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Methodological considerations of priming repetitive transcranial magnetic stimulation protocols in clinical populations

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To the editor:

Repetitive transcranial magnetic stimulation (rTMS) is a neuroplasticity-enhancing technique that modifies brain responsiveness to various therapeutic modalities in clinical psychiatric and neurological applications.[1] Furthermore, its effect can be attributed to long-term potentiation (LTP) or long-term depression (LTD)-like neuroplasticity. However, responsiveness to rTMS is largely variable in healthy and pathological brains[2] and is mediated by complex biological mechanisms. Metaplasticity refers to a higher-order plasticity mechanism in which the direction and magnitude of synaptic plasticity are modified by prior neuronal activity and is believed to be a significant factor leading to the response variability of rTMS.[3] According to its mechanism of action, the threshold for induction of LTP and LTD is dynamically adjusted to the level of prior neuronal activity: a low level of prior neuronal activity slides down the threshold to preferentially induce LTP. By contrast, a high level slides up the threshold to preferentially induce LTD.[4]

The induction of metaplasticity has been demonstrated in the human cortex using rTMS. Successively applying two identical rTMS protocols may lead to the reversal of the aftereffect of the protocol owing to the saturation of LTP/LTD and homeostatic regulation via metaplasticity. By contrast, pairing two non-identical stimulation protocols appears to induce additive neuroplastic effects through therapeutically beneficial metaplasticity induction.[4] Therefore, researchers have used priming protocols to stabilise and increase the aftereffects of the subsequent conditioning session (figure 1A). A total of two kinds of priming protocols for inducing therapeutically beneficial metaplasticity, 'preceding excitation enhances subsequent inhibition' and 'preceding inhibition amplifies subsequent excitation', have been tested with conventional high-frequency/low-frequency rTMS as well as intermittent/continuous theta burst stimulation (iTBS/cTBS) in the M1 of healthy individuals, measured using motor-evoked potential (MEP).[5]

PRIMING PROTOCOLS IN CLINICAL POPULATIONS

Despite the application of rTMS in a wide range of clinical populations,[6] priming rTMS protocols have primarily been used in clinical trials of major depressive disorders (MDDs) and motor stroke. rTMS is a well-established non-pharmacological treatment of depression.[7] A form of inhibitory priming rTMS protocol, which applied 6 Hz high-frequency rTMS priming followed by a conditioning session of 1 Hz low-frequency rTMS, was tested in a randomised controlled trial (RCT) with patients with MDD. This trial demonstrated a superior effect of priming rTMS to the right dorsolateral prefrontal cortex (DLPFC) compared with low-frequency rTMS alone in improving depressive moods.[8] This clinical benefit was attributed to the stronger inhibitory effect of priming rTMS (6 Hz before 1 Hz) on the right DLPFC than that of low-frequency rTMS alone through metaplasticity induction. The fact that the inhibitory rTMS delivered to the right DLPFC is less commonly used in the treatment of MDD compared with the excitatory rTMS delivered to the left DLFPC[9] is worth mentioning. Consequently, the effectiveness of priming rTMS protocols to the left DLPFC compared with non-priming (standard) rTMS protocols for antidepressant treatment remains uncertain.

According to a recent review of priming protocols in healthy human subjects,[5] the

