD Posterior corona radiata (10 ⁻⁶ mm ² /s)	-461,455.03	87,259.39	<0.001

C, Δ(Force)

Parameter	B	SE	P-value
Session=1	690.63	118.59	<0.001
Session=2	686.6	118.22	<0.001
Resistive level=60%	1.58	1.04	0.145
Resistive level=40%	1.76	0.93	0.075
Sex=female	-29.42	5.52	<0.001
Age, years	-2.16	0.55	0.001
Max_Cer_L	0.72	1.12	0.526
Size_Cer_L, (8 mm ³)	1.15x10 ⁻³	7.90x10 ⁻⁴	0.164
Mean_Cer_L	-23.16	5.08	<0.001
Max_M1_L	1.11	0.96	0.263
Size_M1_L, (8 mm ³)	4.13x10 ⁻³	2.51x10 ⁻³	0.118
Mean_M1_L	-7.19	3.84	0.079
Max_PMv_L	4.61	1.45	0.006
Size_PMv_L, (8 mm ³)	1.51x10 ⁻⁴	2.45x10 ⁻³	0.952
Mean_PMv_L	1.46	3.6	0.69
Max_PMd_L	-1.47	1.63	0.381
Size_PMd_L, (8 mm ³)	-3.85x10 ⁻³	2.45x10 ⁻³	0.135
Mean_PMd_L	-2.6	2.65	0.339
Max_S1_L	-1.44	1.2	0.246
Size_S1_L, (8 mm ³)	2.96x10 ⁻³	4.81x10 ⁻³	0.546
Mean_S1_L	6.97	4.18	0.114
Max_SMA_L	-3.08	2.39	0.214
Size_SMA_L, (8 mm ³)	2.57x10 ⁻³	2.32x10 ⁻³	0.283
Mean_SMA_L	-0.54	4.26	0.901
Max_Cer_R	1.9	1.61	0.254
Size_Cer_R, (8 mm ³)	-5.92x10 ⁻⁴	6.65x10 ⁻⁴	0.386
Mean_Cer_R	10.64	2.86	0.002

Table III. Continued.

C, Δ(Force)			
Parameter	B	SE	P-value
Max_M1_R	0.39	1.17	0.746
Size_M1_R, (8 mm ³)	-6.09x10 ⁻⁴	1.29x10 ⁻³	0.644
Mean_M1_R	7.67	2.6	0.009
Max_PMv_R	0.37	1.47	0.803
Size_PMv_R, (8 mm ³)	5.82x10 ⁻³	2.52x10 ⁻³	0.034
Mean_PMv_R	0.81	4.06	0.845
Max_PMd_R	-0.85	1.23	0.503
Size_PMd_R, (8 mm ³)	0.01	2.00x10 ⁻³	0.014
Mean_PMd_R	-0.69	3.73	0.855
Max_S1_R	-0.56	0.69	0.428
Size_S1_R, (8 mm ³)	-1.41x10 ⁻³	3.23x10 ⁻³	0.669
Mean_S1_R	-8.28	4.18	0.064
Max_SMA_R	0.71	1.22	0.572
Size_SMA_R, (8 mm ³)	-6.46x10 ⁻³	2.88x10 ⁻³	0.038
Mean_SMA_R	0.98	3.81	0.8
FA Corticospinal tract	27.6	20.53	0.196
FA Cerebral peduncle	5.48	61.34	0.93
FA Posterior limb of internal capsule	-334.48	58.89	<0.001
FA Posterior corona radiata	-182.63	121.68	0.152
MD Corticospinal tract (10 ⁻⁶ mm ² /s)	105,826.78	37,490.28	0.012
MD Cerebral peduncle (10 ⁻⁶ mm ² /s)	-173259.08	106,242.82	0.121
MD Posterior limb of internal capsule (10 ⁻⁶ mm ² /s)	34,301.53	110,648.92	0.76
MD Posterior corona radiata (10 ⁻⁶ mm ² /s)	-279,777.8	84,242.02	0.004

