Title: Intervention-Induced Changes in Cortical Connectivity and Activity in Severe Chronic Hemiparetic Stroke

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Abstract

Objective: Effective interventions have demonstrated the ability to improve motor function by reengaging ipsilesional resources, which has been shown to be critical and feasible for hand function recovery even in individuals with severe chronic stroke. However, the question remains how these focal activity changes (i.e., changes in activity within motor regions) relate to altered cortico-cortico interactions within/across multiple regions.

Methods: Eight individuals with severe chronic stroke participated in a device-assisted intervention. Pre- and post-intervention, we collected EEG while performing hand opening with/without lifting the paretic arm. We quantified changes in focal cortical activity at movement execution and connectivity during movement preparation.

Results: Post-intervention, individuals displayed a reduction in coupling from ipsilesional M1 to contralesional M1 within gamma frequencies during movement preparation for hand opening. This was followed by a reduction in activity in contralesional primary sensorimotor cortex during movement execution. Meanwhile, during lifting and opening, a more inhibitory coupling within ipsilesional M1 from gamma to beta frequencies was accompanied by an increase in ipsilesional primary sensorimotor cortex activity.

Conclusions: Changes in coupling within or between motor regions during movement preparation complement topographical activity changes at movement execution.

Significance: Our results suggest that changes in cortico-cortico interactions may lead to corresponding changes in focal cortical activity.

Keywords: connectivity, stroke, electroencephalography (EEG), neuroplasticity, dynamic causal modeling (DCM), upper extremity

Abbreviations:

BMS: Bayesian Model Selection

CAR: Cortical Activity Ratio

DCM-IR: Dynamic Causal Modeling for Induced Responses

FMA: Fugl Meyer Assessment

SABD: Shoulder Abduction

UE: Upper Extremity

1. Introduction

Up to 50% of individuals with stroke experience some form of motor impairment in the upper extremity (UE)[1]. This includes deficits in hand control, as well as functional use of the hand in coordination with the rest of the limb. This stroke-induced motor impairment is often associated with changes in brain activity, as demonstrated by changes in both focal (i.e., within-region) cortical activity and network-wide (i.e., between-region) cortico-cortico interactions[2]. Accumulating evidence has demonstrated that effective interventions have the ability to improve functional use of both the hand in isolation and together with the arm[3-6], which has been shown to be accompanied by focal changes in the form of ipsilesional reorganization[7-9]. Presumably, any changes in focal cortical activity would also involve changes on a broader network level. However, the interplay between focal cortical changes and network-wide changes following an intervention have not been investigated, and thus it still remains unknown what changes in network-wide cortico-cortico interactions accompany or lead to the changes in focal activity patterns following an effective intervention.

Stroke-induced changes in focal cortical activity, which is defined here as activity within isolated regions of interest, during hand opening have been widely studied. For instance, individuals with stroke display reduced output from ipsilesional primary motor cortex, which was linked to the impaired hand function[10]. As compensation, individuals demonstrate increased activity not only in ipsilesional secondary motor cortices, but also in contralesional motor cortices, which has been interpreted as an alternative means for generating motor output to spinal cord

motoneurons[11-13]. The compensation pattern tends to align with impairment level, with more mildly impaired individuals usually showing increased activity in neighboring areas that are close to the lesion (i.e., usually involving ipsilesional secondary motor areas) and individuals with more severe impairments usually displaying greater activity in contralesional motor areas[13-16]. Furthermore, the use of contralesional motor areas is not only shown cross-subjects with various impairment, but also demonstrated within-subjects with increased demands of motor control. For example, when lifting against greater loads while reaching, individuals with stroke, especially individuals with more severe impairments, show further increased cortical activity in the contralesional hemisphere[17]. This evidence suggests that stroke does not only cause changes in local activity, but also cortico-cortico connectivity which lead to and are expressed as changes in contralesional cortical activity. Multiple studies taking a network-wide approach have confirmed this by showing that individuals with stroke show altered interhemispheric M1-M1 connectivity and intrahemispheric connectivity within the ipsilesional hemisphere, which correlate with greater motor deficits[2,18-21]. Such changes in cross-hemisphere regions suggest that stroke-induced brain reorganization is not only limited to focal changes, but can also cross different regions, probably via changes in long-distance cortico-cortico communication.

These stroke-induced changes in cortical activity and cortico-cortico communication seem to be reversible. Accumulating evidence has pointed to a return of 'back-to-normal' brain activity as a key to motor recovery[22]. Both spontaneous and effective intervention-induced recovery are associated with increased reliance on the ipsilesional sensorimotor cortex and decreased reliance on the contralesional cortex during movement[7,15]. Furthermore, such increased use of ipsilesional control is critical for motor improvements in individuals with both mild and more severe impairments, especially for hand/arm recovery[8,23]. Similarly, individuals who recover well post-stroke demonstrate a rebalancing of interhemispheric M1-M1 and intrahemispheric connectivity as their deficits improve[18,21], suggesting that changes on a larger network-wide scale also support improved behavior. However, connectivity change following an effective intervention has predominantly involved individuals with mild impairments[24-26]. Additionally, we do not know how these intervention-induced connectivity changes interact with changes in focal activity.

