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Not all brain regions are created equal for improving bimanual coordination in individuals with chronic stroke ☆

Wan-wen Liao [a,*], Jill Whitall [a,b], George F. Wittenberg [c,d], Joseph E. Barton [c], Sandy McCombe Waller [a]

[a] Department of Physical Therapy and Rehabilitation Science, School of Medicine, University of Maryland Baltimore, Baltimore, MD, USA
[b] Faculty of Health Sciences, University of Southampton, Southampton, UK
[c] VA Maryland HealthCare System and Department of Neurology, School of Medicine, University of Maryland, Baltimore, MD, USA
[d] VA Pittsburgh Healthcare System, and University of Pittsburgh, Pittsburgh, PA, USA

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HIGHLIGHTS

- Patients with greater arm/hand impairment improved bimanual coordination with facilitation of contralesional dorsal premotor cortex (cPMd).
- Patients with fewer arm/hand impairment improved bimanual coordination with facilitation of ipsilesional primary motor cortex (iM1).
- Wrist/hand function and the interhemispheric inhibition strength seem to affect responses to cPMd and iM1 facilitation.

ABSTRACT

Objective: The now standard cortical stimulation approach of inhibiting contralesional primary motor cortex (cM1) disrupts bimanual coordination while facilitating ipsilesional M1 (iM1) fails to enhance paretic arm function, in severely impaired individuals. We propose an alternative target, enhancing contralesional dorsal premotor cortex (cPMd) to improve bimanual coordination and compare its effects to iM1.
Methods: Fourteen participants with stroke received 5-Hz repetitive transcranial magnetic stimulation (rTMS) on cPMd or iM1 in a repeated cross-over design. Bimanual force/neuromuscular coordination and cortical excitability were assessed. We also examined the relationship of baseline motor function/interhemispheric inhibition (IHI) to participant's responses to each stimulation target.
Results: We identified two patterns of responses. Participants with more severe impairment and weaker IHI improved bimanual force/neuromuscular coordination, ipsilesional activations and reduced IHI after cPMd-rTMS; whereas, those with milder impairment and stronger IHI improved only after iM1-rTMS.
Conclusions: Cortical stimulation protocols could be tailored to the types of tasks and to individuals' severity of impairment. Facilitation of cPMd may improve bimanual coordination especially for individuals with limited arm/hand function.
Significance: Our study is the first to identify cortical stimulation strategies for improving bimanual coordination for individuals with different level of severity of stroke.

1. Introduction

Each year, over 795,000 people experience a stroke which is the primary cause of long-term disability in the United States (Benjamin et al., 2017). Despite undergoing intervention after a stroke, most people experience residual arm deficits in the chronic phase that greatly affects their ability to accomplish daily living activities (Kwakkel et al., 2004; Winstein et al., 2016). In recent

☆ This work was done at the University of Maryland Baltimore, Baltimore, Maryland, USA.

* Corresponding author at: Department of Occupational Therapy, College of Medicine, Chang Gung University, 259, Wenhua 1st Rd., Guishan Dist., Taoyuan City 333, Taiwan.
E-mail address: wanwenliao@gmail.com (W.-w. Liao).

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decades, one promising approach to enhance post-stroke arm recovery has been to directly modulate the cortical excitability in the brain using non-invasive brain stimulation (NIBS), such as repetitive transcranial magnetic stimulation (rTMS). The premise of NIBS is that cortical plasticity can be induced through repetitive and continuous stimulation of the underlying neuron pools, thus enhancing the brain's functional reorganization after stroke (Klomjai et al., 2015). Current standard NIBS approaches were mostly developed based on the interhemispheric competition model, which emphasizes facilitation of the ipsilesional primary motor cortex (iM1) and/or inhibition of the contralesional M1 (cM1), with the goal of rebalancing interhemispheric inhibition (IHI) (Murase et al., 2004; Nowak et al., 2009).

Although this standard approach of facilitation of iM1/inhibition of cM1 has been effective in improving arm function in mildly-impaired individuals, it fails to generate the same level of improvement in individuals with more severe arm impairments (Ackerley et al., 2010; Hesse et al., 2011; Kakuda et al., 2011; Hao et al., 2013; Levy et al., 2016). These severely-impaired individuals tend to experience extensive ipsilesional cortex damage, leaving them with limited neural resources for activation by stimulating the iM1 (Butefisch et al., 2003; Hedna et al., 2013; Levy et al., 2016; Simis et al., 2016; Touvykine et al., 2016). Alternatively, the contralesional hemisphere, especially the contralesional dorsal premotor cortex (cPMd), facilitates interhemispheric communication and supports paretic arm movements in individuals with moderate to severe impairment (Bestmann et al., 2008; Bestmann et al., 2010). Disruption of the cPMd resulted in delayed reaction time and increased temporal errors compared to those of other contralesional areas such as cM1. This indicated a more likely causal role for the cPMd than other contralesional areas in controlling paretic arm movements (Johansen-Berg et al., 2002; Lotze et al., 2006; Mohapatra et al., 2016; Sankarasubramanian et al., 2017). In addition, one recent study examined the effects of facilitation of the cPMd compared to inhibition of cM1 on single paretic arm reach. It was revealed that facilitation of the cPMd improved the reaching reaction time for individuals with severe hemiparesis (Sankarasubramanian et al., 2017). Therefore, facilitating the cPMd may serve as a plausible alternative approach, in addition to facilitating iM1, to improve recovery of paretic arm movements. To our knowledge, a direct comparison of neuromodulation using rTMS on these two regions has not been conducted in individuals with stroke. Furthermore, it is not known whether individuals with varying degrees of severity will respond differently to one approach over the other.

Another potential caveat of the current neuromodulation protocols is that they are predominantly designed to improve unimanual arm function. Given the high involvement of both arms in daily activities, interventions aimed at improving arm coordination are equally, if not more, important as those which facilitate recovery of solely paretic arm function. For individuals with severe impairment, restoring coordination of the two arms may be most critical for enhancing daily living activities. At this point, only one study about current standard NIBS approaches has examined their effects on bimanual coordination for individuals with stroke. That study reported a negative impact on bimanual finger coordination after using the standard approach of inhibiting cM1 (Takeuchi et al., 2012). This may indicate that current NIBS protocols are not necessarily applicable for enhancing bimanual coordination.

Indeed, when comparing bimanual arm movements to unimanual movements, studies have shown that a more distributed neural network, including motor regions, premotor regions, and the cerebellum, was involved in control of bimanual coordination (Toyokura et al., 1999; Zhuang et al., 2005; Grefkes et al., 2008). In particular, the premotor regions of both hemispheres, such as the PMd, are associated with coordinating and stabilizing bimanual simple and complex hand movements (Gerloff and Andres, 2002; Debaere et al., 2004; van den Berg et al., 2010; Liuzzi et al., 2011). Furthermore, a positive modulation has been found between both the PMd and other brain regions within and between hemispheres (Grefkes et al., 2008). The above suggests that the PMd is a potential neuromodulation target for enhancing bimanual coordination. For individuals with more severe arm impairments, the cPMd may be even more critical for bimanual as well as paretic arm function. As far as we know, no study has examined the neuromodulation effects of the cPMd compared to the iM1 in enhancing bimanual coordination for individuals with chronic stroke. The treatment effects of NIBS on bimanual coordination remain unclear.

The aim of this study was to compare the effects of facilitation of the cPMd and iM1 on bimanual coordination and cortical function in individuals with chronic hemiparesis. We selected the cPMd as the neuromodulation target based on its high relevance to stroke recovery and its critical involvement in bimanual coordination. We compared its stimulation effect to that of the most common neuromodulation target, the iM1. Based on evidence in previous studies, we hypothesized that the beneficial effects of facilitation of the cPMd would depend on the baseline impairment. Participants with greater baseline impairment would demonstrate greater improvement in interlimb force and neuromuscular coordination as well as cortical excitability measures after facilitation of the cPMd. Conversely, participants with fewer baseline impairment would differentially respond to facilitation of the iM1. The overall goal of this study was to provide insights for developing individually-tailored and task-based neuromodulation interventions to assist in recovery of bimanual post-stroke function.

2. Methods

2.1. Participants

Fourteen individuals (9 males, mean age 65 ± 9.89 years, range 43–79 years) were enrolled (Table 1). All participants had experienced a first stroke and demonstrated hemiparesis with residual upper limb deficits. Inclusion criteria were (1) greater than 40 years of age, (2) unilateral ischemic (≥6 months post-stroke) or hemorrhagic (≥12 months post-stroke) stroke, (3) able to demonstrate motor evoked potentials (MEPs) during active muscle contraction of the paretic arm, (4) Fugl-Meyer assessment of upper extremity (FM-UE) score between 20 and 65, and (5) able to perform experimental protocols with both arms. Individuals were excluded if they had (1) stroke involving cerebellum, (2) other concomitant neurological or psychiatric disorders such as brain tumor and dementia, (3) any contraindications to TMS (e.g., history of epilepsy, metallic implants in the head or chest, and implanted shunts/simulators/cardiac pacemakers) (Rossi et al., 2009), and (4) concurrent use of CNS-affecting medications, including antidepressants (Ziemann et al., 2015). All participants provided written informed consent. All study procedures were approved by the Institutional Review Board of the School of Medicine at the University of Maryland, Baltimore and performed in accordance with the Declaration of Helsinki.

