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Cassandra J Fierro March 3, 2019

Reevaluating Structural and Functional Correlates of Chronic Poststroke Motor Impairment

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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
of the requirements of the degree of
Bachelor of Sciences with Honors

Neuroscience and Behavioral Biology

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Abstract

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Stroke is an increasingly critical public health concern now being the leading cause of long-term adult disability in the United States –the most common disability being upper-extremity movement dysfunction. The interhemispheric imbalance model suggests that abnormal inhibition between hemispheres, specifically greater inhibition of the unaffected primary motor cortex (cM1) on the affected motor cortex (iM1), reduces neuroplasticity and limits maximal recovery of normal arm motor production. This study aimed to investigate the relationship between interhemispheric inhibition (IHI) in stroke with the structural integrity of sensorimotor pathways and with measures of behavioral motor outcomes. 13 individuals with chronic ischemic stroke (mean age: 63.5 ± 11 years, 7 males) completed TMS assessments, diffusion-weighted magnetic resonance imaging scans and behavioral motor assessments. IHI was measured in participants using a TMS paired-pulse paradigm from both cM1 to iM1 and iM1 to cM1. A single-pulse TMS condition (SP120) was performed to determine individual baseline cortical excitability. Both TMS conditions recorded motor-evoked potentials (MEPs) from the contralateral FDI hand muscle of the test-stimulus hemisphere. In contrast to the model, greater IHI was seen from iM1 to cM1 in participants. Measures of lower fiber tract integrity of transcallosal sensorimotor projections was associated with less IHI from cM1 to iM1, trending toward facilitation. Measures of lower fiber tract integrity in the ipsilesional CST were also associated with less IHI in the cM1-to-iM1 condition. Behavioral outcomes assessed using the nine-hole peg test, Wolf motor function test and upper-extremity Fugl-Meyer assessment revealed no relationships with IHI. The results of this study do not support the interhemispheric imbalance model. Rather, the results strengthen recent evidence for the differential roles of cM1 in post-stroke motor recovery based on structural reserve as the degree of inhibition from cM1 to iM1 was associated with structural integrity of sensorimotor pathways. The conflicting literature on the imbalance of IHI after stroke may be related to individual post-stroke outcomes which affect the role of cM1 in upper-limb motor rehabilitation, and should be considered for the future of individualized rehabilitation treatments.

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Acknowledgements

I would like to sincerely thank my advisor, Dr. Michael Borich, for supporting all of my research endeavors and for all of the invaluable opportunities and experiences I have received in the lab during the past four years. I would also like to thank Dr. Keith Easterling for always being an enthusiastic professor who has generously offered me much academic and professional guidance these past four years. Thank you, also, to Shiyu Lin for the collaboration and tireless discussions together during this project.

Table of Contents

Background

Stroke is an increasingly critical public health concern now being the leading cause of long-term adult disability in the United States (Mozaffarian et al., 2016). Stroke has a wide range of debilitating effects with upper-extremity movement dysfunction being one of the most common (Lawrence, 2001). Yet, current rehabilitation methods vary in their effectiveness and optimal treatment for each patient remains poorly defined (Langhorne, Coupar, and Pollock, 2009). An imbalance of inhibition between primary motor (M1) cortices is observed after stroke which is thought to reduce neuroplasticity and limit maximum recovery of normal arm motor production (Murase et al., 2004; Sauerbrei et al., 2012; Vuilleumier et al., 1996). This imbalance has been exploited in modern rehabilitation therapies which use repetitive transcranial magnetic stimulation to either increase excitability of the ipsilesional M1 or reduce excitability of the contralesional M1 (Hummel and Cohen, 2006; Muellbacher et al., 2000; Pascual-Leone et al., 1994). However, the efficacy of this approach has been widely disputed and the significance of aberrant interhemispheric inhibition for post-stroke motor recovery is not well understood. Contributing to the characterization of the structure and function of motor pathways involved in interhemispheric inhibition after stroke could help inform the direction of future rehabilitation treatments and contribute to recovery prognosis.

A current theory on motor dysfunction in the paretic upper-limb is outlined by a model of abnormal interhemispheric inhibition (IHI). The model states that an imbalance of IHI occurs between M1 cortices due to ischemic lesioning and subsequent maladaptive cortical reorganization. The ipsilesional motor cortex (iM1) exhibits reduced excitability in relation to the contralesional motor cortex (cM1), which becomes more excitable (Murase et al., 2004; Kirton et al., 2010; Liepert et al., 2000). This phenomenon is thought of as a compensatory

mechanism whereby the unaffected hemisphere increases its inhibition of the affected hemisphere during unilateral motor movement.

Quantification of IHI between M1s can thus be used to assess the function of transcallosal motor pathways in stroke. IHI is measured using transcranial magnetic stimulation (TMS), a type of noninvasive brain stimulation which induces electromagnetic pulses over a specific cortical region. In the IHI dual-coil paradigm, a conditioning-pulse is applied over one hemisphere which inhibits the size of a motor evoked potential (MEP) produced in a target muscle by a test-pulse on the homotopic region of the contralateral hemisphere. Although IHI has been widely investigated and reviewed in the field, it is still not fully understood.

Previous TMS and transcranial direct stimulation studies that have investigated IHI in stroke display large variability in their conclusions about its role in persistent motor impairment –specifically for individuals with greater impairments. Furthermore, recent publications have produced growing evidence refuting the interhemispheric imbalance model as a maladaptive mechanism and suggest that it may, for some individuals, play a supportive role in motor recovery (Bradnam et al., 2013, Di Pino et al., 2014, McCambridge et al., 2017; Plow et al., 2016). The Bimodal Balance Recovery model describes that an imbalance of IHI may be maladaptive in individuals with high levels of intact ipsilesional motor pathways, or 'structural reserve', yet could be beneficial to recovery for individuals with low structural reserve due to vicariation of intact cortical areas (Di Pino et al., 2014).

