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Modulation of poststroke motor cortex activity by metaplasticity-inducted theta burst stimulation: A concurrent TMS-EEG study

Dear Editor,

Metaplasticity is a high-level form of plasticity mechanism which describes how prior neuronal activity level mediates subsequent Hebbian-type synaptic plasticity induction, that is, long-term depression (LTD) or long-term potentiation (LTP) [1]. The pairing of two non-identical repetitive transcranial magnetic stimulation (rTMS) protocols could enlarge after-effects (either LTP- or LTD-like) in human primary motor cortex (M1) presumably via metaplastic mechanisms. The pairing protocol is called priming stimulation, or metaplasticity-inducted stimulation [1,2]. Recently, we have applied inhibitory continuous theta-burst stimulation (cTBS) followed by excitatory intermittent TBS (iTBS), both at a 'conventional' intensity (70 % of the resting motor threshold [RMT]), targeting the poststroke ipsilesional M1. However, priming the iTBS protocol by cTBS was not superior to iTBS alone in improving poststroke upper extremity motor outcomes [3]. A possible explanation is that the cTBS priming, although succeeding in lowering the threshold of LTP induction, also suppressed M1 excitability via LTD-like induction. Thereby, cTBS may have counteracted the LTP-like effect by the subsequent iTBS, especially in poststroke patients with compromised ipsilesional excitability. As both cellular and human studies have shown that metaplasticity can be inducted even in the absence of any LTP/LTD effects [2,4], here we aimed to test whether applying 'low-intensity' cTBS priming could enhance subsequent iTBS-induced excitability-enhancing effects, more than 'conventional' intensity cTBS priming or non-primed iTBS, thereby leading to better behavioral outcomes in poststroke patients.

Nineteen patients with upper extremity hemiparesis due to subcortical stroke (Table S1) participated in three experimental sessions, separated by at least seven days, in a counterbalanced order (Fig. 1a). The maximum lesion overlap was found at the basal ganglia and posterior limb of the internal capsule (Fig. 1b). iTBS was delivered at an intensity of 70 % RMT, while cTBS was delivered at either 55 %, 70 % or 20 % RMT in the three experimental sessions. A 55 % RMT intensity was used as the low-intensity because reducing TBS to 62 % active motor threshold (approximately equaling 55 % RMT) had no effect on corticospinal excitability (i.e., LTP/D like effects) measured by motor-evoked potential (MEP) [5]. A 20 % RMT intensity was employed as sham stimulation, as the induced E-fields were comparable to those of a 90° flip coil—the most widely used sham TMS method in clinical practice.

The primary neurophysiological outcome was P30 amplitude in the TMS-evoked potentials (TEPs) selected from the ipsilesional (stimulated) sensorimotor cortex (SMC) [6], as well as the global mean field power (GMFP) of P30 [7]. Because force control is highly relevant to poststroke motor impairment and indicative of motor recovery [8], secondary behavioral outcome was the force control capability of the hemiplegic arm quantified by the mean and variability of force production at 20 % and 50 % maximum voluntary contraction (MVC) level. Neurophysiological and behavioral outcomes were measured before and immediately after TBS. This study was approved by the Institutional Review Board of Hong Kong Polytechnic University (HSEARS 20231103003-04) and prospectively registered (NCT06241508).

Using permutation tests, we found that P30 amplitude (30–38 ms) over the ipsilesional SMC was significantly enhanced after $cTBS_{55\ \%RMT}$-primed iTBS ($p < 0.0167$ Fig. 1c). The mean amplitude of P30 from the significant time window was therefore extracted for further analysis. Two-way repeated-measures analysis of variance (rmANOVA) on the P30 amplitude showed a significant time effect ($F_{1,18} = 6.86$, $p = 0.017$), and a nonsignificant condition-by-time interaction effect ($F_{2,36} = 0.65$, $p = 0.527$; Table S3). Nonparametric tests showed that only $cTBS_{55\ \%RMT}$-primed iTBS enhanced P30 amplitude ($p = 0.016$; Fig. 1d; Table S4), though between-condition comparisons were not significant. When MEP status was included as a covariate, rmANOVA revealed a significant time effect ($F_{1,17} = 12.32$, $p = 0.003$) and a significant time-by-MEP status interaction ($F_{1,17} = 7.59$, $p = 0.014$). We therefore conducted a subgroup analysis by stratifying participants into MEP+ (n = 7) and MEP− (n = 12) groups. Nonparametric tests showed that $cTBS_{55\ \%RMT}$- and $cTBS_{70\ \%RMT}$-primed iTBS, but not $cTBS_{20\ \%RMT}$-primed iTBS significantly enhanced P30 amplitude in the MEP+ subgroup ($ps = 0.028$; Table S5). In contrast, no significant changes in P30 amplitude were observed following any stimulation protocols in the MEP− subgroup.

