FUNCTIONAL LATERALIZATION OF SENSORIMOTOR CORTEX FOR ASSESSING STROKE NEUROREHABILITATION

A Thesis

Presented to

the Faculty of the Department of Electrical & Computer Engineering

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

in Electrical Engineering

by

Zachery R. Hernandez

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Abstract

Stroke physical therapy effectiveness is typically measured by changes in the functionality, strength, or impairment of the trained upper limb. In addition, brain activation measures can be beneficial, especially since certain therapies induce neuroplastic changes to the brain. The goal for this thesis is to therefore investigate the effect of a neuro-rehabilitation clinical study on sensorimotor lateralization by assessing early and late treatment sessions. Significant lateralization differences were revealed at various time segments, which were generally before movement onset. To account for various arm movement characteristics, a measure of cortical lateralization was compared to each clinical assessment. This exhibited relationships which were not significant, yet offered linear trends which depended heavily on physical upper limb attributes as well as the clinical tests. In all, the results suggest that neuro-rehabilitation does alter lateralization of the sensorimotor cortex, which were specific to both the individual and the type of clinical assessment.

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Chapter 1

Introduction

Stroke is the leading cause of long-term disability in the United States, disrupting the lives of nearly 7 million American adults in 2016 and costing an estimated average of $8,000 per patient in direct medical care in 2014 [1]. Although nearly two-thirds of victims survive up to a year or more post-stroke, about 37% to 49% of these survivors are dependent on others for daily living activities [2]. Part of this dependence is due to motor deficits such as muscle weakness on one side of the body (known as hemiparesis) which impairs the survivor's ability to walk or manipulate objects with their arm or hand. Fortunately, there are a wealth of stroke rehabilitation programs focused on physical therapy that have been effective in improving physical function, strength, or quality of life for the affected individual [3]. Moreover, stroke rehabilitation treatment interventions, especially those involving high repetitions, can increase the process of brain re-organization due to Hebbian plasticity [4], though this warrants further attention [5]. One approach has been to incorporate brain-machine interfaces (BMIs) into existing rehabilitative treatments such as robot-assisted therapy [6], [7], functional electrical stimulation [8], or virtual environments [9], [10]. This approach, sometimes called neurorehabilitation, can enhance task engagement as well as provide clinicians and therapists with an opportunity to monitor the cortical activity driving and responding to the rehabilitation itself [11].

This approach may not be possible if not for the increasing technological advancements in mobile non-invasive brain recording devices such as scalp electroencephalography (EEG) which can record oscillatory electrical activity from the scalp, originating from the summed post-synaptic action of thousands to millions of parallel pyramidal neurons [12]. A multitude of neuroscience and neural signal processing studies have recorded brain activity from humans using scalp EEG within the past decade with the popular goal of forming relationships between behavior and neurophysiology (e.g., so-called neural correlates). This was the focus of one study, where chronic stroke survivors underwent treatment aimed at functional motor recovery of the upper arm. To accomplish this, patients would control the initiation of movements from an upper limb exoskeleton using a feature of EEG activity related to movement intention called motor-related cortical potentials (MRCPs). Using a binary classifier for the real-time closed-loop BMI in latter sessions, the researchers achieved above-chance constant accuracy with a true positive rate of 63% and 67% in the fourth and fifth sessions, respectively. It differed from other relevant studies, which use a more commonly known EEG feature of motor intent known as sensorimotor rhythm for classification, yet were still comparable in performance.

While useful for providing feedback and engaging participants, EEG data could also be analyzed to assess the outcome of a given rehabilitation treatment. This would be similar to the same role that clinical motor tests such as grip/pinch strength, Fugl-Meyer Arm Assessment, and many others play in assessing physical changes in arm movement before and after treatment. One way to assess cortical functional changes may be to measure the dynamics of sensorimotor (SM) lateralization, or differences in left and right primary sensory and motor cortical activity within the brain. SM lateralization was sought out due to its extensive research in regards to the context of stroke motor recovery. In healthy individuals, recruitment of cortical neurons during unilateral extremity movements are typically confined to contralateral SM areas of the brain. While someone recovering from the onset to chronic (post-6 months) stroke weakening one side of the body, both contralateral and ipsilateral SM areas of the brain are likely to be recruited for movement of the paretic limb. In fact, the dynamic nature of contribution from both SM cortex hemispheres can depend on the stage of movement or length of time since the brain injury. For instance, a study by Fang and colleagues used SM lateralization to reveal significant differences not only between stroke survivors and able-bodied controls, but also between planning and execution stages of the arm movement with greater lateralization in the planning stage [13]. In regards to time since stroke on cortical lateralization, the SM activity of stroke patients following a successful motor recovery became lateralized to the lesional hemisphere in the subacute ($<$ 1 wk) stage, more dispersed in the early chronic (2-4 wks) stage, then completely ipsilesional for everyone in the chronic ($>$ 4 wks) stage of stroke [14]. This may not always hold true, as equally bilateral SM activity could account for successful recovery in people with chronic stroke as well [15]. Nonetheless, varying levels of SM lateralization account in one way or another to the success of motor recovery for someone with chronic stroke. The neurophysiologic origins remain unclear, though several studies have observed high connectivity between SM hemispheres and highly lateralized connectivity between the ipsilesional hemisphere and the target limb muscle [16, 17]. This is further explained by the so-called interhemispheric imbalance model, which posits balanced cortical inhibition between both SM hemispheres during a unilateral task [18]. A focal lesion can therefore disrupt this balance, leading to increased excitation in the contralesional hemisphere, which results in increased inhibition of the ipsilesional hemisphere. This further indicates the dynamic and altering role that SM bilateral activity, especially through interhemispheric inhibition, contains in regards to stroke recovery.

Thus while much is known about the functional lateralization of the sensorimotor or primary motor cortex, its dynamics under various settings for stroke survivors, especially rehabilitation treatments, remain unknown. Though the stroke event itself as a disruption of blood flow to brain regions leading to cellular death is neuroplastic in nature, so too would be any recovery and physical therapy treatment that follows after the event. And while such dynamical processes may be governed by different mechanisms, the research explained above provides one of many ways neuron populations in the brain re-organize and strengthen new connections that result in arm or hand motor recovery based on either functionality, strength, or level of paresis or any combination thereof. But methods for assessing such recovery through physical rehabilitation depend on clinical outcome metrics that measure only physical attributes of the affected limb. Given the inherent nature of stroke, attributing rehabilitative outcomes to structural or functional changes in the brain can allow physical therapists to better understand the fundamental causes underlying any rehabilitative treatment. For this, EEG recorded from a chronic stroke neurorehabilitation clinical study was used for assessing such changes in brain function. The treatment itself was similar to the experiment protocol described in [7] where a BMI controlled the initiation of movement for an arm exoskeleton within the context of robot-assisted therapy. Since source estimation has been utilized in past studies to localize small regions of activity for stroke survivors performing upper-limb tasks [19, 13], this could be applied to extracted motor-related cortical potentials (MRCPs), slow-wave EEG activity (0.1-1 Hz) from the sensorimotor cortex, in order to obtain a measure functional lateralization known as the SM lateralization ratio. Thus, two aims were proposed for this masters thesis: 1) investigate the changes within sensorimotor cortical activity between left and right hemispheres within early and late rehabilitation treatment session groups and 2) compare beginning-to-end treatment differences between motor-related brain activity and clinical motor test measures.

Chapter 2

Methods

2.1 Subject Information

Five (4M/1F) out of ten subjects with chronic ($>$ 6 months) stroke were selected from a National Institutes of Health (NIH) clinical study (ClinicalTrials.gov Identifier: NCT01948739), primarily because all five had a subcortical stroke which left cortical surfaces without any missing anatomical structure. This was beneficial to the thesis for two reasons: 1) the ability to successfully generate a boundary element method (BEM) model of the cerebral cortex to conduct source estimation, and 2) general consistency in the anatomical structure of the brain. All five subjects participated within the study protocol were approved by the Institutional Review Boards of University of Houston, University of Texas Health Science Center, Rice University, and Methodist Hospital and provided written informed consent prior to the study. The inclusion/exclusion criteria for this study can be found in Tables 2.1 and 2.2 and subject demographics can be found in Table 2.3.

2.2 Clinical Motor Assessments

A variety of clinical assessments was performed on each subject to determine motor impairment, function, and strength before and after the treatment as well as 2 months after the treatment. Motor impairment was measured using the Fugl-Meyer Arm Assessment (FMA, score range 0-66) where the highest score indicates a lack of impairment. The Action Research Arm Test (ARAT, score range 0-57) assesses arm motor function in addition to coordination and dexterity where the highest score indicates intact arm function. Similarly, the Jebsen-Taylor Hand Function Test (JTHFT, time range 0-120 seconds per subtest) measures activities of daily living and functionality of the hand by timing the displacement of identical items within each subtest. A dynamometer and pinch gauge were used to measure grip and pinch strength, respectively. The initial scores and measurements from all clinical assessments described above, in addition to arm weakness left/right side information, could be found in Table 2.4 for each subject.