Presumably, cortico-cortico interactions should shape focal activity. For instance, the neural processes that initiate movement are known to begin over 500 ms before the actual movement itself, and involve a combination of activity in both secondary and primary motor regions[27]. In individuals with stroke, upper limb motor-related cortical activity already shows differences even 400 ms before movement onset, with severely impaired individuals demonstrating overlapped regions largely in contralesional motor areas related to different parts of the arm compared to controls[28]. This suggests that changes in cortico-cortico interactions during motor preparation are possibly contributing to the observed abnormal activity present at movement onset post-stroke.

Previously, we demonstrated the feasibility of improving the hand/arm function in individuals with moderate to severe chronic stroke via a device-assisted intervention[29], and eliciting ipsilesional cortical reorganization[8]. In this study, we hypothesized that this reengagement of ipsilesional resources is the result of intervention-induced changes in cortico-cortico interactions during movement preparation that shape changes in focal activity at movement execution. To test this hypothesis, we examined changes in both cortical activity within isolated motor regions at movement execution and dynamic cortical connectivity between motor regions during movement preparation following an effective device-assisted intervention in individuals with severe chronic hemiparetic stroke. Through this combined approach, we could observe how the interactions between regions during movement preparation gave rise to any intervention-induced activity changes. We applied a frequency-based connectivity approach, since regions that synchronize in phase or power at the same frequency (i.e., linear coupling) or across different frequencies (i.e., nonlinear coupling) are considered to be directly or indirectly connected[30,31]. Additionally, the well-established physiological underpinnings of specific frequency bands within the motor system would provide insight into the underlying neural mechanisms that may be shaping cortical activity at movement execution[32-35]. Finally, we examined these changes in relation to both hand opening and hand opening while lifting the arm since effective UE interventions have shown improvements in both hand control and coordination between the shoulder and hand due to a reduced expression of the flexion synergy during functional tasks[36-38].

The EEG-data related to pure hand opening, have been reported before[8]. Here, we re-analyzed these data to further investigate the cortico-cortico interactions. Other data related to hand opening while lifting the arm are original.

2. Methods

2.1 Stroke participants

Eight individuals with chronic hemiparetic stroke (mean age: 63.5±4) with subcortical lesions and severe impairment (UEFMA: 11-24) participated in this study. Participant information and the methods of the intervention have been reported before[8,29]. We re-state this information here to make this paper self-contained. All individuals were screened for inclusion by a licensed physical therapist. Inclusion criteria included a UEFMA between 10 and 30 out of 66, no botulinum toxin within the last 6 months, MRI compatibility, the ability to elicit enough EMG activity at wrist/finger extensors, the ability for the FES to generate a hand opening of at least 4 cm between thumb and index finger, the ability to lift the paretic arm, and the ability to give informed consent. See Table 1 for full demographics. This study was approved by the Northwestern University institutional review board, and all participants gave informed written consent.

Table 1. Participant demographics and clinical characteristics

Participant	Age	Time Since Stroke (yrs)	Affected Hand	Lesion Location	UE FMA	CMSA
P01	64	9	R	IC	23	3
P02	62	8	L	IC, BG	12	3
P03	68	3	L	Par, Occ, IC	17	3
P04	61	22	L	IC, BG, Thal	11	3
P05	61	13	L	Occ, IC	24	3
P06	70	20	R	IC, BG, Thal	13	3
P07	59	6	R	IC, BG	24	3

P08	63	9	R	IC, Thal	22	4

Note: BG=basal ganglia, CMSA=Chedoke-McMaster Stroke Assessment, FMA=Fugl-Meyer Assessment, IC=Internal Capsule, Occ=Occipital Lobe, Par=Parietal Lobe, Thal=Thalamus, UE=Upper Extremity.

2.2 Intervention Design

Individuals took part in a 7-week intervention with 3 sessions per week lasting approximately 2 hours. During each session, individuals completed 20-30 trials of a reach-grasp-retrieve-release task with a jar while seated at a table. A novel EMG-FES device, called ReIn-Hand[39], was used to assist paretic hand opening since these individuals lacked sufficient finger extension ability to complete the task without the stimulation. The novelty of this device is that it can detect hand opening intent and drive the paretic hand open even during lifting and reaching movements that typically increase expression of the flexion synergy at the elbow[36], wrist, and fingers[37,38]. Briefly, this device recorded EMG activity from eight muscles (deltoid, biceps brachii, triceps, extensor communis digitorum, extensor carpi radialis (ECR), flexor digitorum profundus, flexor carpi radialis (FCR), and abductor pollicis), and used EMG features to detect hand opening intent in real-time to trigger an Empi transcutaneous electrical neuro-stimulation device (Vista, CA, USA). The stimulation electrodes were applied to the wrist/finger extensors with the following settings: biphasic symmetrical waveform, frequency = 50 Hz $\pm$ 20%, pulse width = 300 μs, amplitude = sufficient for maximum hand opening without discomfort, and duration = 3 s. The ReIn-Hand device allows for intuitive control since the same muscles the participant is attempting to drive (i.e. finger/wrist extensors) are being used to control the stimulation. All participants could successfully use the device to complete the described task.