2.2. Experimental design

This study employed a single-blind, repeated measures, crossover design. None of the participants had experience with rTMS before this study. Participants underwent two experimental conditions, including cPMd stimulation for the first two visits and iM1 stimulation for the last two visits. The two conditions were presented in a systematic order to minimize the impact of

Table 1
Study participant demographics and clinical characteristics.

ID	Gender Male (M)/Female (F)	Time since stroke (years)	Paresis Right (R)/Left (L)	Stroke subtype	Lesion location	FM-UE Shoulder/elbow	FM-UE Wrist/hand
1	M	16	L	Ischemic	Cortical	17	20
2	F	16	R	Ischemic	Subcortical	20	5
3	M	5	R	Ischemic	Cortical/Subcortical	20	22
4	F	7	L	Ischemic	Cortical/Subcortical	25	4
5	F	8	L	Ischemic	Subcortical	31	23
6	F	15	L	Ischemic	Cortical/Subcortical	17	19
7	M	14	R	Hemorrhage	Cortical/Subcortical	25	16
8	M	5	R	Ischemic	Pontine	18	12
9	M	7	L	Ischemic	Subcortical	28	23
10	F	9	L	Ischemic	Subcortical	31	23
11	M	7	R	Ischemic	Cortical/Subcortical	20	8
12	M	1	L	Ischemic	Basal ganglia	26	22
13	M	1	L	Ischemic	Cortical/Subcortical	16	10
14	M	2	R	Ischemic	Basal ganglia	28	24

FM-UE, Fugl-Meyer assessment of upper extremity score.

between-session variability on responses to rTMS. Each experimental condition (cPMd or iM1) consisted of two visits, one to assess intracortical and interhemispheric excitability and the other to assess interlimb force and neuromuscular coordination during a bimanual isometric force task. Within each session, participants received baseline assessment, repetitive stimulation of cPMd or iM1, and post-stimulation assessment (Fig. 1). Thus, a total of four sessions were required for each participant, with each separated by at least 48 hours to minimize carryover effects. The Fugl-Meyer assessment scale of upper extremity (FM-UE) was used at the first visit to evaluate the motor function of the paretic arm.

2.3. Electromyography

Two bipolar Ag-AgCL surface electrodes were placed on the belly of biceps brachii (BB) muscle of each arm. Muscle activation was recorded using a wireless electromyography (EMG) system (TeleMyo Direct Transmission System, Noraxon, USA). EMG signals were bandpass filtered between 5 and 400 Hz using a zero-phase Butterworth filter, sampled at 1000 Hz, and stored on a PC for off-line analysis using MATLAB (Math Works™ Inc., Natick, USA).

2.4. Motor task: bimanual isometric elbow flexion task

Participants were seated in a cushioned reclining chair with elbows positioned at 90° flexion with forearms stabilized in arm cuffs in a neutral position. They performed bimanual, isometric elbow flexion tasks in a common-goal condition (a single target line corresponding to the total force of both arms). In the common-goal condition, the two arms shared a single focus, and they had to coordinate with each other to accomplish tasks. Before testing, participants performed bimanual maximal voluntary force contraction in isometric elbow flexion condition (bimanual MVC). The target force level to match for testing was 20% of the bimanual MVC. Participants were instructed to isometrically flex both elbows to match to the target force level as closely as possible (a single target line corresponding to the total force of both arms) and hold this continuously for 10 seconds (s). The force performance during this 10-s period was used to analyze the interlimb force and neuromuscular coordination. Real-time, visual feedback of force performance was displayed on a computer screen placed 1 meter in front of the participant. There were three to five practice trials to ensure that the correct movements were performed. A total of three trials was collected at the baseline and the post-stimulation evaluation period, respectively. Rest breaks were provided between trials if needed.

2.5. Repetitive transcranial magnetic stimulation

The rTMS was delivered to the cPMd or iM1 using a biphasic rapid stimulator with 70-mm double air film coil (MagstimRapid2, Magstim Co, UK). The coil was held tangentially to the scalp, with the handle pointing backward, and laterally at a 45° angle in the sagittal plane. The rTMS involved a train of 50 pulses (10 s) at 5 Hz with an inter-train interval of 30 s, repeated 24 times (Goh et al., 2015). The total number of stimulations was 1200 pulses, and the duration of intervention was 930 s. The optimal site for stimulation (hotspot) and the active motor threshold (AMT) were determined according to guidelines in the literature (Rothwell et al., 1999; Rossini et al., 2015). AMT was defined as the lowest intensity-producing MEP amplitudes exceeding 200 μV in ≥5 of 10 consecutive stimulations, while participants performed the isometric elbow flexion task using a single arm at 20% MVC. A neuronavigation system (Brainsight, Rouge Research, Canada) was used to ensure accurate coil placement throughout the experiment.

The cPMd location was defined as 2.5 cm anterior to the hotspot of the non-paretic BB muscle (Fink et al., 1997; Picard and Strick, 2001). To further isolate cPMd from the contralesional M1, we

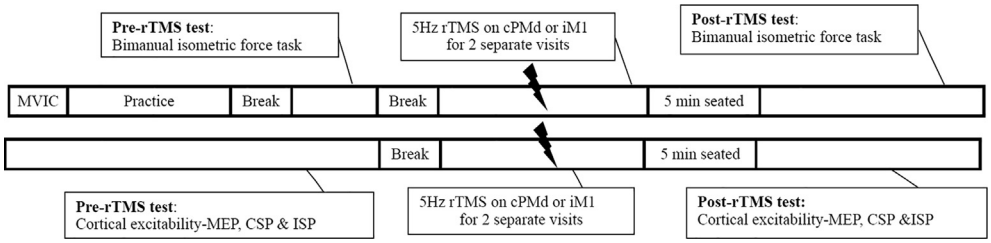

Fig. 1. Experimental flow. Each participant had four visits. There were two visits to assess interlimb force and neuromuscular coordination during bimanual tasks and two visits to evaluate cortical excitability. Abbreviations: MVIC, maximal voluntary isometric contraction; cPMd, contralesional dorsal premotor cortex; iM1, ipsilesional primary motor cortex; MEP, motor evoked potential; CSP, cortical silent period; ISP, ipsilateral silent period.

applied a single-pulse TMS on the cPMd location to ensure that (1) there was no MEP activity recorded over the non-paretic BB muscle, and (2) there were no visually-apparent muscle twitches in the forearm or hand. EMG activity of the non-paretic arm was also monitored during rTMS intervention to ensure that stimulation effects were focused on cPMd and did not spread to the contralesional M1 (Meehan et al., 2013).

To determine the ideal rTMS intensity for the cPMd and iM1, we performed pilot tests using an intensity from 70% to 90% AMT of the BB muscle in non-disabled individuals. For PMd, we found that 70% AMT could increase MEP amplitudes. It was the most tolerable intensity for all individuals, given that the premotor cortex was on the crown of the precentral gyrus, which was closer to the stimulating coil than the motor cortex and more sensitive to stimulation (Gerschlager et al., 2001). Thus, the rTMS intensity for the cPMd was set as 70% AMT of the non-paretic BB muscle. For the iM1, rTMS was applied to paretic BB muscle hotspot. To allow equal comparison between two experimental conditions (cPMd and iM1), the rTMS intensity for the iM1 was also based on the AMT of the non-paretic BB muscle. It was set at 90% AMT based on our pilot tests and safety guidelines for high-frequency rTMS (Wassermann, 1998). EMG signals were continuously monitored to ensure no muscle activity was evoked during rTMS.

There was a 5-min rest period before and after rTMS intervention to allow for consolidation of stimulation effects after rTMS intervention (Bienenstock et al., 1982; Thickbroom, 2007; Gentner et al., 2008; Ridding and Ziemann, 2010). Participants were seated comfortably in a cushioned reclining chair with their neck supported in the neck rest and their arms resting in the arm trough during this 5-min period and the rTMS intervention.

2.6. Behavioral measurement: interlimb force coordination

The force produced by each arm was recorded by two force transducers

(Transducer Techniques, CA, USA) mounted under the armrests. The force signal was sampled at 1000 Hz and filtered by a zero-phase low pass filter with a cutoff frequency of 10 Hz. Data acquisition was controlled using a customized MATLAB script. As described in Section 2.4, *Motor task*, participants isometrically flexed their elbow to match the target force line for 10 s in a total of three trials. The initial 2 s and the last 3 s of each trial were removed from analyses to account for initial adjustment and potential early force termination. Interlimb force coordination was quantified by assessing the correlation of force between the arms during the bimanual task using the Pearson's correlation coefficient function. A moving window correlation method with a window length of 200 ms that moved one sample at a time was used to calculate the correlation of force between the arms across time. This method was selected because it could account for variances over time for non-stationary time series data (Boker et al., 2002). Therefore, the resulting Pearson's correlation coefficient represented the degrees of interlimb force coordination of each trial.