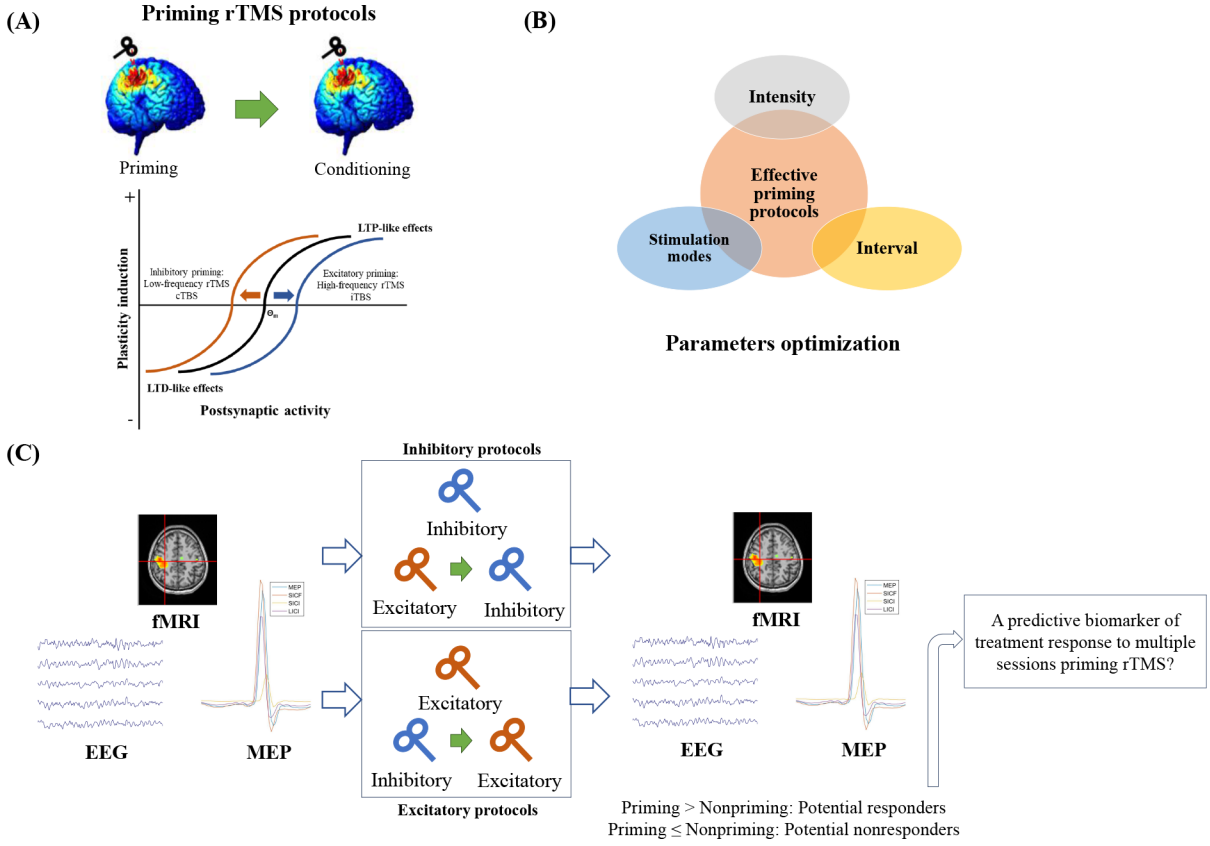

Figure 1 (A) Design of priming rTMS protocol and its underlying sliding threshold model: a low level of neuronal activity induced by low-frequency priming using low-frequency rTMS or cTBS can slide down the threshold (θ_m) to preferentially induce LTP-like effects. By contrast, a high level of neuronal activity induced by high-frequency priming using high-frequency rTMS or iTBS slides up the threshold to preferentially induce LTD. (B) Parameter optimisation of priming protocols. (C) Using the brain response to priming rTMS relative to non-priming rTMS to predict its treatment response. cTBS, continuous theta burst stimulation; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; iTBS, intermittent theta burst stimulation; LICI, long-interval intracortical inhibition; LTD, long-term depression; LTP, long-term potentiation; MEP, motor-evoked potential; rTMS, repetitive transcranial magnetic stimulation; SICF, short-interval intracortical facilitation; SICI, short-interval intracortical inhibition.

superiority of priming stimulation over non-priming stimulation has frequently been demonstrated in modulating the M1 excitability, measured by MEP. Therefore, priming rTMS may show clinical benefits for motor recovery following neurological disorders, although evidence is currently limited to post-stroke rehabilitation. Cassidy *et al* applied the same priming inhibitory rTMS protocol (6 Hz before 1 Hz) to the contralesional M1 in patients who had a stroke.[10] The study found that single-session priming rTMS significantly decreased the duration of the cortical silent period and short-interval intracortical inhibition over the ipsilesional M1 compared with the non-priming control. However, superiority was not observed in the outcome of paretic hand functions. Another team has recently validated an excitatory form of iTBS priming for stroke rehabilitation.[1] The RCT of patients post-stroke compared 10-session priming iTBS (cTBS prior to iTBS), non-priming iTBS (sham cTBS prior to iTBS) and sham stimulation (sham cTBS prior to sham iTBS) that was delivered to the ipsilesional M1, in combination with robot-assisted motor training, on upper extremity motor and neurophysiological outcomes. The primary analysis demonstrated that priming with iTBS was equivalently effective compared with non-priming iTBS in boosting motor outcomes in patients with stroke. Furthermore, priming iTBS demonstrated clinical superiority in improving upper extremity impairment in patients who had a stroke with a higher functioning upper extremity compared with non-priming iTBS and sham stimulation.[1]