2.3 EEG Experiment and Behavioral Task

Participants took part in an EEG experiment within one week prior to and following the intervention. Participants sat in a Biodex chair (Biodex Medical Systems, Shirley, NY) with straps crossing the chest and abdomen to limit potential trunk movements. The participant's paretic arm was placed in a forearm-hand orthosis attached to the end effector of an admittance controlled robotic device (ACT^{3D}) instrumented with a six degree of freedom (DOF) load cell (JR^3 Inc., Woodland, CA). At the beginning of each trial, participants moved their hand to a home position, with the shoulder at 85° abduction, 40° flexion, and the elbow at 90° flexion angle. The participant received an auditory cue once they reached the home position. Following

the cue, the participant relaxed at the home position for 5-7 s and then self-initiated one of 2 movements: 1) maximum paretic hand opening with the arm resting on a haptic table, or 2) maximum paretic hand opening while lifting against 50% of their maximum shoulder abduction (SABD) force. This shoulder abduction level was used since it is roughly equivalent to the weight of the limb in moderate to severe chronic stroke participants, thus making it a functionally relevant shoulder abduction level for translation to many activities of daily living that require simultaneously using the hand while lifting the arm. Participants were instructed to avoid eye movements by focusing on a point and movements of other body parts during the performance of each trial, which was confirmed by electrooculogram (EOG) traces and visual inspection by the experimenter, respectively. Participants performed 60-70 trials of each condition, which were separated into blocks (one block consisted of 20-30 trials of a particular condition). Blocks were randomized to minimize any order effects. Rest periods varied between 15 to 60 seconds between trials and 10 minutes between blocks.

Scalp recordings were made with a 160-channel High Density EEG system using active electrodes (Biosemi, Inc., Active II, Amsterdam, The Netherlands) mounted on a stretchable fabric cap based on a 10/20 system. The impedance was kept below 50 kΩ for the duration of the experiment. Simultaneously, EMGs were recorded from the extensor carpi radialis, flexor carpi radialis, and deltoid of the paretic arm, which were used to detect movement onset for post-processing purposes. All data were sampled at 2048 Hz. Additionally, the positions of EEG electrodes on the participant's scalp were recorded with respect to a coordinate system defined by the nasion and pre-auricular notches using a Polaris Krios handheld scanner and reflective markers (NDI, Ontario, Canada). This allowed for coregistration of EEG electrodes with each participant's anatomical MRI data.

2.4 Structural Imaging of the Brain

Participants participated in MRI scans at Northwestern University's Center for Translation Imaging on a 3 Tesla Siemens Prisma scanner with a 64-channel head coil. Structural T1-weighted scans were acquired using an MP-RAGE sequence (TR=2.3s, TE=2.94ms, FOV=256x256mm^2) producing an isotropic voxel resolution of 1x1x1 mm^3. Visual inspection of

acquired images was performed immediately following the data acquisition to guarantee no artifacts and stable head position.

2.5 Data Analysis for Cortical Topography

EEG data were aligned to the earliest EMG onset of the 3 muscles and segmented from -2200 to +200 ms (with EMG onset at 0 ms) using Brain Vision Analyzer 2 software (Brain Products, Gilching, Germany). Data were then visually inspected for the presence of artifacts. Trials exhibiting artifacts (e.g., eye blinks) were eliminated from further analysis. The remaining EEG trials were baseline-corrected (from -2180 to -2050 ms), low pass filtered at 70 Hz, and ensemble-averaged. The averaged EEG signals were down-sampled to 256 Hz and imported into CURRY 6 (Compumedics Neuroscan Ltd., El Paso, TX). The cortical current density strength ($\mu A/mm^2$) from 150 ms to 100 ms prior to EMG onset was computed using the standardized low-resolution electromagnetic brain tomography (sLORETA) method (Lp = 1) based on a subject-specific boundary element method model with the regulation parameter automatically adjusted to achieve more than 99% variance accounted for. Possible sources were located on a cortical layer with 3 mm distance between each node. Although the inverse calculation was performed over the whole cortex, only the activity in the specific regions of interest (ROIs) was further analyzed. These ROIs included bilateral primary sensorimotor cortices (primary motor cortex (M1) + primary sensory cortex (S1)) and secondary motor cortices (supplementary motor area (SMA) + premotor area (PM)).

We quantified a cortical activation ratio $CAR = \frac{\sum_1^N s_n}{\sum_1^M s_m}$ for each of the 4 ROIs, where s_n represents the current density strength of the nth node, and n and m are the indices of nodes in a specific ROI and the whole sensorimotor cortices, respectively. The cortical activity ratio reflects the relative strength from one ROI as normalized by the total combined strength of the 4 ROIs.

2.6 Statistical Analysis for Cortical Activity

Statistics were performed using SPSS (IBM, V24). A 2 (time) x 2 (task) x 4 (region) repeated measures ANOVA was performed on the cortical activity ratio after checking the data did not violate Mauchly's sphericity test. We performed post-hoc paired t-tests when a main ANOVA

effect or interaction was found. Significance was set a $p < .05$. Individual data are depicted for significant findings.