2.3 Experiment Protocol

The treatment intervention for this study consisted of 14 sessions in total. In all sessions, the subject was seated in a chair facing a computer screen while a powered elbow exoskeleton held their impaired arm. They also wore a scalp electroencephalographic (EEG) cap for recording brain activity. Each subject would view a graphical user interface (GUI) that consisted of a solid green ball mapped to the exoskeleton's elbow joint angle and circles with crosshairs representing the targets each subject must move the green balls towards by moving at the elbow joint (Fig. 2.1). While these characteristics were universal of every session, others were more specific to sessions at different stages of the treatment intervention. For instance, subjects would control the exoskeleton with an above-threshold elbow joint velocity while brain activity was passively collected during the first two sessions. On the third session, the experimenter would use EEG data collected from the first two sessions to begin calibrating parameters of the real-time BMI scheme. Once adjusted, sessions 4 through 14 comprised of subjects using the closed-loop real-time BMI to replace the joint

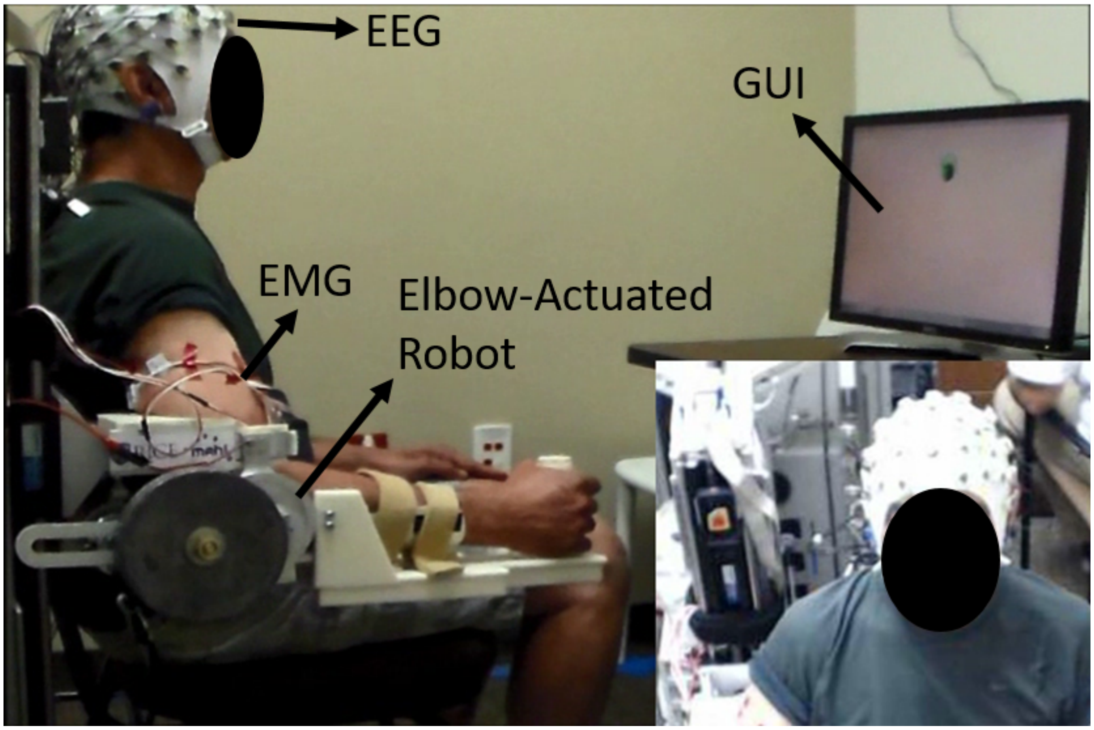

Figure 2.1: Subject in data recording and feedback setup for each treatment session.

velocity-activated movement with motor-related cortical potentials (MRCPs) originating from central regions of the brain. The subject was instructed only move the impaired arm during sessions by mentally anticipating the movement before execution in order to generate the MRCPs necessary for initiating exoskeleton movement. The number of trials varied between each session, ranging from 95 to 148 (or on average 123±13) trials per session.

2.4 EEG Preprocessing

A 64-channel active-electrode EEG system was used for collecting brain activity (actiCAP, Brain Products GmbH) with a sampling rate of 500 Hz. Electrodes were configured to the international 10-20 montage with unipolar reference and ground electrodes attached to the subject's impaired and non-impaired earlobes, respectively. Eight of the 64 active EEG channels (FT7-10, TP7-10) were bypassed using a splitter box (EIB-64A, Brain Products) to record bipolar electromyographic (EMG) activity from the biceps and triceps brachii muscles of both arms. The ground electrode to all four EMG pairs were all connected to the same ground on the splitter box and attached to the subject's lateral malleolus at the ankle joint. Both EEG and EMG signals were therefore synchronized because of this bypass configuration. All EEG channel positions in 3-dimensional space were acquired using the Polhemus digitization system.

During the closed-loop BMI sessions (sessions 4-14), movement onset event markers related to a successful motor intent were generated by the upper limb exoskeleton and recorded into the EEG system by means of auxiliary transistor-transistor logic (TTL) trigger inputs. A successful motor intent occurred when the subject produced MRCPs from central regions of the brain, following EMG activity from the arm indicating physical movement, within 15 seconds after display of target onset on the computer screen.

The following pre-processing steps were performed within the MATLAB (MathWorks Inc.) environment using functions from the FieldTrip Toolbox [20]. After removing the eight EMG channels from the 64-channel dataset, the remaining 56 EEG channels were first high pass filtered ($f_c = 0.1$ Hz) using a zero-phase 4th order Butterworth filter (Fig.2.2A). A blind source separation method known as independent component analysis (ICA) was performed next on the filtered EEG channels in order to extract and remove eye blink artifacts [21] that could dominant the centrally located MRCPs when estimating sources. Reconstructed EEG signals were then low pass filtered ($f_c = 1$ Hz) and spatially filtered using the surface Laplacian to obtain the MRCPs that will be used for later analysis. Signals were divided into movement epochs using the movement onset event markers sent from the exoskeleton throughout each treatment session. To maintain the radial positioning symmetry of EEG electrodes over the head, a spline interpolation was computed over channels neighboring the missing channels FT7-8 and TP7-8 due to the aforementioned EMG substitution. The EEG dataset would finally consist of spatially smoothed slow cortical potentials with readiness potentials over the central areas of the head. This will be used to localize the sources that generate the MRCPs which will be discussed in later sections.

2.5 MRI Preprocessing

One magnetic resonance imaging (MRI) T1-weighted brain scan was acquired by each participant from either the Houston Methodist Research Institute (HMRI) or the University of Texas Health Science Center at Houston (UT Health) using the same 3 Tesla full body scanner manufacturer and model (Philips Ingenia). Parameters universal at both sites included a repetition time (TR) of 8 milliseconds, 256 x 256 field of view, one-millimeter slice thickness, and slice direction in the sagittal plane. Parameters specific to the HMRI site included a 240 x 222 acquisition matrix (AM), duration time (DT) of 335 seconds, 8 degree flip angle (FA), and 0.938 millimeter reconstructed in-plane resolution (RIPR) (AM = 256 x 256; DT = 305 s; FA = 6; RIPR = 1 mm for UT Health site). MRI scans were obtained from all five subjects for this thesis, as this would be necessary for estimating distributed sources across the cortex surface. Before estimating sources using the preprocessed EEG data, the subject's brain structure was motion-corrected, Talairach transformed, segmented, intensity normalized, and parcellated using the Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/) which ran on a Linux virtual machine (Fig.2.2B). The Freesurfer results were imported into the Brainstorm

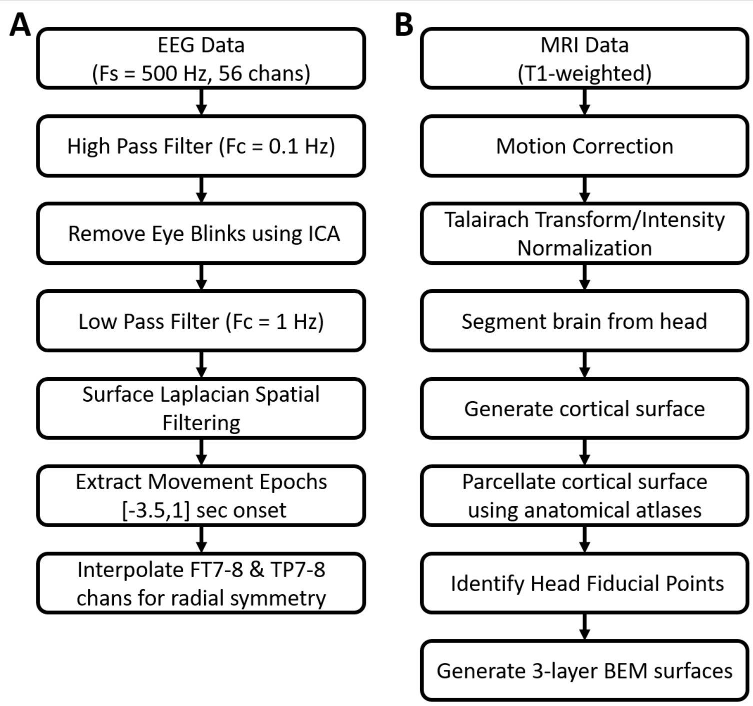

Figure 2.2: **(A)** EEG and **(B)** MRI preprocessing steps.

Toolbox, which is a software library and graphical user interface application for analyzing brain recordings developed in both MATLAB and Java environments [22]. During the import process, six head fiducials (nasion, left/right pre-auricular point, anterior/posterior commissure, interhemispheric point) were identified and the head or scalp surface was generated for EEG-MRI co-registration. Lastly, three head layers (scalp, outer and inner skull) were segmented from the MR images in order to generate boundary element method (BEM) surfaces, which will be necessary, along with the cortex surface, for generating the forward model for source analysis.

2.6 Source Analysis: Pre-processing

Electrode position data were co-registered with the MRI data using: 1) the head surface model as a surface to project electrode position points onto and 2) the nasion and left/right pre-auricular points as fiducial landmarks for EEG position/MRI spatial alignment. Since multiple EEG electrode locations were recorded for each subject (for some or every treatment session), each electrode position data file was co-registered with the subject's MRI and visually inspected for proper alignment and projection on the head surface and the best aligned and evenly-space data file was selected per subject. The aligned channels, in addition to the 3-layer BEM and cortex surface models were used for computing the forward head model using the OpenMEEG BEM software [23] within the Brainstorm Toolbox. The forward head model would then contain thousands of points across the cortical surface that represent the dipoles, or sources, of electrical activity over the cortex. EEG epochs were averaged per session, and the data and noise covariance were calculated based on the concatenation of all epochs at times 3.5 to 2.5 seconds before, and 2.5 seconds before to 1 second after movement onset, respectively.