In order to characterize the structural state of neuronal pathways involved in motor movement, current methods in diffusion-weighted magnetic resonance imaging (DW-MRI) can be used to reconstruct neuronal tract images through the measurement of water diffusion within white matter tissue. Microstructural properties of these neural tracts can be described with

diffusion metrics and are have been widely used to quantify structural white matter pathway integrity and degeneration in stroke (Lindenberg et al., 2010; Stinear et al., 2007; Werring et al., 2000). Both transcallosal and corticospinal motor pathways were investigated.

The corpus callosum is the major brain commissure connecting homologous cerebral cortices. This white-matter structure, which facilitates interhemispheric communication, is implicated in modulating motor movement (Takeuchi et al., 2010). The model of IHI implicates the corpus callosum as the major pathway by which motor cortices can send excitatory projections onto inhibitory interneurons of the contralateral motor cortex to evoke inhibition. This is evidenced from studies of individuals with callosal agenesis who were unable to elicit interhemispheric inhibition (Meyer et al., 1995). Furthermore, somatosensory and motor cortices run bilaterally through the callosum and often suffer damage after stroke leading to upper extremity motor impairments. The relationship between transcallosal sensorimotor fiber status and IHI in stroke has not been elucidated. Evaluating transcallosal primary motor and somatosensory tracts may reveal potential structural communication factors as underlying mechanisms of unbalanced IHI post-stoke.

The corticospinal tract (CST) is also an essential pathway for motor output from M1 to the periphery. DW-MRI is commonly used to assess the structural differences between the ipsilesional and contralesional CST post-stroke. Previous studies have produced much evidence showing relationships between CST integrity and upper-extremity motor function in stroke (Jang et al., 2014; Stinear et al., 2007; Werring et al., 2000). Specifically, positive correlations have been revealed between higher metrics of fiber tract integrity in the CST and increased motor function in individuals with chronic stroke (Jang et al., 2014). Furthermore, structural asymmetries between bilateral CST projections have been associated with levels of IHI in stroke

(Cunningham et al., 2015). By evaluating properties of bilateral CST projections with IHI, this study will contribute to the understanding of the relationship between structure and function of IHI pathways as well add to findings of previous literature.

The aim of the present study is to assess associations between physiological function of motor pathways and integrity of sensorimotor tract structure in stroke. Secondly, this study aims to characterize the relationship between measures of sensorimotor pathway structure and function with chronic poststroke motor outcomes. By adding to the current knowledge of the structure and function of motor pathways in the stroke-affected brain, insights into the role of IHI for motor rehabilitation can lead to advancements in treatment approaches and recovery prognosis.

Methods

Participants.

Thirteen participants with chronic ischemic stroke (mean age: 63.5 ± 11 years, 7 males) completed MRI scans, TMS assessments, and behavioral motor assessments (Table 1). Exclusion criteria included: hemorrhagic stroke, history of multiple clinically-significant strokes, neurodegenerative disorders or psychiatric diagnosis, age outside the range of 18-85 years, or contraindications to MRI or TMS. Participants provided written informed consent in accordance with the Declaration of Helsinki. The Emory Institutional Review Board approved all study procedures.

Table 1. Stroke Participant Characteristics

ID	Sex	Age (y)	PSD (mo)	Stroke Hemisphere	Lesion Location	UEFMA score
S01	M	73	9	R	R IC/BG	45
S02	F	48	11	R	R IC/BG	60
S03	F	74	14	R	R IC/BG	40
S04	F	44	22	R	R PLIC	55
S05	F	62	164	L	L IC	61
S06	M	80	54	R	R MCA*	35
S07	F	64	53	R	ACA	58
S08	M	66	156	L	L BG	66
S09	M	50	66	L	L MCA	60
S10	M	74	23	L	L Brainstem (pons)	51
S11	M	72	34	R	L Brainstem (pons)	54
S12	M	56	69	R	L Frontal, Parietal, cortical/subcortical WM	53
S16	F	63	42	L	L PLIC, striatum	35
	M= 7	63.5 ± 11	56.3 ± 56	LH = 5		51.8 ± 10

Abbreviations: F, female; M, male; L, left; R, right; LH, left hemisphere; PSD, poststroke duration; IC, inner capsule; BG, basal ganglia; PLIC, posterior limb of the inner capsule; MCA, middle cerebral artery; ACA, anterior cerebral artery; WM, white matter. Group value is expressed as mean ± SD.

*Diffusion imaging suggests lesion may, in fact, not be from an MCA ischemia. Possible hemmoragic stroke.

TMS assessment.

A two-coil, paired-pulse, TMS protocol was performed to measure interhemispheric inhibition between M1 cortices. Procedure employed two TMS monophasic stimulators (2002, Magstim Company Ltd.) attached to figure-of-eight coils (Magstim 70mm P/N 9790, Magstim Co., UK) to induce electromagnetic pulses over primary cortical motor regions (M1s). M1s were in reference to lesion location (iM1/cM1). M1 hotspots were localized for ~50μV motor evoked potentials (MEPs) in the first dorsal interosseous (FDI) hand muscle. Hotspot localization applied each participant's T1-weighted scan to co-register anatomical landmarks for real-time stereotactic neuronavigation (Brainsight®, Rouge Research Inc.). Resting motor threshold (RMT) was determined bilaterally according to standard protocol (Rossini et al., 2015).

Two TMS conditions were used to evaluate cortical excitability and interhemispheric inhibition. The first TMS condition (SP120) involved 20-30 suprathreshold single-pulses

delivered at rest over M1 (120% RMT, ≤ 0.25 Hz) to measure individual cortical excitability of each hemisphere. The second TMS condition employed standard IHI procedure consisting of 20-30 suprathreshold double-pulses (120% RMT, ≤ 0.25 Hz) delivered to bilateral M1 cortices. The first conditioning-pulse was applied to an M1 hemisphere followed by a test-pulse over the contralateral M1 with a 10ms interstimulus interval (ISI) in between. This ISI is an established timing which is known to evoke inhibition (Ferbert et al., 1992). The conditioning-pulse inhibits the size of the MEP amplitude produced by the test-pulse. IHI is measured both from the contralesional to ipsilesional M1 (cM1-to-iM1 condition) and from the ipsilesional to contralesional M1 (iM1-to-cM1 condition). The MEP evoked from the hand contralateral to the test-pulse hemisphere is used for the IHI calculation. The test-pulse MEP is converted into a ratio of the average test-pulse MEP amplitude over the average SP120 MEP amplitude from the equivalent hemisphere. This ratio is interpreted as the amount of MEP amplitude suppression, or inhibition, induced by the conditioning-pulse hemisphere where a higher ratio indicates less inhibition and a lower ratio indicates greater inhibition.