2.7 Dynamic causal modeling for induced responses

We used dynamic causal modeling for induced responses (DCM-IR)[40] to model the task-related time-varying changes in power both within and across a range of frequencies by estimating the coupling parameters within and between sources in a network. This approach has been used in previous hand movement tasks to elucidate the dynamic interactions within a motor network[41-43].

2.7.1 Definition of model space

Our motor network model consisted of 5 ROIs, including bilateral primary motor cortex (M1), bilateral premotor cortex (PM), and supplementary motor area (SMA). Locations of each of these regions were adapted from the Human Motor Area Template (HMAT)[44] and are shown in Table 2. Bilateral primary sensory cortices were not included to reduce the computational demand and complexity of the model. Bilateral SMAs were treated as a single source due to their mesial position on the cortices. SMA also served as the input to the modelled network. It was chosen due to its critical role in movement preparation during self-initiated motor tasks[45,46], and has previously been demonstrated to be an appropriate input for self-initiated motor tasks using DCM-IR[41-43].

Different within- and cross-frequency connections between these 5 sources were used to create 12 models as shown in Supplementary Figure 1 which have successfully been used before in a similar motor task in healthy controls[41]. These 12 models were separated into 2 groups. Group 1 (models 1 to 6) allowed nonlinear and linear extrinsic (between region), but only linear intrinsic (within region) connections. Group 2 (models 7 to 12) allowed both nonlinear and linear connections for both extrinsic and intrinsic connections. Within each group, the 6 models consisted of 1 fully connected model, and the other 5 models missing 1 or 2 connections that were from one premotor area (PM) to either the other PM or to M1. Using this model, we tested the importance of nonlinear frequency interactions within regions as well as the importance of various connections to premotor regions.

Table 2. Coordinates of motor network

Sources	MNI-Coordinates (X,Y,Z)
Left M1	-37 -26 60
Right M1	37 -26 60
Left PM	-35 -4 60
Right PM	35 -4 60
SMA	-2 -7 60

Note: Coordinates were adapted from Mayka et al., 2006

2.7.2 DCM Preprocessing

EEG data were preprocessed using SPM12 (SPM12, Wellcome Trust Centre for Neuroimaging, www.fil.ion.ucl.ac.uk/spm/) in the same manner, as described in section 2.5, up until trial averaging. Artifact free trials were projected from channel space to the sources using the generalized inverse of the lead-field matrix using an equivalent current dipole for our chosen sources (see below)[40]. The spectrogram from 4 to 48 Hz at each source was computed using a Morlet wavelet transform (wavelet number: 7). This range includes theta (4-7 Hz), alpha (8-12 Hz), beta (13-30 Hz), and gamma (31-48 Hz) frequencies. The spectrogram was then averaged over all trials, cropped between -1000 to 0 ms, and then baseline-corrected by subtracting the frequency-specific power of the first 1/6 samples of the time window (-1000 to -833 ms). The input from SMA to the whole network was modelled as a gamma function with a peak at 400 ms prior to EMG onset with a dispersion of 400 ms. These values were chosen in order to capture the peak of the bereitschaftspotential during a self-initiated movement[27]. The model simulation was restricted to the time leading up to EMG onset (-1000 to 0 ms) to capture purely the motor preparation and command, rather than any potential sensory feedback related to the task. The dimensionality of the spectrogram was then reduced to four modes using singular value decomposition (SVD). The four modes preserved > 96% of the data variance on average. This dimensionality reduction both reduced the computational demand of the model inversion and denoised the data.

2.7.3 Calculation of coupling parameters

For each of the models shown in Supplementary Figure 1, the dynamics of the spectrogram were evaluated using the following equation for each model described above:

$$\tau\dot{g}(t) = \tau\begin{bmatrix}\dot{g}_1\\ \vdots \\ \dot{g}_J\end{bmatrix} = \begin{bmatrix}A_{11} & \dots & A_{1J}\\ \vdots & \ddots & \vdots \\ A_{J1} & \dots & A_{JJ}\end{bmatrix} g(t) + \begin{bmatrix}C_1\\ \vdots \\ C_J\end{bmatrix} u(t),$$

where vectors g and $\dot{g}$ represent the instantaneous power and its first derivative at each of the modes (results of SVD) for each of the sources in the motor network. The A matrix contains the coupling parameters within and across different modes between any 2 regions within the J=5 regions, and the C matrix contains the weights of the extrinsic input u from SMA. Each of the elements in the coupling A matrix refers to the influence of power at a specific frequency in one motor region on the power at another frequency in another region. Positive (i.e. excitatory) or negative (i.e. inhibitory) coupling suggests changes in power in the first frequency and region lead to the same directional or opposite change, respectively, in power in the second frequency and region. τ is a scaling factor and t represents time. Using the above equation and the output of the SVD, the DCM-IR method optimizes the A and C matrices to best describe the spectrogram of the measured data. The quality of a model and the estimated A and C matrices was quantified by the accounted variance from the predicted spectrogram.