2.7 Source Analysis

There could be two approaches to EEG source localization [24]. In the equivalent current dipole (ECD) modeling approach, few dipoles were estimated across the entire time, which assumes the dipole(s) to be invariant to time. By contrast, linearly distributed (LD) modeling assumes that EEG would be composed of a linear combination of cortical sources. Dipoles could also be estimated anywhere over the scalp surface as well as invariant to time. Due to characteristics of the EEG-based MRCP time-series signals, the latter approach was selected for source localization.

Source analysis was therefore achieved by solving the inverse problem between EEG sensors and cortical sources. This solution is impossible to compute directly since an infinite number of source dipoles could generate the electrical activity measured by the EEG channels. Hence, sources were estimated by use of the minimum norm imaging approach[25]. Significance of estimated source current densities were observed though a normalization method known as standardized low resolution brain electromagnetic tomography (sLORETA) [26] to allow for within and between subject comparisons. For computational efficiency and to maintain the anatomical structure of pyramidal neurons near the cortex surface, source dipole directions were assumed to be perpendicular to the cortex surface.

2.8 Source Analysis: Post-processing

Source values from left/right pre- and post-central gyrus cortical regions were selected and grouped using the Desikan-Killiany anatomical atlas [27] for its relation to the primary sensory and motor, or S1 and M1, cortices, which play a role in sensorimotor function. These grouped sources were further clustered into early and late session groups. The first (session 4, 5, 6) and last (session 12, 13, 14) three closed-loop BMI treatment sessions were selected and averaged to create these two groups in order to compare activity between early and late rehabilitation treatment. The natural logarithm of ipsilesional source activity from each M1 and S1 cortex divided by its contralesional source activity was calculated at small time segments to obtain a time-based sensorimotor lateralization measure to compare between the subject's early and late session groups as well as the subject's clinical motor assessment scores.

2.9 Statistical Analysis of Current Source Densities

A paired or repeated measures t-test was computed in order to test any significant changes between each subject's early and late treatment session groups per time point. A linear regression (with calculated R^2 and p values) was applied across all subjects and between the early-late treatment difference of each SM lateralization time segment measure and the pre-post treatment difference of each clinical assessment measure.

Table 2.1: Inclusion/exclusion criteria for NIH clinical study NCT01948739.

Inclusion Criteria	**Exclusion Criteria**
Diagnosis of unilateral cortical and subcortical stroke confirmed by brain CT or MRI scan	Orthopedic limitations of either upper extremity that would affect performance on the study;
Subacute or chronic stroke; interval of at least 3month and interval of at least 6 months from stroke to time of enrollment, respectively	Untreated depression that may affect motivation to participate in the study;
No previous clinically defined stroke	Subjects who cannot provide self-transportation to the study location.
Age between 18-75 years	
Upper-extremity hemiparesis associated with stroke (manual muscle testing score of at least 2, but no more than 4/5 in the elbow and wrist flexors)	
No joint contracture or severe spasticity in the affected upper extremity: i.e., significant increase in muscle tone against passive ROM is no more than of full range for given joint e.g., elbow, wrist and forearm movements	

Table 2.2: Inclusion/exclusion criteria for NIH clinical study NCT01948739.

Inclusion Criteria (Continued)
Sitting balance sufficient to participate with robotic activities
No neglect that would preclude participation in the therapy protocol
Upper limb proprioception present (as tested by joint position sense of wrist)
No history of neurolytic procedure to the affected limb in the past four months and no planned alteration in upper-extremity therapy or medication for muscle tone during the course of the study
No medical or surgical condition that will preclude participation in an occupational therapy program, that includes among others, strengthening, motor control and functional re-training of the upper limbs
No contraindication to MRI
No condition (e.g., severe arthritis, central pain) that would interfere with valid administration of the motor function tests
English-language comprehension and cognitive ability sufficient to give informed consent and to cooperate with the intervention.

Table 2.3: Subject demographics.

Subject ID	**Gender**	**Age (yrs.)**	**Post-Stroke Age (mos.)**	**Stroke Type**	**Lesion Location**
9010	F	54	72	Ischemic	R thalamus
9012	M	58	10	Ischemic	L thalamus
9014	M	61	9	Hemorrhagic	L thalamus, claustrum
9020	M	64	15	Ischemic	R thalamus, putamen
9023	M	44	17	Hemorrhagic	L thalamus

Table 2.4: Subject baseline clinical motor assessment scores.

Subject ID	**Paretic Arm**	**FMA (0-66)**	**ARAT (0-57)**	**JTHFT (items/sec)**	**PS (%)**	**GS (%)**
9010	Left	35	45	1.85	47.8	50.0
9012	Right	33	39	1.49	50.0	39.1
9014	Right	32	30	1.73	49.1	25.9
9020	Left	17	9	0.00	0.00	4.09
9023	Right	32	12	0.50	46.2	21.1

Chapter 3

Results

3.1 Within-Subject Comparison of Early-to-Late Treatment Sessions

3.1.1 Time-Series Source Current Densities

Figures 3.1 to 3.5 depicted the mean and variance between all source dipoles within a given region (left/right M1 or S1) and across three treatment sessions from either the early or the late portions of the treatment intervention. When performing the paired t-test between the early and late treatment source values per subject, there appeared to be a large variation in the time regions that were significant when observing across subjects. For instance, subjects 9010 and 9012 (Figs. 3.1 & 3.2) contained significant times mostly prior to movement onset, with the most notable difference between session groups on the ipsilesional side between onset and 1500 milliseconds before onset. Significance in subjects 9014 and 9020 (Figs. 3.4 & 3.5) were distributed among times around and up to 500 milliseconds post-movement or times around 1 second before movement. By comparison, the entire time-series of the ipsilesional sensorimotor cortex for subject 9023 (Fig. 3.5) was significant while significance for the contralesional side focused primarily around 500 milliseconds before movement. Despite significance, all time-series source current densities followed the same deflection around movement onset followed by a peak or growing increase in source current magnitude up to 500 milliseconds after the movement. Overall,

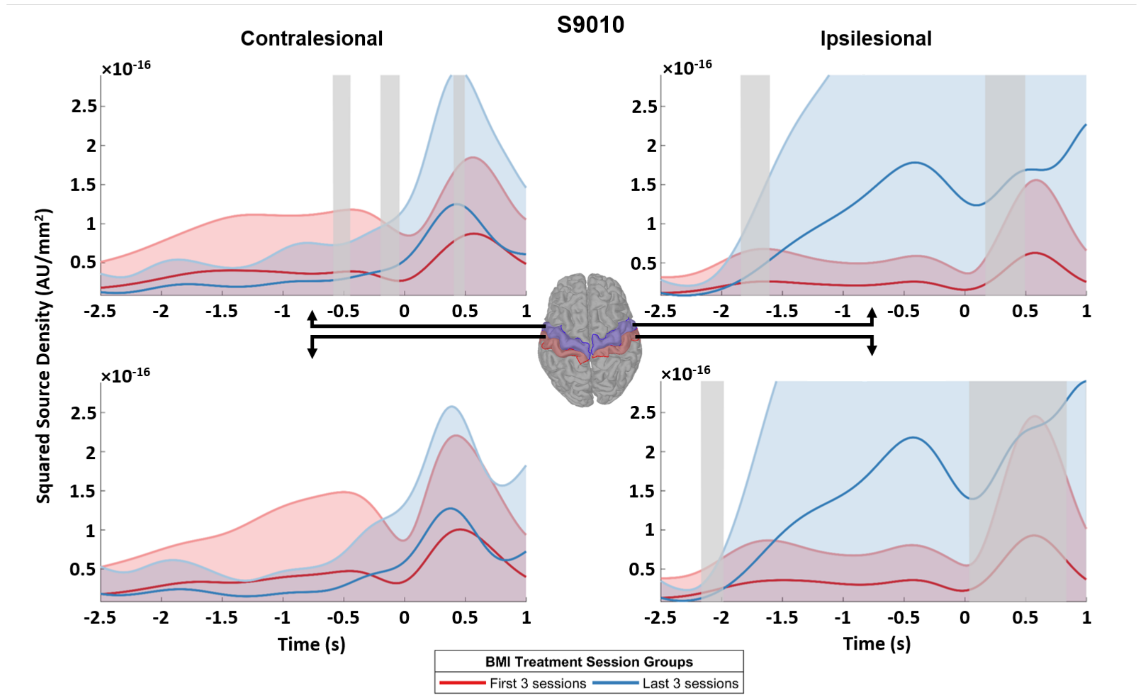

Figure 3.1: Differences between early (red) and late (blue) treatment session groups for subject 9010 across the sensorimotor cortex. Non-shaded areas denote statistical significance.

significant differences in source current magnitude occurred thus indicating changes in the sensorimotor cortex as a result of the neuro-rehabilitation treatment.

