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# Combined rTMS and Virtual Reality Brain-Computer Interface Training for Motor Recovery after Stroke

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## Abstract

**Objective—**Combining repetitive transcranial magnetic stimulation (rTMS) with brain-computer interface (BCI) training can address motor impairment after stroke by downregulating exaggerated inhibition from the contralesional hemisphere and encouraging ipsilesional activation. The objective was to evaluate the efficacy of combined rTMS+BCI, compared to sham rTMS+BCI, on motor recovery after stroke in subjects with lasting motor paresis.

**Approach—**Three stroke subjects approximately one year post-stroke participated in three weeks of combined rTMS (real or sham) and BCI, followed by three weeks of BCI alone. Behavioral and electrophysiological differences were evaluated at baseline, after three weeks, and after six weeks of treatment.

**Main Results—**Motor improvements were observed in both real rTMS+BCI and sham groups, but only the former showed significant alterations in inter-hemispheric inhibition in the desired direction and increased relative ipsilesional cortical activation from fMRI. In addition, significant improvements in BCI performance over time and adequate control of the virtual reality BCI paradigm were observed only in the former group.

**Significance—**When combined, the results highlight the feasibility and efficacy of combined rTMS+BCI for motor recovery, demonstrated by increased ipsilesional motor activity and improvements in behavioral function for the real rTMS+BCI condition in particular. Our findings also demonstrate the utility of BCI training alone, as demonstrated by behavioral improvements for the sham rTMS+BCI condition. This study is the first to evaluate combined rTMS and BCI training for motor rehabilitation and provides a foundation for continued work to evaluate the potential of both rTMS and virtual reality BCI training for motor recovery after stroke.

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## 1. Introduction

Stroke is a sudden and devastating condition affecting nearly 800,000 Americans each year [1]. Those cases resulting in lasting motor impairment, in particular, can have a significant impact on quality-of-life. The clinical standard-of-care for stroke rehabilitation focuses mainly on the affected limb, without significant attention paid to the neural origin or the resulting alterations in brain network dynamics. The potential for functional recovery may be increased by identifying pathological cortical network changes and developing treatment strategies tailored to individual subjects to address network level changes in neural activity.

Previous studies have demonstrated that, in many cases, atypical and compensatory patterns of neural activity can arise after a stroke [2,3], and that generally increased contralesional activation during recovery is associated with poorer function of the paretic limb [2,4–6]. While such compensatory contralesional activation may be related to the volume of damaged tissue within the lesioned hemisphere, studies have also recently shown using functional MRI (fMRI) that shifts in cortical activity from contralesional to ipsilesional motor areas over the course of treatment are associated with improved outcomes [2,6]. Brain-based treatment strategies should ideally encourage ipsilesional activity during paretic limb movement for optimal improvement. Recent studies have also shown that maladaptive plasticity after stroke can lead to undesirable alterations in neural network dynamics, including neurotransmitter changes and modulations in inter-hemispheric interactions. Hemiparesis after stroke results not only from neuronal loss due to the vascular insult within the lesioned hemisphere but also the downregulation of remaining neurons within the lesioned hemisphere resulting from excessive inter-cortical inhibition from the healthy hemisphere (Figure 1) [7,8] or from learned non-use [9]. Thus, subjects recovering from strokes are hypothesized to be “doubly-disabled”, due not only to the loss of function from to the vascular insult but also from downregulation of surviving neurons. Treatment strategies aimed to improve motor function after stroke should optimally address this downregulated excitability ipsilesionally by encouraging activity within the lesioned hemisphere and by suppressing the inhibition from the healthy hemisphere.

Non-invasive brain stimulation (NIBS) has been explored in recent years in multiple forms to enhance motor recovery after stroke, especially repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) [10,11]. Application of rTMS or tDCS is generally aimed towards increasing excitability within the lesioned hemisphere, either directly through facilitatory stimulation or indirectly through suppressive stimulation to the contralesional hemisphere. rTMS applied in a suppressive fashion to the contralesional side has been utilized in several studies and is hypothesized to increase excitability within the lesioned hemisphere by reducing IHI from the contralesional side [12–15]. Several studies have evaluated rTMS specifically for motor recovery after stroke, and have demonstrated promising results with respect to motor improvement on the paretic side [16–20]. While such studies have demonstrated the promise of NIBS in stroke recovery, the optimal treatment strategies are far from understood. Additionally, the optimal parameters for inclusion of successive therapy in other forms, such as physical therapy or constraint induced movement therapy, has not been fully elucidated.

Brain-computer interface (BCI) has also been explored in recent years as a potential treatment strategy for hemiparesis following stroke [21,22]. BCI systems record neural signals, typically via non-invasive EEG measurements, and translate recorded activity patterns into a meaningful form of feedback conveyed to the subject [23,24]. As BCI technologies can be used to detect user intent, even without corresponding action, BCIs can be used to provide subjects with a meaningful form of feedback before physical movement is possible. Success within the BCI task informs users that the brain state created was desirable, whether or not it led to a noticeable motor movement at the same time. Standard physical therapy approaches rely on motor outputs as an indication of correct activation, which can be discouraging in the initial stages of motor recovery when motor output is inherently limited despite strong effort by the subjects. EEG or MEG-based BCI systems, in particular, have been associated with improvements in hand motor function in previous studies [25–29]. BCI training coupled with functional electrical stimulation (FES) or robotic orthoses or exoskeletons have begun to be explored in patient populations, however, the ideal BCI paradigms, subject characteristics, and complementary treatments are not yet well understood.

Despite the research completed towards developing rTMS or BCI training separately as treatment strategies for motor recovery after stroke, no study to date has combined the complementary treatments of rTMS and BCI training for stroke rehabilitation. The objective of this study was to evaluate the efficacy of combined rTMS and BCI training, vs. sham rTMS and BCI training, vs. BCI training alone on motor recovery after stroke in subjects with lasting motor paresis. The advantage of using BCI in conjunction with rTMS for motor recovery is that such a two pronged approach combines low frequency rTMS to reduce inter-hemispheric inhibition (IHI) and motor imagery based BCI to encourage excitability within the lesioned hemisphere, as shown in Figure 1. This addresses both of the aforementioned causes of motor impairment after stroke, namely reduced ipsilesional excitability due to non-use as well as excessive IHI from the contralesional motor cortex. We hypothesized that subjects receiving real rTMS+BCI training or BCI training alone (sham rTMS+BCI) would show improvements in motor function, with the real rTMS+BCI condition demonstrating greater functional improvement in hand motor ability over time as well as a reduction of contralesional to ipsilesional IHI.

## 2. Materials and methods

### 2.1 Participants

The study was approved by the University of Minnesota Institutional Review Board. All participants provided written informed consent prior to participation. We recruited subjects 18-70 years old with a history of a first-ever stroke 3-12 months prior to the date of enrollment. Other inclusion criteria included the presence of an ipsilesional motor-evoked potential (MEP), and impaired but at least 10 degrees of active finger movement on the paretic side. Exclusion criteria included a personal history of epilepsy or seizures within the past 2 years, MRI-incompatible implanted devices, bilateral motor paresis and any other condition that would require significant management beyond that of a stable outpatient. Each participant completed a screening visit in which the Beck Depression Inventory (BDI)[30],

Upper-Extremity Fugl Meyer Assessment (UE-FM)[31], Edinburgh Handedness Inventory (EHI)[32], Modified Ashworth Scale (MAS)[33], and Mini-Mental Status Examination (MMSE)[34] were assessed, along with screening for an ipsilesional MEP, tactile sensation, and kinesthesia in the paretic limb. These scores, along with a pertinent medical record history, were evaluated by the study physician for each participant to determine eligibility. For safety, blood pressure and pulse were assessed on each of the testing days prior to application of rTMS. Subjects also completed a report of symptoms at the beginning and end of each test session to assess for adverse events.