EMG Recording and Preprocessing.

Surface electromyography data (EMG) were continuously recorded bilaterally from the first dorsal interosseous (FDI) muscles using a three-channel EMG device (Rogue Research Inc., Canada). EMG data were processed through a written program in MATLAB 2016a. Peak-to-peak amplitudes of motor evoked potentials (MEP) were automatically quantified and manually reviewed for accuracy.

Diffusion-weighted magnetic resonance imaging.

Diffusion-weighted magnetic resonance imaging (DW-MRI) was acquired on a Siemens 3T Trim Trio whole-body scanner. Six non-weighted images (b-value: 0 s/mm2), 128 weighted and phase encoded images (64 gradient directions; b-value: 1000 s/mm2; TR/TE: 8700/93ms; FOV 256 mm; resolution of 2x2x2 mm3; and 64 slices with no gap), and structural T1-weighted anatomical scans (TR= 2300 ms, TE= 2.89 ms, flip angle θ = 8°, FOV = 256 x 256 mm, 176 slices, 1 mm3 isotropic voxel) were obtained.

ExploreDTI software (Leemans et al., 2009) was used to convert the 2D DW-MRI images slices into a 4D nifti file and a corresponding b-matrix text file. Both files were then exported to FSL software (PsychINFO Database Record © 2016 APA) for further preprocessing. Corrections for distortions (subject motion and eddy current distortion) and image merging were performed to augment the image quality. Merging procedure entailed a two-step process. Non-weighted images with reversed phase-encoded polarities were initially used to estimate the susceptibility-induced off-resonance field. The field parameters were then fed in an FSL eddy tool to merge and correct the weighted images for each participant. The resultant file was then used for image visualization, corpus callosum partitioning, CST delineation, and whole-brain fiber tractography in ExploreDTI.

To map the structural connectivity of transcallosal pathways, whole brain deterministic tractography was run on the corrected images in ExploreDTI. Constrained Spherical Deconvolution (CSD), a non-tensor based model, was used to estimate fiber tract orientations for tractography at each voxel (seedpoint resolution of 2 x 2 x 2 mm3, 0.2 mm step size, and angle threshold of > 30°). This model was preferred to tensor-based alternatives due to its ability to estimate non-Gaussian diffusion processes and reconstruct crossing fibers (Tournier et al., 2004).

After performing whole-brain tractography, fiber tracts in both the corpus callosum and part of the CST were obtained.

In examining the corpus callosum, the commissure was partitioned into five regions representing transcallosal projections between homologous cortical regions (Hofer and Frahm, 2006) (Figure A). Partitions III and IV were of interest, containing projections between the primary motor and sensory cortices, respectively. The partitions were used as the region of interest (ROI) and was manually delineated with AND masks. A NOT mask was drawn above and below the corpus callosum to minimize the presence of non-transcallosal reconstructed fiber tracts.

CST tracts were extracted bilaterally using AND masks around the internal capsules at the inferior and superior levels of the pons and at the level of the precentral gyrus. Regions were then flanked with NOT masks to prevent extraction of non-corticospinal tracts.

Four diffusion metrics were obtained from these regions of interest: mean diffusivity (MD) as a scalar measure of average diffusion, fractional anisotropy (FA) as an index of the degree of restricted diffusion, fiber volume (FV), and fiber number (FN). These metrics were used as quantitative analyses of water diffusion behavior within tracts and of fiber quantity which thus indexed white matter tract integrity.

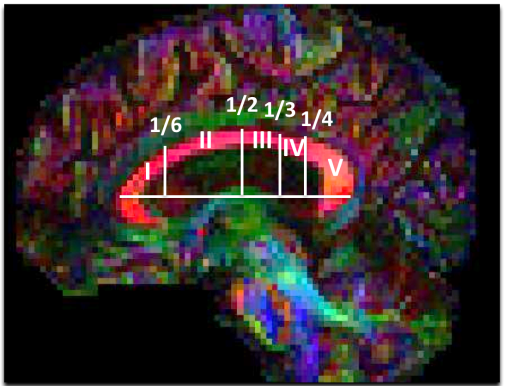

Figure 1. The corpus callosum was partitioned into different cortical regions (regions I-V) where homologous fibers transverse the corpus callosum. Regions of interest (ROIs) were delineated for partitions III and IV in the mid-sagittal plane, representing primary motor and somatosensory cortical tracts. Fiber tracts were reconstructed for these regions and diffusion metrics were extracted to assess structural characteristics of pathways.

Upper-Extremity Motor Assessments.

Three behavioral assessments were administered to the stroke cohort: Wolf motor function test (WMFT), upper extremity Fugl-Meyer assessment (UEFMA) and nine-hole peg test (NHPT) which each provided indices of upper extremity motor function, level of physical impairment, and manual dexterity, respectively. Tests were performed by a licensed physical therapist (M.R.B).

Paretic and non-paretic performance were assessed for the WMFT. Participants completed 15 timed motor tasks, which were averaged and used in a task rate calculation for a projected mean rate of individual task performance. Individuals who could not complete a task in under 120 s were ascribed a mean rate of zero. The mean WMFT rate has been validated as a measure of upper extremity motor function in stroke-affected individuals (Wolf et al., 2001). To measure upper extremity motor impairment, the UEFMA is scored off 33 items testing motor

functioning, sensory functioning, balance, and joint range of motion. Each item is ranked on a scale of 0-2, where higher scores indicate less impairment (Duncan et al., 1983). The NHPT for manual dexterity is a bilateral timed test which requires participants to use their thumb and forefinger to remove, and then replace, nine pegs from a board at their fastest pace. An average rate for each hand is calculated per individual.