3.1.2 Sensorimotor Cortex Lateralization-Based Measures

After calculating the log ratio of ipsilesional-to-contralesional localized cortical activity per subject, the following plots were generated by calculating the mean ratio across time segments of 100 milliseconds from a shortened epoch of -1500 milliseconds to zero seconds corresponding to movement. This shortened epoch was chosen as a constraint since a past study [7] revealed the existence of MRCPs during this treatment from -1.5 to zero seconds prior to arm movement where the negative peak would occur between 0 to 600 milliseconds before onset. In contrast to the

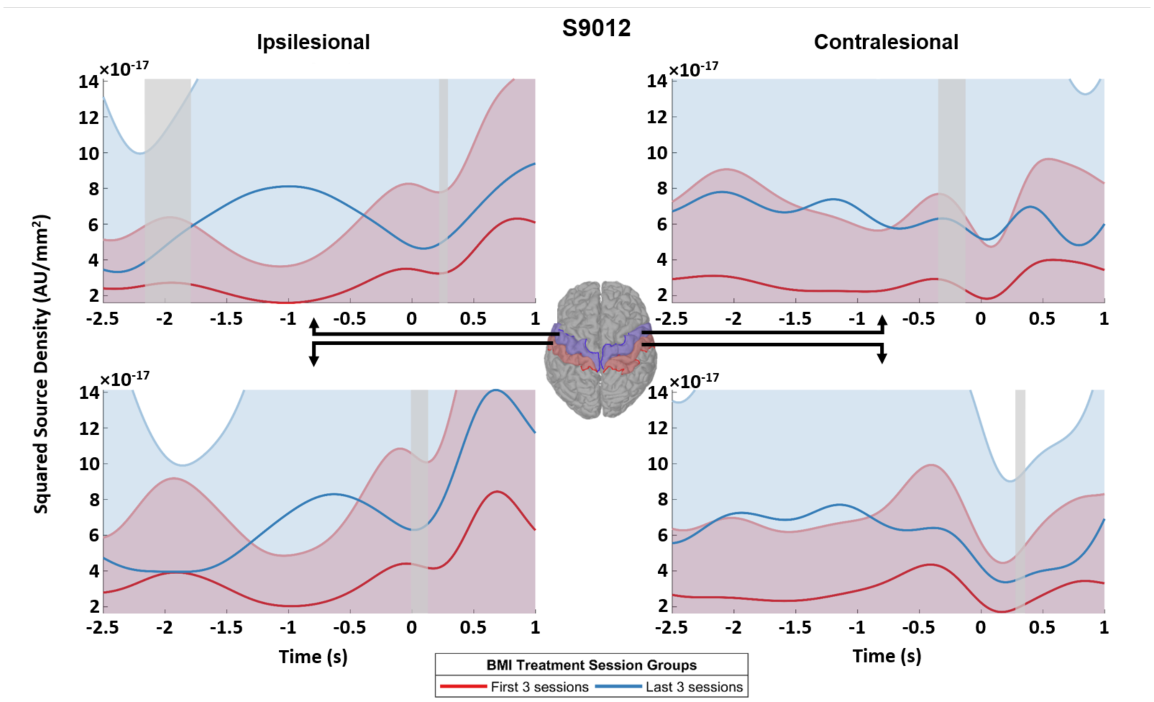

Figure 3.2: Differences between early (red) and late (blue) treatment session groups for subject 9012 across the sensorimotor cortex. Non-shaded areas denote statistical significance.

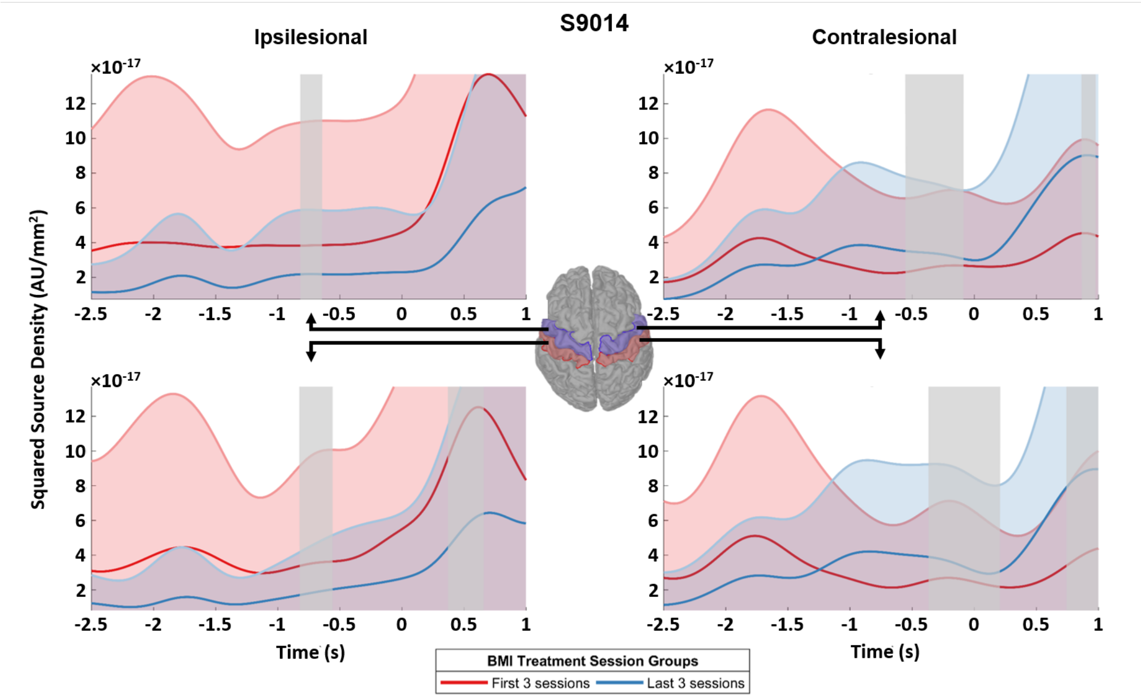

Figure 3.3: Differences between early (red) and late (blue) treatment session groups for subject 9014 across the sensorimotor cortex. Non-shaded areas denote statistical significance.

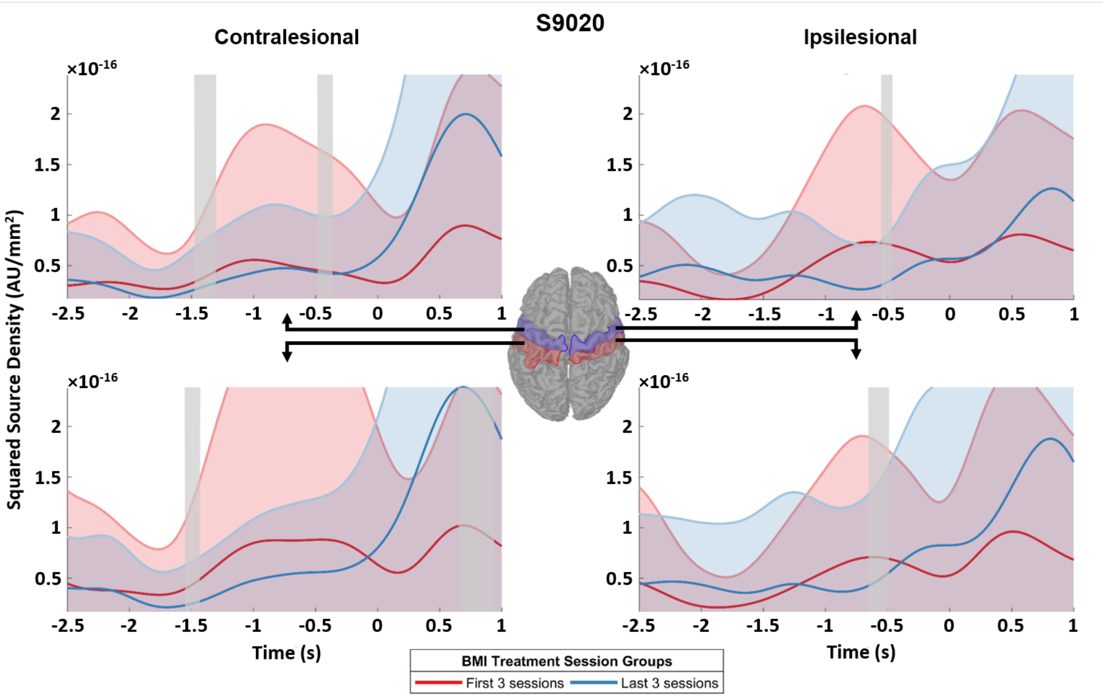

Figure 3.4: Differences between early (red) and late (blue) treatment session groups for subject 9020 across the sensorimotor cortex. Non-shaded areas denote statistical significance.

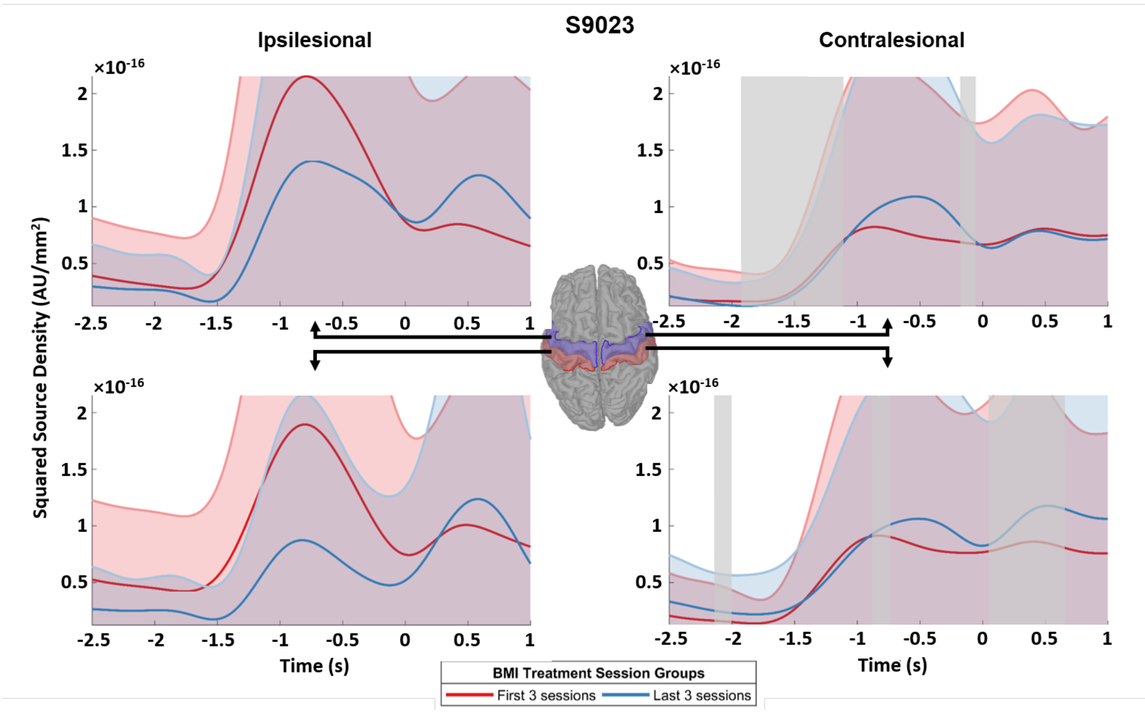

Figure 3.5: Differences between early (red) and late (blue) treatment session groups for subject 9023 across the sensorimotor cortex. Non-shaded areas denote statistical significance.