Three individual subjects participated in and completed the study. Two participants were randomly assigned to the real rTMS+BCI condition, and one subject was randomly assigned to the sham rTMS+BCI condition. Table I provides demographic and enrollment information for each of the participants. All participants remained blinded to their treatment condition, and tolerated all treatment and testing procedures well. No decrements in motor or cognitive function were noted and no adverse effects reported for any of the participants.

## 2.2 Study Design

The study design included two different treatment conditions, each with two phases of treatment, as shown in Figure 2. Treatments occurred approximately three times per week over a six-week period for each participant. For both conditions, the first nine sessions (over three weeks) consisted of combined rTMS and BCI training, with rTMS applied immediately prior to BCI training. rTMS was applied in either a real or sham manner, depending on the subject group, which was randomly assigned. The second nine sessions (over three weeks) consisted of BCI training only, and was identical for both subject groups. Testing was conducted at baseline, prior to any treatments, along with after the rTMS+BCI phase (post-test 1) and after the BCI only phase (post-test 2). Testing visits consisted of behavioral tests, IHI testing, as well as functional MRI. Participants, testers, and treaters conducting BCI training were blinded to the TMS treatment condition.

## 2.3 Testing Procedures

**2.3.1 Behavioral Measures—**Behavioral outcome was assessed at each testing time point using the Box and Block Test and Finger Tracking Test [35]. The Box and Block test requires subjects to grasp, lift, and release 2.5 $cm^3$ cubes in order to move the cubes from one compartment to another. The score is determined as the number of blocks transferred correctly within a 60 second period. At each test visit, participants completed three 60 second trials. The finger tracking test [35] provides a measure of fine motor movements through tracking a sinusoidal target over time through movements of the index finger. Subjects completed the finger tracking test while inside of the MRI scanner and while fMRI scans were simultaneously collected. Subjects wore custom electro-goniometer braces on each hand, each of which included a potentiometer signaling extension and flexion of the index finger metacarpophalangeal joint. Subjects were presented with target stimuli with a random sinusoidal waveform and were instructed to move the corresponding index finger to match the target trace as the cursor moved across the screen with a constant velocity. The waveform was adjusted to correspond to a range of 25-75% of the range of motion for each subject. Each fMRI scan consisted of six 30 second runs, three on each hand, along with

seven interspersed 30 second rest runs. One to two scans of tracking test data, along with corresponding fMRI, were collected for each participant at each testing visit. Outcome measures from the tracking test include an accuracy index, which is calculated using a ratio of the error to the standard deviation of the target, normalized to the range of motion for each subject [35].

**2.3.2 Inter-hemispheric Inhibition—**IHI was assessed at each testing time point using two Magstim 200 stimulators with a Bi-Stim connecting module along with two 50mm figure-of-eight coils (Magstim Company, Spring Gardens, UK). Subjects were seated in a reclining chair, and earplugs were applied prior to application of TMS. Surface EMG electrodes were applied bilaterally to the first dorsal interosseous muscle, and EMG activity was recorded via a custom LabVIEW based software and a National Instruments data acquisition system (National Instruments, Austin, TX) with a sampling frequency of 6,400 Hz and a gain of 300. Background EMG activity was monitored bilaterally throughout the testing to ensure TMS measures were taken at rest. Initial locations of the bilateral motor areas were determined via scalp measurements, while the motor hotspot was determined as the location on the scalp with the lowest resting motor threshold (rMT), defined as the lowest TMS intensity resulting in a motor-evoked potential (MEP) of at least 50μV in at least 5 out of 10 successive trials. Each coil was positioned at an angle of approximately 45° posterior and lateral to the midsagittal plane. The rMT was determined for bilateral motor hotspots, along with the 1mV threshold, defined as the lowest TMS intensity resulting in an MEP of at least 1mV in at least 5 out of 10 successive trials. In the event that a 1mV threshold could not be determined, 130% of the rMT for the corresponding side was used. IHI testing involved collecting 60 trials, applied in a randomized order, consisting of 10 trials of each of the following conditions: (1) single pulse to ipsilesional primary motor cortex (M1), (2) single pulse to contralesional M1, paired-pulse to ipsilesional M1 followed by contralesional M1 separated by (3) 10ms and (4) 40ms, and paired-pulse to contralesional M1 followed by ipsilesional M1 separated by (5) 10ms and (6) 40ms. All pulses were applied at the corresponding 1mV threshold or 130% rMT when required. IHI was assessed via offline analysis by comparing the paired-pulse peak-to-peak MEP amplitudes to the corresponding single pulse MEP amplitudes for each direction and time interval.

**2.3.3 MRI—**Anatomical and functional MRI scans were acquired on a 3.0 Tesla scanner (Magnetom Trio (n=1) or Magnetom Prisma (n=2), Siemens, Munich, Germany) equipped with a 32 channel head coil. A high resolution (1 mm isotropic voxels) T1-weighted magnetization prepared rapid acquisition gradient echo (MP-RAGE) anatomical scan (TR = 2150 ms, FA = 8°, TA = 04:58 min) was acquired during rest. Functional scans were collected subsequently during (1) rest and (2) while performing the finger tracking test previously described for each subject at each testing visit. Functional data were collected using T2* weighted images of the blood oxygen level dependent (BOLD) signal measurements with 3 mm isotropic voxels using a gradient echo planar imaging (gEPI) sequence (TR = 3000ms, TE = 30ms, FA = 90°, TA = 08:45 min). A block design was used for the functional scans, with 30-second alternating blocks of tracking with each hand independently, interleaved with 30-second rest blocks after each movement block.

## 2.4 Treatment Procedures

**2.4.1 rTMS—**rTMS was applied using a 70mm figure-of-eight air film coil and a Magstim Rapid2 stimulator (Magstim Company, Spring Gardens, UK). Subjects were seated in a reclining chair, and earplugs (Howard Leight Max, 33dB NRR, Honeywell, Morris Plains, NJ) were inserted prior to application of TMS. The EEG cap was applied prior to rTMS, to enable subsequent BCI training. Surface EMG electrodes were applied to the extensor digitorum muscle on the non-paretic side, and EMG activity was recorded via a custom LabVIEW based software and a National Instruments data acquisition system. The motor hotspot and rMT of the contralesional hemisphere were determined as described previously, and rTMS was applied for 10 minutes at a rate of 1Hz and an intensity of 90% rMT. After determining rMT, the treater disconnected the real rTMS coil and either reconnected the real coil (real rTMS+BCI condition) or connected the sham coil (sham rTMS+BCI condition) so that the patient was blinded. The sham coil was also a 70mm figure-of-eight air film coil (Magstim Company, Spring Gardens, UK) which mimicked the sound of the coil clock without generating an appreciable significant magnetic field.