DISCUSSION

In summary, preliminary evidence from RCTs in disease populations supports the utility of priming rTMS for both psychiatric and neurological applications to achieve superior neuromodulatory outcomes. Despite the potential for prolonged treatment sessions, the clinical application of priming rTMS protocols remains highly viable, particularly when employing accelerated protocols such as TBS. The significance of priming rTMS protocols can be summarised as follows. First, experimental studies using priming rTMS have demonstrated the history state dependence of the aftereffect of rTMS in both healthy and pathological brains.[4] Second, by using the metaplastic

mechanism, priming rTMS offers a clinically feasible solution to induce more robust neuromodulatory effects in the brain. This can lead to improved therapeutic outcomes in psychiatric and neurological rehabilitation.[1 8] Therefore, priming rTMS protocols have the potential to overcome the limitations faced by patients who do not adequately respond to standard rTMS protocols.

Although metaplasticity-elicited priming rTMS protocols have shown promise in enhancing therapeutic responses, many unknowns remain. First, the optimal parameters for the priming protocols have not been well studied. Several parameters must be considered (figure 1B). (1) Interstimulation interval: the induction of metaplasia occurs only within a certain time window. A priming transcranial direct current study investigated an interstimulation interval of 3 min, but not of 0 min and 30 min,[11] resulting in metaplasticity-induced effects. By contrast, a TBS study established that an interval of 5 min between two iTBS sessions, but not of 15 min, led to a metaplasticity-induced effect.[12] No study has systematically investigated the influence of time intervals on the effect of rTMS priming using two non-identical protocols. (2) Intensity: in animal studies, the metaplasticity of hippocampal neurons can be elicited even when priming stimulation does not induce any LTP/LTD effects;[13] however, the rationale has yet to be tested in the human cortex. Murakami *et al*,[14] who conducted the only study concerning the intensity, documented that low-intensity TBS priming at 70% active motor threshold (AMT) was not superior to high-intensity TBS priming at 80% AMT, with MEP outcomes; thus, evidence regarding the impact of intensity on the effect of priming rTMS remains inconclusive. (3) Stimulation modes: although priming protocols using conventional rTMS and TBS have demonstrated metaplasticity-induced effects, clinical evidence comparing different modes of stimulation or for developing a hybrid mode of priming stimulation (eg, TBS primed rTMS) is not yet available. Note that experimental evidence concerning parameter selection in priming rTMS is primarily derived from studies conducted on healthy adults. As a result, parameter optimisation for priming rTMS protocols in disease populations remains largely unknown and requires further systematic investigation. A thorough investigation of the parameters that determine the effectiveness of priming rTMS will open up new avenues for optimising therapeutic brain stimulation strategies. By identifying the optimal timing, intensity and stimulation modes for priming rTMS, clinicians and researchers will be able to expand the range of options available for patients who have limited responses to conventional rTMS protocols.

In addition, neural biomarkers that can assess metaplasticity in healthy and pathological brains and predict treatment responses are lacking. Carey *et al*[15] conducted a single-group pre–post experiment using priming rTMS (6 Hz before 1 Hz) to the contralesional M1 in patients who had a stroke. They reported that the extent of preservation of the ipsilesional posterior limb of the internal capsule (PLIC) predicted an improvement in paretic hand function in patients after receiving priming rTMS. However, the structural reserve in the PLIC is more likely to be a general biomarker reflecting the potential for motor recovery following stroke, but not the brain capacity to induce therapeutically beneficial metaplasticity. Quantified by various measures, such as electroencephalography, functional magnetic resonance imaging (fMRI) or MEP (single-pulse and paired-pulse outcomes), the brain response to priming rTMS appears to be a promising method to evaluate the acute neuroplasticity induced by priming stimulation relative to the non-priming control, and it may be further used to predict the therapeutic response of multiple session priming protocols (figure 1C). The approach using predictive biomarkers also offers a possible solution for identifying patients who may exhibit a more favourable therapeutic response to priming protocols than to conventional non-priming protocols. Longitudinal studies incorporating neural biomarkers are required to substantiate this hypothesis. However, conducting such studies with biomarkers in disease populations presents specific challenges. First, recruiting enough participants and ensuring their repeated measures can be difficult. Collaboration with multiple centres, including acute hospitals, community rehabilitation facilities and patient advocacy groups, would help address this challenge. Second, analysing longitudinal data requires sophisticated statistical techniques. Recent advancements in machine learning and artificial intelligence modelling offer opportunities to develop reliable and efficient prediction models using multimodal neural biomarkers.