previously mentioned average source current density signals, only subject 9020 (Fig. 3.9) reported an area of no significant difference between session groups between the time segments of the aforementioned MRCP activations (-600 to 0 ms) for the primary somatosensory cortex (S1). Otherwise, all subjects reported significant differences in SM lateralization measures at early and late treatments, especially for the primary motor cortex (M1). There was no general trend across all five subjects for differences between the stages of treatment. For instance, while subjects 9010 and 9012 (Figs. 3.6 & 3.7) were observed to transition from increased contralesional to increased ipsilesional activity by the end of the treatment, the opposite occurred for the other three subjects. In fact for subjects 9014 and 9020 (Figs. 3.8 & 3.9), ipsilesional activity was more prominent at the beginning of treatment but became more contralesional by the end of the treatment. Subject 9023 (Fig. 3.10) was the only individual that exhibited ipsilesional activity at the beginning and end of treatment, but similar to subjects 9014 and 9020 (Figs. 3.8 & 3.9), this activity decreased to near equal bilateral activity by the end of the treatment. Despite such differences among subjects, functional lateralization activity from the sensorimotor cortex varied significantly across most of the -1.5 to 0 second time segment by comparison of early and late treatment sessions.

3.2 Comparison of Cortical to Clinical Motor Assessment Measures

Since cortical sensorimotor activity exhibited alterations during treatment sessions, yet varied in direction of alteration (i.e., ipsi- toward more contra-lateral activity or vice versa), a linear regression was applied to the difference between pre- and post-treatment measurements of each clinical assessment and the difference between

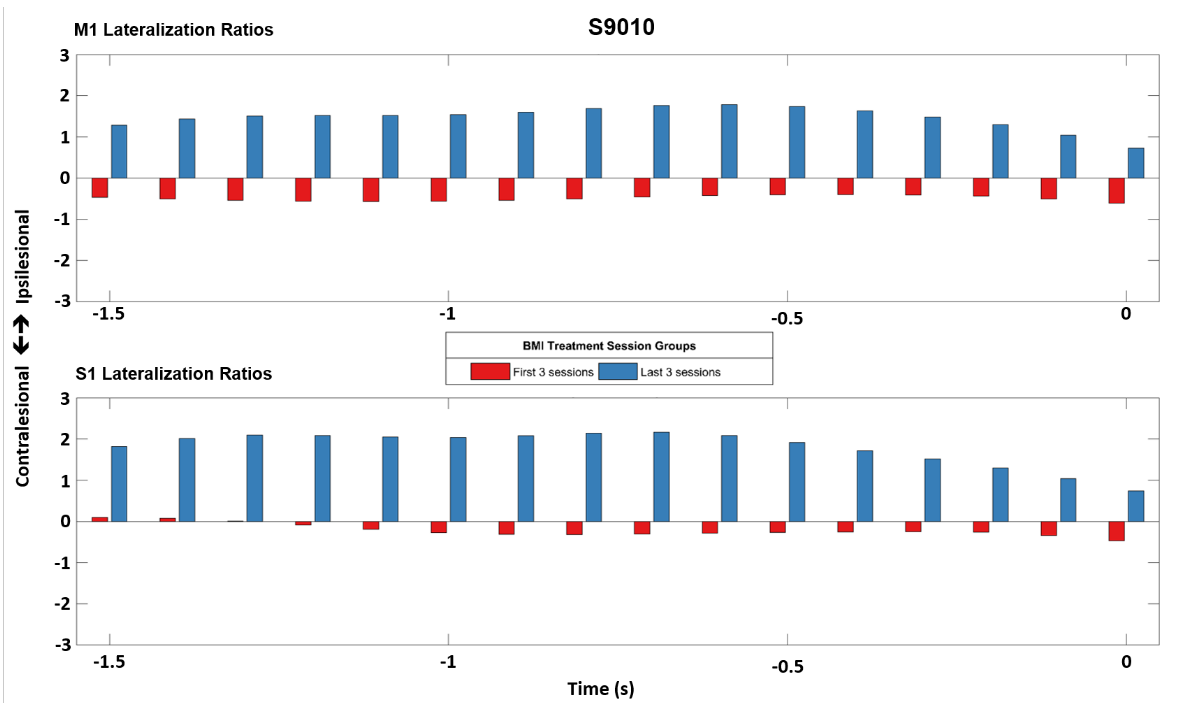

Figure 3.6: Lateralization differences between early (red) and late (blue) treatment session groups for subject 9010 for primary motor (top) and sensory (bottom) cortex. Non-shaded areas denote statistical significance.

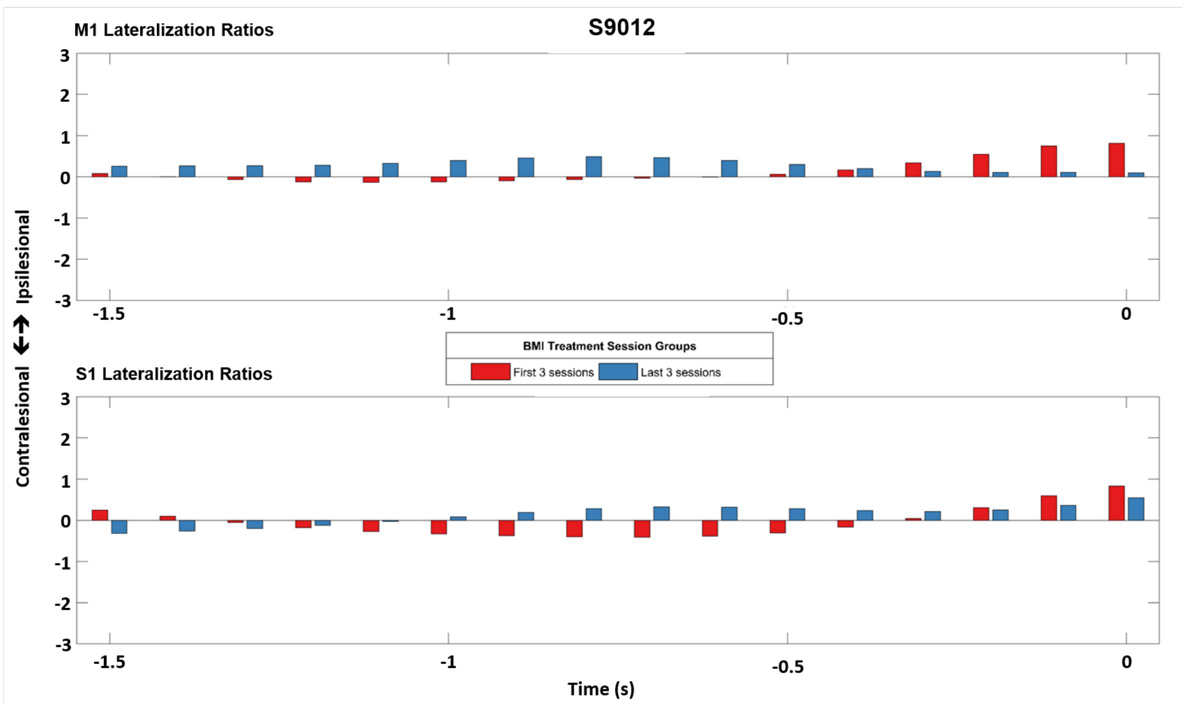

Figure 3.7: Lateralization differences between early (red) and late (blue) treatment session groups for subject 9012 for primary motor (top) and sensory (bottom) cortex. Non-shaded areas denote statistical significance.