2.7. Neuromuscular coordination measurement: Intermuscular coherence

In addition to interlimb force coordination, we also assessed the arms' neuromuscular coordination during bimanual tasks. The neuromuscular coordination between the arms was defined as the synchronization of EMG signal of BB muscles of the two arms in the frequency domain and assessed by the coherence between the two EMG signals. This intermuscular EMG-EMG coherence provided information on the degree of common neural drive from the cortex to muscle pairs, which represented the motor synchrony/binding between muscles during a specific motor task (Farmer et al., 1998; Grosse et al., 2002). It has also been used to characterize functional coordination between muscles in non-disabled individuals and those with stroke (Boonstra et al., 2007; Farmer et al., 2007; Kisiel-Sajewicz et al., 2011; Dai et al., 2017).

To calculate the intermuscular coherence during the bimanual task, raw EMG signal were first extracted from the same trials used to analyze interlimb force coordination, then high-pass filtered at 250 Hz and full-wave rectified in accordance with published recommendations (Boonstra and Breakspear, 2012; Ward et al., 2013; Farina et al., 2016). The magnitude squared of coherence (C) was estimated by using the mscohere function of MATLAB, with a Hanning window of 2048 samples per segment, with an overlap of 75% (Frequency resolution = 0.49 Hz). It was converted to Fisher's values using the following algorithm:

$$FZ = \arctan h\left(\sqrt{C}\right)$$

The Fisher's Z transformation was used as a normalization procedure to stabilize the coherence distribution variance (Brillinger, 1974) and has been used in several previous studies (Maris and Oostenveld, 2007; Danna-Dos Santos et al., 2010; Lee et al., 2014). This z-transformed intermuscular coherence represented the strength of neuromuscular coupling between the two arms. The increment of this value after rTMS would indicate an enhanced neural drive from the cortex to both BB muscles, leading to a stronger neuromuscular synchronization of the arms during bimanual tasks. In our study, we calculated the z-transformed coherence within the β band (15–30 Hz) because changes in the β originated primarily from the cortex and were associated with promoting stable motor output (Kilner et al., 2000; Gilbertson et al., 2005; Perez et al., 2006; Kristeva et al., 2007; Fisher et al., 2012). The z-transformed coherence in the β band was averaged across trials for each participant and represented the strength of neuromuscular coordination of both arms during bimanual tasks.

In addition to evaluating the strength of intermuscular coherence, we also evaluated intermuscular coherence quality by calculating the rate of significant intermuscular coherence above 95% confidence interval (CL) in the β band following the formula below (Halliday et al., 1995; Amjad et al., 1997; Mima et al., 2001; Schmied et al., 2014):

$$\mathrm{L} = \text{numbers of segments. } \alpha = 0.05$$
$$\mathrm{CL} = 1 - \alpha^{1/(\mathrm{L}-1)}$$

The rate of significant intermuscular coherence was defined as the number of coherences above CL, divided by the total number of coherences in the β band expressed as a percentage (%). The rate of significant intermuscular coherence was averaged across trials for each participant and compared between experimental conditions.

2.8. Measurement of cortical excitability and intracortical and interhemispheric inhibition

2.8.1. MEP amplitude of the ipsilesional and contralesional M1

MEP amplitude was assessed using a 70-mm figure-eight coil attached to the stimulator. A single-pulse TMS was applied to the paretic and non-paretic BB muscle hotspots at 120% AMT, while participants performed isometric elbow flexion tasks using a single arm at 20% MVC. A total of 12 trials were collected for each hemisphere at the baseline and after rTMS. The post-rTMS MEP was standardized by dividing it into the baseline MEP value (mean MEP amplitude at the baseline) and expressed as a MEP ratio. A higher value (>1) would indicate increased cortical excitability after rTMS and vice versa.

2.8.2. Contralateral silent period (CSP) of the ipsilesional and contralesional M1

To quantify the contralateral silent period (CSP), the EMG was full-wave rectified. The CSP onset was defined as the point when the rectified EMG dropped and stayed below the pre-stimulus EMG level (defined as the averaged EMG activity of 100-ms window, from 150 to 50 ms prior to TMS onset) for at least 10 ms (Harris-Love et al., 2011). The CSP offset was defined as the point when rectified EMG returned and stayed above the pre-stimulus level for at least 10 ms. The CSP duration was defined as the onset of MEP to the offset of CSP (Curra et al., 2002). The CSP duration was standardized by dividing it into MEP size to reduce between-participant variability (Orth and Rothwell, 2004; Orth et al., 2005). The value of CSP ratio indicated the degrees of intracortical inhibition.

2.8.3. Ipsilateral silent period (ISP)

To evoke the ipsilateral silent period (ISP), a single-pulse TMS was applied to the hotspot of the non-paretic BB muscle at 150% AMT, while participants performed isometric elbow flexion tasks using their paretic arm at 30% MVC. The onset of ISP was defined as the point when the rectified EMG dropped and stayed below the pre-stimulus level for at least 5 ms. ISP offset was defined as the point when the rectified EMG returned and stayed above the pre-stimulus level for at least 5 ms (Harris-Love et al., 2016). We calculated the ISP inhibition based on the formula below (Harris-Love et al., 2016):

$$\%\ \text{Inhibition} = [1 - (\text{mean EMG during ISP}/\text{mean EMG pre-stimulus})] * 100$$

A higher value indicated a stronger inhibition from the contralesional to ipsilesional hemisphere and vice versa. The EMG signals were continuously monitored to ensure there was no voluntary activity of the non-paretic arm. A total of ten trials was collected for evaluation of ISP at baseline and after rTMS. The ISP inhibition indicated the percentage of interhemispheric inhibition (IHI) from the contralesional to the ipsilesional hemisphere.

2.9. Statistical analysis

To identify responders to each type of stimulation (cPMd or iM1), we first used a hypothesis-driven hierarchical cluster analysis to group participants into two, three, and four clusters according to (1) baseline motor impairments using FM-UE shoulder/elbow, FM-UE wrist/hand, and FM-UE total score; (2) baseline ISP inhibition; and (3) responsiveness to cPMd- and iM1-rTMS defined as the MEP ratio of the ipsilesional hemisphere after cPMd- and iM1-rTMS (Thompson-Butel et al., 2014). The squared Euclidean distance was used as the distance measure, and the averaged linkage method was used to classify clusters (Kaufman and Rousseeuw, 1990). The raw score of the above outcomes were standardized to Z score. Then, we inspected the results to determine the optimal clusters that could distinguish between responders to cPMd-rTMS and responders to iM1-rTMS. A one-way analysis of variance, with Bonferroni-corrected post hoc comparison in cases of significance, was further used to examine whether the clusters significantly differed from each other in terms of the responsiveness to cPMd and iM1-rTMS (the ipsilesional MEP ratio of cPMd- and iM1-rTMS). Participants continually classified into the same cluster were the same group of responders, and their measurements of behavioral, neuromuscular, and cortical excitability were analyzed together as a group (cPMd-responders or iM1-responders) and compared between cPMd- and iM1-rTMS conditions.

We also performed a linear regression analysis to examine the relationship between baseline motor impairment and interhemispheric interaction to participants' responsiveness to cPMd- and iM1-rTMS. The explanatory variables were FM-UE shoulder/elbow, FM-UE wrist/hand, FM-UE total score, and ISP inhibition. The dependent variables were the ipsilesional MEP ratio of cPMd- and iM1-rTMS. In addition, a linear regression analysis was also implemented to investigate whether time (years) since stroke onset could affect responsiveness to cPMd- and iM1-rTMS. R^2 measured the goodness-of-fit for this model.

The Shapiro–Wilk test was used to examine the distribution of all data, and the natural log transformation was used to transform data that were not normally-distributed into normal distributed data. In addition, the paired t test was used to examine differences of all outcomes at the baseline between cPMd- and iM1-rTMS conditions. Two-way, repeated measures, analysis of variances (ANOVA) with factors of conditions (cPMd-rTMS vs. iM1-rTMS) and side of hemisphere (ipsilesional vs. contralesional) was used to evaluate the MEP ratio. Two-way repeated measures ANOVA with factors of time (baseline vs. post-stimulation) and conditions (cPMd-rTMS vs. iM1-rTMS) was also used to evaluate the CSP ratio of each hemisphere and ISP inhibition.

For behavioral and neuromuscular measurements, Pearson's correlation coefficient was converted into normally-distributed data using the Fisher r-to-z transformation following recommendations from the literature and averaging within each participant (Fisher, 1915; Silver and Dunlap, 1987). Two-way repeated measures ANOVA with factors of time (baseline vs. post-stimulation) and conditions (cPMd-rTMS vs. iM1-rTMS) were used to examine interlimb force correlation (z-transformed correlation of coefficient) and intermuscular coherence (intermuscular coherence strength and rate of significant intermuscular coherence). In the case of significant interaction effects, the paired t test with the Bonferroni correction procedure was used for post hoc analysis to evaluate directional changes of outcomes in terms of time (baseline vs. post-stimulation) or hemisphere (ipsilesional vs. contralesional) for each condition. Figures were presented using the original data (without natural log transformation) with mean ± standard errors of the mean. For all statistical tests, alpha level was set as 0.05.