2.7.4 Bayesian model selection

We performed Bayesian model selection (BMS) with random effects[47] on the 12 models described above for both the hand opening and the simultaneous lifting and opening conditions using the data from all of the participants to assess which model best explained the observed data. BMS with random effects was chosen since it is better equipped to handle potential heterogeneity associated with the study of a diseased population such as stroke[47], and it contains a complexity term that penalizes a model based on the number of parameters it uses. The winning model, which was then used for further analysis of intervention-induced changes, was chosen based on the highest posterior exceedance probability (i.e. the probability that a given model is more likely than any of the other models tested).

2.7.5. Inference on coupling parameters

Predicted spectra and A matrices from the four modes were projected back to frequency domain allowing for characterization of the coupling parameters as a function of frequency for the winning model. The coupling matrices for each intrinsic and extrinsic connections in the winning model for each participant were further smoothed with a Gaussian kernel (full-width half-maximum of 8 Hz) for each condition. These matrices include the frequency-to-frequency (both within- and cross-frequency) coupling values for each connection. T-statistics were used to calculate statistical parametric maps separately for each connection and condition pre/post intervention. Significance for intervention-induced changes in specific coupling parameters was set at $p < 0.05$ with family wise error (FWE) correction.

3. Results

ReIn-Hand assisted reaching-grasping training improved the score of Box and Block test significantly, as well as scores in other clinical assessments[8,29]. The results included here will focus exclusively on the observed cortical neural changes pre- versus post-intervention.

3.1 Changes in Cortical Activity Ratio (CAR)

We first tested for any intervention-induced changes in cortical activity for the 2 tasks related to movement execution. A 2 (time) x 2 (task) x 4 (region) repeated measures ANOVA found a significant Time * Task ($F[1,7] = 8.03$, $p = 0.025$, $\eta_p^2=0.53$) and Time * Region ($F[3,21] = 4.64$, $p = 0.012$, $\eta_p^2=0.40$) interaction. Post hoc paired t-tests found that following the intervention there was a significant decrease in the cortical activation in contralesional M1/S1 ($p = 0.042$) during hand opening (See Figure 1A). For the simultaneous lifting and opening condition, a significant increase in cortical activation in ipsilesional M1/S1 ($p = 0.025$) was observed (See Figure 1B).

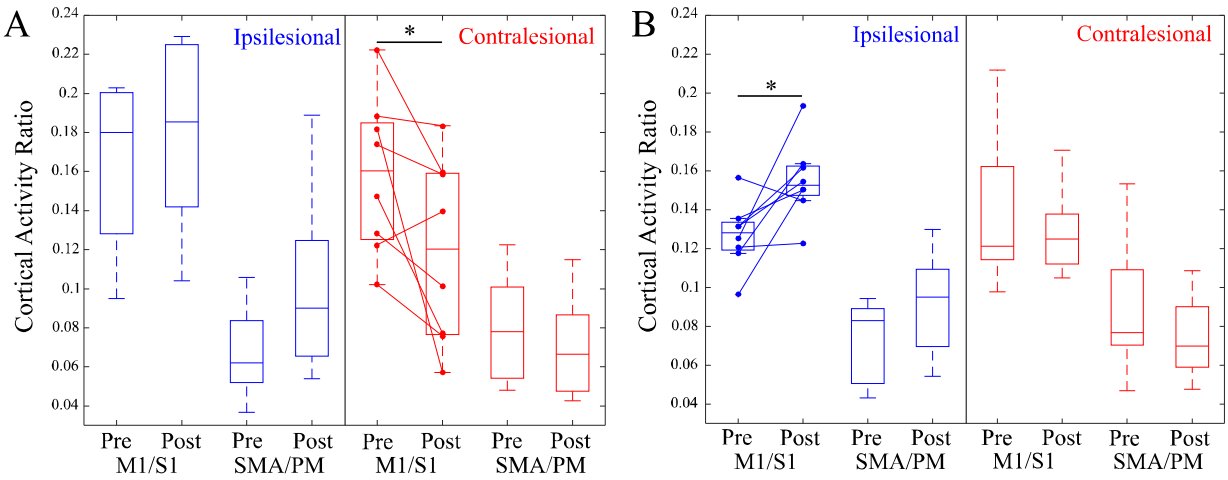

Figure 1. Box plots depicting cortical activity ratio Pre/Post Intervention for (A) hand opening on the table and (B) hand opening while lifting. Regions include combined primary motor cortex and primary sensory cortex (M1/S1) and combined supplementary motor area and premotor area (SMA/PM) for both the ipsilesional (Blue) and contralesional (Red) hemispheres. Participants demonstrated a decrease in contralesional primary sensorimotor cortex activity for hand opening following the intervention (left) and an increase in ipsilesional primary sensorimotor cortex activity for hand opening while lifting following the intervention (right). * indicates $p < 0.05$.