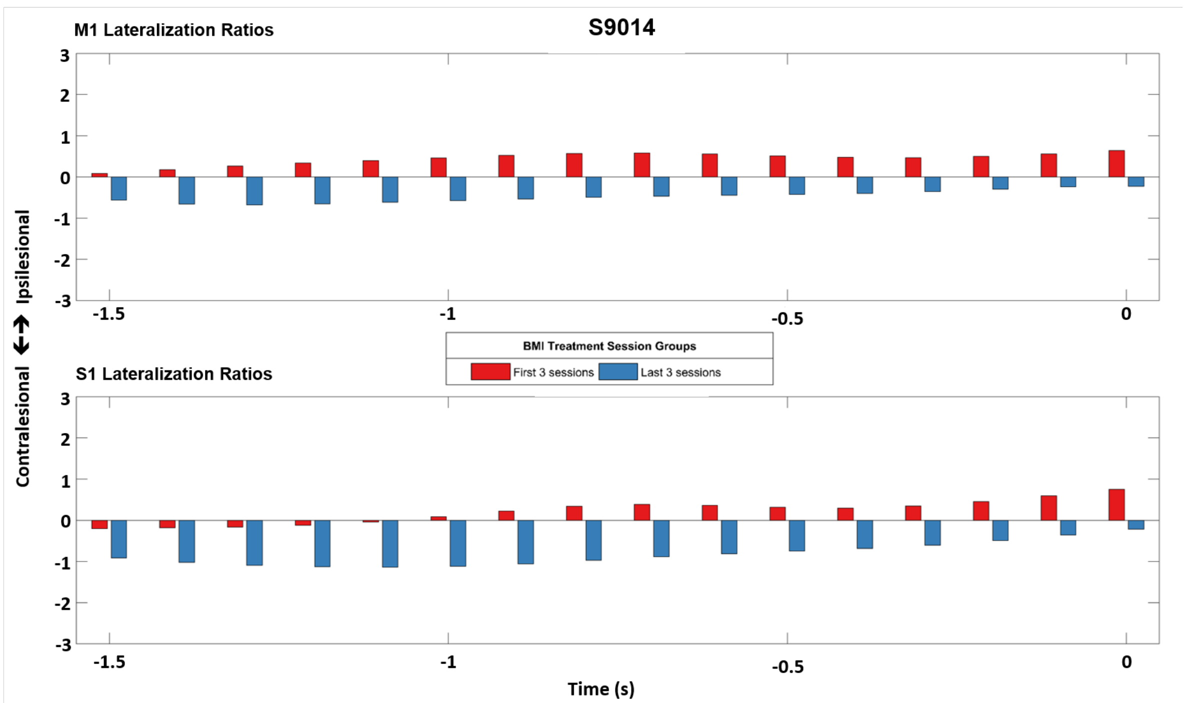

Figure 3.8: Lateralization differences between early (red) and late (blue) treatment session groups for subject 9014 for primary motor (top) and sensory (bottom) cortex. Non-shaded areas denote statistical significance.

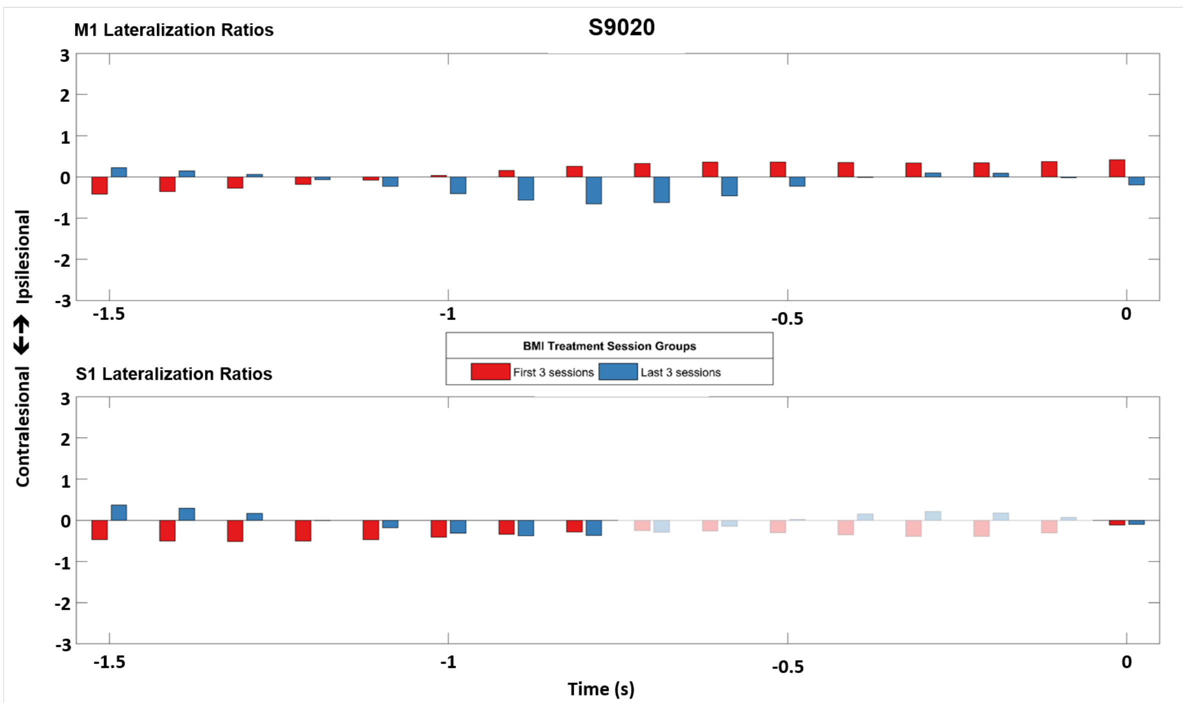

Figure 3.9: Lateralization differences between early (red) and late (blue) treatment session groups for subject 9020 for primary motor (top) and sensory (bottom) cortex. Non-shaded areas denote statistical significance.

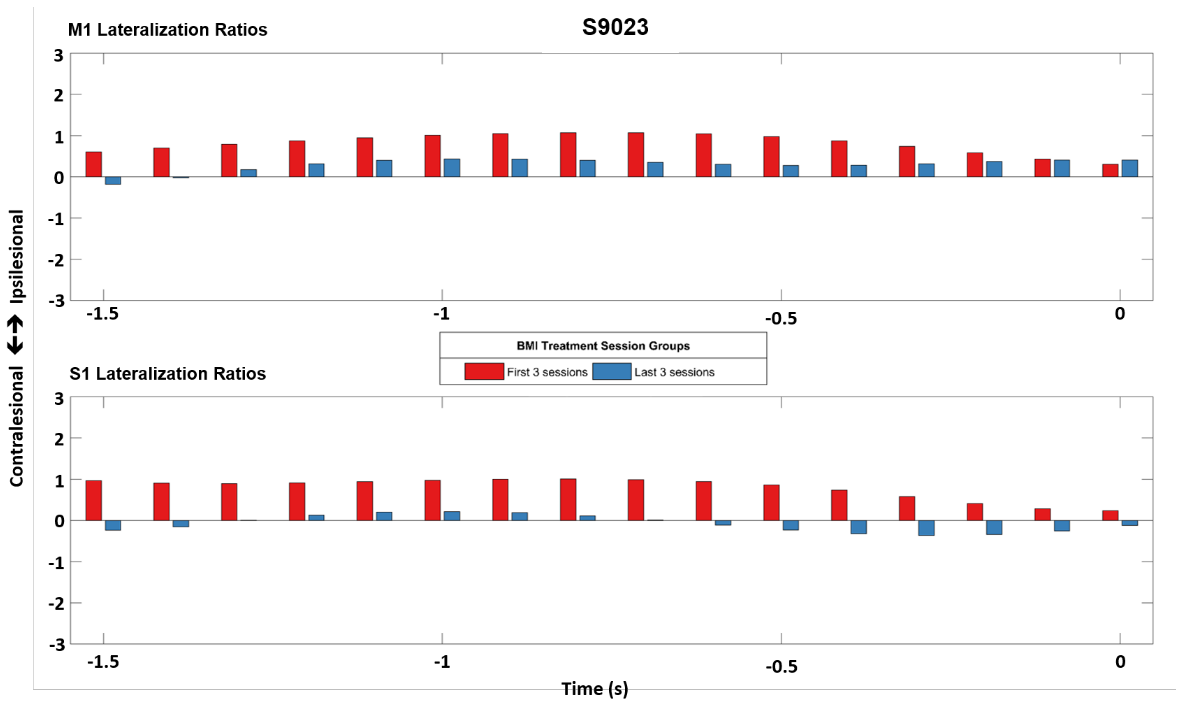

Figure 3.10: Lateralization differences between early (red) and late (blue) treatment session groups for subject 9023 for primary motor (top) and sensory (bottom) cortex. Non-shaded areas denote statistical significance.

early and late session groups of the M1 cortical lateralization ratio at 100-millisecond time segments ranging from 1500 to zero milliseconds before movement onset. The results below are divided based on the primary outcome measured by each clinical assessment. This would include motor impairment, strength, and function/daily living activities, before and after the neurorehabilitation treatment period.

3.2.1 Cortical Lateralization Activity versus Motor Impairment

There appeared to be minimal to no relationship between motor impairment and the cortical lateralization activity when comparing the pre-post treatment differences between Fugl-Meyer Arm Assessment scores and early-late treatment differences between functional lateralization ratio of the M1 region. This relationship, illustrated in Figure 3.11, was invariant to the movement epoch, where R^2 values ranged from 1.1e-5 (t = [-1.1, -1.0], $p = 0.995$) to 0.044 (t = [-1.5, -1.4], $p = 0.734$). However, this effect was attributed to the near-lack of change in motor impairment due to the treatment itself and may not necessarily reflect on the changes in cortical lateralization activity.