Statistical analyses.

All statistical analyses will be performed using GraphPad Prism (version 8.00 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com). Non-parametric one-sample and two-sample Wilcoxon signed rank tests were performed to evaluate within and between group differences. Linear regression was used to analyze the association between the magnitude of conditioning pulse MEP amplitudes with IHI. Linear regression was also performed to delineate relationships between diffusion metrics with dependent variables of behavioral motor assessments and IHI. Significance level is set at $p< 0.05$ for all statistical comparisons.

Results

SP120 MEP amplitudes are significantly different between hemispheres.

The SP120 condition was administered to index individual resting cortical excitability for each hemisphere. SP120 MEP amplitudes were used in the IHI calculation, but also to assess whether baseline excitability differed between lesioned and non-lesioned hemispheres. Significantly smaller MEP amplitudes were seen for iM1 which suggests that the affected hemisphere has reduced cortical excitability compared to the unaffected hemisphere (Figure 2).

Figure 2.

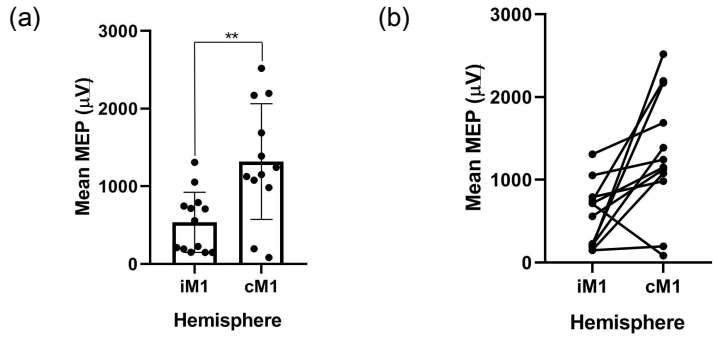

Figure 2. Less cortical excitability in iM1 compared to cM1. (a) Single-pulse TMS at 120% RMT (SP120) over iM1 resulted in a significantly smaller MEP amplitudes than SP120 over cM1. A nonparametric Wilcoxon matched-pairs signed rank test was performed to determine significance (n= 12/group, Mean ± SD, $p<0.01$). (b) Matched participant hemispheres show lower mean MEP amplitudes for iM1 compared to cM1.

Less inhibition is seen from cM1 to iM1 than from iM1 to cM1.

To investigate inhibitory activity between motor cortices after stroke, the IHI paired-pulse TMS paradigm was performed bi-directionally; the degree of inhibition was measured both from the unaffected M1 (cM1) to the affected M1 (iM1) and from the affected M1 to the unaffected M1. The iM1-to-cM1 condition produced significantly smaller IHI ratios, indicating greater MEP suppression, and therefore inhibition, than the cM1-to-iM1 condition (Figure 3). Namely, the lesioned hemisphere showed more inhibition of the non-lesioned hemisphere than the converse.

Figure 3.

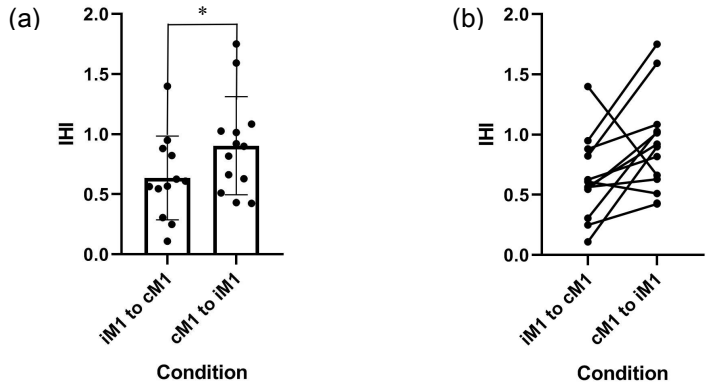

Figure 3. Lower inhibition found in the cM1-to-iM1 condition. In the paired-pulse TMS procedure for assessing IHI, the iM1-to-cM1 condition resulted in significantly lower IHI ratios indicating greater inhibition from iM1 to cM1 than from cM1 to iM1. Nonparametric Wilcoxon matched-pairs signed rank test was performed to determine significance (n= 12-13/group, Mean ± SD, *$p<0.05$). (b) Matched participant data show trends of greater interhemispheric inhibition in the iM1 to cM1 condition and less interhemispheric inhibition in the cM1 to iM1 condition (n=12).

A robust regression and outlier removal (ROUT) method analysis was used to determine outliers in the IHI ratios. No significant outliers were found for either the cM1-to-iM1 or iM1-to-cM1 condition.

MEP amplitudes from conditioning-pulses are not significantly different from SP120 MEP amplitudes for both hemispheres.

To assess the consistency of the magnitude of conditioning-pulse MEPs, conditioning-pulse MEP amplitudes were compared to SP120 MEP amplitudes of the equivalent hemisphere as both conditions apply single-pulse TMS at 120% RMT. A one sample Wilcoxon signed rank

test determined that the ratios of conditioning-pulse MEPs over SP120 MEPs did not significantly differ from 1 in both the iM1-to-cM1 and cM1-to-iM1 conditions (n=12; p=0.380, 0.677). This evidences that conditioning-pulse responses were consistent with baseline SP120 responses.

No associations found between conditioning-pulse MEP ratios with degree of IHI for both cM1-to-iM1 and iM1-to-cM1 conditions

In order to improve upon current analyses in IHI studies, this investigation sought to examine the relationship between the magnitude of conditioning-pulse MEP amplitudes and subsequent test-pulse MEP amplitudes. It is hypothesized that greater conditioning-pulse MEP amplitudes may be related to greater test-pulse MEP amplitudes and therefore could confound quantification of IHI. To test this hypothesis, conditioning-pulse MEP amplitudes were plotted against IHI values. Linear regression revealed no relationships between these two variables (Figure 4).

Figure 4.