3. Results

3.1. Hierarchical cluster analysis

Two, three, and four clusters were generated based on our hypothesis-driven cluster analysis models. Four participants were consistently classified into the same cluster throughout all models. These participants demonstrated increased cortical excitability in the ipsilesional hemisphere after cPMd-rTMS (mean MEP ratio = 1.65 ± 0.1) with almost no changes after iM1-rTMS (mean MEP ratio = 1 ± 0.09). Significant differences were also found in the ipsilesional MEP ratio between this cluster of four participants and other clusters for both cPMd- and iM1-rTMS conditions across all models ($P < 0.05$). These participants had limited paretic arm function, particularly in the distal part of the arm (mean FM-UE total score = 27 ± 1.83; mean FM-UE wrist/hand score = 6.75 ± 2.75), compared to the other ten participants (mean FM-UE total score = 46.3 ± 9.75; mean FM-UE wrist/hand = 20.4 ± 3.81). Their baseline ISP inhibition was also lower (mean = 35 ± 6.15) than that of the other ten participants (mean = 55.25 ± 6.33).

The other ten participants were classified into one, two, and three clusters. However, no significant difference was found in the ipsilesional MEP ratio of cPMd- and iM1-rTMS between these

clusters across all models ($P > 0.05$), meaning these participants shared similar response patterns. These participants demonstrated increased cortical excitability after iM1-rTMS (mean MEP ratio = 1.60 ± 0.19) but decreased excitability after cPMd-rTMS (mean MEP ratio = 0.73 ± 0.23). Overall, based on hierarchical cluster analysis models, we identified two major groups of responders, with one showing positive responses to cPMd-rTMS (cPMd-responder group: n = 4) and the other demonstrating positive responses to iM1-rTMS (iM1-responder group: n = 10). As a result, we divided participants into two subgroups, and their behavioral, neuromuscular, and cortical excitability data were analyzed together as a group and compared between rTMS conditions.

3.2. Relationship between baseline FM-UE score and baseline ISP inhibition to ipsilesional

3.2.1. MEP ratio after cPMd- and iM1-rTMS

We found a significant negative relationship between the ipsilesional MEP ratio of cPMd-rTMS to the FM-UE total score ($F_{(1,13)} = 18.44$, $R^2 = 0.61$, $P = 0.001$) (Fig. 2a) and to the FM-UE wrist/hand score ($F_{(1,13)} = 27.03$, $R^2 = 0.69$, $P < 0.001$) (Fig. 2b). There was also a significant negative relationship between the ipsilesional MEP ratio of cPMd-rTMS to baseline ISP inhibition ($F_{(1,13)} = 15.24$, $R^2 = 0.56$, $P = 0.002$) (Fig. 2c). No relationship was found between the ipsilesional MEP ratio of cPMd-rTMS to the FM-UE shoulder/elbow score ($F_{(1,13)} = 3.5$, $R^2 = 0.23$, $P = 0.09$).

Conversely, a significant positive relationship was found between the ipsilesional MEP ratio of iM1-rTMS to FM-UE total score ($F_{(1,13)} = 17.65$, $R^2 = 0.59$, $P = 0.001$) (Fig. 2d) and to the FM-UE wrist/hand score ($F_{(1,13)} = 23.31$, $R^2 = 0.66$, $P < 0.001$) (Fig. 2e). The ipsilesional MEP ratio of iM1-rTMS was also positively correlated with baseline ISP inhibition ($F_{(1,13)} = 8.97$, $R^2 = 0.43$, $P = 0.01$) (Fig. 2f). Again, no relationship was found between the ipsilesional MEP ratio of iM1-rTMS and the FM-UE shoulder/elbow score ($F_{(1,13)} = 3.5$, $R^2 = 0.23$, $P = 0.07$). There was no correlation between time since stroke onset and the ipsilesional MEP ratio of cPMd- ($R^2 = 0.001$, $P = 0.93$) and iM1-rTMS ($R^2 = 0.02$, $P = 0.61$) in all participants.

3.3. Behavioral data

3.3.1. Interlimb force coordination

There was a significant interaction effect of time and condition for interlimb force correlation for both cPMd- ($F_{(1,3)} = 72.98$, $P = 0.003$) and iM1-responders ($F_{(1,9)} = 56.7$, $P < 0.001$) (Fig. 3). For iM1-responders, interlimb force correlation increased after iM1-rTMS ($t_{(9)} = -5.28$, $P = 0.001$, Baseline $\rho = 0.48 \pm 0.1$; Post-rTMS $\rho = 0.79 \pm 0.1$) but decreased after cPMd-rTMS ($t_{(9)} = 4.25$, $P = 0.002$, Baseline $\rho = 0.64 \pm 0.09$; Post-rTMS $\rho = 0.38 \pm 0.06$). In contrast, for cPMd-responders, interlimb force correlation increased after cPMd-rTMS ($t_{(3)} = -3.42$, $P = 0.04$, Baseline $\rho = 0.28 \pm 0.04$, Post-rTMS $\rho = 0.53 \pm 0.11$) but showed no significant change after iM1-rTMS ($t_{(3)} = 2.65$, $P = 0.08$, Baseline $\rho = 0.38 \pm 0.06$; Post-rTMS $\rho = 0.2 \pm 0.01$). No differences were found in the baseline interlimb force correlation between conditions for either group of responders (cPMd-responders: $t_{(3)} = 1.08$, $P = 0.36$; iM1-responders: $t_{(9)} = -1.6$, $P = 0.14$).

3.3.2. Intermuscular coherence

Fig. 4a illustrates an example of change of intermuscular coherence in one representative participant. There was a significant interaction effect of time and condition for the intermuscular

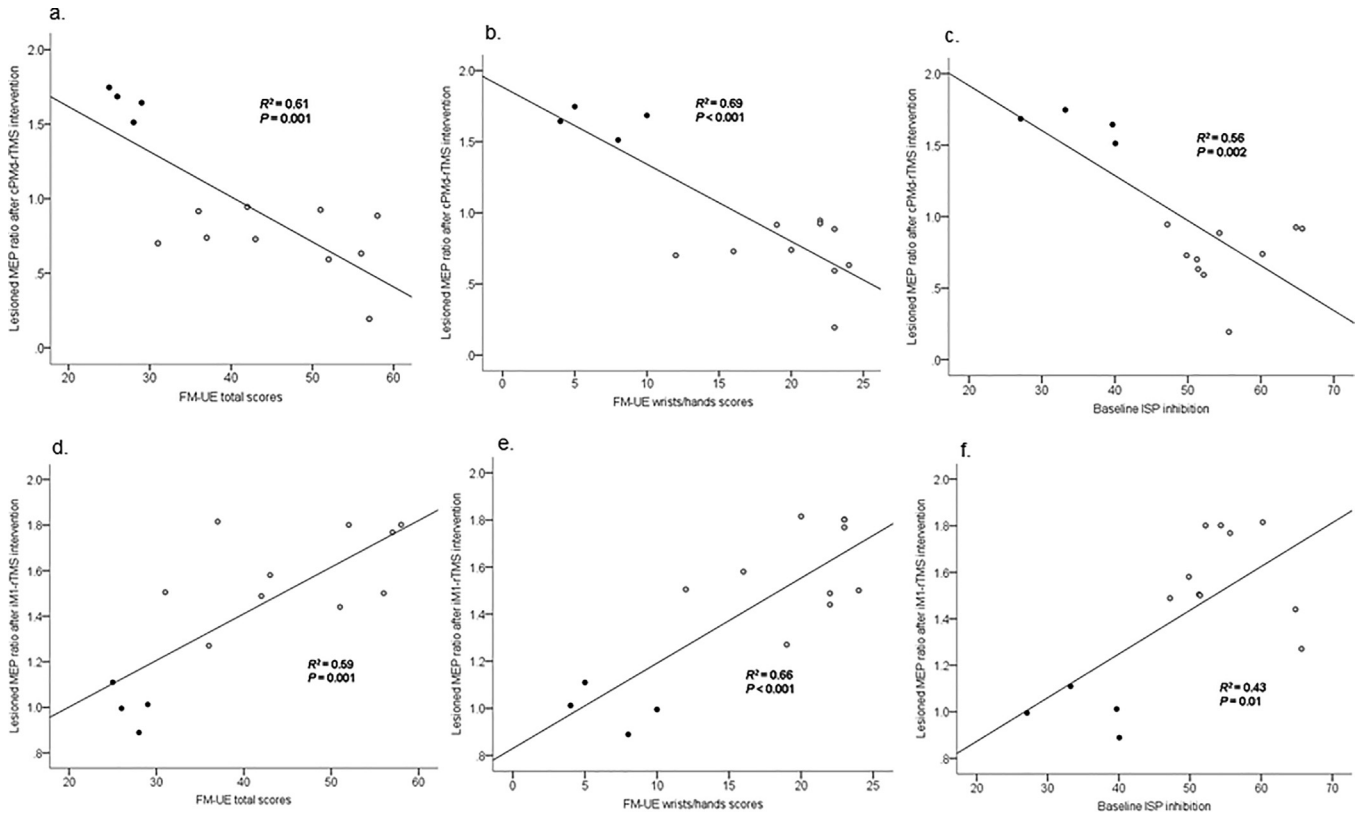

Fig. 2. A negative correlation was found between the baseline FM-UE total score (a), wrist/hand score (b), and ISP inhibition (%) (c) to the ipsilesional MEP ratio after cPMd-rTMS. A positive correlation was found between the same outcome variables (d-f) after iM1-rTMS. Each circle represents a participant's data (N = 14). The filled circles are cPMd-responders (n = 4), and the open circles are iM1-responders (n = 10). FM-UE, Fugl-Meyer assessment of upper extremity score.