**2.4.2 BCI Training—**BCI training was conducted using 64 channel TMS-compatible EEG Caps (Fast N' Easy Caps, Brain Products GmbH, Munich, Germany) along with a BrainAmp MR amplifier (Brain Products GmbH, Munich, Germany). Subjects were seated in a comfortable chair and wearing 3D red/blue glasses in front of a stimulus presentation box, in which they would place their hands. The box contained an angular mounted screen with a 3D virtual reality stimulus of hands reaching out to grasp and lift a cup on the left or right side of the screen. The stimulus presentation box was constructed in an attempt to align the 3D virtual reality hands with the perception of their own hands concealed within the box. The EEG cap was placed according to the 10-20 international system, and electrode impedances were lowered to <10kΩ. EEG data was recorded via Brain Vision Recorder (Brain Products GmbH, Munich, Germany), digitized at a sampling rate of 5000Hz, and filtered online from 0.1 – 500Hz. BCI2000 [36] was used to control the BCI stimulus using the streaming EEG activity. The BCI cursor velocity and direction was determined by a weighted sum of μ band activity at 12Hz in the C3 and C4 electrodes over bilateral motor cortex. A large Laplacian filter was also applied to C3 and C4, in which an equally weighted sum of the four next-to-nearest neighboring electrodes were subtracted from the central electrode to enhance the signal-to-noise ratio. An online normalizer implemented within BCI2000 [36] was used to correct in real time for any inherent difference in signal strength between the two sides resulting from the stroke. A Java application using NetBeans IDE (Oracle Corporation, Redwood City, CA) was used to connect the standard 1D cursor stimulus of BCI2000 to the 3D virtual reality display, in which the position of the virtual hand on the left and right was mapped to correspond to the position of the 1D cursor in BCI2000 running in the background [37]. During BCI, subjects received an auditory and visual cue indicating the target location for each trial (left or right) and were instructed to perform motor imagery of the corresponding hand (via imagining opening and closing the hand repetitively) for the duration of the trial. The speed of the cursor and trial duration were optimized over time for each subject to minimize the occurrence of trials that timed-out prior to hitting a target. Within each BCI session, subjects completed 8-10 runs, each consisting of 20 trials, 10 each for left and right targets presented in a randomized fashion. Both left and

right targets were included in BCI training, as the purpose of the BCI training was not only to encourage activation within the lesioned hemisphere motor cortex, but also to encourage differential activation between left and right handed trials, as many subjects may have quite limited activity within the lesioned cortex. Such differential activation is desirable to encourage the users to relearn to use and balance activity within both hemispheres. Lastly, trials involving imagination of the non-paretic limb also serve as a useful counterpoint to interleave with paretic limb trials, rather than exclusively rest blocks.

### 2.5 Data Analysis

**2.5.1 fMRI analysis—**fMRI analysis was completed using the statistical parametric mapping (SPM 12) toolbox (Wellcome Trust Centre for Neuroimaging, London, UK) within the Matlab (MathWorks, Natick, MA) environment. Functional images were preprocessed using a standard pipeline within SPM, including slice timing correction, realignment, co-registration with anatomical images, normalization, and smoothing. Anatomical images were also segmented and normalized to the MNI template for each subject. 1$^{st}$ level analysis was completed using a general linear model and a block design, with contrasts to compare movement blocks comprised of the finger tracking test with rest blocks. Head movement parameters were included as regressors with in the general linear model. The significance threshold was set to $p<0.001$.

**2.5.2 Statistical Analysis—**Statistical testing was performed using R Statistical Software, version R i386 3.2.4 [38]. Welch two-sample one-sided t-tests were used to evaluate statistical significance of changes in study measures over the course of treatment, from baseline to post-test 1, post-test 1 to post-test 2, as well as from baseline to post-test 2 for each treatment condition. T-tests were used, rather than a repeated measures ANOVA, as the testing data over time for each subject and group reflects two treatment phases, namely TMS+BCI from baseline to post-test 1 and BCI only from post-test 1 to post-test 2. Welch t-tests were selected as the testing data was not assumed to have equal variances, and one-sided tests were performed to specifically assess whether significant improvements were observed. Two sided t-tests were also performed, but the p-values are not reported. The significance threshold was set at $p<0.05$. Bonferroni correction was performed as well, and all tests with $p<0.01$ survived Bonferroni correction.

## 3. Results

### 3.1 Behavioral Measures

Box and Block test results are shown in Figure 3A. Individual results demonstrated one subject within the real rTMS+BCI condition significantly improved from post-test 1 to post-test 2 (covering the phase of BCI training only, without preceding rTMS) ($p<0.05$), while the sham subject demonstrated significant gains from baseline to post-test 1 ($p<0.05$), post-test 1 to post-test 2 ($p<0.05$) and baseline to post-test 2 ($p<0.01$, Bonferroni corrected). When combined on a condition level, the real rTMS+BCI condition demonstrated positive trends, though not significant, over time, with a relative improvement of 73% from baseline to post-test 1 and 40% from post-test 1 to post-test 2. The sham rTMS+BCI condition also improved in the Box and Block Test over time, passing significance thresholds but with lower relative

improvement of 24% from baseline to post-test 1 and 22% from post-test 1 to post-test 2 compared to the real rTMS+BCI group. Tracking test results for the paretic hand for each subject are shown in Figure 3B, normalized to the measured range of motion at each test visit. Significant improvements were seen in the normalized accuracy index from baseline to post-test 1 ($p<0.01$, Bonferroni corrected $p<0.05$) and from baseline to post-test 2 in one real rTMS+BCI subject ($p<0.01$, Bonferroni corrected) and one sham rTMS+BCI subject ($p<0.001$ for both, Bonferroni corrected), with positive trends noted in the remaining real rTMS+BCI subject. When averaged on a condition level, significant improvements are noted from baseline to post-test 2 for the real rTMS+BCI condition ($p<0.01$, Bonferroni corrected $p<0.05$), with an average of 51% and 24% improvements from baseline to post-test 1 to post-test 2 for the real rTMS+BCI condition. Additionally, significant improvements are noted from baseline to post-test 1 (77%) and post-test 2 ($p<0.001$) for the sham rTMS+BCI condition, along with a 9% improvement from post-test 1 to post-test 2. However, when analyzed at the unit scale, the overall improvement in finger tracking test accuracy is greater in magnitude for the real rTMS+BCI Condition relative to the overall change of the sham rTMS+BCI condition.

### 3.2 Inter-hemispheric Inhibition

IHI measures, indicated by a paired pulse to single pulse peak-to-peak amplitude ratio, are shown in Figure 4. For this analysis, inhibition is indicated as a reduction in MEP size in paired-pulse trials compared to single-pulse trials (PP/SP ratio), thus reduced IHI is indicated by an increase in the PP/SP ratio and vice versa for increased IHI. Individual results in both real rTMS+BCI subjects demonstrate trends towards reduced inhibition from the contralesional hemisphere acting upon the ipsilesional hemisphere, with accompanying trends towards increased inhibition from the ipsilesional hemisphere acting upon the contralesional hemisphere ($p<0.05$ for S01). The sham rTMS+BCI subject displayed significant increases in inhibition from the contralesional hemisphere acting upon the ipsilesional hemisphere ($p<0.001$, Bonferroni corrected), with no appreciable changes in the ipsilesional to contralesional direction. When combined on a condition level, significant increases in inhibition are observed in both conditions, but in the direction of ipsilesional to contralesional for the real rTMS+BCI condition (average 35.8% ratio decrease from baseline, $p<0.01$, Bonferroni corrected $p<0.05$) and in the direction of contralesional to ipsilesional for the sham rTMS+BCI condition (average 65.4% ratio decrease from baseline, $p<0.001$, Bonferroni corrected).