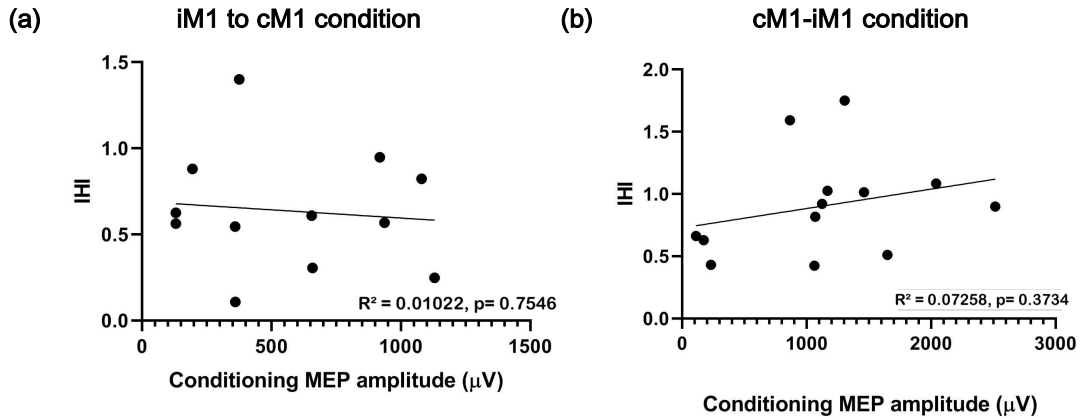

Figure 4. Level of IHI is not associated with magnitude of conditioning-pulse MEPs. Conditioning-pulse MEP amplitudes were not related ($p>0.05$) to the amount of IHI produced in either the (a) iM1-to-cM1 ($R^2=0.01022$) or (b) cM1-to-iM1 condition ($R^2=0.07258$). Linear regression analyses were performed to test significance of associations (n= 12/group).

Diffusion metrics of bilateral corticospinal tracts are asymmetric for FA and MD but not FV or FN.

After stroke, lesions can cause hemispheric deficits to the ipsilateral CST. To evaluate asymmetries between the fiber tracts of the ipsilesional CST (iCST) and contralesional CST (cCST), differences in the values of diffusion metrics between the tracts were calculated (cCST subtracted from iCST). Both FV and FN showed similar values between tracts. FA and MD values, however, are significantly different between hemisphers with lower fiber tract integrity in the iCST. This result indicates equivalent fiber tract structure, but asymmetric fiber tract integrity between hemispheres (Figure 5).

Figure 5.

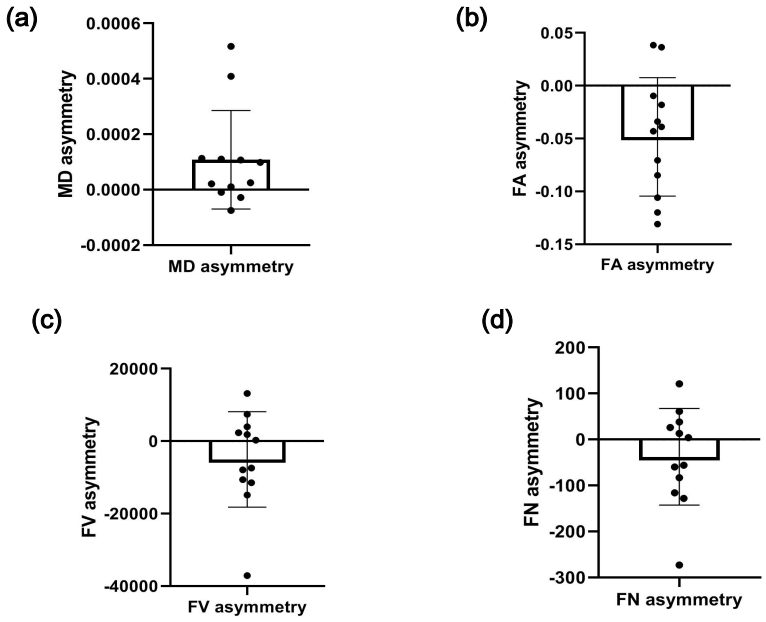

Figure 5. Measures of fiber tract integrity show differences between ipsilesional and contralesional corticospinal tract projections. A non-parametric one-sample Wilcoxon test determined differences between (a) mean diffusivity (MD) and (b) fractional anisotropy (FA) of bilateral CST projections to be significantly different from zero, indicating an asymmetry between ipsilesional and contralesional CST integrity where the ipsilesional tracts had lower fiber tract integrity (n= 12/group; Mean ± SD, $p<0.05$). (b) Fiber volume (FV) and (c) fiber number (FN) were not determined to be significantly different between bilateral CST (n= 12/group; Mean ± SD).

Impairments in upper-limb motor movement and manual dexterity are seen in stroke cohort.

The NHPT and UEFMA were evaluated in the participants to confirm that the cohort expressed a degree of motor impairment. Additionally, these two assessments and the WMFT served to each evaluate different components of motor movement. NHPT rates of the paretic

hand were significantly slower than the nonparetic hand indicating a degree of impairment in paretic hand dexterity. The UEFMA is an assessment of upper-extremity motor impairment where a score of 61 and below indicates an impairment. The average UEFMA for the group was 51.8 which additionally suggests that the group displayed a level of overall motor impairment.

Figure 6.