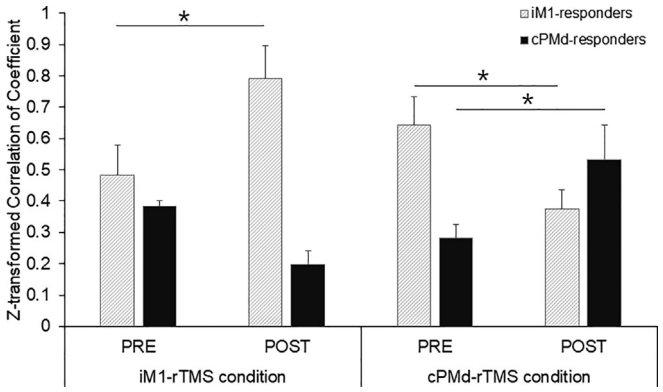

Fig. 3. Interlimb force correlation changed from pre- to post-rTMS. iM1-responders are the gray dashed bars. cPMd-responders are the black closed bars. $^{*}P \leq 0.05$.

coherence strength for cPMd- ($F_{(1,3)} = 637.1$, $P = 0.04$) and iM1-responders ($F_{(1,9)} = 161.225$, $P < 0.001$) (Fig. 4b). For iM1-responders, there was a significant increase of intermuscular coherence strength after iM1-rTMS ($t_{(9)} = -15.86$, $P < 0.001$, Baseline = 0.52 ± 0.01; Post-rTMS = 0.63 ± 0.01) but a decrease after cPMd-rTMS ($t_{(9)} = 5.2$, $P = 0.001$, Baseline = 0.57 ± 0.01; Post-rTMS = 0.49 ± 0.02). In contrast, for cPMd-responders, there was a significant increase of intermuscular coherence strength after cPMd-rTMS ($t_{(3)} = -14.39$, $P < 0.001$, Baseline = 0.46 ± 0.03; Post-rTMS = 0.65 ± 0.03) but no significant change after iM1-rTMS ($t_{(3)} = 2.75$, $P = 0.07$, Baseline = 0.55 ± 0.01; Post-rTMS = 0.53 ± 0.01). No differences were found in the baseline intermuscular coherence strength between conditions for either group of responders (cPMd-responders: $t_{(3)} = 2.41$, $P = 0.1$; iM1-responders: $t_{(9)} = -0.14$, $P = 0.7$).

We also found a significant interaction effect of time and condition for the rate of significant intermuscular coherence for both groups of responders (cPMd-responders: $F_{(1,3)} = 14.9$, $P = 0.03$; iM1-responders: $F_{(1,9)} = 52.78$, $P < 0.001$) (Fig. 4c). For iM1-responders, the rate of significant intermuscular coherence increased after iM1-rTMS ($t_{(9)} = -6.97$, $P < 0.001$, Baseline = 0.35 ± 0.02; Post-rTMS = 0.46 ± 0.01) but reduced after cPMd-rTMS ($t_{(9)} = 3.61$, $P = 0.006$, Baseline = 0.4 ± 0.01; Post-rTMS = 0.35 ± 0.02). Conversely, for cPMd-responders, the rate of significant intermuscular coherence increased after cPMd-rTMS ($t_{(3)} = -3.86$, P = 0.03, Baseline = 0.36 ± 0.01; Post-rTMS = 0.46 ± 0.01) but remained nearly unchanged after iM1-rTMS ($t_{(3)} = 2.93$, P = 0.07, Baseline = 0.39 ± 0.03; Post-rTMS = 0.35 ± 0.02). No differences were found in the baseline rate of significant intermuscular coherence between conditions for either group of participants (cPMd-responders: $t_{(3)} = 1.51$, $P = 0.23$; iM1-responders: $t_{(9)} = -1.9$, $P = 0.09$).

3.4. Cortical excitability data

3.4.1. MEP data

For iM1-responders, there was a significant interaction effect of condition and hemisphere ($F_{(1,9)} = 77.78$, $P < 0.001$) for MEP ratio (Fig. 5a). The ipsilesional MEP ratio was greater in the iM1- than

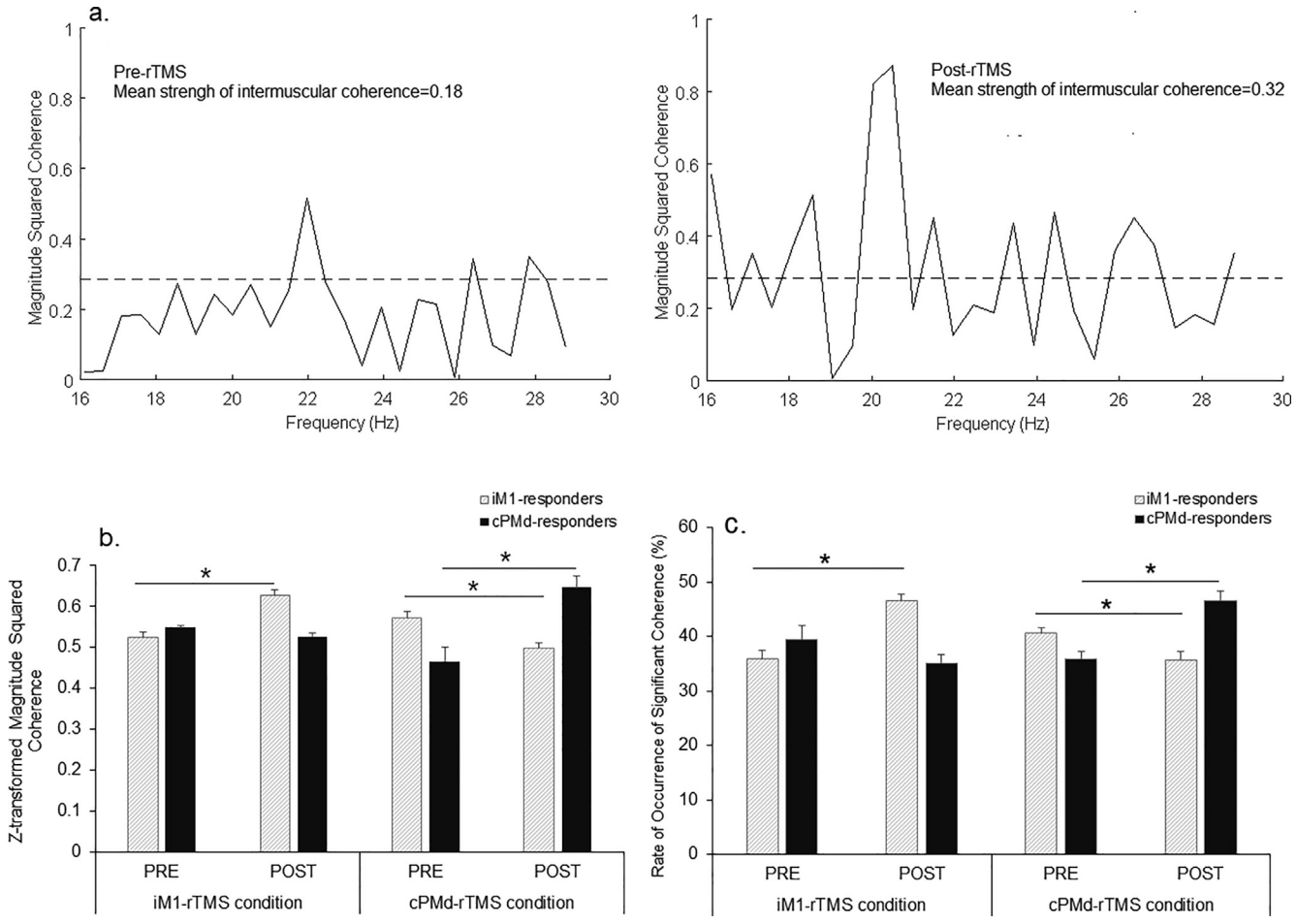

Fig. 4. Intermuscular coherence changed from pre- to post-rTMS. (a) An example from one participant of the raw intermuscular coherence of the β band before (on the left) and after (on the right) iM1-rTMS. The dashed line is the level of significant coherence. (b) Changes of intermuscular coherence strength. (c) Changes of rate of significant intermuscular coherence (%). iM1-responders are the gray dashed bars. cPMd-responders are the black bars. $^{*}P \leq 0.05$.