### 3.3 BCI Performance

Measures of BCI performance are shown in Figure 5. The percent valid correct (PVC) (Figure 5A) demonstrates that both subjects within the real rTMS+BCI condition achieved higher overall accuracy in the BCI only phase compared to the rTMS+BCI phase, with a significant difference for S01 (+11.2%, $p<0.001$, Bonferroni corrected). The sham rTMS +BCI subject did not exhibit any significant trends in BCI performance over time. When combined for each condition and treatment phase (Figure 5B), a significant improvement in performance (+7.5%, $p<0.001$, Bonferroni corrected) is observed from the rTMS+BCI phase to the BCI only phase for the real rTMS+BCI condition only, with a slightly negative trend in the sham rTMS+BCI condition. BCI performance differences between targets on the non-

paretic side and targets on the paretic side (Figure 5C) are generally positive for subjects within the real rTMS+BCI condition, indicating reduced performance on paretic side trials. Additionally, S03 demonstrated a significant ($p<0.05$) increase in PVC difference between the rTMS+BCI and BCI only phase. The sham rTMS+BCI subject exhibited negative BCI performance differences, indicating reduced performance on the non-paretic side trials. Overall, the real rTMS+BCI condition exhibited positive differences in performance between the non-paretic and paretic sides for both phases of treatment, while the sham rTMS +BCI subject exhibited negative differences for both phases of treatment (Figure 5D).

### 3.4 fMRI

fMRI activation maps are shown in Figure 6A for each subject at each testing visit for paretic hand tracking relative to rest. All subjects demonstrated some level of ipsilesional activation during paretic hand tracking, accompanied in some subjects (S02, S03) by contralesional activation. fMRI activation maps were influenced by not only the range of motion during the Finger Tracking Test, which was considerably lower for both real rTMS +BCI subjects, but also head movement corresponding to paretic tracking periods, particularly for S01. To assess the relative activation of both hemispheres during movement, the laterality index for the precentral gyrus was calculated and is shown for both paretic hand tracking (Figure 6B upper) and non-paretic hand tracking relative to rest (Figure 6B lower). Both real rTMS+BCI subjects exhibited positive laterality indices, indicating primarily ipsilesional activation during paretic hand tracking, with increased recruitment of ipsilesional areas over time noted for S03 and exclusively ipsilesional activation over time for S01. The laterality index is not shown for post-test 2 for S01 as no activation overlapped with the ipsilesional or contralesional precentral gyrus R01. The sham rTMS+BCI subject exhibited a negative laterality index at post-test 1 compared to baseline and post-test 2, indicating increased activation of contralesional cortex. Interestingly, when evaluated for non-paretic hand tracking periods relative to rest blocks (Figure 6B lower), a slight decrease is observed from baseline to post-test 1 only in the two real rTMS+BCI subjects, suggesting increased recruitment of ipsilesional areas even during non-paretic tracking. In the sham rTMS+BCI subject, the non-paretic laterality index exhibited increased over time, suggesting an overall reduction in bilateral activation during non-paretic tracking.

## 4. Discussion

This study investigated the combination of contralesional rTMS followed by BCI training to enhance motor function following stroke. The study included two conditions, namely real rTMS+BCI and sham rTMS+BCI training, to elucidate the influence of combined rTMS and BCI training compared to that of BCI training alone. Only real rTMS+BCI training led to reduced IHI from the contralesional to ipsilesional hemisphere and increased IHI from the ipsilesional to contralesional hemisphere, as hypothesized. Additionally, maximal or increasing ipsilesional fMRI activation during paretic hand tracking was only observed for the real rTMS+BCI condition, with trends towards opposite increased contralesional activation for the sham rTMS+BCI group. Additionally, BCI performance demonstrated significant improvements over time for the real rTMS+BCI group only, which may reflect increased learning potentially due to an added difficulty of early BCI training immediately

after rTMS. The results support the role of rTMS in modifying inter-hemispheric interactions and potentially increasing ipsilesional activity, however behavioral testing indicated significant improvements for both treatment conditions over time. For the finger tracking test, significant improvements were observed for both conditions while improvements were only observed for the sham rTMS+BCI condition for the Box and Block test, which was not in alignment with our original hypothesis. This improvement suggests that BCI training alone may have an appreciable effect in subjects, which is particularly interesting given that the sham rTMS+BCI subject also began with only minor deficits in hand function. While improvements in behavioral measures were noted for the subjects within the real rTMS+BCI condition, they were more subtle in magnitude. However, the subjects within the real TMS+BCI condition also exhibited considerably reduced function on the paretic side at baseline, which could account for the difference in score improvement over time between conditions. The Box and Block test, while clinically accepted and easy to administer, represents a relatively coarse measure of motor function in subjects with remaining spasticity or difficulty opening or closing the hand. While the Finger Tracking Test can detect subtle changes in fine motor skill, the application and relevance of the measure is still limited by the effective range of motion of the subject, which was limited for both subjects within the real rTMS+BCI condition. In future studies, it may be worthwhile to include more sensitive measures of subtle motor function changes, such as a transition from scooping to grasping blocks for the Box and Block test, which may lead to changes in quality of life but not significant changes in scores. It is also unclear whether the improvements in either group were due to the treatments alone or potentially also due to a training effect; though at least three practice rounds were completed prior to each testing visit to avoid such a training effect.

While IHI testing results agreed with our initial hypothesis, in that subjects within the real rTMS+BCI condition exhibited reduced inhibition from the contralesional to ipsilesional hemisphere and increased inhibition from the ipsilesional to contralesional hemisphere, we did not expect the sham rTMS+BCI subject to exhibit increased IHI from the contralesional to ipsilesional hemisphere. Given that the rTMS was applied in a sham fashion, this may reflect noise affiliated with the inherent fluctuations in MEP size in both single pulse and paired-pulse trials. Additionally, despite the fact that the pulse intensities for IHI testing are applied at individualized intensities, it is possible that the stimulation thresholds, and the difference in threshold between the paretic and non-paretic side, could have an effect on the resultant IHI ratios. The subject within the sham rTMS+BCI condition exhibited minor impairments at baseline on the paretic side, and not surprisingly exhibited a smaller difference in 1mV thresholds between the ipsi- and contralesional sides than the other two subjects.

The BCI performance results demonstrated that subjects were able to control the virtual reality stimulus, with high performance seen for both subjects within the real rTMS+BCI condition in multiple sessions. Interestingly, a slight negative trend in performance was initially observed for subjects within the real rTMS+BCI condition during the rTMS+BCI phase, with significantly ($p<0.001$, Bonferroni corrected) lower overall PVC during the rTMS phase for the real condition. These results indicate that rTMS applied immediately prior to BCI may effectively increase difficulty of the BCI task. Real rTMS was also noted

to affect performance differences between target locations, with generally reduced performance on the paretic side for subjects within the real rTMS+BCI condition. It is unclear whether this performance difference results from the considerable impairment on the paretic side in those subjects, potentially leading to increased difficulty performing motor imagination of the paretic limb, or from the carryover effects of the rTMS treatment. The rTMS is intended to down-regulate the contralesional hemisphere, but may lead to increased difficulty performing paretic movements or imaginations in subjects who may rely on some degree of compensatory contralesional activation associated with the paretic limb.

fMRI revealed ipsilesional activation in all subjects during paretic hand tracking, with maximal or increasing recruitment of ipsilesional areas over time only for both real rTMS +BCI subjects. This highlights the potential role of the rTMS treatment in encouraging ipsilesional activation by modifying inter-hemispheric interactions, as the sham rTMS+BCI subject did not demonstrate similar increases in ipsilesional activation. However, the fMRI analysis was limited by head motion during paretic hand tracking in all subjects, particularly in S01. While motion correction was included in preprocessing and movement parameters were included as regressors, the effects of head motion may have appreciably reduced the active voxels during paretic hand tracking. Interestingly, both real rTMS+BCI subjects also demonstrated a reduction in laterality index from baseline to post-test 1 for non-paretic hand tracking, indicating increased ipsilesional activation during non-paretic hand tracking and suggesting a potential additional influence of rTMS on fMRI activation patterns associated with the contralesional side.