3.2 Bayesian model selection and model fit

In order to determine any intervention-induced changes in connectivity, we first had to evaluate which DCM model tested best explained the observed data. BMS with random effects clearly preferred model 12 for each condition (see Supplementary Table 1), which had full connections between the 5 motor regions of interest and allowed both within- and cross-frequency interactions for intrinsic and extrinsic connections. Exceedance probabilities were .973 for the opening condition and .975 for the simultaneous lifting and opening condition. Supplementary Figure 2 depicts both the observed and predicted spectrograms in each of the 5 motor regions using the winning model for one participant during the hand opening condition. Comparison of these two spectrograms shows the overall similarity between the observed data (i.e., power changes over time) and the model-predicted data. Overall, this model explained ~85% of the original spectral variance for each condition, indicating that it was suitable for evaluating any intervention-induced changes.

3.3 Intervention-induced changes in coupling parameters

Once we determined the model that best explained the observed data, we examined whether any intervention-induced changes in connectivity for any of the region-region connections occurred. We found that the intervention induced two significant changes in the coupling parameters, one for each motor task. After the intervention, participants demonstrated significantly less excitatory coupling from ipsilesional M1 to contralesional M1 in gamma frequencies (47 Hz → 36 Hz) during hand opening (see Figure 2A). When looking at the individual coupling values for this particular regional coupling, we found that prior to the intervention, 6 out of 8 participants demonstrated positive coupling values, indicating that increases in gamma in ipsilesional M1 led to increases in gamma in contralesional M1 (see Figure 2B). However, following the

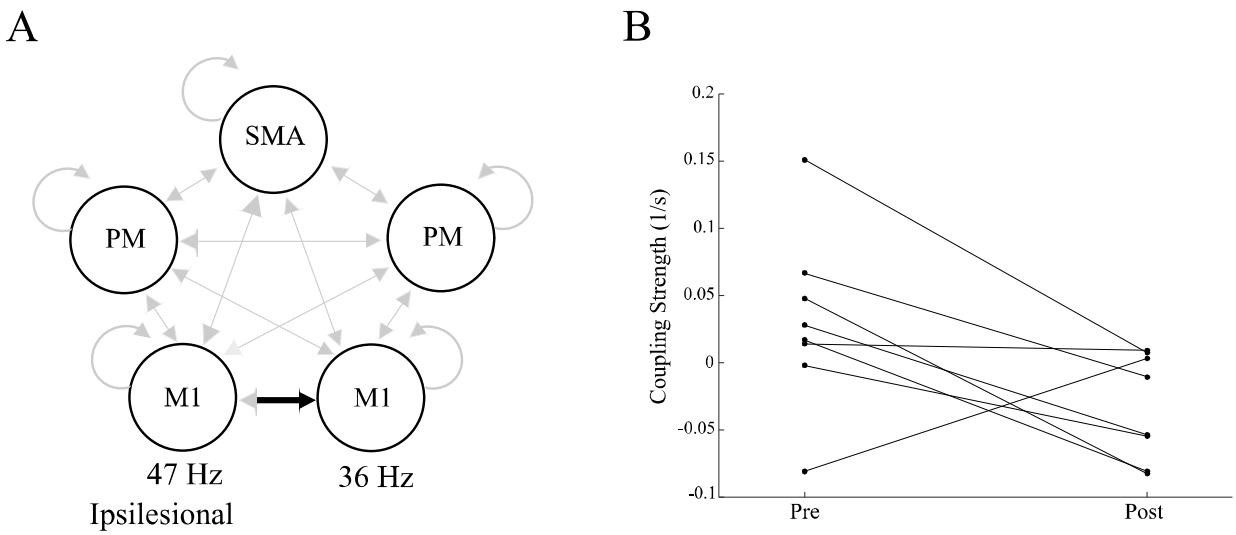

Figure 2. Reduced interhemispheric coupling following the intervention for hand opening on the table. (A) Schematic of significant decreases in coupling (black) from ipsilesional M1 (47 Hz) to contralesional M1 (36 Hz) within the motor network (light gray) following the intervention. None of the other region interactions (light gray arrows) showed significant changes pre to post intervention. (B) Individual coupling strength data pre/post intervention for the connection depicted in A. 6 out of 8 subjects demonstrate a reduction in coupling strength for this M1-M1 connection within gamma frequencies. Positive values indicate excitatory coupling, while negative values indicate inhibitory coupling.

intervention, 5 out of 8 participants showed zero or negative coupling, indicating that increases in gamma in ipsilesional M1 no longer led to increases in gamma in contralesional M1 (see Figure 2B).

For the task of simultaneous lifting and opening, the intervention induced significantly more negative or inhibitory coupling within ipsilesional M1 from gamma to beta (44 Hz → 25 Hz) (see Figure 3A). When looking at the individual coupling values for this particular regional coupling, we found that prior to the intervention, 6 out of 8 participants showed positive coupling values, indicating that increases in gamma power within ipsilesional M1 led to subsequent increases in beta power also within ipsilesional M1 (see Figure 3B). However, following the intervention, 7 out of 8 participants showed negative or inhibitory coupling, indicating that increases in gamma power within ipsilesional M1 led to subsequent decreases in

