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Evaluating interhemispheric cortical responses to transcranial magnetic stimulation in chronic stroke: A TMS-EEG investigation

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Abstract

TMS-evoked cortical responses can be measured using simultaneous electroencephalography (TMS-EEG) to directly quantify cortical connectivity in the human brain. The purpose of this study was to evaluate interhemispheric cortical connectivity between the primary motor cortices (M1s) in participants with chronic stroke and controls using TMS-EEG. Ten participants with chronic stroke and four controls were tested. TMS-evoked responses were recorded at rest and during a typical TMS assessment of transcallosal inhibition (TCI). EEG recordings from *peri-central* gyral electrodes (C3 and C4) were evaluated using imaginary phase coherence (IPC) analyses to quantify levels of effective interhemispheric connectivity. Significantly increased TMS-evoked beta (15–30 Hz frequency range) IPC was observed in the stroke group during ipsilesional M1 stimulation compared to controls during TCI assessment but not at rest. TMS-evoked beta IPC values were associated with TMS measures of transcallosal inhibition across groups. These results suggest TMS-evoked EEG responses can index abnormal effective interhemispheric connectivity in chronic stroke.

Keywords

Stroke; TMS; EEG; TMS-EEG; Connectivity; Coherence; GABA; Beta; Rehabilitation; Motor; cortex

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.neulet.2016.02.047>.

1. Introduction

Persistent arm disability following stroke is the result of direct ischemic loss of neurons combined with maladaptive brain reorganization [35]. Evidence from animal models and humans suggests there is widespread reorganization of cortical network activity patterns remote to the lesion that extend into the contralesional hemisphere during stroke recovery [16,20,34]. In preclinical rodent models of acute stroke, neuronal tissue surrounding the lesion is hypoexcitable [18]. The ability to characterize and modulate specific mechanisms of cortical reorganization could be exploited to modify recovery trajectories after stroke.

Electroencephalography (EEG) is a low-cost, non-invasive, well-tolerated brain imaging modality that directly characterizes post-synaptic potentials associated with coherent neural activity [22]. Ongoing synchronized neuronal network activity in M1 generates oscillations in the beta frequency range observable at rest [1] and during sustained isometric contractions [13]. During volitional hand movement, beta oscillations decrease in amplitude prior to movement [25]. Beta oscillations appear to be directly controlled by increased γ -aminobutyric acid (GABA) activity [9,12]. Administering a GABA-A receptor agonist (e.g. Diazepam) decreases M1 movement-related beta activity [10,19]. Thus, beta oscillatory activity could be a surrogate marker of GABA activity and neuronal excitability within movement-related human brain networks. In individuals with chronic stroke, preliminary evidence shows movement-related beta activity attenuation in iM1 that correlates with greater arm motor impairment [30]. However, it is not known if a stroke alters interhemispheric M1 connectivity in the beta range during movements.

Transcranial magnetic stimulation (TMS) indexes neuronal excitability in the human brain. Following stroke, iM1 cortical excitability decreases while contralesional (c)M1 excitability increases; this interhemispheric imbalance may interfere with recovery [38]. GABAergic activity modulates interhemispheric inhibition (IHI) between M1s [11]. During paretic hand movements, individuals with chronic stroke show increased TMS-induced IHI from cM1 onto iM1 immediately before and at the onset of movement [17]. Single-pulse TMS applied over M1 induces synchronized local beta oscillatory activity in healthy individuals [23]. Yet, TMS-evoked oscillatory behavior has not been studied in individuals with stroke.