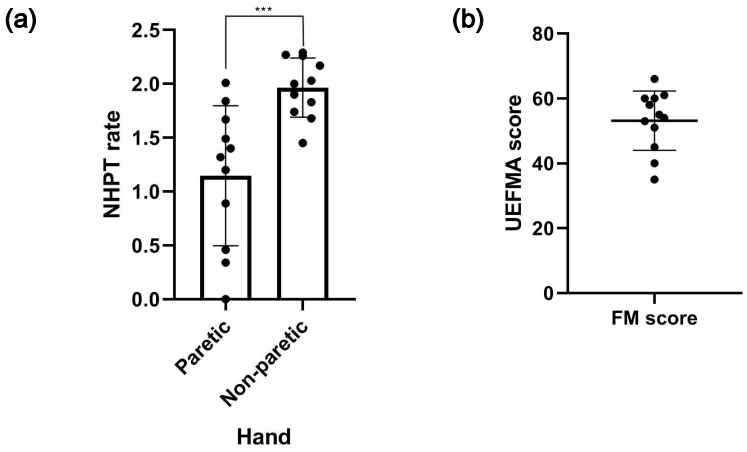

Figure 6. Motor impairment confirmed in stroke cohort. The NHPT is an assessment of hand dexterity where individuals are asked to place and then remove 9 plastic pegs from 9 holes in a board using only their index and fore-finger. The rate of task completion was recorded from both hands. (a) A Wilcoxon matched pairs signed rank test determined that the paretic NHPT rate was significantly slower than the nonparetic rate ($p=0.001$) indicating impairment in paretic hand dexterity in the cohort. (b) Additionally, the UEFMA is an assessment of upper-extremity motor impairment scored out of 66, where any score below 61 is considered impaired. The mean group score for the assessment was 51.8 ± 10 which suggests that the cohort overall displayed motor impairments.

Transcallosal MD and FA are associated with IHI from cM1 to iM1.

The level of IHI measured from cM1 to iM1 is relevant for unilateral movement of the paretic arm, which is facilitated by transcallosal sensorimotor projections. To investigate the relationship between the structural reserve of transcallosal pathways and IHI involved in paretic movement, diffusion metrics (MD, FA, FV and FN) were extracted and compared to the level of IHI. Measures of transcallosal MD and FA were evidenced to be related to IHI. Participants with higher transcallosal FA and lower transcallosal MD values, indicating higher fiber tract integrity, had lower IHI ratios meaning greater inhibition from cM1 to iM1. Individuals with the lowest values of FA and highest values of MD –signifying lower fiber tract integrity –showed high IHI ratios, expressing facilitation (IHI ratios greater than 1) rather than inhibition (Figure 7).

Figure 7.

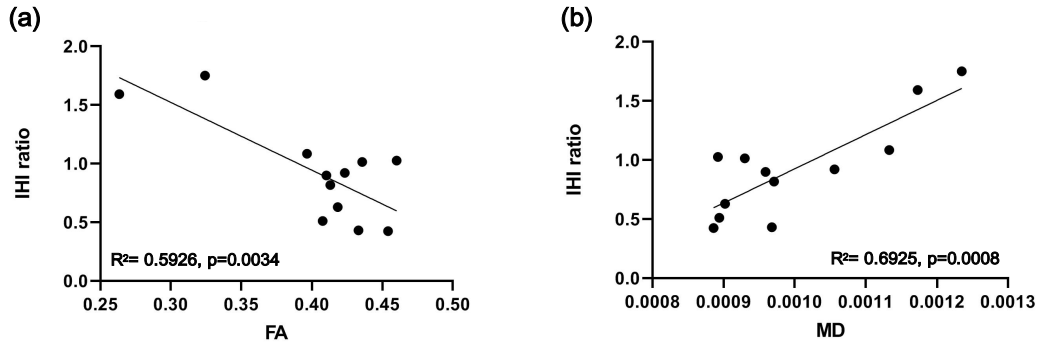

Figure 7. IHI is associated with metrics of transcallosal fiber tract integrity in the cM1-to-iM1 condition. Linear regression of measures of transcallosal (a) mean diffusivity (MD) and (b) fractional anisotropy (FA) revealed relationship to the degree of IHI produced from cM1-to-iM1 (n=12/group). Participants with smaller FA and greater MD values, implying lower fiber tract integrity, show less inhibition from cM1-to-iM1 than individuals with higher fiber tract integrity.

Transcallosal diffusion metrics are associated with IHI from iM1 to cM1.

To further delineate the relationship between the structural integrity of transcallosal projections and IHI, diffusion metrics of transcallosal sensorimotor tracts were compared with levels of IHI in the iM1-to-cM1 condition. Indices of higher fiber tract integrity (higher FA, lower MD, greater FN and greater FV) were associated with less inhibition from iM1 to cM1 (Figure 8).

Figure 8.

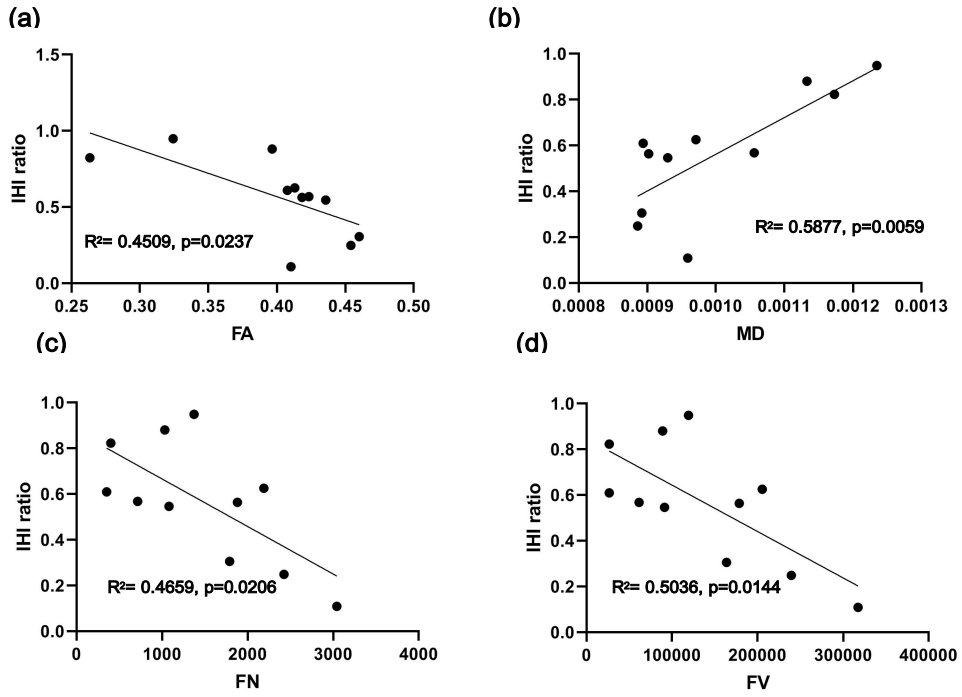

Figure 8. IHI from iM1-to-cM1 is associated with metrics of transcallosal sensorimotor tract integrity. Linear regression of diffusion metrics of transcallosal sensorimotor projections revealed relationships with the degree of IHI produced in the iM1-to-cM1 condition. (a) Lower fractional anisotropy (FA), (b) higher mean diffusivity (MD), (c) lower fiber number (FN) and (d) lower fiber volume (FV) were associated with the higher IHI ratios, or less inhibition, in the iM1-to-cM1 condition (n= 11/group; $p<0.05$).