L, left; R, right; Cer_L/R, cerebellar left/right hemisphere; M1_L/R, primary motor cortex left/right hemisphere; PMv_L/R, ventral premotor cortex left/right hemisphere; PMd_L/R, dorsal premotor cortex left/right hemisphere; S1_L/R, primary sensory cortex left/right hemisphere; SMA_L/R, supplementary motor area left/right hemisphere; max, maximum activation; size, cluster size; mean, average activation; B, regression coefficient; SE, standard error; FA, fractional anisotropy; MD, mean diffusivity.

contralesional activations are equal, whereby the functional role of a region (such as planning compared with execution) is key to understanding its impact on motor performance.

Cluster size associations further illuminate neural efficiency mechanisms. Smaller, focused activations in ipsilesional SMA and M1 were found to be associated with superior FMA-UE and Force, suggesting that functional recovery relies on streamlined, instead of diffuse, engagement of primary motor regions. Ward *et al* (50) previously demonstrated that motor recovery was correlated with renormalization of activity toward ipsilesional M1 and reduced diffuse recruitment of non-primary regions, suggesting a shift from compensatory to more efficient processing. By contrast, larger clusters in

Table IV. Comparison of model fit across motor assessments using -2 log likelihood values.

Motor	Fugl-Meyer assessment for upper extremity	Box and blocks test	Force
Assessment model	652.998	790.758	880.792
Prediction model	210.889	251.080	257.632

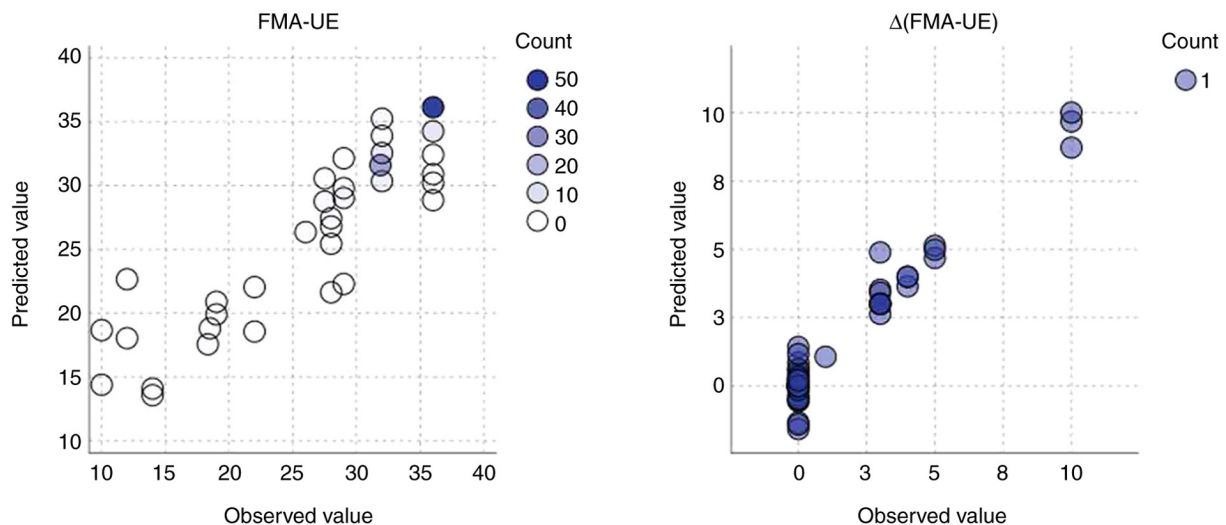


Figure 3. Circular scatter plots comparing observed values with generalized linear mixed model-predicted FMA-UE and $\Delta(\text{FMA-UE})$ values. Circle color (counts) reflect the number of overlapping data points at that location (i.e., the frequency of identical value pairs). FMA-UE, Fugl-Meyer assessment upper extremity.

the ipsilesional Cer and contralesional SMA were associated with poorer performance, potentially reflecting compensatory efforts or reduced network specificity. Consistent with the present findings, previous studies also noted that cerebellar overactivation may reflect attempts to compensate for impaired corticocortical or corticostriatal connectivity (50-53), whilst contralesional SMA hyperactivity was associated with poor motor outcomes in patients with chronic stroke (54). By contrast, the positive role of ipsilesional SMA suggests activation across motor scales underscores its importance in motor planning and execution, corroborating its known involvement in internally guided movements (55,56).