Interactions between brain regions and network connectivity can be characterized by EEG coherence in healthy individuals [32,37] and individuals with stroke [24,36,39]. EEG approaches have the advantage of excellent time resolution allowing evaluation of cortical network interactions on neurobiologically relevant timescales. The linear relationship between oscillatory activity in two EEG channels or sources at a specific frequency is measured as coherency. A common problem of standard EEG coherence analyses is that evaluation of coherent networks must overcome volume conduction. Volume conduction (whether due to noise or physiological signal) can promote artificial coherence and inaccurate estimates of connectivity between regions. Using the imaginary part of coherency (IPC) as a measure of brain connectivity overcomes the problem of volume conduction [21]. A non-vanishing IPC requires phase delays between two sensors that cannot be caused by volume conduction [21]. IPC is sensitive to synchronization of two processes that are phased lagged to each other at a specific frequency and is insensitive to non-interacting sources of

activity [21]. Using this approach, movement-related interhemispheric interactions have been reported in healthy individuals [21]. Given the dependence of IPC on phase delays, this coherence approach is insensitive to instantaneous sources of artifact such as the large electromagnetic artifact associated with TMS pulse delivery. Thus, IPC provides an index of functional connectivity within cortical networks that overcomes some challenges associated with recording TMS-evoked EEG responses. At present, TMS-evoked IPC has not been studied. However, it is now possible to use concurrent TMS-EEG to evaluate causal interactions within M1 to study changes in functional connections that underpin persisting motor dysfunction.

The primary objective of this investigation was to characterize TMS-induced interhemispheric IPC in the beta frequency range as a neurophysiologic marker of interhemispheric inhibition and then employ this marker to study differences in connectivity between the primary motor cortices after stroke during an active motor state.

2. Material and methods

2.1. Participant characteristics

10 right-handed participants with chronic ischemic stroke (age: 66.6 ± 4.1 years, Fugl-Meyer Upper Extremity (FMUE) Score [5]: 41.3 ± 23.3 , range: 8–66, 8 subcortical, 5 left hemisphere, 10 males) and 4 right-handed healthy control participants (age: 62.5 ± 8.1 , 3 males) (Table 1) completed a single visit comprised of FMUE assessment performed by a licensed physical therapist and TMS-EEG testing. The University of British Columbia Ethics Committee approved all testing procedures. Informed consent was obtained in accordance with the Declaration of Helsinki.

2.2. TMS procedures

Following FMUE assessment, participants were seated comfortably in a reclining chair for all TMS-EEG testing procedures. TMS was delivered using a monophasic stimulator (200², Magstim Company Ltd.) connected to a 70 mm hand-held figure-of-eight coil positioned to induce a posterior-anterior current in M1. Identification of the M1 hotspot for the extensor carpi radialis (ECR) and determination of the resting motor threshold (RMT; % of maximum stimulator output) was performed bilaterally using standard protocols [29]. During TMS, real-time stereotactic neuronavigation (BrainSight[®], Rogue Research Inc.) was used for targeting stimulation over the ECR motor representation in M1 using each participant's magnetic resonance imaging (MRI) T₁-weighted scan. Earplugs were worn during assessments to minimize TMS-induced auditory artifacts. Stimuli were delivered at a frequency not greater than 0.25 Hz during all TMS procedures.

2.3. EEG recording of cortical responses to TMS

EEG data were recorded using a 64-channel DC amplifier (Neuro Prax EEG[®], neuroConn GmbH). Signals were collected continuously (sampling frequency: 2000 Hz, impedance: $<5\text{k}\Omega$, frequency range: 0–1200 Hz, 0.5 $\mu\text{V/bit}$ resolution).

2.4. Evaluation of TMS-evoked EEG responses at rest

Single TMS pulses ($N = 20$, intensity: ~ 1 mV peak-to-peak MEP amplitude) were applied with ECR at rest. Electromyographic (EMG) data collected from the ECR were evaluated on- and off-line to confirm there was no volitional activity during this condition. If a RMT or 1 mV response could not be established ($N = 3$) due to a lack of quantifiable MEP, then thresholds from the cM1 were used. Peak-to-peak MEP amplitudes were used as an EMG-based assessment of cortical excitability during rest.