cPMd-rTMS condition ($t_{(9)}$ = 7.68, P < 0.001, ipsilesional MEP ratio: iM1-rTMS = 1.59 ± 0.06, cPMd-rTMS = 0.73 ± 0.07). The contralesional MEP ratio was lower than the pre-stimulus level after iM1- than cPMd-rTMS ($t_{(9)}$ = −2.59, P = 0.03, contralesional MEP ratio: iM1-rTMS = 0.71 ± 0.04, cPMd-rTMS = 0.91 ± 0.05). In addition, there was a significant difference in the MEP ratio between hemispheres for both rTMS conditions. For iM1-rTMS, there was a greater MEP ratio in the ipsilesional than the contralesional hemisphere ($t_{(9)}$ = 14.2, P < 0.001). In particular, the MEP ratio was higher than pre-rTMS level in the ipsilesional hemisphere (MEP ratio = 1.59 ± 0.06), but it decreased and stayed below the pre-rTMS level in the contralesional hemisphere (MEP ratio = 0.71 ± 0.04). Conversely, for cPMd-rTMS, the MEP ratio was lower than the pre-rTMS level for both hemispheres, with a

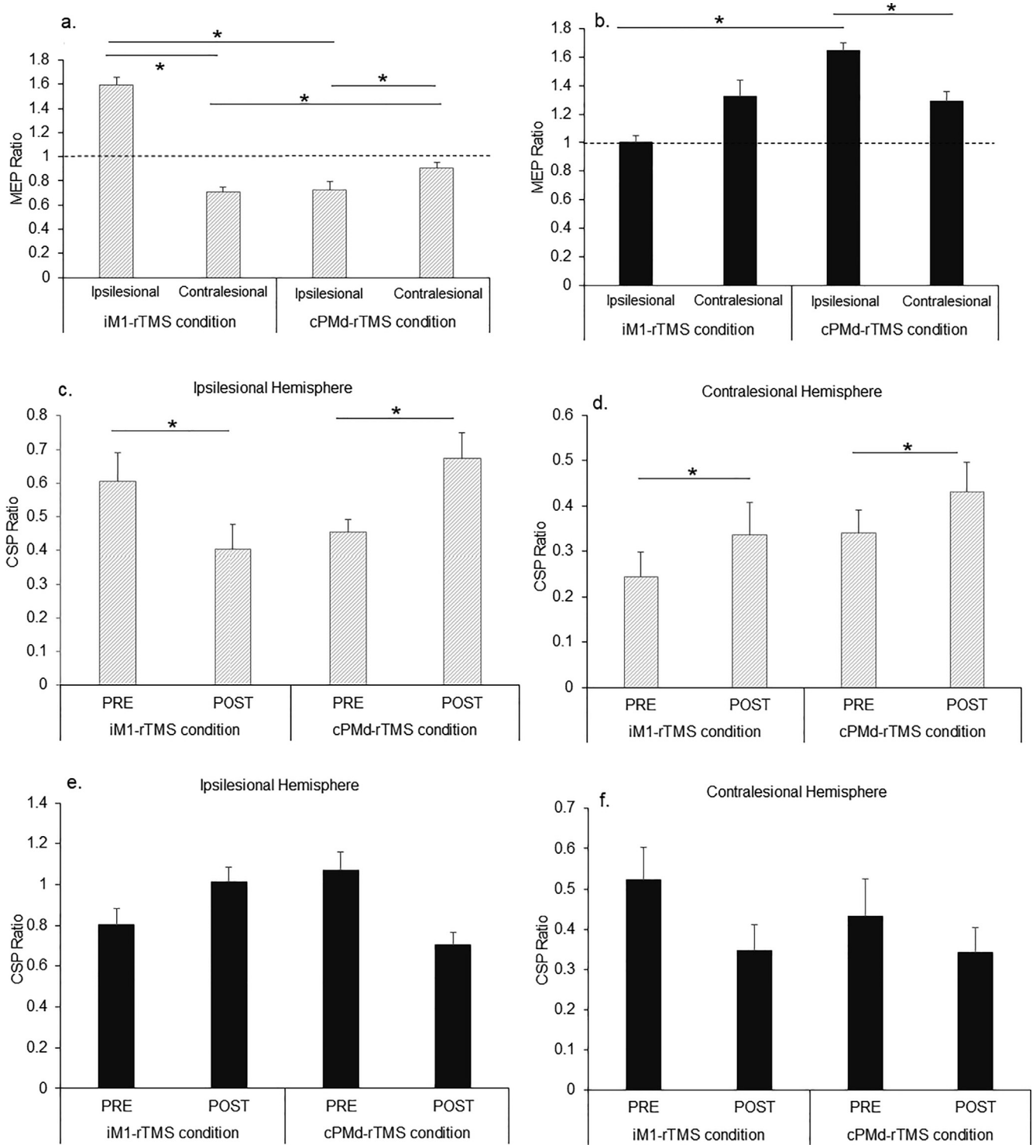

Fig. 5. Top: MEP ratio of both hemispheres in iM1-responders (a) and cPMd-responders (b). Middle: CSP ratio of both hemispheres from pre-to post-rTMS in iM1-responders (c, d). Bottom: CSP ratio of both hemispheres from pre- to post-rTMS in cPMd-responders (e, f). iM1-responders are the gray dashed bars. cPMd-responders are the black bars. $^{*}P \leq 0.05$.

significantly greater reduction in the ipsilesional (MEP ratio = 0.73 ± 0.07) than contralesional (MEP ratio = 0.91 ± 0.05) hemisphere ($t_{(9)} = -3.68$, $P = 0.005$). We also identified a main effect of condition ($F_{(1,9)} = 40.51$, $P < 0.001$) that showed a greater MEP ratio in the iM1-rTMS (MEP ratio = 1.29 ± 0.03) than cPMd-rTMS condition (MEP ratio = 0.81 ± 0.06), and a main effect of hemisphere ($F_{(1,9)} = 41.41$, $P < 0.001$) with a greater MEP ratio in the ipsilesional (MEP ratio = 1.16 ± 0.03) than contralesional (MEP ratio = 0.95 ± 0.02) hemisphere.

For cPMd-responders, there was a significant interaction effect of condition and hemisphere for the MEP ratio ($F_{(1,3)} = 14.11$, $P = 0.03$) (Fig. 5b). The ipsilesional MEP ratio was greater in the cPMd- than iM1-rTMS condition ($t_{(3)} = -42.96$, $P < 0.001$, ipsilesional MEP ratio: cPMd-rTMS = 1.65 ± 0.05, iM1-rTMS = 1 ± 0.05). However, the contralesional MEP ratio was similar for cPMd- and iM1-rTMS condition ($t_{(3)} = 0.18$, $P = 0.87$, contralesional MEP ratio: cPMd-rTMS = 1.29 ± 0.07, iM1-rTMS = 1.32 ± 0.12). In addition, there were significant differences in the MEP ratio between hemispheres only for the cPMd-rTMS condition ($t_{(3)} = 4.1$, $P = 0.03$). The MEP ratio was greater in the ipsilesional (MEP ratio = 1.65 ± 0.05) than contralesional (MEP ratio = 1.29 ± 0.07) hemisphere. However, we did not find hemispheric differences in the MEP ratio of the iM1-rTMS condition ($t_{(3)} = -2.24$, $P = 0.11$, ipsilesional MEP ratio = 1 ± 0.05, contralesional MEP ratio = 1.32 ± 0.12). We also identified a significant main effect of condition ($F_{(1,9)} = 11.64$, $P = 0.04$) that showed a greater MEP ratio in the cPMd-rTMS (MEP ratio = 1.47 ± 0.04) than the iM1-rTMS condition (MEP ratio = 1.16 ± 0.05).

3.4.2. CSP ratio

For iM1-responders, there was a significant interaction effect of time and condition for the ipsilesional hemisphere ($F_{(1,9)} = 102.15$, $P < 0.001$). There was a decreased ipsilesional CSP ratio from baseline to post-rTMS after iM1-rTMS ($t_{(9)} = 5.17$, $P = 0.001$, Baseline = 0.6 ± 0.09, Post-rTMS = 0.4 ± 0.07) but an increase after cPMd-rTMS (Fig. 5c) ($t_{(9)} = -5.94$, $P < 0.001$, Baseline = 0.45 ± 0.04, Post-rTMS = 0.68 ± 0.08). In contrast, for the contralesional hemisphere, there was a main effect of time ($F_{(1,9)} = 24.47$, $P = 0.001$) that showed an increased contralesional CSP ratio from baseline to post-stimulation for both iM1- ($t_{(9)} = -5.48$, $P < 0.001$) and cPMd-rTMS ($t_{(9)} = -2.23$, $P = 0.05$) conditions (Fig. 5d). No differences were found in the baseline CSP ratio of both hemispheres between conditions for iM1-responders (Ipsilesional hemisphere: $t_{(3)} = -1.31$, $P = 0.22$; Contralesional hemisphere: $t_{(3)} = -2.08$, $P = 0.07$).