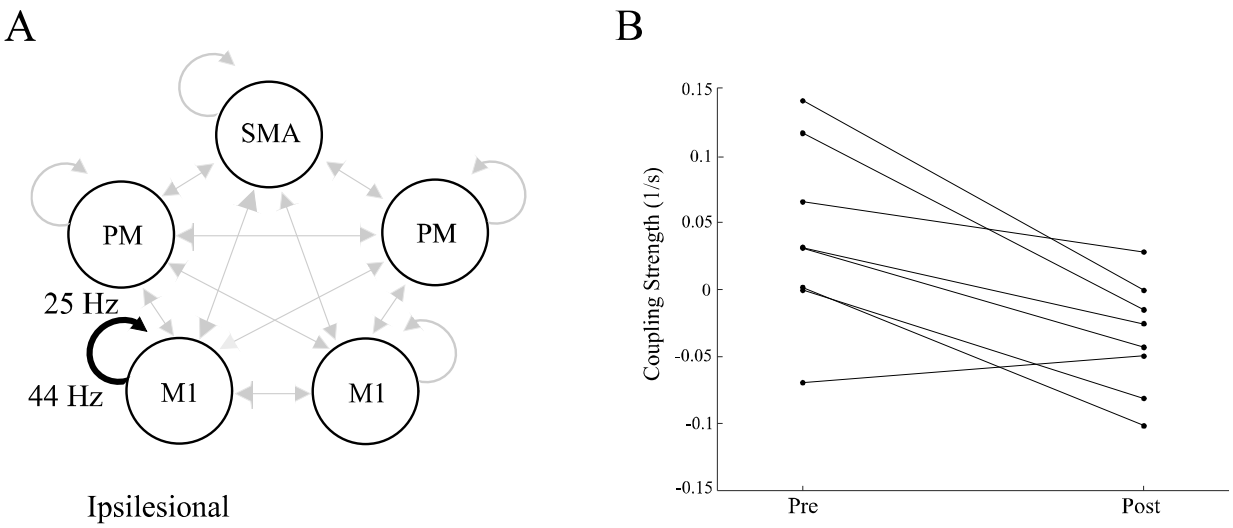

Figure 3. Altered intrinsic coupling within ipsilesional motor cortex following the intervention for hand opening while lifting. (A) Schematic of significant decreases in intrinsic coupling (black) in ipsilesional M1 (44 Hz to 25 Hz) within the motor network (light gray) following the intervention. None of the other region interactions (light gray arrows) showed significant changes pre to post intervention. (B) Individual coupling strength data pre/post intervention for the connection depicted in A. 7 out of 8 subjects demonstrate negative coupling within ipsilesional M1 from gamma to beta frequencies following the intervention. Positive values indicate excitatory coupling, while negative values indicate inhibitory coupling.

beta power within ipsilesional M1 (see Figure 3B).

4. Discussion

The current study quantified changes in both cortical activity in isolated regions at movement execution and connectivity between cortical regions during movement preparation related to paretic hand opening with and without coordination of shoulder abduction following a device-assisted intervention. Overall, we observed that reengagement of the ipsilesional motor cortex at

movement execution following the intervention was accompanied by similar changes in dynamic connectivity during movement preparation in movement-related gamma and beta frequency bands for both movements.

4.1 Intervention-Induced Changes Related to Paretic Hand Opening

As we reported previously, participants demonstrated decreased contralesional primary sensorimotor activity related to paretic hand opening following the intervention. In this study, we further demonstrated that following the intervention, these individuals demonstrated a reduction in coupling from ipsilesional M1 to contralesional M1 within gamma frequencies.

In healthy controls, gamma band power increases in contralateral primary sensorimotor cortex just before the onset and during movement[48-53]. This increase in gamma power has been shown to facilitate movement in studies using transcranial alternation current stimulation (tACS) to artificially increase gamma power over the contralateral primary sensorimotor cortex[54-56]. Typically, gamma is associated with local intracortical processing, particularly within GABAergic interneuronal circuits[57,58], with increases in gamma power related to movement associated with decreases in $GABA_A$[55]. However, gamma synchronization is notable usually confined to a small area in the contralateral primary sensorimotor cortex in controls[48,51,59], rather than bilateral increases in gamma during movement as observed here prior to the intervention.

Before the intervention, individuals with severe chronic stroke showed positive gamma coupling (as demonstrated by the positive coupling shown in Figure 2B) from ipsilesional M1 to contralesional M1. This abnormal initial positive gamma coupling between ipsilesional and contralesional M1 may indicate abnormal intercortical communication between the two hemispheres (via callosal or subcortical means[60]) and may give rise to the initial increased contralesional activity in these individuals. This is supported by previous findings in stroke showing weaker GABAergic inhibition from the ipsilesional to the contralesional hemisphere following stroke[61-64], and that this imbalance is associated with greater abnormal contralesional activity during paretic hand movements[65].

Following the intervention, we found that the abnormal interhemispheric gamma coupling decreased in 6 out of 8 participants (see Figure 2B), which supports the intervention-induced reduction in contralesional activity in the primary sensorimotor cortex (see Figure 1A). The intervention-induced decrease in positive gamma coupling between ipsilesional and contralesional M1 may underlie the subsequent decrease in CAR in contralesional primary sensorimotor cortex and reflect a return to a more normal state as observed in healthy controls.