The subtlety of the improvements observed in subjects could be due to use of motor imagination only during BCI training. Previous studies have explored using FES [39] or robotic exoskeletons [22,25,27] along with BCI training to integrate movement of the paretic limb into the treatment, whether through passive or active movement, with the intent of capitalizing on resultant Hebbian plasticity. While BCI training and contralesional rTMS offer complementary benefits, it is possible that the cortical activity generated during motor imagination, without moving the paretic limb, does not enhance ipsilesional activity and plasticity as strongly as movement of the paretic limb could. While robotic exoskeletons [22,25,27,40] offer passive movement of the paretic limb, recent research studies have highlighted the utility of active movement [41,39], whether initiated by the user or via FES, along with neuromodulation to enhance plasticity. Future studies will be required to establish the optimal combination of motor intention, paretic limb movement, and cortical dynamics to enhance recovery.

Additionally, the BCI control paradigm could be modified to incorporate additional levels of control based on the relationship between ipsilesional and contralesional activation. In our study, we utilized a one-dimensional control strategy based on the weighted difference between the event-related activity at 12Hz in left and right motor cortex [37,42–45]. While this paradigm would require differences in cortical activity between paretic and non-paretic trials, it does not rule out the potential for subjects to control the BCI stimulus using modulations within the contralesional or ipsilesional side alone [23,24]. In future studies, additional signal processing techniques could be used to target particular brain regions [46] to force subjects to activate ipsilesional cortex alone, while also ensuring subjects are able to

achieve adequate control of such a stimulus. In this study, the BCI control parameters were kept largely constant with the intention of encouraging subjects to learn to control the stimulus, and only settings such as overall trial time and an additional velocity gain factor for each trial were varied to ensure subjects had adequate time to reach a target. It is also possible to adapt the control paradigm, including the electrode(s) and frequency band, for each subject in real time. Such adaptation may compensate for differences in activation patterns amongst subjects depending on the lesion size and location.

It is also possible that contralesional rTMS and/or BCI training may only be appropriate for a subset of subjects with excessive IHI from the contralesional hemisphere and difficulty achieving independent brain activation patterns for paretic and non-paretic limb movement. Additional studies are needed to examine the optimal rehabilitation strategies to promote brain reorganization in stroke subjects, perhaps adapted to the subject's network dynamics over time, such as IHI ratios. It is likely that subjects with similar impairments after stroke may benefit from different treatment strategies due to differences in the affected neural networks. In this way, facilitative or suppressive TMS could be applied to targets outside of primary motor cortex if the cortical dynamics indicated a potential alternative target to achieve a desired therapeutic effect. Additionally, the application of TMS for stroke rehabilitation is appropriate for limited patient populations, as many may be excluded due to a history of epilepsy, certain medications, or other concurrent medical conditions. While TMS has been generally well received in patient populations to date, the exclusion criteria do significantly limit the extent of patients who may receive the therapy. In this way, BCI could be a particularly valuable potential therapy, as it is relatively portable and has very few exclusion criteria generally.

While the results of our study are in general agreement with previous studies of contralesional rTMS or BCI training for motor recovery after stroke, the distinctive feature of our study was the combined approach to enhance excitability and activity within the lesioned cortex. While generally positive behavioral changes were observed, we cannot draw strong conclusions due to the limited patient population. However, treatment-specific behavioral results were observed, particularly in the real rTMS+BCI group in the IHI, fMRI, and BCI results. The hypothesized TMS-specific alterations in inter-hemispheric interactions were only observed in the real rTMS+BCI group, along with maximal or increasing ipsilesional fMRI activity for the real rTMS+BCI group only. BCI training also indicated significant improvements over time and differences between paretic and non-paretic performance only for the real rTMS+BCI group, highlighting the potential effect of preceding rTMS on subsequent BCI training. Additionally, both groups demonstrated improvements on behavioral tests over time, highlighting the potential of not only combined rTMS+BCI, but also BCI alone to result in functional improvements in subjects who have otherwise completed the standard-of-care physical and occupational therapy. Therefore, with respect to the original objective of comparing rTMS+BCI training to sham rTMS+BCI training, the IHI, fMRI, and BCI results have highlighted the effects of real rTMS, while the behavioral improvements suggest combined rTMS+BCI treatments or even BCI alone can lead to functional improvement. Given the novelty of combining rTMS with BCI training for motor recovery after stroke, along with the novelty of the virtual-reality BCI training, we believe that the treatment-specific results highlight the potential of this combined therapy,

particularly with respect to inter-hemispheric interactions. We believe the combination of neuromodulation with subsequent brain computer interface training holds promise as a brain-based therapy for motor recovery and merits further research in the future.

### 4.1 Study Limitations

We acknowledge several limitations of the present study. The small sample size of three subjects does not accurately reflect the spectrum of subjects with motor impairments following stroke. The sample size of three subjects also resulted in an unbalanced number of subjects randomly assigned to each condition (real rTMS+BCI or sham rTMS+BCI). Additionally, both subjects randomly assigned to the real rTMS+BCI condition exhibited considerably reduced paretic motor function at baseline compared to the subject within the sham rTMS+BCI condition, who exhibited subtle impairment in motor function. Thus, the results of the study cannot completely evaluate the difference between conditions due to the unbalanced assignment to conditions and considerable inter-individual differences in baseline function. Additionally, with regard to the statistical analysis, we acknowledge the difficulty of applying a t-test on a limited number of samples. Although a limited number of samples, in some cases as low as three, cannot accurately approximate a distribution, such t-tests do provide a measure of the statistical basis for differences over time. The p-values reported are prior to correction for multiple comparisons, however Bonferroni correction was performed and all tests with $p<0.01$ survived the conservative correction. While other advanced statistical methods, such as a repeated measures ANOVA, could be employed to further separate the effects of treatments across groups over time, t-tests were selected as the most appropriate method given that the treatments given between baseline and post-test 1 and between post-test 1 and post-test 2 are actually different (TMS+BCI vs. BCI only). Future work with additional patients could include more detailed statistical analysis to further separate the effects of treatment type over time. However, despite these challenges, this study establishes the feasibility and potential for efficacy in combining rTMS and BCI training for motor rehabilitation. Additional research will be necessary to build upon the current work and establish the efficacy of combined rTMS and BCI training in a larger patient cohort. Additionally, it is noted that, as the study design did not include a control condition, the behavioral improvements observed in subjects could be unrelated to the treatment but resulting from spontaneous recovery following stroke or possible placebo effects associated with rTMS or BCI treatments. However, given that all of the subjects were nearly one-year post-stroke at enrollment and were not pursuing any other forms of rehabilitative training, we believe the behavioral improvements observed are indeed reflective of the study treatments. Finally, we would like to emphasize the difficulty in identifying eligible subjects for the study, as subjects were required to be less than 12 months from the date of stroke, with an ipsilesional MEP and some finger extension, and also not pursuing outside therapy while participating. This combination of factors excludes many subjects who may benefit from the combined therapy. Future studies should include chronic stroke subjects or include subacute stroke subjects completing physical or occupational therapy along with a control condition to assess the level of improvement in motor function expected from standard-of-care therapy alone.