For the cPMd-responders, there was no interaction effect (Ipsilesional hemisphere: $F_{(1,3)} = 7.93$, $P = 0.07$; Contralesional hemisphere: $F_{(1,3)} = 0.41$, $P = 0.35$) or main effects of time (Ipsilesional hemisphere: $F_{(1,3)} = 2.1$, $P = 0.24$; Contralesional hemisphere: $F_{(1,3)} = 6.1$, $P = 0.09$) or condition (Ipsilesional hemisphere: $F_{(1,3)} = 0.32$, $P = 0.61$; Contralesional hemisphere: $F_{(1,3)} = 0.32$, $P = 0.61$) for either hemisphere (Fig. 5e, Fig. 5f). No difference was found in the baseline CSP ratio of either hemisphere between conditions for cPMd-responders (Ipsilesional hemisphere: $t_{(3)} = -2.48$, $P = 0.09$; Contralesional hemisphere: $t_{(3)} = 1.18$, $P = 0.32$).

3.4.3. ISP inhibition

For iM1-responders, there was a significant interaction effect of time and condition ($F_{(1,9)} = 94.03$, $P < 0.001$) (Fig. 6a). ISP inhibition was reduced from baseline to post-rTMS after iM1-rTMS ($t_{(9)} = 14.54$, $P < 0.001$, Baseline = 55.25 ± 2, Post-rTMS = 41.45 ± 2.15); however, it increased after cPMd-rTMS ($t_{(9)} = -3.39$, $P = 0.008$, Baseline = 54.29 ± 2.02, Post-rTMS = 59.67 ± 1.42). There was a significant main effect of condition ($F_{(1,9)} = 14.94$, $P = 0.004$) that showed greater ISP inhibition in the cPMd- (ISP inhibition = 56.98 ± 1.55) than iM1-rTMS condition (ISP inhibition = 48.35 ± 2.02) and a significant main effect of time ($F_{(1,9)} = 24.23$, $P = 0.001$) that showed greater ISP inhibition before rTMS (ISP inhibition = 54.77 ± 1.63).

For cPMd-responders, there was a significant interaction effect of time and condition ($F_{(1,3)} = 161.83$, $P = 0.001$) (Fig. 6b). ISP inhibition was reduced from baseline to post-rTMS ($t_{(3)} = 6.4$, $P = 0.008$, Baseline = 44 ± 2.92, Post-rTMS = 29.2 ± 2.91) after cPMd-rTMS; however, it was similar before and after iM1-rTMS ($t_{(3)} = -2.94$, $P = 0.06$, Baseline = 37.5 ± 1.58, Post-rTMS = 44.12 ± 1.97). No difference was found in the baseline ISP inhibition between conditions for either group of participants (iM1-responders: $t_{(9)} = 0.41$, $P = 0.69$; cPMd-responders: $t_{(3)} = -2.12$, $P = 0.13$).

4. Discussion

In this study, we proposed an alternative neuromodulation target, cPMd, to facilitate recovery of bimanual coordination post-stroke. We compared its effects to the common neuromodulation target, iM1, to determine which one of these two areas could be better for enhancing bimanual performance. Consistent with our hypothesis, we found that facilitation of both areas could enhance temporal coordination of the two arms during bimanual tasks; however, they appeared to work differently for participants depending on their baseline level of arm/hand impairment as well as their baseline interhemispheric interaction. We found that facilitation of cPMd produced beneficial effects on interlimb force and neuromuscular coordination exclusively for participants with greater arm/hand impairment and weaker baseline IHI. Facilitating iM1 worked better for participants with milder arm/hand impairment and stronger baseline IHI.

To our knowledge, this was the first study to demonstrate that bimanual arm coordination could be enhanced through cortical stimulation in individuals with chronic stroke. We found improvements not only in cortical excitability levels but also in behavioral and neuromuscular control of the arms during bimanual tasks. This result indicated that cortical stimulation could strengthen the common neural drive from cortex to muscle pairs of both arms. Therefore, it could help with functional coordination between the arms during bimanual tasks (Kilner et al., 2000; Fisher et al., 2012; Dai et al., 2017). A similar finding of increased neural drive to muscle pairs was reported in one previous NIBS study that applied anodal transcranial direct current stimulation (tDCS) (Power et al., 2006). However, that study examined stimulation effects of one cortical area only under unimanual isometric force contraction conditions for non-disabled individuals and did not assess behavioral changes. Our study expanded this earlier study by showing that targeted stimulation of two different areas, cPMd and iM1, could enhance both the behavioral and neuromuscular drive of the two arms during bimanual tasks for individuals with stroke.

The fact that facilitation of both cPMd and iM1 led to improved bimanual coordination indicated that potential neuromodulation targets responsible for bimanual coordination were not limited to one specific region for individuals with chronic stroke. Indeed, studies have shown that multiple brain regions, such as bilateral motor and premotor regions, were involved in controlling bimanual tasks, and these areas were organized into a functional neural network to coordinate movement of the two arms (Gerloff and Andres, 2002; Debaere et al., 2004; Zhuang et al., 2005; Grefkes et al., 2008). It was possible that stimulation of one of these involved regions, cPMd and iM1 in this study, could strengthen intra- and/or interhemispheric connections of this functional network, therefore leading to bimanual performance improvements (Sale et al., 2015). This concept has been demonstrated in studies

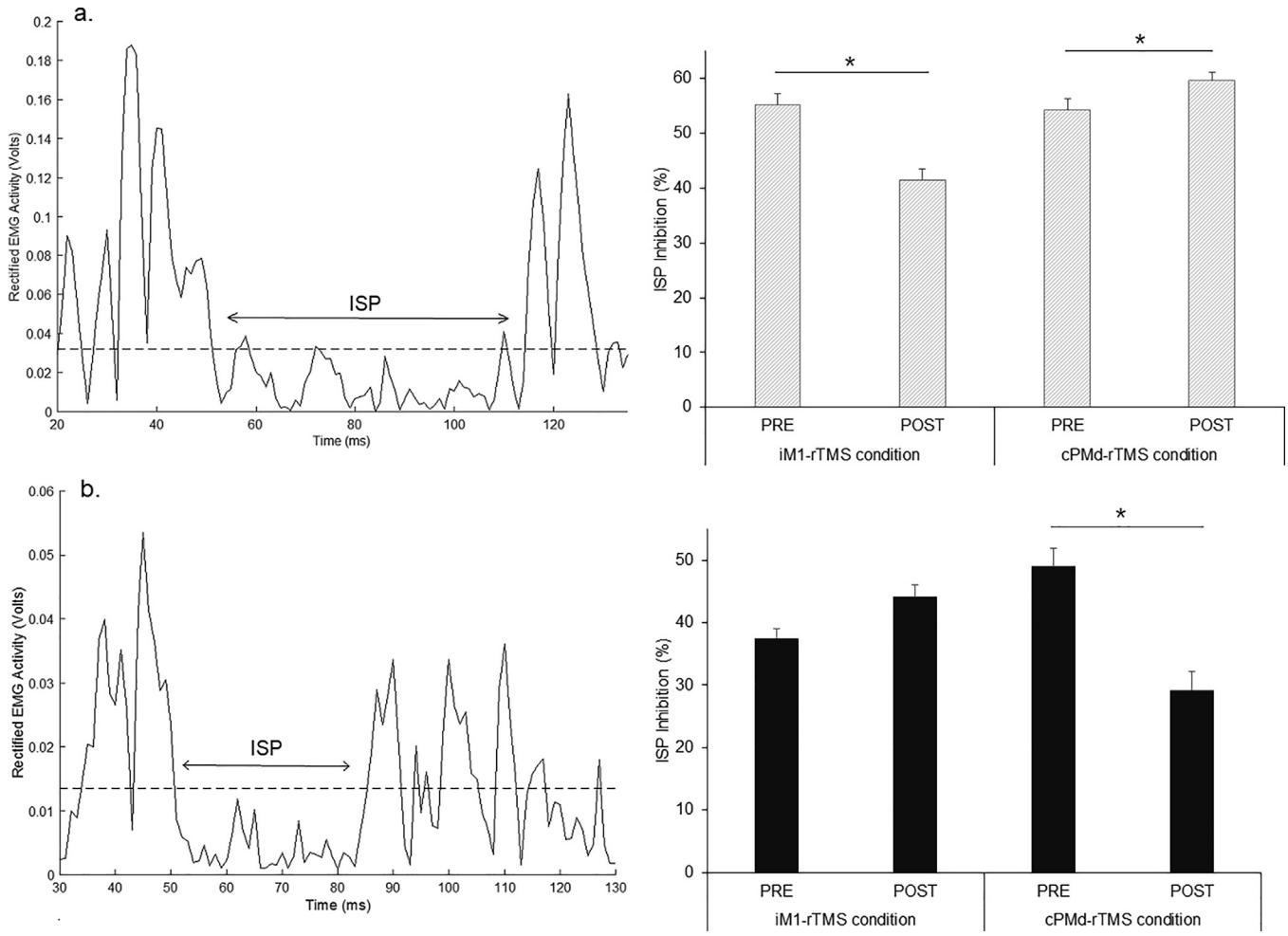

Fig. 6. ISP inhibition changes from pre-to post-rTMS. (a) An example of raw ISP from one iM1-responder (left) and group data of ISP inhibition of iM1-responders (right, gray dashed bars). (b) An example of raw ISP inhibition of one cPMd-responder (left) and group data of ISP inhibition of cPMd-responders (right, black closed bars). $^{*}P \leq 0.05$.