4.2 Intervention-Induced Changes Related to Paretic Hand Opening While Lifting

For the simultaneous lifting and opening task, we observed increased ipsilesional primary sensorimotor activity following the intervention. This focal activity change during the lifting and opening task was supported by an altered coupling, in which the intervention induced a shift from positive to negative coupling between gamma and beta within ipsilesional M1 (see Figure 3B). This intervention-induced change in cross-frequency coupling is particularly relevant since gamma and beta power are typically inversely related in healthy controls during movement[32]. Whereas gamma tends to increase in power prior to and during the onset of movement, beta decreases in power[49,66]. This decrease in beta power during movement preparation in healthy controls has been linked with the reduction of inhibition in M1 just prior to movement to release the motor command[67,68]. Consequently, movements executed during elevated beta synchrony are slower[69], and increasing beta power using tACS has been shown to impair movement in healthy controls[54,70]. Importantly, stroke individuals show less decreases in beta during movement compared to controls[71], and persistence of inhibition in ipsilesional M1 during movement preparation[72]. Therefore, the shift from positive to negative coupling between gamma and beta in ipsilesional M1 following the intervention may reflect a return to a more typical pattern seen in healthy controls.

Prior to the intervention, individuals with severe chronic stroke demonstrated increased gamma power associated with increased beta power in ipsilesional M1 (as demonstrated by positive coupling between gamma and beta power in 6/8 participants, see Figure 3B). This positive coupling shifted to negative after the intervention, where increases in gamma power were associated with decreases in beta power. Importantly, decreases in beta power are inversely

related to BOLD activity in the sensorimotor cortex, suggesting some interplay or association between these two physiological processes[73,74]. Given beta's role in descending layer V pyramidal neurons[75,76], the observed intervention-induced increase in CAR may reflect increased drive and use of remaining descending ipsilesional motor resources during the lifting and opening condition following the intervention, rather than purely an intracortical change. This is significant since reliance on descending tracts from the contralesional hemisphere has been linked with synergy-induced impairments[77,78], particularly during tasks involving lifting at the shoulder[17,36], as examined here. Meanwhile, increased use of descending corticospinal tract from the ipsilesional hemisphere has been shown to be crucial for improved function following stroke[13,79,80], especially for independent control of multijoint movements of the upper extreminty[81]. Although contralesional corticobulbar pathways can support more proximal paretic arm movements such as reaching[82], they do not offer sufficient control of independent joints during multijoint movements[83,84]. Thus, the ability to maintain ipsilesional recruitment during combined shoulder-hand tasks is critical for potential functional improvement since ipsilesional corticospinal tract, unlike contralesional corticobulbar tracts, has more specific branching in the spinal cord that allows for independent control of the different parts of the arm[84-87].

4.3 Limitations

One of the major limitations of the current study is the small sample size (N=8). However, these participants are fairly homogeneous in that they are each severely impaired (FMA: 10-24; Chedoke McMaster: 3-4) with subcortical lesions in the chronic phase. The robotic setup during the EEG experiment also allowed for a well-controlled environment to investigate cortical activity related to the paretic arm and hand, thus minimizing potential session to session variability.

There are numerous methods to analyze connectivity besides DCM-IR when measuring EEG. Methods such as correlation or coherence between two time-series are the most commonly used metrics. However, unlike DCM-IR, these are limited to within-frequency relationships. Methods evaluating both within and cross-frequency relationships are rarer, including bicoherence, n:m phase synchrony, and multi-spectral phase coherence methods[88-91]. However, these methods

either do not evaluate directionality, like correlations and coherence, or do not directly link to cortical regions. DCM-IR allowed us to evaluate both linear and nonlinear relationships between regions within a network, while also looking at directionality. However, DCM-IR only examines the temporal dynamics of power, but does not contain information of phase, which has been shown to play a potential role in cortical communication[30]. Lastly, DCM is limited by the models tested, and it is possible that there is a better model not considered here.

EEG is inherently limited in its spatial resolution, particularly in comparison to fMRI. However, using our high-density EEG setup, along with the sLORETA inverse calculation based on subject-specific boundary element models created with individual's anatomical MRI, we have demonstrated a resolution of roughly 5 mm[92,93]. This is suitable for distinguishing primary sensorimotor cortex and secondary motor areas as investigated here in our topographical analysis and allowed us to investigate multi-joint movements which would have been impractical inside an MRI scanner. Meanwhile, the source reconstruction in DCM is based on an equivalent current dipole (ECD) method using the coordinates chosen based on our previous cortical activity findings in combination with standardized locations from the literature. Although these dipoles capture a smoothed portion of the cortex, it is possible that additional activity is not captured within the 5 regions investigated. It is worth noting that these 2 independent inverse approaches (sLORETA and ECD) yielded complementary results in the regions investigated.

5. Conclusion

The current study demonstrates that intervention-induced changes in coupling both within and between motor regions during movement preparation in movement-related frequencies complement changes in focal cortical activity at movement execution related to both the hand and arm. Together, these findings suggest that changes network-wide cortico-cortico interactions may lead to corresponding changes in focal cortical activity.

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