## 5. Conclusions

In summary, our findings demonstrate the feasibility and efficacy of combined rTMS with BCI training in stroke subjects, as demonstrated by statistically significant improvements in the finger tracking test over time, alterations in IHI as hypothesized, maximal or increasing ipsilesional fMRI activation during paretic hand tracking, and significant increases in BCI performance over time for the real rTMS+BCI group. In contrast to our original hypothesis, however, the real rTMS+BCI training was not superior to sham rTMS+BCI training in all measures, as functional gains in behavioral tests were observed for both conditions, indicating that BCI training alone may lead to improvement in motor function in some subjects. Interestingly, IHI testing revealed significant changes in IHI for both conditions but in opposite directions, with increased inhibition in the desired direction from the ipsilesional to contralesional hemisphere for the real rTMS+BCI condition only, supporting the directionality of rTMS induced effects. BCI performance demonstrated subjects were able to achieve adequate control of the virtual reality BCI paradigm, with peak daily performance above 70% and significantly higher performance overall for real rTMS+BCI. fMRI results demonstrate maximal or increased ipsilesional recruitment over time for real rTMS+BCI, further highlighting the unique effects of the combined rTMS+BCI therapy relative to BCI alone. Our findings lay a foundation for continued research to evaluate the potential of both rTMS and virtual reality BCI training for motor recovery after stroke and elucidate the ideal parameters, schedule, and combinations of brain-based treatments to maximize motor rehabilitation following stroke.

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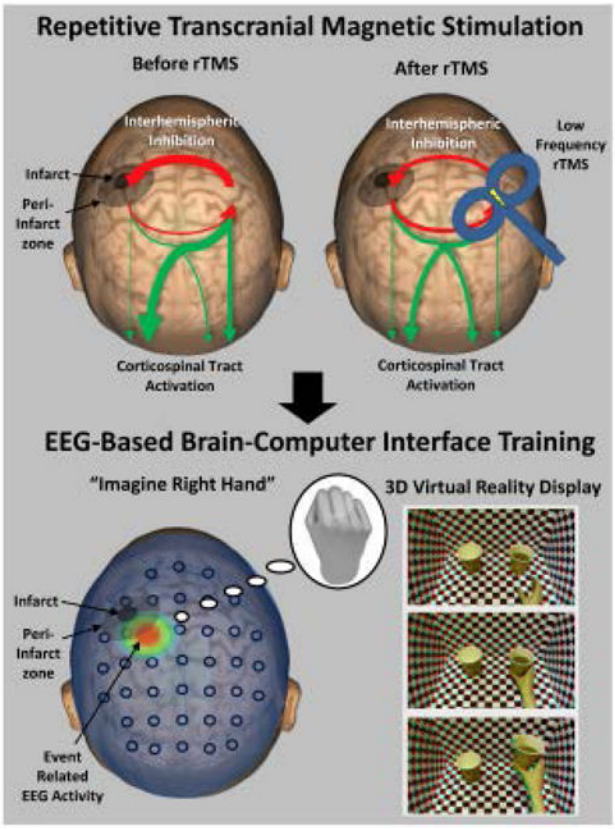


**Figure 1.**

Schematic illustrating rationale for contralesional rTMS (upper) and BCI training (lower). (upper) After a stroke, the interhemispheric inhibition from the contralesional hemisphere acting upon the ipsilesional hemisphere can further reduce the excitability of the lesioned hemisphere, reducing corticospinal activity (as indicated by arrow thickness). The rationale for this study is based, in part, on the notion that applying low frequency rTMS to the contralesional side can reduce excitability of the contralesional side, thus reducing interhemispheric inhibition and effectively increasing excitability within the lesioned hemisphere. (lower) EEG-based BCI training uses motor-imagination to generate event-related changes in recorded EEG activity on both sides, which controls a 3D virtual reality stimulus. The BCI training is intended to both increase excitability within the lesioned hemisphere over time as well as discourage compensatory contralesional activation during ipsilesional motor imaginations.

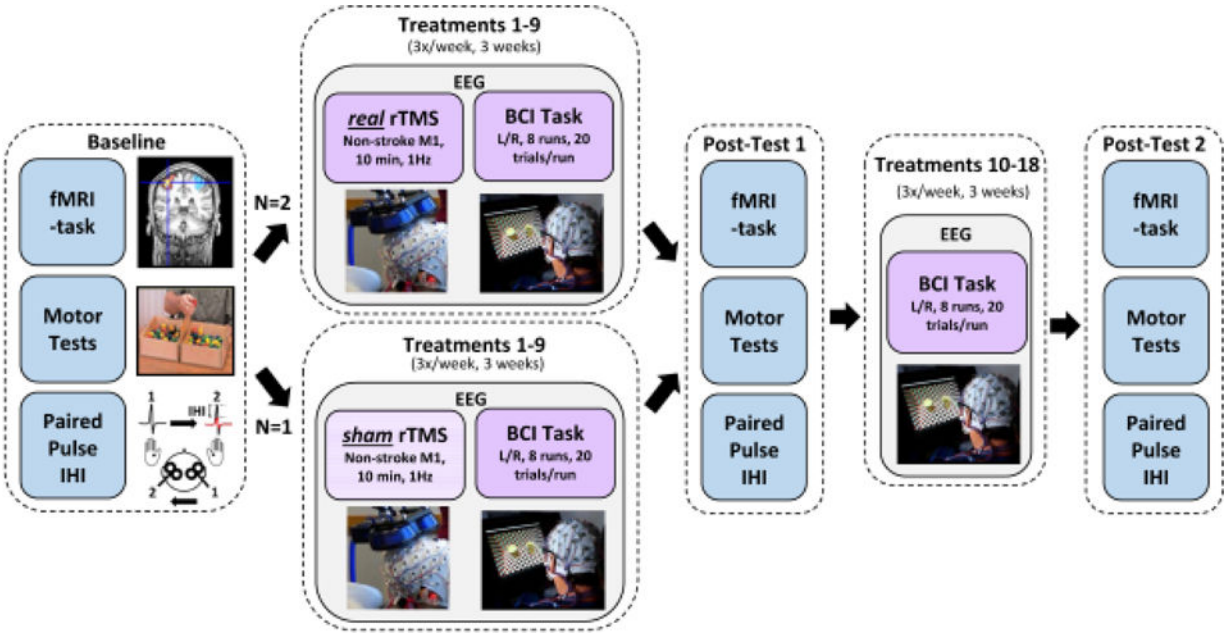


**Figure 2.**

Study schedule in which participants received two different types of treatments, first combined rTMS and BCI training followed by BCI training alone over a period of six weeks. Testing visits including fMRI, motor tests, and IHI testing were interspersed at baseline, after 3 weeks (post-test 1), and after 6 weeks (post-test 2).