rmANOVA on GMFP of P30 further showed a significant condition-by-time interaction ($F_{2,36} = 3.62$, $p = 0.037$; Table S3). MEP status was not a significant covariate when analyzing GMFP. Nonparametric tests showed that GMFP was increased after $cTBS_{55\ \%RMT}$-primed iTBS (pre vs. post: $p = 0.044$) but decreased after $cTBS_{70\ \%RMT}$-primed iTBS (pre vs. post: $p = 0.014$), respectively (between-condition difference: $p = 0.007$; Fig. 1e; Table S4). Responder analysis was conducted using two thresholds (>10 % and >30 % change from baseline) to define facilitation, no change, or inhibition. The $cTBS_{55\ \%RMT}$-primed iTBS protocol consistently resulted in a significantly higher percentage of responders showing facilitation and a lower percentage showing inhibition compared to the $cTBS_{70\ \%RMT}$-primed protocol. Using a >10 % change from baseline, facilitatory effects were observed in 11 of 19 participants (57.9 %) receiving $cTBS_{55\ \%RMT}$-primed iTBS, compared to only 3 of 19 participants (15.8 %) receiving $cTBS_{70\ \%RMT}$-primed iTBS. Conversely, inhibitory responses were observed in 4 of 19 participants (21.1 %) and 14 of 19 participants (73.7 %), respectively ($p = 0.004$). Using a >30 % change threshold, the percentage of facilitatory responses remained higher for the $cTBS_{55\ \%RMT}$-primed iTBS protocol (7/19, 36.8 % vs. 3/19, 15.8 %), while the rate of inhibitory responses was lower, compared to $cTBS_{70\ \%RMT}$-primed iTBS protocol (1/19, 5.3 % vs. 8/19, 42.1 %; $p =$

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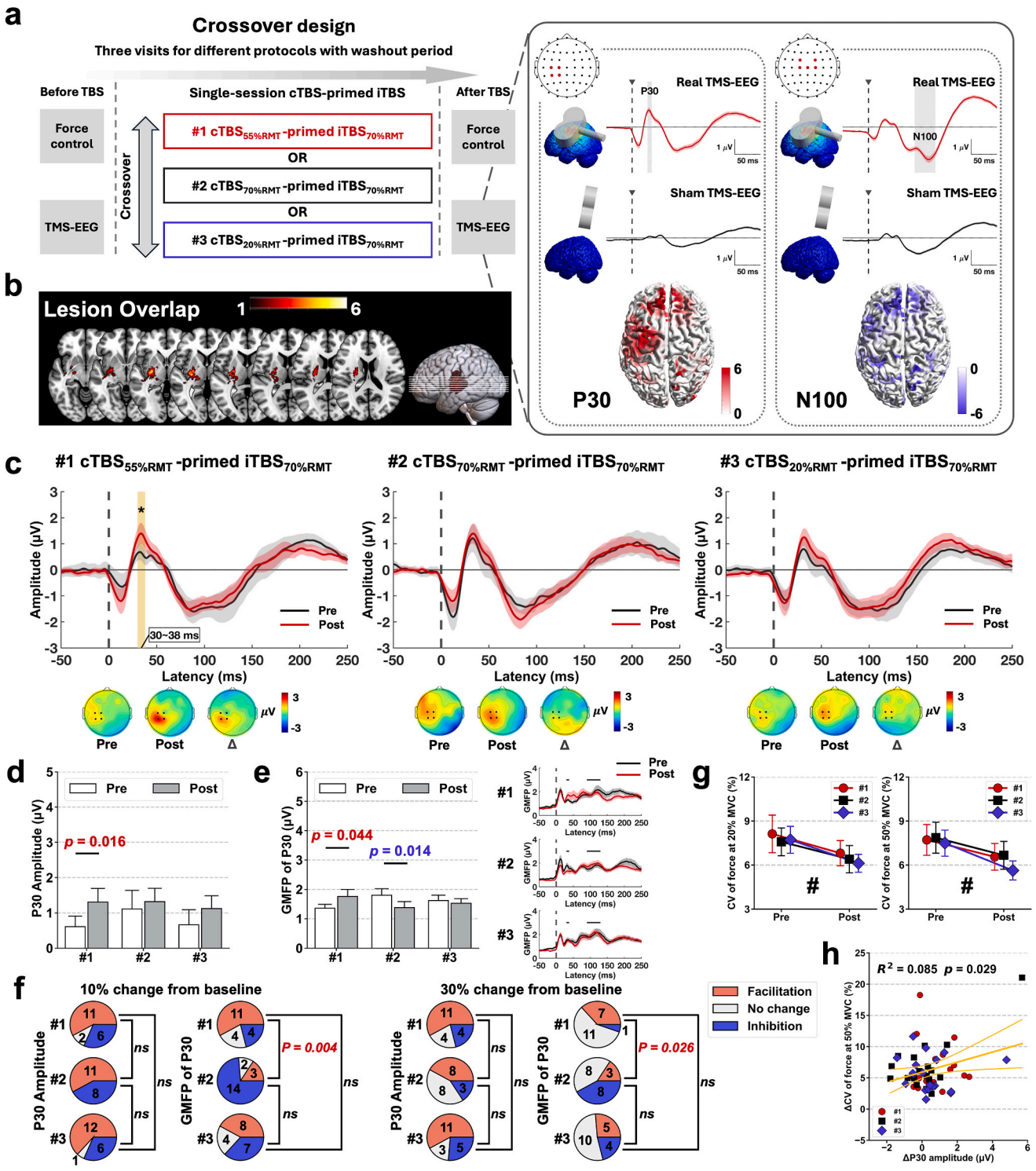