Asymmetries in CST integrity are related to IHI in the cM1-to-iM1 condition.

The iCST showed significantly lower fiber tract integrity given by lower FA and higher MD values. To test whether these asymmetries were related to the degree of inhibition of the unaffected hemisphere (cM1) on the affected hemisphere (iM1), asymmetries of diffusion metrics were plotted against degree of IHI in the cM1-to-iM1 condition. Greater CST asymmetry in FA and MD values was associated with less IHI, trending toward facilitation (Figure 9).

Figure 9.

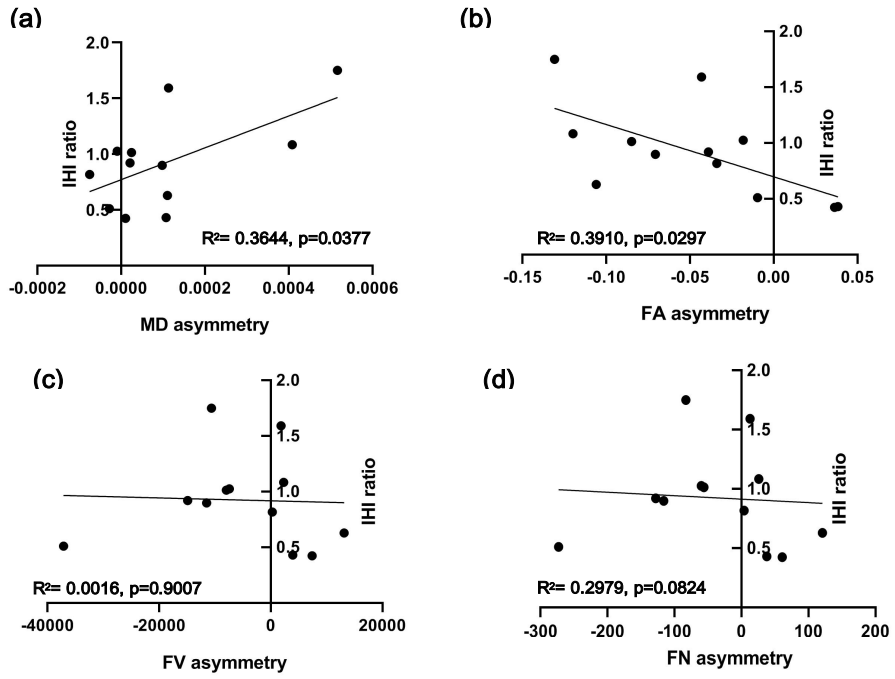

Figure 9. FA and MD CST asymmetry show associations to IHI from cM1 to iM1. Linear regression of (a) mean diffusivity (MD) and (b) fractional anisotropy (FA) asymmetry revealed significant associations to IHI in the cM1-to-iM1 condition where greater asymmetry was related to less inhibition (higher IHI ratios) (n= 11/group, $p<0.05$). (c) Fiber volume (FV) and (d) fiber number (FN) CST asymmetries did not show associations to IHI from cM1 to iM1 (n=11/group).

Wolf motor function, Upper-extremity Fugl-Meyer and nine-hole peg test scores are not associated with IHI.

Given that IHI is thought to be a mechanism significant for unilateral movement of the upper-limb, assessments of motor function and dexterity were administered and scores of the paretic limb were compared to IHI from cM1-to-iM1 to determine whether levels of IHI were related to the degree of paretic motor movement, dysfunction and deterity. Linear regression analyses of WMFT, UEFM and NHPT scores gave no significant associations to IHI for the cM1-to-iM1 condition. Measures of upper-extremity motor function were not found to be related to IHI.

Nine-hole peg test of the paretic limb is related to mean diffusivity in both transcallosal tracts and CST projections.

To elucidate relationships between motor function and the structural integrity of IHI pathways, indices of motor function were compared to both transcallosal and CST diffusion metrics. No relationships were found between WMFT and UEFMA scores and CST or transcallosal fiber tract diffusion metrics. The NHPT, however, revealed a relationship between the paretic limb rate with the degree of transcallosal MD and with the degree of MD asymmetry of the CST. Higher MD values of transcallosal sensorimotor tracts and greater MD asymmetries between the bilateral CST, indicating lower structural integrity, were related to a slower paretic limb NHPT rate (Figure 10).

Figure 10.

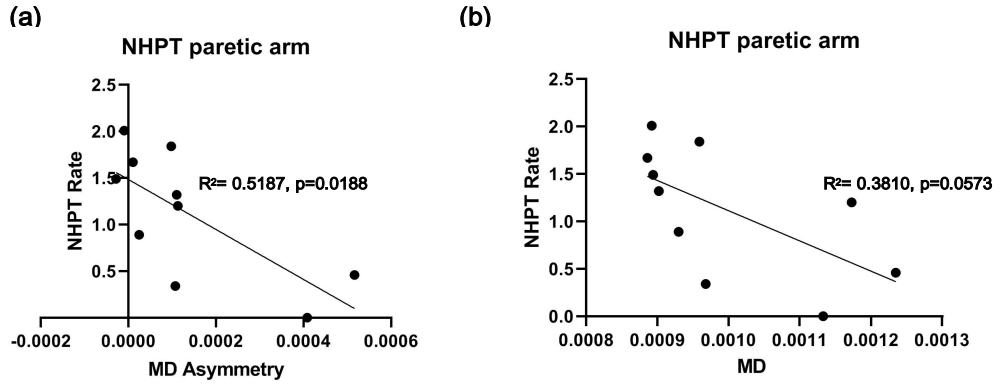

Figure 10. Nine-hole peg test scores using the paretic arm are related to transcallosal and corticospinal mean diffusivity. Linear regression revealed significant relationships between nine-hole peg test (NHPT) rates of the paretic limb and (a) degree of CST asymmetry for mean diffusivity (MD) (n=12; p=0.0188) as well as with (b) transcallosal sensorimotor tract MD values (n=12; p=0.0573). Longer NHPT rates, signifying less distal motor dexterity, were related to greater MD asymmetry of the CST and higher transcallosal MD –indications of lower fiber tract integrity.