Diffusion metric findings highlight structural underpinnings of these functional patterns. Higher FA in corticospinal tracts and posterior limb of the internal capsule, markers of white matter integrity, likely facilitate efficient signal transmission, supporting motor performance (57). However, increased FA in posterior corona radiata, a region integrating sensorimotor fibers, may disrupt feedback loops critical for motor control or it could reflect maladaptive tissue reorganization, such as gliosis scarring (58). These results extend current models, by integrating functional reorganization with structural connectivity, proposing that both focused ipsilesional activation and preserved white matter integrity are pivotal for optimal motor function.

The overall pattern of associations underscores the importance of lateralized, focused recruitment within the ipsilesional hemisphere for achieving improvements in upper-limb function. Positive association of left M1 with $\Delta(\text{FMA-UE})$

suggest that re-engagement of the primary motor area on the stroke-affected side can facilitate fine motor control, consistent with motor assessment evidence that normalization of ipsilesional activity is beneficial (59). In addition, the mixture of positive and negative associations within ipsilesional premotor and sensory cortices indicates that excessive or diffuse engagement of these secondary areas may not always be adaptive. These findings collectively suggest that whilst SMA overactivation may reflect inefficient compensation, as previously observed in studies linking diffuse recruitment during poorly performed tasks to maladaptive neural resource allocation (60,61), PMv engagement represents a more targeted adaptive mechanism for motor recovery. This aligns with its role in higher-order motor planning and bilateral coordination, demonstrated in previous studies where preserved PMv activity supported grasp posture encoding and compensated for compromised primary motor pathways (62).

Contralesional recruitment emerged as variably supportive. Although positive association in the right PMd aligned with prior reports of an ancillary contribution from premotor regions in the unaffected hemisphere (63,64), negative association in right PMv and positive ones in right SMA suggest that each contralesional region may differentially influence distinct facets of motor recovery. The fact that right somatosensory cortex activation is positively associated with changes in gross dexterity suggests that contralesional sensory processing can aid performance when ipsilesional pathways are compromised, but such recruitment may be less crucial for fine motor tasks (65,66).

White matter diffusion metrics corroborated these aforementioned functional observations, showing that the structural integrity of critical descending pathways (corticospinal tract, internal capsule) may have different impact on fine compared with gross motor recovery. Negative associations of FA in the cerebral peduncle and posterior limb of the internal capsule with $\Delta(\text{FMA-UE})$, and a negative association of FA in the posterior limb of the internal capsule with $\Delta(\text{Force})$, but positive ones for $\Delta(\text{BBT})$, suggest that microstructural reorganization in these tracts may support certain compensatory strategies (such as improved motor speed or gross upper-limb function) at the expense of refined upper-limb coordination (67). By contrast, the positive association of FA in the posterior corona radiata with $\Delta(\text{FMA-UE})$, a measure of fine motor recovery, suggests that diffuse connectivity changes in this region may selectively enhance sensorimotor integration, which is critical for tasks requiring refined coordination (including finger individuation or selective movement) (68). This aligns with the posterior corona radiata's role in integrating corticopontine and associative fibers that facilitate cross-modal connectivity between sensory feedback and motor planning (69). However, the negative associations of posterior corona radiata FA with $\Delta(\text{BBT})$ and $\Delta(\text{Force})$, which are measures of gross dexterity and strength, indicate that diffuse reorganization here may divert resources from task-specific corticospinal pathways, which are more directly involved in force generation and rhythmic movements (70). Therefore, the inverse associations of FA in the posterior corona radiata with $\Delta(\text{FMA-UE})$ compared with $\Delta(\text{BBT})$ may seem contradictory. However, this likely reflects the dual role of this region in integrating sensory and motor signals. Higher FA in this area may facilitate fine motor coordination (such as finger individuation), supporting improvements in FMA-UE, whilst potentially disrupting the streamlined corticospinal output necessary for gross dexterity tasks, such as the BBT. These findings underscore the importance of interpreting diffusion metrics within the specific motor domains they influence.