2.5. Transcallosal inhibition (TCI) assessment

Single pulses ($N = 20$, 150% RMT) were delivered during an isometric grip force contraction (50% maximum voluntary contraction) of the hand ipsilateral to stimulation site to evaluate TCI [14] (Fig. 1A). A strain gauge based hand-held isometric dynamometer (MLT004/ST, ADInstruments Ltd.) measured and recorded grip force. Using a custom MATLAB program, signals were digitized and displayed on a computer screen in front of the participant to provide real-time visual feedback of force production. Rest periods (30 s) were provided after every five trials to minimize fatigue-related effects.

All TMS-EEG testing procedures were conducted for cM1 and iM1 with hemisphere and TMS condition (TCI vs. rest) order randomized across individuals. The same procedures were completed for the dominant (d) and non-dominant (nd) M1 in controls. EMG responses were recorded and analyzed offline to quantify the ipsilesional silent period (iSP) magnitude (mean iSP ratio: mean EMG during iSP/mean EMG during -100 ms prior to TMS delivery) and duration using methods previously described [14].

2.6. EEG data processing and analysis

All data were pre-processed in EEGLAB, a MATLAB-based, open-source, freely available software environment [2]. EEG data were resampled (1000 Hz), filtered (0.3–100 Hz), and re-referenced (linked mastoids). Data epochs (-1000 to 4000 ms with respect to TMS delivery) were extracted for subsequent IPC analyses [21].

2.7. IPC analysis of interhemispheric interactions following TMS

Using custom MATLAB routines, post-TMS (0–300 ms) IPC values between electrodes overlying M1 bilaterally (left: C3 and right: C4) were calculated within the beta frequency range (15 and 30 Hz) as the primary dependent measure of TMS-evoked interhemispheric connectivity (Fig. 1B). TMS-evoked interhemispheric (C3/C4) beta IPC values were determined for stimulation of each hemisphere in each participant.

2.8. Statistical analysis of interhemispheric beta IPC

Post-TMS interhemispheric beta IPC values were expressed relative to the pre-stimulus interval (-1000 – 0 ms with respect to TMS delivery). IPC values were calculated for each trial for all subjects. To reduce the effects of inter-subject variability in coherent responses and unequal sample sizes between groups, trial-by-trial IPC values from the subjects within each group were resampled without replacement to an even number of trials per subject per condition according to the bootstrap procedure [3]. Descriptive statistics and Levene's Test

for Equality of Variances evaluated the assumptions of normality and homogeneity of variance. Independent *t*-tests assessed group (Stroke, Controls) differences in IPC where TMS over iM1 was compared to responses to ndM1 TMS and TMS over cM1 were compared to dM1 TMS as reported previously [14]. Paired *t*-tests evaluated hemispheric (iM1 vs. cM1) differences in TMS-evoked IPC in the Stroke group for the Rest and TCI conditions separately. A critical α level of $p < 0.01$ was used for statistical comparisons to adjust for multiple comparisons.

2.9. Statistical analysis of EMG-based measures of cortical excitability and transcallosal inhibition

Two-way (Group $\times$ Hemisphere) analyses of variance (ANOVAs) were conducted for TCI measures (iSP ratio and iSP duration) and MEP amplitude at rest. Simple effects analyses were performed for significant interaction effects. Significance level was set to $p < 0.05$.

2.10. Evaluation of the relationship between EEG and EMG measures of interhemispheric interactions

Bivariate correlations using Pearson's *r* were performed to investigate the relationship between iSP ratio and iSP duration with TMS-evoked interhemispheric beta IPC. Significance level was set to $p < 0.05$.

3. Results

The assumptions of normality and homogeneity of variance were not violated based on inspection of descriptive statistics outputs (histogram of sample distribution, skewness/kurtosis values, Q-Q plot) and non-significant *F* statistic for Levene's test.