CONCLUSION

Metaplasticity-elicited priming rTMS protocols are likely to achieve superior efficacy in terms of sensorimotor and emotional outcomes in neurological and psychiatric applications compared with conventional rTMS. Further studies are required to investigate parameter optimisation and identify biomarkers that evaluate the brain reserve of therapeutically beneficial metaplasticity.

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REFERENCES

1 Zhang JJ, Bai Z, Fong KNK. Priming intermittent theta burst stimulation for hemiparetic upper limb after stroke: a randomized controlled trial. *Stroke* 2022;53:2171–81.
2 Magnuson J, Ozdemir MA, Mathieson E, *et al*. Neuromodulatory effects and reproducibility of the most widely used repetitive transcranial magnetic stimulation protocols. *PLoS One* 2023;18:e0286465.
3 Müller-Dahlhaus F, Ziemann U. Metaplasticity in human cortex. *Neuroscientist* 2015;21:185–202.
4 Sack AT, Paneva J, Küthe T, *et al*. Target engagement and brain state dependence of transcranial magnetic stimulation: implications for clinical practice. *Biol Psychiatry* 2023:S0006-3223(23)01571-8.
5 Hassanzahraee M, Zoghi M, Jaberzadeh S. How different priming stimulations affect the corticospinal excitability induced by noninvasive brain stimulation techniques: a systematic review and meta-analysis. *Rev Neurosci* 2018;29:883–99.
6 Somani A, Kar SK. Efficacy of repetitive transcranial magnetic stimulation in treatment-resistant depression: the evidence thus far. *Gen Psychiatr* 2019;32:e100074.
7 Wang S, Tang S, Huang J, *et al*. Rapid-acting antidepressants targeting modulation of the glutamatergic system: clinical and preclinical evidence and mechanisms. *Gen Psychiatr* 2022;35:e100922.
8 Fitzgerald PB, Hoy K, McQueen S, *et al*. Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. *J Clin Psychopharmacol* 2008;28:52–8.
9 Kan RLD, Padberg F, Giron CG, *et al*. Effects of repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex on symptom domains in neuropsychiatric disorders: a systematic review and cross-diagnostic meta-analysis. *Lancet Psychiatry* 2023;10:252–9.
10 Cassidy JM, Chu H, Anderson DC, *et al*. A comparison of primed low-frequency repetitive transcranial magnetic stimulation treatments in chronic stroke. *Brain Stimul* 2015;8:1074–84.
11 Fricke K, Seeber AA, Thirugnanasambandam N, *et al*. Time course of the induction of homeostatic plasticity generated by repeated transcranial direct current stimulation of the human motor cortex. *J Neurophysiol* 2011;105:1141–9.
12 Tse NY, Goldsworthy MR, Ridding MC, *et al*. The effect of stimulation interval on plasticity following repeated blocks of intermittent theta burst stimulation. *Sci Rep* 2018;8:8526.
13 Huang YY, Colino A, Selig DK, *et al*. The influence of prior synaptic activity on the induction of long-term potentiation. *Science* 1992;255:730–3.
14 Murakami T, Müller-Dahlhaus F, Lu MK, *et al*. Homeostatic metaplasticity of corticospinal excitatory and intracortical inhibitory neural circuits in human motor cortex. *J Physiol* 2012;590:5765–81.
15 Carey JR, Deng H, Gillick BT, *et al*. Serial treatments of primed low-frequency rTMS in stroke: characteristics of responders vs. nonresponders. *Restor Neurol Neurosci* 2014;32:323–35.

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