3.2.2 Cortical Lateralization Activity versus Motor Strength

Two clinical metrics used for measuring motor strength were grip and pinch strength and the difference in strength, measured in pounds, depicted an overall general direct relationship for pinch grip and inverse relationship for grip strength at certain time segments. For pinch strength (Fig. 3.12) this was most prominent in time segments of [-1.5, -1.4] ($R^2 = 0.46$, $p = 0.208$) and [-1.4, -1.3] ($R^2 = 0.36$, $p = 0.28$) seconds prior to movement onset. In contrast, time segments for grip strength

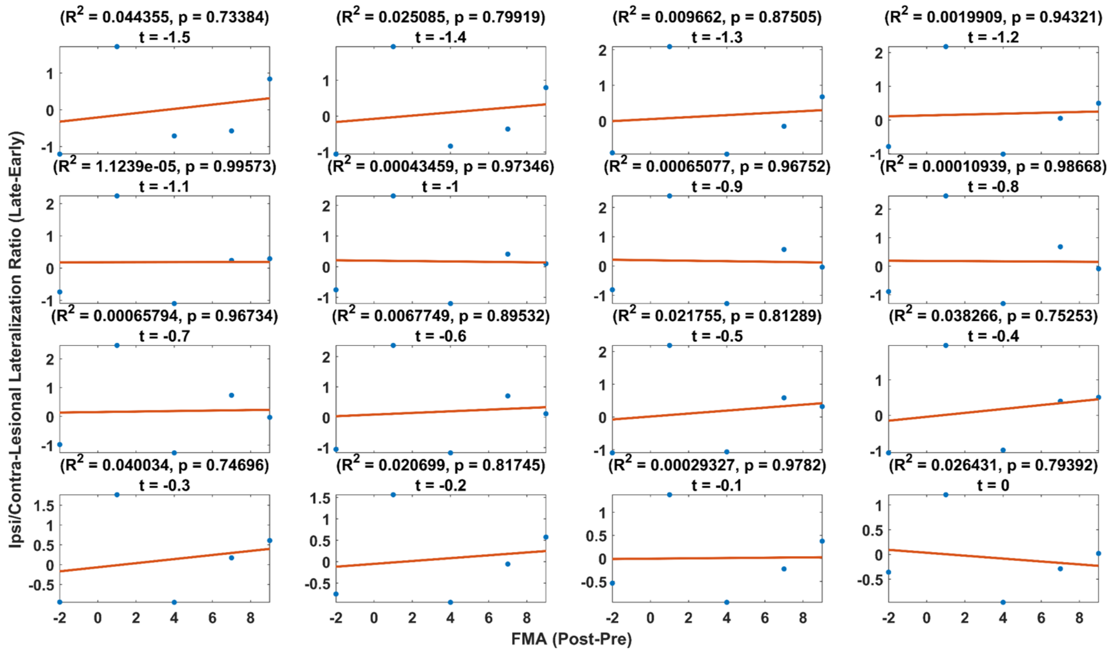

Figure 3.11: Linear regression treatment differences between Fugl-Meyer Arm Assessment score (x-axis) and 100-ms time segment Cortical Lateralization Ratio measures across -1.5 to 0 seconds pre-movement.

had the strongest inverse relationship at [-0.6, -0.5] and [-0.5, -0.4] (both with $R^2 = 0.49$, $p = 0.19$) seconds before arm movement. The relationship between grip strength and M1 cortical lateralization activity treatment differences showed that increases in grip strength correlated to negative lateralization (or increased contralesional) activity among the five subjects and vice versa for decreased grip strength (led to increased ipsilesional activity) due to the treatment intervention. The opposite effect was true for pinch strength, where increased strength correlated to increased ipsilesional activity and vice versa for decreased strength, though the residual variance from the regression line was greater than that of the cortical lateralization activity-to-grip strength residual variance.

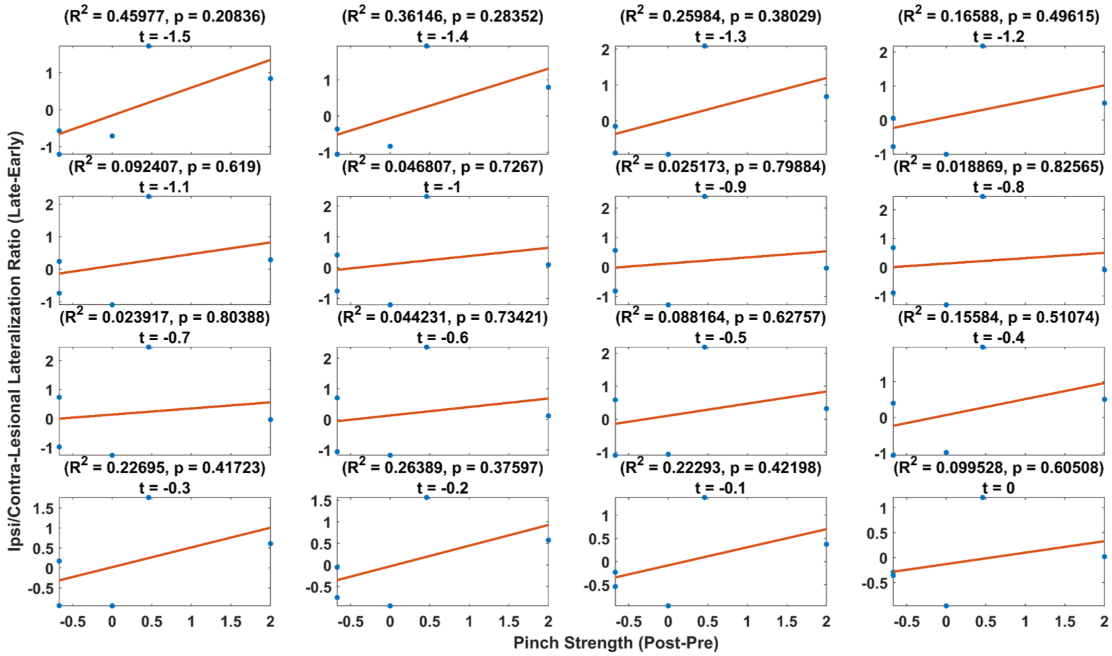

Figure 3.12: Linear regression treatment differences between Pinch Strength (x-axis) and 100-ms time segment Cortical Lateralization Ratio measures across -1.5 to 0 seconds pre-movement onset.

3.2.3 Cortical Lateralization Activity versus Motor Function

Similarly to the relationship between cortical activity and strength, the relationship with motor function was direct or inverse depending on the clinical test. When comparing brain activation time segments with the Arm Research Action Test (ARAT), a direct relationship could be observed, where cortical activity at time segments -800 to -600 milliseconds ($R^2 = 0.38$, $p = 0.26$) correlated the most with ARAT scores (Fig. 3.14). Specifically, higher ARAT score differences (signifying more intact motor function) related to greater ipsilateral activity differences whereas the converse was also true (lower ARAT = less ipsilesional activity). The opposite effect (inverse relationship) held true for the Jepsen-Taylor Hand Function Test (JTHFT) where the greatest correlation between the clinical test and cortical activity occurred between -600 and -400 milliseconds pre-movement onset, as shown in

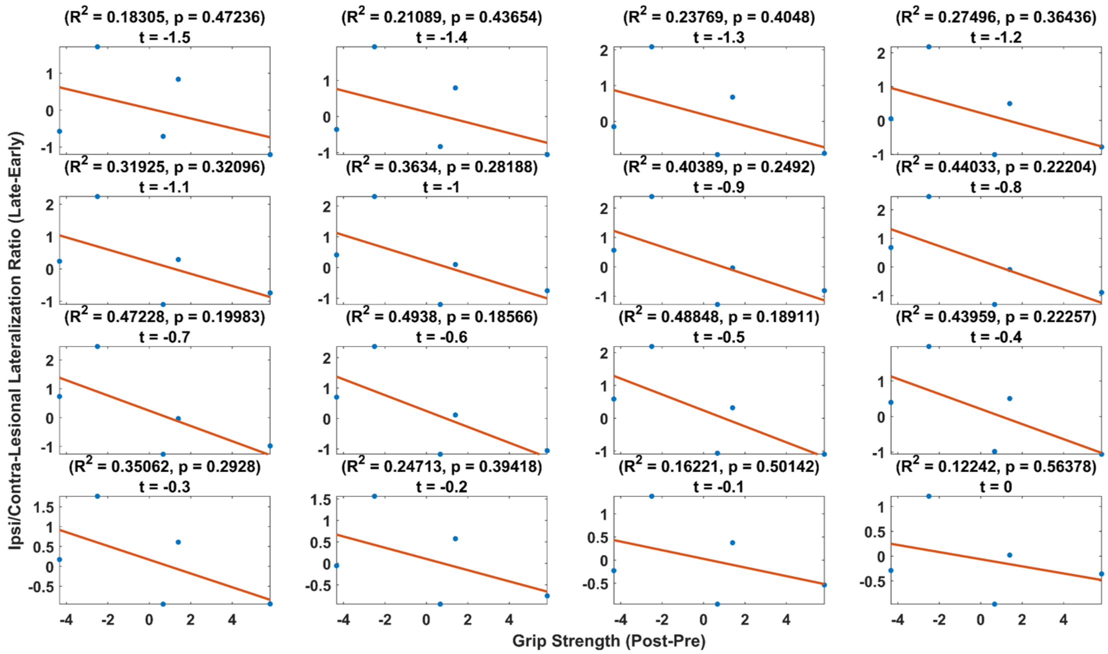

Figure 3.13: Linear regression treatment differences between Grip Strength (x-axis) and 100-ms time segment Cortical Lateralization Ratio measures across -1.5 to 0 seconds pre-movement.

Figure 3.15 ($R^2 = 0.27$, $p = 0.36$). Within this time, an increase in the number of items per second (indicating greater motor function) related to less ipsilesional (or more contralesional) activity while a reduction of this clinical metric related to more ipsilesional activity over the treatment intervention period.