3.1. TMS-evoked interhemispheric IPC during TCI but not rest is increased in chronic stroke

During TCI, post-TMS beta IPC values were significantly larger in the stroke group during TMS over iM1 compared to TMS over ndM1 in controls ($t(12) = 4.41$, $p = 0.001$, Mean Difference $CI_{95\%}$: 0.036–0.105) (Fig. 1C). A group difference was not observed for the Rest condition for either hemispheric comparison (iM1/ndM1: $p = 0.812$ and cM1/dM1: $p = 0.119$). No other significant differences in TMS-evoked interhemispheric IPC were observed between or within groups.

3.2. Transcallosal inhibition is reduced in chronic stroke

Significant reductions in iSP ratio ($F_{1,24} = 4.53$, $p = 0.044$) and duration ($F_{1,24} = 4.49$, $p = 0.045$) were noted in the stroke group regardless of hemisphere stimulated. An effect of hemisphere was observed ($F_{1,23} = 6.84$, $p = 0.015$) where iM1 stroke/ndM1 control MEP values were lower than cM1 stroke/dM1 control values. This difference appeared to be primarily due to MEP values from iM1 stimulation in the stroke group despite the lack of a significant interaction effect ($F_{1,23} = 2.82$, $p = 0.107$).

3.3. Magnitude of TCI is associated with TMS-evoked beta interhemispheric IPC across participants

A significant positive correlation ($r = 0.470$, $p = 0.018$) was observed between iSP ratio and IPC values during the TCI condition (Fig. 1E). Duration of the iSP was not significantly associated with IPC values ($r = -0.101$, $p = 0.625$).

4. Discussion

This is the first study of interhemispheric interactions during an active (TCI) and a resting motor state using IPC analyses of cortical responses to TMS in neurologically intact persons and participants with chronic stroke. Our findings indicate increased beta coherence between hemispheres when TMS was delivered over the M1 ipsilateral to the hand engaged in a sustained contraction compared to rest. Participants with chronic stroke showed significantly greater TMS-evoked interhemispheric beta IPC values when stimulating over iM1 compared to stimulation over the ndM1 in matched controls. By directly evaluating cortical responses to TMS, these findings extend previous methodological approaches to measure levels of transcallosal inhibitory activity. These results also provide the first report of abnormal interhemispheric interactions in chronic stroke using TMS-EEG associated with recovery (or lack thereof) of function.

4.1. What is the significance of using concurrent TMS-EEG approaches to study effective cortical connectivity?

There is a single published report of concurrent TMS-EEG approaches to investigate neurophysiologic markers of cortical dysfunction after stroke [15]. Using TMS-evoked potentials (TEPs) recorded from individual EEG channels, it was shown that direct measurement of cortical responses may augment information already available from standalone TMS measures of corticospinal functional pathway integrity [33] used as a prognostic factor during the acute phase of stroke recovery [15]. Single channel-based TEPs provide estimates of discrete, local cortical responses to TMS but do not provide a measure of regional cortico-cortical connectivity. Additionally, evaluation of cortical excitability and connectivity is often performed during rest whereas significant changes in cortical activity and connectivity patterns are observed during various active motor states [4] such as a steady-state muscle contractions employed in this study. Both task-based and resting functional connectivity have been evaluated using fMRI. Analytical modeling approaches have been applied in an effort to determine directionality/causality of connectivity patterns after stroke (for review: Ref. [7]). It is now possible to elucidate causal cortical connectivity patterns in a classical “perturb-and-measure” approach with TMS-EEG to characterize information flow under different brain states. Here, we provide evidence of abnormal interhemispheric causal connectivity between M1s during iM1 stimulation associated with motor-related transcallosal inhibitory signaling. These differences in connectivity were not present at rest suggesting a state dependence for this effect.