Discussion

The interhemispheric imbalance model predicts that, after stroke, the unaffected hemisphere (cM1) will produce abnormally high inhibition onto the affected hemisphere (iM1) as a compensatory mechanism which impedes motor rehabilitation. Substantial evidence for higher excitability of cM1 and lower excitability of iM1 has supported this model. The current study, as well, found higher cortical excitability in cM1 compared to iM1. Yet, our measures of IHI conversely found significantly greater inhibition from iM1 to cM1 in the study cohort. The maladaptive role of cM1 in paretic upper-limb recovery is currently being debated as some

evidence for its supportive influence in the recovery process is being discovered. Furthermore, studies using animal models of stroke have shown evidence for differential effects of cM1 reorganization that depend on lesion characteristics and method of rehabilitation treatment (Jones et al., 2013; Dancause et al., 2015). This may suggest that the roles of cM1 in humans with stroke may also be different depending on individual structural and behavioral characteristics (Buetefisch, 2015).

This study specifically investigated the relationship of individual structural integrity of cortical pathways involved in IHI with the degree of inhibition from cM1 to iM1. Individuals with low transcallosal fiber tract integrity, exhibiting of low FA and high MD, had less IHI from cM1 to iM1. Furthermore, greater FA and MD asymmetries in the bilateral CST, which specified lower iCST integrity, was also associated with less IHI in the cM1-to-iM1 condition. This result can be potentially attributed to differential cortical reorganization rather than lesion-based fiber degeneration as fiber volume and fiber number were not significantly different between hemispheres for both the CST and transcallosal projections. Overall, individuals with less structural integrity of cortical IHI pathways had low amounts of inhibition from cM1 to iM1 and, in some cases, even showed facilitation from cM1 to iM1. This result suggests that IHI and the role of cM1 may be different in individuals with lower or higher post-stroke structural integrity.

Relationships between lower structural integrity of cortical pathways were also seen with slower rates of manual dexterity. The NHPT, which requires fine-motor coordination of the digits and hand muscles, was related to the structural integrity of CST pathways and transcallosal sensorimotor pathways. Particularly, faster rates using the paretic arm were associated with more standard values of transcallosal MD and more symmetric MD values between bilateral corticospinal tracts. However, the WMFT and the UEFMA, which also assess proximal and

gross motor movement, did not reveal significant associations with fiber tract structure. One conceivable explanation for this result is the differential demand on skillfulness tested in the NHPT than in the WMFT and UEFMA. Substantial evidence has shown that both ipsilateral and contralateral M1 projections contribute to skilled unilateral upper-extremity motor function (Chen et al., 1997; Gerloff et al., 1998; Hummel et al., 2003; Perez and Cohen, 2008; Bradnam et al., 2013). Additionally, activation of ipsilateral M1 pathways are evidenced to be modulated by the level of precision of a task (Hummel et al., 2003; Buetefisch et al., 2014). It is therefore possible that individuals with higher integrity bilateral corticospinal tracts and transcallosal pathways may be better able to employ the ipsilateral M1 to assist in fine-motor dexterity of the paretic hand.

Further work may consider investigating the function of inhibitory intracortical networks and their relationship to motor pathway structure and poststroke behavioral motor outcomes to better understand the mechanisms of low interhemispheric inhibition seen in individuals with low fiber tract integrity in this study. Prospective studies may also consider parsing behavioral assessments into proximal and distal movement scores to further define the association between transcallosal sensorimotor tract integrity and motor outcomes in chronic stroke.

In a stroke population, individuals have a wide variation in their functional, structural, and behavioral characteristics. Conflicting literature about the role of IHI in upper-extremity motor recovery and function after stroke suggests that differences in individual post-stroke outcomes may be related to the different roles seen for cM1. This study evidenced relationships between the structural integrity of an individual's cortical IHI pathways with degree of IHI from cM1 to iM1. Additionally, these differences in structure may be related to behavioral outcomes relevant to fine-motor tasks. This study suggests that post-stroke variation in functional and

behavioral outcomes could be related to individual structural integrity of the CST and interhemispheric sensorimotor tracts. This is relevant for the Bimodal Balance Recovery model which proposes that the level of structural reserve after stroke may determine whether interventions targeting interhemispheric imbalance support motor recovery. Particularly, individuals with low structural reserve may not benefit from such interventions. Further research into the contribution of structural integrity of cortical motor pathways on post-stroke function and behavior can help inform the future of individualized rehabilitation treatments.

Limitations

The present study used several linear regression models to assess the significance of associations between variables of sensorimotor tract structure and motor pathway function. Corrections for multiple comparisons were not incorporated and thus there is potential for inclusion of false-positive associations in the results. However, these associations were tested under the premise of directed hypotheses and the aims of the study were largely exploratory. In addition, the preprocessing of our EMG recordings was not thoroughly robust in correcting for all residual artifacts and noise. Two participants exhibited the need for possible further filtration of movement artifact and 60-cycle Hz noise. This suggests the potential for some imprecise evaluations of MEP amplitudes for the SP120 and IHI assessments. Furthermore, in regard to the structural DW-MRI, ROIs on the images were manually delineated for each participant for both the transcallosal sensorimotor tracts and the bilateral CST. This leaves room for human error and bias which could affect the quantification of diffusion metrics for these pathways. Lastly, the number of participants in the study was small and did not reach criterion for using parametric

statistical analyses. A larger study cohort would more strongly support our results and provide sufficient statistical power.

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