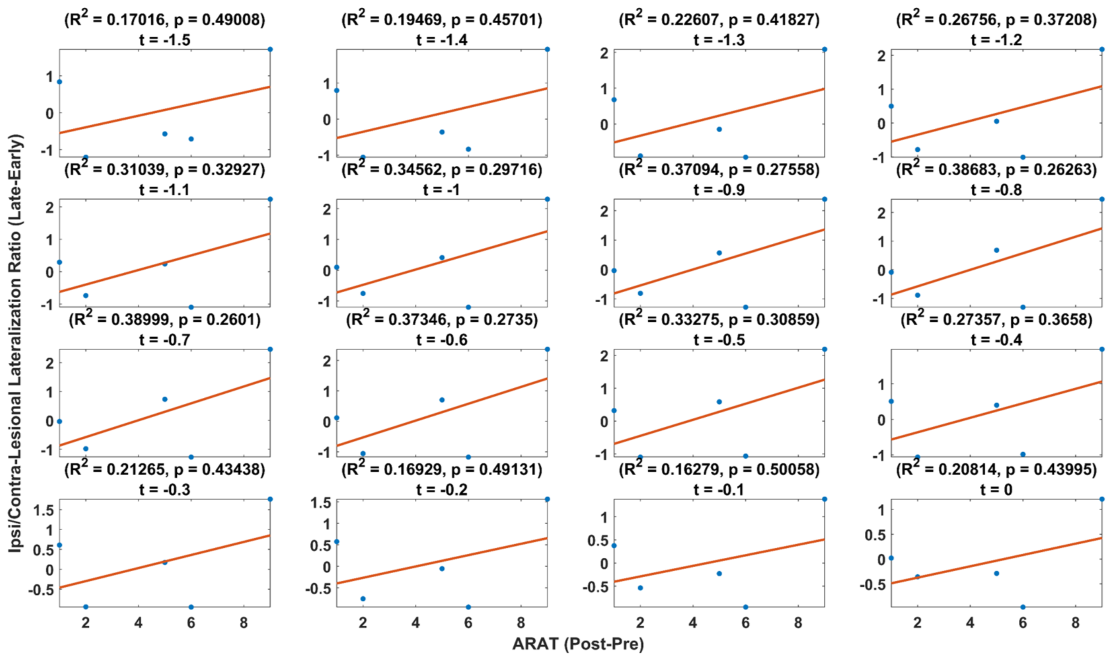

Figure 3.14: Linear regression treatment differences between Action Arm Research Test (ARAT) (x-axis) and 100-ms time segment Cortical Lateralization Ratio measures across -1.5 to 0 seconds pre-movement.

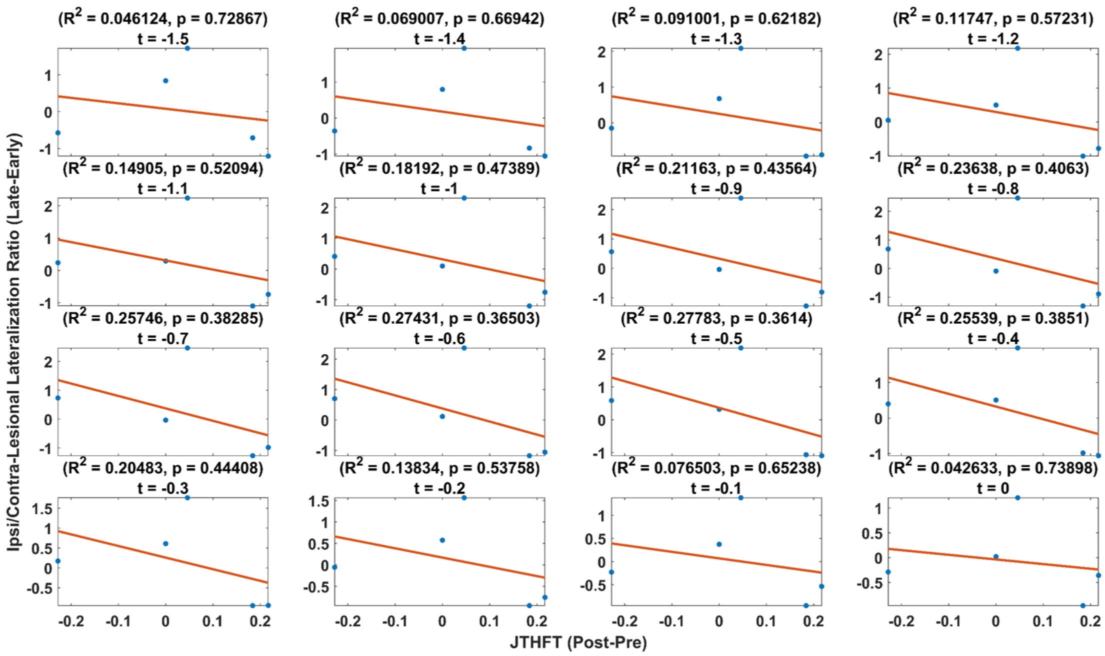

Figure 3.15: Linear regression treatment differences between Jepsen-Taylor Hand Function Test (JTHFT) (x-axis) and 100-ms time segment Cortical Lateralization Ratio measures across -1.5 to 0 seconds pre-movement.

Chapter 4

Discussion

4.1 Neurorehabilitation Treatment Influences Lateralization of Motor-Related Cortical Potentials

The results from Section 3.1 reveal significant differences between the beginning and end of the 10-session, closed-loop BMI treatment intervention. These differences varied by subject, and did not reveal any significant differences between session stages when grouped together across subjects. There could be two different factors causing for this. One factor may simply be a result of small sample size, since most stroke studies tend to collect data from 10 or more stroke survivors. Another more probable factor is that any lateralization variation due to rehabilitation treatment may be specific to the individual and therefore not a common feature among people who have had a stroke. This is reasonable given the various studies depicting such differences between subjects. Even studies involving lateralization effects in stroke recovery [14, 15] have resulted in different outcomes where there appears to be lateralization shifts due to the neuroplastic nature of recovery immediately following the stroke event. Furthermore, other underlying factors such as lesion location, severity of injury, or baseline physical motor attributes could influence the type of outcome each participate experiences throughout the treatment and therefore the measures produced as a result of such influence. Such factors were considered by first constraining the pool of 10 participants from the NIH clinical study to those with only focal subcortical lesions. Fortunately the lesion location for all 5 subjects happened to be within left or right hemispheres of the thalamus, which relieves this study of placing lesion location as a confounding factor. Since not all subjects acquired the same type of injury (3 ischemic/2 hemorrhagic) or volume of damaged tissue (two subjects possessed additional damage in putamen/claustrum regions), the severity of damage might be a major factor which could not be controlled in the outcome of cortical lateralization due to the treatment sessions. Since the type of injury has been shown to have no effect on treatments outcomes [28], the influence of ischemic and as compared to hemorrhagic stroke would not be considered a factor toward cortical and physical changes related to the rehabilitation. Furthermore, though infarct location may play a large role in determining recovery and treatment outcomes, infarct size plays minimal to no role [29]. Lastly, it was understood that various characteristics of upper limb activity such as functionality, strength and impairment could be a potential factor in treatment outcome as well as any cortical lateralization-based differences. Instead of accounting for such differences, the relationship between cortical and physical attributes were explored in order to further understand the magnitude of each effect.

4.2 Treatment Changes in Clinical Outcome Measures Follow Cortical Lateralization Dynamics

Two types of relationships were observed when comparing cortical and arm motion-based metrics. For attributes such as motor impairment, hardly any relationship existed with cortical lateralization activity, whereas various direct and inverse relationships occurred for other attributes such as strength and function of the affected (as well as trained) arm and hand. The low to non-existent relationship between brain activation and motor impairment treatment differences via the Fugl-Meyer Arm Assessment suggests that motor lateralization treatment differences have little to no effect on the level of arm impairment. In fact, even if subjects did improve greatly as a result of the treatment, this didn't correspond to any general trend in increased or decreased ipsilesional (or contralesional) M1 cortical activity. This doesn't infer a lack of neural mechanisms for motor impairment changes, but rather that such changes may be the result of different neural oscillations such as alpha (8-12 Hz) activity motor regions of the brain [30]. Additionally, the Fugl-Meyer Arm score might not be a reliable measure of motor impairment outcomes since only elbow joint movements were trained during the treatment. For this, Fugl-Meyer scores more specific to movements at the elbow could potentially yield stronger relationships with cortical lateralization of the sensorimotor cortex.

Conversely, opposing relationships were observed for both motor strength and function responses to the cortical lateralization activity ratio measure. In regards to motor strength, the opposing relationships where increased ipsilesional activity corresponded to increased pinch grip, but decreased grip strength, could indicate a separation of lateralized MCRPs involved in coarser or finer strength. Hence, finer movements such as finger pinching could involve more ipsilesional motor regions while more gross movements such as grip may recruit contralesional motor regions to assist the movement of more muscles working in synchrony to perform a heavier task. Thus the relationship between lateralization activity and motor strength presents a variation from activity localized to the contra-hemisphere during a unilateral low muscle group-based movement, to bilateral activity utilized to assist in unilateral movements involving many muscle groups coordinating in unison, which will be necessary in future investigations. The contrast in relationships involving either the ARAT score or JTHFT items per second treatment differences might suggest various covert factors contributing to either direct or inverse relationships. For instance, the increased contralesional activity necessary for improving the number of items per second for the JTHFT may be a result of time (specifically performing items quickly) necessitating greater recruitment of the primary motor cortex in performing such timed hand/arm tasks. Obtaining ARAT scores have no such time constraint, since scoring is based on the ability to movement and complete each task. Thus, ipsilesional activity differences suggest a relation to the method of measuring motor function, where merely performing each task is a result of less motor recruitment as compared to more recruitment when timing or speed of the upper limb task becomes crucial to the clinical test.

Overall, the results revealed that a robot-assisted rehabilitation treatment guided using BMIs does in fact induce changes in sensorimotor lateralization that is subject-specific in terms of both brain activity itself as well as the various characteristics of arm motor activity. Though none of the relationships between each clinical motor assessment and cortical lateralization ratio were deemed significant ($p < 0.05$), the general trend at areas with the lowest p-values indicate possible significant relationships if more subjects were acquired for this thesis. Nonetheless, though sensorimotor lateralization may become more utilized in stroke rehabilitation, especially in conjunction with BMIs [31, 32], its use in monitoring treatment outcomes may offer a different perspective which could further inform physical therapists and clinicians toward rehabilitation treatments better tailored to the individual patient.

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