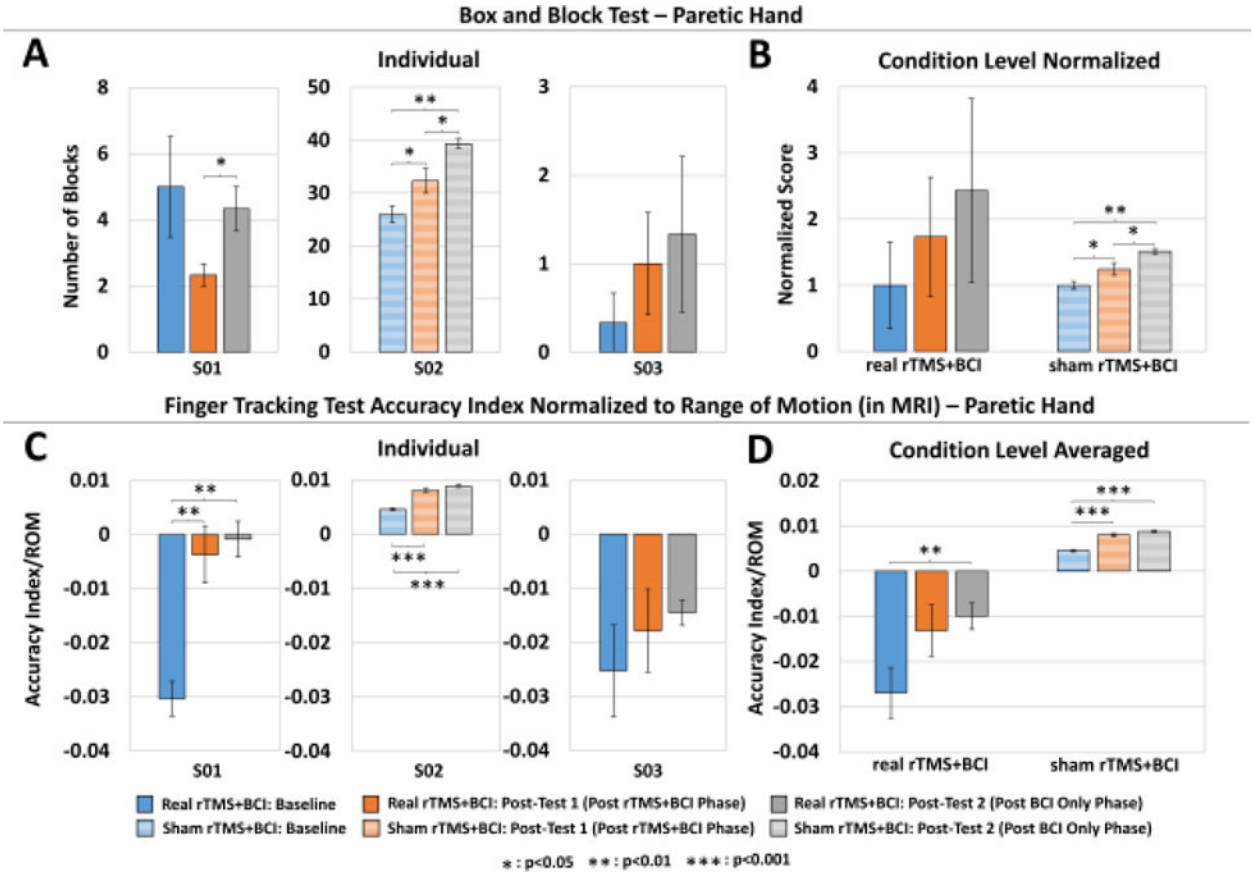


**Figure 3.**

Box and Block Test scores of the paretic hand (mean ± standard error of 3 trials) for each subject (A) and each condition normalized to baseline (B). Finger Tracking Test accuracy index values (mean ± standard error of 3 trials) of the paretic hand normalized to the range of motion (ROM) for each subject (C) and for each condition (D).

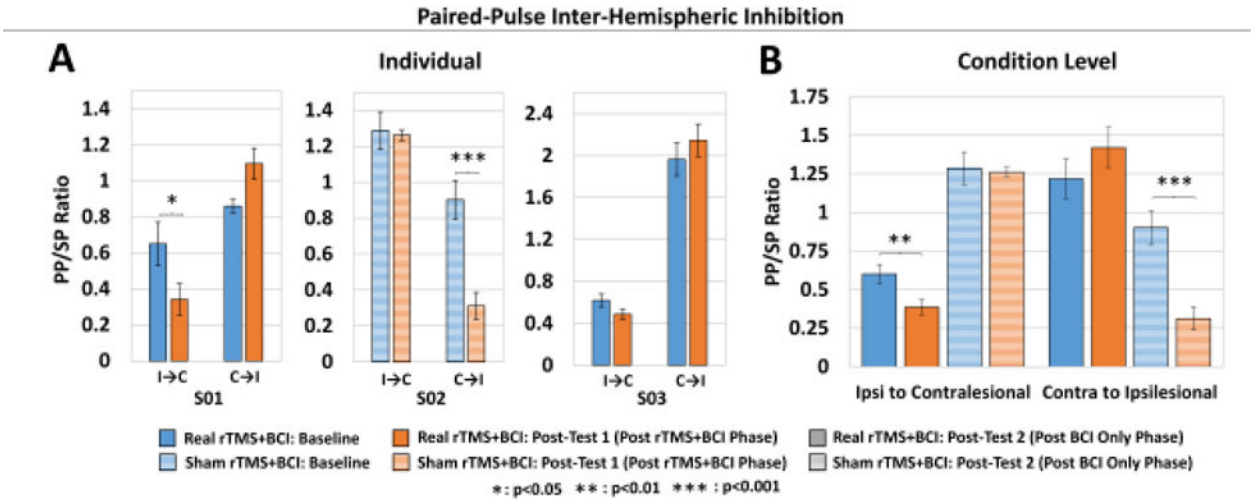


**Figure 4.**

IHI paired-pulse to single-pulse (PP/SP) MEP amplitude ratios (mean ± standard error of 20 trials) in each direction for each subject (A) and each condition (B). I: Ipsilesional hemisphere, C: Contralesional hemisphere.

