REVIEW ARTICLE

Critical role of glutamatergic and GABAergic neurotransmission in the central mechanisms of theta-burst stimulation

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Abstract

Theta-burst stimulation (TBS) is a varied form of repetitive transcranial magnetic stimulation (rTMS) and has more rapid and powerful effects than rTMS. Experiments on the human motor cortex have demonstrated that intermittent TBS has facilitatory effects, whereas continuous TBS has inhibitory effects. Huang's simplified model provides a solid basis for elucidating such after-effects. However, evidence increasingly indicates that not all after-effects of TBS are as expected, and high variability among individuals has been observed. Studies have suggested that the GABAergic and glutamatergic neurotransmission play a vital role in the aforementioned after-effects, which might explain the interindividual differences in these after-effects. Herein, we reviewed the latest findings on TBS from animal and human experiments on glutamatergic and GABAergic neurotransmissions in response to TBS. Furthermore, an updated theoretical model integrating glutamatergic and GABAergic neurotransmissions is proposed.

KEYWORDS

GABA, glutamate, mechanisms, repetitive transcranial magnetic stimulation, theta-burst stimulation

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FIGURE 1 (a) Standard pattern of intermittent and continuous theta-burst stimulation (iTBS and cTBS, respectively). (b) After-effects of iTBS and cTBS on motor-evoked potential (MEP). According to a recent meta-analysis, cTBS reduces MEP amplitudes lasting up to 60 min (a pooled standard mean difference [SMD] of -0.9 , $p < .00001$), whereas iTBS increases MEP amplitudes lasting up to 30 min (SMD = 0.71 , $p < .00001$) (Chung et al., 2016) * $p < .00001$

1 | INTRODUCTION

1.1 | Theta burst stimulation overview and LTP-/LTD-like after-effects

Theta-burst stimulation (TBS) is a patterned form of repetitive transcranial magnetic stimulation (rTMS). The basic elements of TBS include 50-Hz tripulse burst trains given at intervals of 200 ms (i.e., 5 Hz; the theta range in electroencephalography [EEG] terminology; Figure 1a). TBS is more efficient in terms of time and energy than conventional rTMS protocols for producing after-effects on the human motor cortex through a synaptic plasticity-like mechanism (Huang, Chen, Rothwell, & Wen, 2007; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Huang et al., 2017).

In the mammalian brain, neurons and synapses are interconnected in a complex manner. This complex neuronal network is flexible and can be modulated by the plastic nature of synaptic transmissions between two neurons. The major long-term forms of synaptic plasticity, referred to as long-term potentiation (LTP) and long-term depression (LTD), are induced by changes in the postsynaptic Ca^{2+} concentration (Blitzer, Iyengar, & Landau, 2005). Based on the simplified postsynaptic mechanism of the glutamatergic synapses proposed by Huang, Rothwell, Chen, Lu, and Chuang (2011), intermittent TBS (iTBS), which denotes short trains of intermittent bursts, leads to the Ca^{2+} influx-related excitatory effect (through postsynaptic NMDA receptors) and produces the LTP-like effect. By contrast, continuous TBS (cTBS), which involves continuous application of TBS trains, enables intensification of the interneuron-activated inhibitory effect, thereby overcoming the excitatory effect and producing an LTD-like effect (Huang et al., 2011). Short bursts of high-frequency axonal stimulation, mimicking a common pattern of hippocampal pyramidal neuronal discharge, induce LTP in the hippocampus only when the stimuli are repeated at intervals less than 2 s; the optimal interval seems to be 200 ms, which is in the theta EEG frequency range (Larson & Lynch, 1986).

TBS is originally used in animal brain slices to induce changes in synaptic plasticity (Larson & Lynch, 1986, 1989). A single burst of axonal stimulation in the hippocampus was found to produce a spatially diffuse "priming" effect that prolongs responses to subsequent bursts given at a theta rhythm, thus triggering synaptic modifications (Larson & Lynch, 1986). Theta-rhythm stimulation facilitated synaptic plasticity of hippocampal pyramidal neurons if high Ca^{2+} levels were provoked and inhibited depression of synaptic plasticity when stimulation was insufficient to result in high calcium levels in the theta phase (Saudargiene, Cobb, & Graham, 2015). In addition, the presynaptic changes in GABA release are critically involved in TBS-induced potentiation or depression of synaptic plasticity (Larson & Munkacsy, 2015; Nishiyama, Togashi, Aihara, & Hong, 2010). A detailed discussion of the role of GABAergic activities in the mechanisms of TBS is provided in this article.