4.2. What is the significance of increased interhemispheric beta IPC in stroke?

We observed greater beta IPC during iM1 stimulation compared to TMS applied over the non-dominant hemisphere in matched controls that could reflect functional reorganization

within the motor system after stroke. It has been hypothesized that synchronous beta oscillatory activity reflects neural mechanisms in the motor system that favor maintaining the current state over information processing of new movements [6]. This theory may explain, in part, the neural substrates of motor impairments observed in other neurologic disorders [4]. Previous work provided evidence that beta oscillatory activity generated from bilateral sensorimotor regions is under direct control of GABA [9,12]. Increased interhemispheric beta IPC between M1s during an active motor state in participants with stroke suggests altered GABAergic activity and could provide a surrogate imaging marker of GABA activity. The implications of these findings remain to be determined. However, exploratory analyses suggest greater IPC levels are present in those individuals with greater levels of persistent upper extremity impairment (Fig. 1F).

Abnormal beta coherence in participants with chronic stroke may reflect compensatory reorganizational mechanisms engaged to overcome lesion-induced dysfunction within the affected hemisphere by recruiting contralesional areas during task execution [8,27]. It remains unclear if bilateral cortical activation patterns contribute to persisting impairments observed after stroke or contribute to better recovery in some cases. Most previous work has relied on correlative imaging approaches, such as fMRI. By utilizing combined TMS-EEG, it is possible to characterize the spatiotemporal characteristics of sensorimotor reorganization in the human brain during recovery after stroke; this approach may allow the identification of causal cortical connectivity patterns that result in better functional outcomes.

4.3. Limitations and future directions

Scalp-based channel recordings provide limited spatial resolution of patterns of TMS-evoked and induced cortical activity. However, substantial evidence exists for M1 as a cortical generator of potentials measured with C3/C4 electrodes and central beta oscillatory activity likely arises primarily from sensorimotor cortical activity [26,28]. Future work can incorporate source decomposition and spatial localization approaches to anatomically localize normal and abnormal patterns of TMS-evoked cortical activity. The sample size in both cohorts was limited. Although there were small sample sizes in both groups, which preclude definitive conclusions, our findings extend previous work showing abnormal network connectivity after stroke. We conducted a post-hoc analysis that included an additional matched control group (N = 6) collected separately. The results observed support the primary findings reported here of abnormal interhemispheric interactions during an active motor state in chronic stroke (see Supplementary materials for additional details). There is the potential that non-significant group differences in interhemispheric interactions during rest were due to our limited sample size. The ability to investigate the influence of the lesioned hemisphere was also not addressed in this investigation due to limited sample sizes but is an important factor to consider in future larger scale studies.

The major obstacle to concurrent TMS-EEG approaches is the potential for multiple sources of an artifact [31]. Steps were taken to minimize artifact presence during data collection (e.g. earplugs to minimize auditory evoked potentials) but residual artifacts remain a challenge. One benefit of the imaginary coherence analysis approach is that results are relatively

immune to large amplitude, quasi-instantaneous artifacts (e.g. TMS pulse-related electrical confounds) making it a potentially promising approach for future TMS-EEG studies employing standard and/or clinical EEG amplifier systems.

5. Conclusions

A comprehensive characterization of the neural substrates underlying persistent functional disability in the majority stroke survivors remains elusive. Concurrent TMS-EEG is a technique now available to probe causal patterns of cortical connectivity across various motor states in an effort to better understand the systems-level substrates supporting and/or limiting motor recovery after stroke. The results reported here suggest TMS-EEG is a feasible approach to study cortical activity and connectivity in the human brain after stroke and supports further work to identify salient markers of functional recovery that ultimately contribute to better functional outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

TMS	transcranial magnetic stimulation
EEG	electroencephalography
IPC	imaginary phase coherence
TCI	transcallosal inhibition
M1	primary motor cortex
FMUE	Fugl-Meyer Upper Extremity Assessment
ECR	extensor carpi radialis
TEP	TMS-evoked potential

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HIGHLIGHTS

- Abnormal interhemispheric connectivity likely contributes to disability after stroke.
- TMS-evoked EEG responses used to evaluate interhemispheric motor connectivity.
- Increased interhemispheric motor connectivity observed after stroke during activity.
- Abnormal TMS-evoked interhemispheric connectivity may relate to motor impairment.
- Novel approach to probe network connectivity underlying stroke-related disability.