Fig. 1. a. Study design. The coil placements during TMS-EEG recording and the time series of TEP extracted from two predefined spatial clusters are presented. (P30: C1-C3-CP1-CP3, N100: FC1-FC2-C1-C2-Cz). Source activity of P30 and N100 is shown from one representative participant. b. Lesion overlap of 18 poststroke patients in the MNI space (one participant did not complete magnetic resonance imaging scanning). The maximum overlap was at the level of the basal ganglia and the posterior limb of the internal capsule. Lesions in the right hemisphere were flipped to the left hemisphere. c. TBS induced local grand-averaged TEPs and topographical distribution of P30 over the ipsilesional SMC. The curves and the shaded area represents mean and standard error, respectively. A yellow bar with an asterisk indicates a significant time window during which P30 amplitude (30-38 ms) over the ipsilesional SMC increased significantly after stimulation ($p < 0.0167$). d. Mean P30 amplitude (30–38 ms). Error bars indicate the standard error. e. Mean GMFP of P30 (30–38 ms). The bar chart shows data that have been averaged across subjects; error bars represent the standard error. f. Responder analysis for P30. h. TBS induced changes in force variability. Hashes indicate significant time effects revealed by the rmANOVA. Data are shown as mean ± standard error. g. The relationship between ΔP30 amplitude and Δforce variability at the 50 % MVC level is illustrated. The solid yellow line represents the linear regression, while the shaded area depicts the 95 % confidence intervals. Abbreviations: c/iTBS, continuous/intermittent theta burst stimulation; CV, coefficient of variation; GMFP, global mean field power; MVC, maximum voluntary contraction; RMT, resting motor threshold; SMC, sensorimotor cortex; TBS, theta burst stimulation; TEPs, TMS-evoked potentials; TMS-EEG, transcranial magnetic stimulation and electroencephalography.

0.026; Fig. 1f).

Permutation tests showed no significant N100 time window, so we used a predefined window (90–130 ms). Table S3–S4 revealed no significant within- or between-condition differences for N100.

In terms of behaviors, rmANOVAs only showed a significant effect of time on force variability (20 % MVC: $F_{1,17} = 10.86$, $p = 0.004$; 50 % MVC: $F_{1,17} = 11.28$, $p = 0.004$; Fig. 1g). Stepwise multivariate regression revealed that ΔP30 amplitude was the only signficant predictor of Δforce variability at 50% MVC (R^2=0.085, $\beta = 0.291$, $p = 0.029$; Fig. 1h), with no contribution from N100.

We demonstrated that 1) priming iTBS with low-intensity cTBS, but not 'conventional' intensity cTBS-primed iTBS, over the stimulated ipsilesional SMC induced LTP-like after-effects in patients with subcortical stroke by enhancing the global cortical reactivity. However, no statistical difference in TEP outcomes was observed between $cTBS_{55\ \%RMT}$-primed iTBS and $cTBS_{20\%RMT}$-primed iTBS. This finding indicates that the use of low-intensity priming is likely to achieve the desired facilitatory effect in a metaplasticity-inducted stimulation protocol, while avoiding the unwanted inhibitory effect in association with the preceding priming stimulation. 2) The local modulatory effect of both low- and 'conventional' intensity primed iTBS seems to be associated with the level of corticospinal structural integrity in the ipsilesional hemisphere. 3) The change of intracortical excitation measured by P30 correlated with the change of force variability.