of non-disabled individuals in bimanual tasks where bimanual performance improved during sequential sensorimotor and typing tasks after facilitation of both M1s (Gomes-Osman and Field-Fote, 2013; Pixa et al., 2017). However, no studies have examined the effects of facilitating PMd alone on coordinating bimanual movements in non-disabled individuals and those with stroke. Our study revealed that both cPMd and iM1 could be potential neuromodulation targets for improving bimanual coordination for individuals with stroke.

Furthermore, as hypothesized, the effectiveness of facilitating cPMd and iM1 on bimanual coordination was associated with participants' baseline impairment and interhemispheric interaction. We found that facilitation of cPMd was beneficial only for participants with greater arm/hand impairment and weaker baseline IHI. This finding was in accordance with literature showing that cPMd supported recovery, particularly for individuals with more severe residual arm impairments (Johansen-Berg et al., 2002; Lotze et al., 2006; Bestmann et al., 2010; Mohapatra et al., 2016; Sankarasubramanian et al., 2017). Rather than inhibiting the ipsilesional hemisphere, cPMd could enhance functional reorganization of the remaining neural network and subsequently promote neural plasticity in these more-impaired individuals (Bestmann et al., 2010; Sankarasubramanian et al., 2017). Our results supported this phenomenon and showed that ipsilesional cortical excitability increased and IHI decreased after facilitating cPMd in these more-impaired participants. Moreover, this finding of increased ipsilesional excitability followed by changes of interhemispheric, but not intracortical, interactions implied that cPMd enhanced activity of the ipsilesional cortex through facilitatory transcallosal influence. This facilitatory transcallosal influence from PMd to the opposite cortex has been demonstrated in studies of humans and primates during resting, unimanual, and bimanual tasks (Koch et al., 2006; Grefkes et al., 2008;, Bestmann et al., 2010; Fujiyama et al., 2016; Cote et al., 2017). Several studies have shown that PMd stimulation facilitated contralateral brain regions, including M1 and supplementary motor areas, during the preparation phase and performance of various kinds of bimanual tasks (Toyokura et al., 1999; Grefkes et al., 2008; Liuzzi et al., 2011; Fujiyama et al., 2016). This enhanced interhemispheric integration, provided by PMd stimulation, could be one key factor that promoted recovery of bimanual coordination in this group of participants.

In addition to the transcallosal pathways, it was also possible that facilitating

cPMd could modulate the ipsilateral pathways, as the cPMd projections terminated at the intermediate zone of cervical elements of the spinal cord and directly onto propriospinal neurons (PNs) (Dum and Strick, 2002). A recent study also revealed that these PNs were associated with recovery of the hand after corticospinal (CST) lesions (Tohyama et al., 2017). Furthermore, cPMd could produce remote effects on cM1 that indirectly influenced contralesional, intracortical, and interhemispheric interaction, subsequently leading to IHI reduction in this study (Rizzo et al., 2004). No matter which pathways were involved, our results indicated that facilitating cPMd could be an alternative neuromodulation

approach for improving bimanual coordination and cortical excitability, especially for individuals with greater arm/hand impairment. Further investigations may be needed to elucidate details of cPMd's influence on these pathways.

Alternatively, we found that facilitating iM1 was more beneficial for participants with milder arm/hand impairment and stronger baseline IHI. After facilitating iM1, participants showed improved bimanual coordination as well as increased ipsilesional excitability, decreased ipsilesional intracortical inhibition, and decreased IHI. This finding was in line with the premise of the IHI model showing that facilitating iM1 could enhance ipsilesional output and restore interhemispheric inhibitory balance (Murase et al., 2004; Nowak et al., 2009). This restored balance of IHI could have contributed to recovery of bimanual coordination for these participants because IHI modulation was critical to coordinating between-arm movements during bimanual tasks (Daffertshofer et al., 2005; Fling and Seidler, 2012; Gooijers and Swinnen, 2014). Conversely, facilitating cPMd seemed to aggravate the already unbalanced IHI from the contralesional to the ipsilesional hemisphere, thus deteriorating bimanual coordination in these participants. Our findings that facilitating cPMd and iM1 worked differentially for individuals with different levels of stroke severity supported the bimodal balance-recovery model proposed by Di Pino et al. (2014). Further, it suggested that cortical stimulation protocols could be individualized to each recipient with respect to their impairment levels as well as the targeted motor tasks.

Interestingly, we found that wrist/hand impairment was associated with effects of cPMd and iM1. Indeed, previous studies demonstrated that wrist/hand function could reflect the integrity of corticospinal (CST) and/or M1 (Stinear et al., 2007; Zhu et al., 2010; Rosso et al., 2013). More impaired wrist/hand function could indicate greater injury in ipsilesional CST and/or iM1. Therefore, stimulating iM1 might not be optimal for these individuals (Zhu et al., 2010; Touvykine et al., 2016). Surprisingly, we did not find a relationship between initial FM-UE shoulder/elbow score and participant's responses to cPMd- and iM1-rTMS, although rTMS was applied to the proximal arm muscle hotspots. This indicated that CST integrity (reflected in FM-UE wrist/hand score), rather than the initial proximal arm impairment, could determine responsiveness to cPMd- and iM1-rTMS. This finding was consistent with evidence in the literature that CST integrity affected whether motor recovery would be proportional to initial arm impairment (Byblow et al., 2015; Feng et al., 2015; Buch et al., 2016). The baseline wrist/hand impairment possibly functioned as a predictor for effects of iM1- and cPMd-rTMS. Future studies may examine if the FM-UE wrist/hand score would be a useful screening test in a larger population of individuals with stroke.

Another unique feature of this study was that we performed cluster analysis as a subgrouping method to categorize participants based on their clinical characteristics and responses to facilitating cPMd and iM1. Although cluster analysis has been used in various types of research in multiple fields, only a few NIBS studies to date have used this method to examine responses to cortical stimulation, and they were all performed in non-disabled adults (Pellegrini et al., 2018). Our study provided an example of how cluster analysis could be used to identify responders to different types of cortical stimulation in individuals with stroke. This may help future researchers to design individually-tailored cortical stimulation protocols for people with stroke.

Four limitations should be considered for this study. First, our bimanual tasks are designed to be like a bimanual cooperative task where the two arms are required to coordinate with each other to achieve a common-goal for both arms. The findings of our study may not necessarily translate to other types of bimanual tasks; for example, the dual-goal task where each arm corresponds to its own goal or complicated bimanual movement tasks. Second, although we provide neurophysiological evidence of changes in cortical excitability after cPMd- and iM1-rTMS, it may be also beneficial for future studies to incorporate neural imaging techniques, such as diffusion tensor imaging, to examine the connectivity or structural differences between responders or non-responders to cPMd-rTMS. Third, based on the results of our pilot test, the intensity used for facilitating cPMd is lower than that of iM1. This may be because the cPMd's location has been shown to be more superficial than the scalp, and it may be more sensitive to stimulation (Foerster, 1936; Gerschlager et al., 2001). However, we find distinct and opposite response patterns between cPMd and iM1-responders where these participants only respond to one type of stimulation but not the other. Increasing the stimulation intensity may strengthen these distinct response patterns, but it probably does not change the direction of responses and may be less likely to affect the interpretation of this study. Fourth, we do not include a sham stimulation site in this study. Instead, the cPMd and iM1 serve as active stimulation controls for each other to minimize potential sensory side effects and placebo effects. Adding a sham stimulation control may provide more comprehensive information about the non-specific effects of rTMS in individuals with stroke (Duecker and Sack, 2015).

5. Conclusions

Our study demonstrates that bimanual arm coordination may be enhanced through facilitating two different brain areas, cPMd and iM1, in individuals with chronic stroke. Facilitating cPMd benefits individuals with more severe arm/hand impairment, and facilitating iM1 works for those with milder arm/hand impairment. These findings provide strategies for the future design of individually-tailored NIBS interventions to enhance bilateral arm coordination after stroke.

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Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

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