Fig. 1.

(A) Schematic of TCI experimental set-up. Stimulation over the primary motor cortex (M1) elicits a motor evoked potential (light blue) in the contralateral (green line) extensor carpi radialis muscle and, via transcallosal pathways, evokes a transient disruption (depicted by flat line in the illustration also in light blue) in ongoing volitional activity in the ipsilateral arm (blue line). (B) Time-frequency plot of group mean data demonstrating larger beta imaginary phase coherence (IPC) values between electrodes (inset: scalp topographic plot of C3 and C4 electrodes) in a region overlying the primary motor cortex (M1) in the left (C3)

and right (C4) hemisphere during TMS over ipsilesional (i) M1 in the stroke group compared to TMS over non-dominant M1 in controls. Data: -1000 ms to 4000 ms from TMS delivery (triangle). Solid black line represents bin of data (0-300 ms) extracted for statistical analyses. Dotted black lines indicate the frequency band range (15-30 Hz) of interest. Warmer colors indicate greater levels of IPC. (C) TMS-evoked beta interhemispheric IPC values were larger in the stroke group during TCI (* $p = 0.001$) but not during the Rest condition. (D) In the stroke group, significant hemispheric (iM1 vs. cM1 TMS) differences in IPC were not observed for either condition. (E) Larger iSP ratios (mean iSP amplitude/mean pre-stimulation amplitude), representing lesser interhemispheric inhibition, were positively correlated with larger TMS-evoked interhemispheric beta IPC values ($p = 0.018$) across all participants. A significant relationship was not observed in either group alone. (F) Time-frequency plot showing qualitatively higher TMS-evoked interhemispheric beta IPC values (warmer colors) in individuals with severe arm impairment ($N = 5$, median Upper Extremity Fugl-Meyer (UEFM) score: 16)(left) compared to participants with mild arm impairment ($N = 5$, median UEFM score: 57) (right). Data: -1000 ms to 4000 ms from TMS delivery (triangle). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1

Participant characteristics.

ID	Age (y)	Stroke Hemisphere	Months post stroke	UEFMA (/66)	RMT (iM1 or ndM1)	RMT (cM1 or dM1)	Lesion location
S01	61	L	91	16	89	53	Internal Capsule/Thalamus
S02	69	R	15	57	>100	56	PLIC/Corona Radiata
S03	64	R	145	16	72	60	Cortical/Subcortical, Prefrontal/Parietal
S04	64	R	94	56	40	40	Corona Radiata
S05	71	L	34	31	65	54	Broca's area
S06	61	L	42	15	>100	49	Subcortical, MCA distribution
S07	67	R	82	60	65	53	Thalamus
S08	62	L	85	8	>100	48	Cortical/Subcortical, Prefrontal/Parietal
S09	68	R	15	66	55	46	Cortical/Subcortical, Prefrontal/Parietal
S10	73	L	142	62	47	41	Pontine
Mean	66 ± 4		75 ± 47	39 ± 23	73 ± 23 ^a	50 ± 6	
H01	69	–	–	–	48	47	–
H02	55	–	–	–	40	39	–
H03	70	–	–	–	43	43	–
H04	56	–	–	–	53	52	–
Mean	63 ± 8	–	–	–	46 ± 6	45 ± 6	–

UEFMA: Upper extremity Fugl-Meyer Assessment, RMT: resting motor threshold (% maximum stimulator output), iM1: ipsilesional primary motor cortex, cM1: contralesional M1, ndM1: non-dominant and dominant M1 in control participants, PLIC: posterior limb of internal capsule, MCA: middle cerebral artery.

^aMean iM1 RMT value includes an RMT of 100% for S02, S06 and S08 due to an inability to elicit an MEP at maximum stimulator output.