Taken together, these findings highlight a dynamic interplay between lateralized, focused activation of ipsilesional motor regions and selective recruitment of contralesional premotor and sensory areas, all modulated by the structural state of relevant white matter tracts. Although contralesional engagement can provide some compensatory support, particularly in sensory processing or force production, sustained gains in upper-limb function appear most strongly associated with ipsilesional reactivation. Future rehabilitation strategies may therefore focus on facilitating the targeted activation of ipsilesional M1 and optimizing microstructural integrity in key motor pathways, whilst also tailoring contralesional involvement to each patient's specific deficit profile.

The present study has limitations that warrant consideration. The small sample size limited statistical power and generalizability, particularly for outcomes, such as grip strength, where only a few patients demonstrated measurable improvements. However, the use of GLMM enhanced statistical robustness by accounting for repeated measures and within-subject variability. By excluding individuals with significant cognitive or sensory impairments, where conditions that can affect $\leq 50\%$ of chronic stroke survivors and frequently co-occur with motor deficits, the present cohort does not fully represent the broader stroke

population observed in clinical practice. Future trials should include participants with mild to moderate sensory and cognitive comorbidities to assess the generalizability of the present neuroimaging biomarkers in real-world settings. The present study also focused exclusively on patients with left middle cerebral artery infarcts, which limits the generalizability to other stroke subtypes and lesion locations. Additionally, the observational design and absence of a control group constrain causal inference. Whilst including healthy or mildly impaired controls can introduce ceiling effects and minimal variability, future studies should consider matched chronic stroke control groups receiving standard care as a more appropriate comparator. Finally, neuroimaging data were acquired at a single institution using a specific robotic and imaging protocol, which may limit reproducibility across settings. To address these limitations, future research should recruit larger and more clinically heterogeneous cohorts, encompass diverse lesion sites and functional baselines, whilst integrating peripheral physiological markers (such as electromyography or kinematic analysis) to refine predictive models and enhance applicability.

The present study builds upon prior knowledge by identifying neuroimaging signatures (such as ipsilesional M1 cluster size and posterior corona radiata FA/MD) as potential biomarkers for predicting response to MRI-compatible robotic training, offering a bridge between neuroplasticity theories and device-based rehabilitation outcomes. It refines the understanding of contralesional contributions, revealing region-specific effects (adaptive right PMd compared with maladaptive PMv/M1 activation) that nuance earlier dichotomous interpretations of compensatory mechanisms (47,49,62). By mapping motor scales, such as FMA-UE, BBT and Force, to distinct neural circuits, the present study provides a framework for interpreting heterogeneous recovery patterns, whilst the inverse relationship between posterior corona radiata FA and outcomes challenges assumptions regarding diffuse white matter reorganization. Methodologically, the integration of real-time neuroimaging during robotic training and a predictive GLMM framework offered preliminary tools for patient stratification, distinguishing efficient, focused ipsilesional reorganization from maladaptive compensatory recruitment. Although modest in scale, these findings highlight interactions between structural connectivity and task-specific functional activation, advancing precision in post-stroke rehabilitation targeting. They also indicate that the integration of fMRI and DTI with robotic rehabilitation provides a novel framework for identifying neural correlates and predictors of recovery, emphasizing the potential for personalized therapeutic strategies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MM and LGA analyzed the data and prepared the manuscript. SE selected and trained the patients, collected and curated the data. AAT designed the study. SE and AAT confirm the authenticity of all the raw data. All authors read and approved the final version of this manuscript.

Ethics approval and consent to participate

Institutional review board approval of the study was granted by the Partners Human Research Committee (approval no. 2005P000570) serving Massachusetts General Hospital (Boston, USA) and all participants provided informed consent for participation in the study, including data collection, anonymized data analysis, and publication of the results.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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