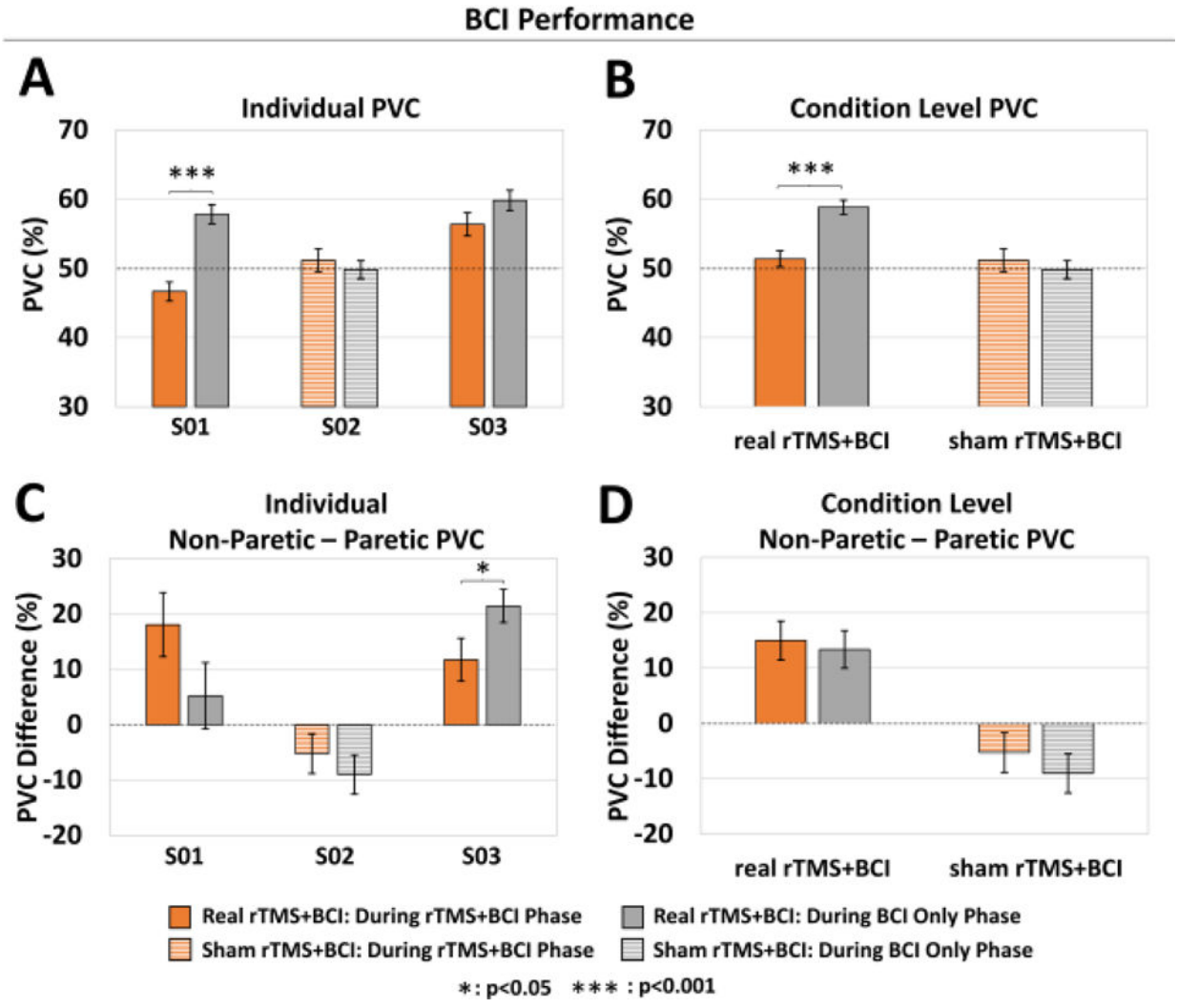


**Figure 5.**

BCI PVC (mean ± standard error) during each treatment phase for each subject (A) and each condition (B). BCI PVC difference between non-paretic and paretic trials (mean ± standard error) during each treatment phase for each subject (C) and each condition (D). Dotted line: chance.

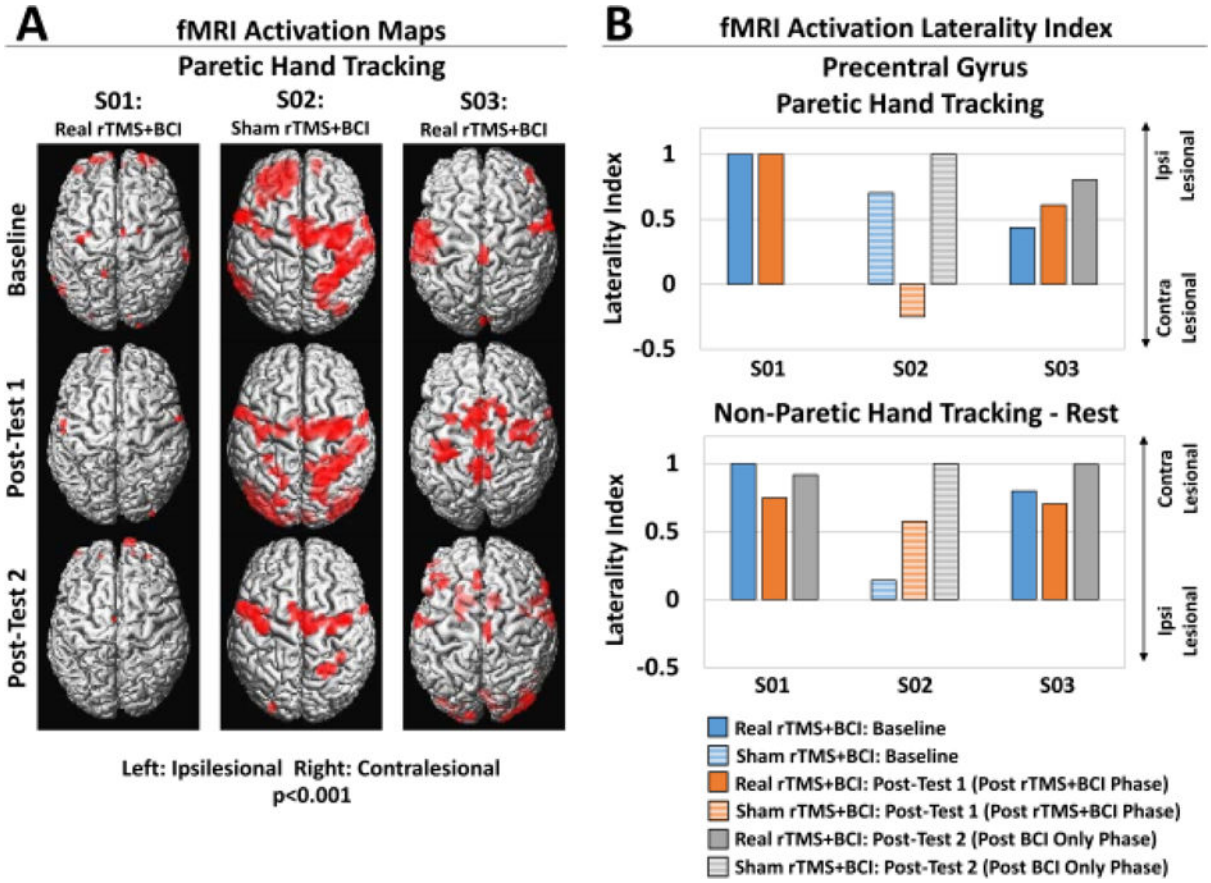


**Figure 6.**

(A) fMRI activation maps during paretic hand tracking relative to rest for each subject at each time point ($p<0.001$, $k>10$ voxels for S02/S03 for display) overlaid on individual anatomy. (B) fMRI laterality index for each subject at each time point during paretic hand tracking (upper) and non-paretic hand tracking relative to rest (lower).

**Table I**

Participant Demographics

| Subject Number | 1 | 2 | 3 |
|---|---|---|---|
| **Sex** | Male | Female | Female |
| **Age** | 60 | 37 | 69 |
| **Time Post Stroke** | 11m, 21d | 11m, 24d | 11m, 18d |
| **Stroke Type** | Ischemic, Sub-Cortical | Ischemic, Sub-Cortical | Ischemic, Sub-Cortical |
| **Stroke Location** | Left BG/ICA/M-2 | Right BG/M-1 | Left CR/P/M-1 |
| **Affected Side** | Right | Left | Right |
| **Mini-Mental Status Exam** | 24 | 30 | 28 |
| **Beck Depression Inventory** | 1 | 22 | 12 |
| **Edinburgh Handedness Inventory** | −0.6 | 0.9 | 0.2 |
| **Upper Extremity Fugl Meyer** | 29 | 60 | 28 |
| **Modified Ashworth Scale** | 0 | 1 | 3 |

BG: Basal Ganglia, ICA: Internal Carotid Artery, M-1: horizontal segment of the middle cerebral artery, M-2: Insular segment of middle cerebral artery, CR: Corona radiata, P: Putamen