Measured by GMFP of P30, iTBS-induced LTP-like plasticity was amplified using low-intensity cTBS priming, more so than with 'conventional' intensity cTBS priming. This superiority may be attributed to metaplasticity, which occurs even in the absence of excitability changes (i.e., LTD-like effects) when using low-intensity priming. The 'conventional' intensity cTBS-primed iTBS even showed possible inhibitory effects on global cortical reactivity, which supports our hypothesis that cTBS may counteract the LTP-like effect by iTBS in poststroke patients. Additionally, analyses of MEP status suggested that metaplasticity-induced effects may be mediated by the degree of preserved corticospinal integrity poststroke, where greater preservation may correlate with a more robust neuromodulatory effect. Of note, because no statistical between-condition difference was found between $cTBS_{55\ \%RMT}$- and $cTBS_{20\ \%RMT}$-primed iTBS, we cannot rule out the possibility that metaplastic interaction also happened using 'ultra-low' intensity priming, although the effect might be less robust [9].

Results further showed that intracortical excitation of the ipsilesional SMC correlated with force variability, which is consistent with a previous study showing that greater motor variability was correlated with iTBS-induced LTP-like plasticity [10]. This finding supports the notion that excitatory stimulation alone creates a time window with enhanced variability, which favors neuroplasticity induction in a non-task-specific manner. However, we acknowledged that the observed TEP changes did not fully align with Δforce variability, which may be attributed to the nature of the behavioral task (The task was designed to test the control of proximal muscles, rather than the muscle directly stimulated by TBS.). Further research is needed to examine the clinical relevance of P30, particularly in poststroke rehabilitation, such as combining excitatory stimulation with task-specific training over multiple sessions.

In conclusion, the intensity of priming stimulation appears to be a determinant of successful metaplastic induction in the poststroke motor cortex.

CRediT authorship contribution statement

Jack Jiaqi Zhang: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Roy Rongyue Zeng:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Michael Tang:** Writing – review & editing, Methodology, Investigation. **Zhongfei Bai:** Writing – review & editing, Supervision, Software, Resources, Project administration, Investigation, Funding acquisition, Formal analysis. **Ruixuan Lin:** Writing – review & editing, Visualization, Validation, Methodology, Investigation. **Youxin Sui:** Writing – review & editing, Validation, Methodology, Investigation. **Yongan Gong:** Writing – review & editing, Visualization, Methodology, Conceptualization. **Tommy LH. Lam:** Writing – review & editing, Methodology, Investigation. **David MA. Mehler:** Writing – review & editing, Visualization, Methodology, Funding acquisition. **Ulf Ziemann:** Writing – review & editing, Validation, Supervision, Methodology, Investigation. **Kenneth NK. Fong:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Conceptualization.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2025.10.008.

References

[1] Müller-Dahlhaus F, Ziemann U. Metaplasticity in human cortex. Neuroscientist 2015;21(2):185–202.
[2] Murakami T, Müller-Dahlhaus F, Lu MK, Ziemann U. Homeostatic metaplasticity of corticospinal excitatory and intracortical inhibitory neural circuits in human motor cortex. J Physiol 2012;590(22):5765–81.
[3] Zhang JJ, Bai Z, Fong KNK. Priming intermittent theta burst stimulation for hemiparetic upper limb after stroke: a randomized controlled trial. Stroke 2022;53(7):2171–81.
[4] Huang YY, Colino A, Selig DK, Malenka RC. The influence of prior synaptic activity on the induction of long-term potentiation. Science 1992;255(5045):730–3.
[5] Dieler AC, Dresler T, Joachim K, Deckert J, Herrmann MJ, Fallgatter AJ. Can intermittent theta burst stimulation as add-on to psychotherapy improve nicotine abstinence? Results from a pilot study. Eur Addict Res 2014;20(5):248–53.
[6] Bai Z, Zhang JJ, Fong KNK. Immediate effects of intermittent theta burst stimulation on primary motor cortex in stroke patients: a concurrent TMS-EEG study. IEEE Trans Neural Syst Rehabil Eng 2023;31:2758–66.
[7] Bai Z, Zhang JJ, Ti ECH, et al. Loss of stimulation intensity- and cortical activity-dependent TMS-evoked reactivity in poststroke primary motor cortex. Brain Stimul 2024;17(6):1286–9.
[8] Kang N, Cauraugh JH. Force control in chronic stroke. Neurosci Biobehav Rev 2015;52:38–48.

[9] Opitz A, Legon W, Mueller J, Barbour A, Paulus W, Tyler WJ. Is sham cTBS real cTBS? The effect on EEG dynamics. Front Hum Neurosci 2015;8:1043.
[10] Teo JT, Swayne OB, Cheeran B, Greenwood RJ, Rothwell JC. Human θ burst stimulation enhances subsequent motor learning and increases performance variability. Cereb Cortex 2011;21(7):1627–38.

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