Experiments on the human motor cortex have demonstrated that iTBS has facilitatory effects and cTBS has inhibitory effects on the amplitude of motor-evoked potential (MEP) elicited by a single pulse of TMS (Figure 1b), and the underlying mechanisms may be similar to the LTP and LTD observed in laboratory experiments. For example, Huang et al. (2005) reported that one session of cTBS reduced short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) in parallel with a decrease in the MEP amplitude for approximately 20 and 10 min, respectively, whereas iTBS enhanced SICI for approximately 10 min. The researchers therefore proposed that cTBS reduces the effectiveness of synaptic connections, whereas iTBS does the opposite in both glutamatergic and GABAergic circuits under the TMS coil (Huang et al., 2005). A comprehensive meta-analysis indicated that cTBS reduced the MEP amplitude for up to 60 min (pooled standard mean difference [SMD] of -0.9 , $p < .00001$), whereas iTBS increases the MEP amplitude for up to 30 min (pooled SMD = 0.71 , $p < .00001$) (Chung, Hill, Rogasch, Hoy, & Fitzgerald, 2016) (Figure 1b). By contrast, findings on the effects of TBS on SICI and ICF have been inconsistent, with the exception of a reported decrease in SICI during the initial 5 min of cTBS (SMD = 0.42 , $p = .00036$) (Chung et al., 2016). The changes in corticospinal excitability may involve LTP- and LTD-like effects on the cortical synapses (Huang et al., 2009, 2011, 2017; Huang, Rothwell, Edwards, & Chen, 2008).

Because theta-rhythm rTMS is more efficient in terms of time and energy than conventional high-frequency or low-frequency rTMS (Huang et al., 2011), it has been used to treat patients with neurological and psychiatric disorders, including major depression and medication-resistant depression. Based on a meta-analysis conducted from January 2001 to September 2016, Berlín et al. (2017) reported a significant and large antidepressant response favoring active TBS, and the pooled Hedges' g for pre-post change in depression scores was 1.0 ($p = .003$). Li et al. (2014) published the first randomized sham-controlled study comparing various prefrontal TBS protocols and determined that protocols involving iTBS over the left dorsolateral prefrontal cortex (DLPFC) were more effective than others for treating medication-resistant depression. Recently, Blumberger et al. (2018) conducted a randomized, multicenter clinical trial and determined that 3 min of prefrontal iTBS was not inferior to 37.5 min of 10-Hz rTMS for treating treatment-resistant depression.

1.2 | The expected effects: iTBS as excitatory and cTBS as inhibitory?

Studies have indicated that not all after-effects of cTBS are inhibitory and that not all those of iTBS are facilitatory (Chung et al., 2016; Hinder et al., 2014; Jannati, Block, Oberman, Rotenberg, & Pascual-Leone, 2017; Lopez-Alonso, Cheeran, Rio-Rodriguez, & Fernandez-Del-Olmo, 2014). For example, Hinder et al. (2014) studied intraindividual reliability and interindividual variability in response to iTBS in 30 healthy subjects, establishing that 73.3% of the subjects exhibited the expected excitatory responses in two sessions 1–3 weeks apart. Lopez-Alonso et al. (2014) studied various noninvasive brain stimulation protocols in 56 healthy subjects and found that only 43% of them exhibited the expected responses to iTBS. The differences in the population of recruited and activated neurons may explain the difference in TBS's after-effects. After examining the effects of cTBS and iTBS protocols in 56 healthy subjects, Hamada, Murase, Hasan, Balaratnam, & Rothwell, 2013) indicated that the TBS responses were highly variable between individuals, and only approximately one-quarter of their participants exhibited the expected inhibitory response after cTBS or the excitation response after iTBS. The researchers found that participants with a large latency difference between MEPs evoked by lateromedial and anterior–posterior coil stimulation, indicative of recruitment of later I waves of the corticospinal volley, exhibited the “expected” inhibition after cTBS and facilitation after iTBS. The researchers concluded that much of the interindividual variation in response to TBS protocols is attributable to differences in neuronal population activated by each TMS pulse rather than differences in the intrinsic amounts of synaptic plasticity in cortical neurons. Finally, the researchers indicated that the recruitment of later I waves is crucial for the expected responses.

TMS of the human motor cortex evokes descending corticospinal activity, and the earliest wave (i.e., the D wave; Figure 2) that can be observed after stimulation originates mainly from direct activation of the axon of large pyramidal tract neurons (PTN) located in cortical layer 5 (Di Lazzaro et al., 2012). The later waves (i.e., later I waves; Figure 2) evoked by cortical stimulation originate from indirect transynaptic activation of the PTN (Di Lazzaro et al., 2012). However, at lower intensities (e.g., active motor threshold), TMS using a figure-of-eight coil and a posterior-to-anterior (PA)-induced current in the brain was found to evoke a pure I-1 wave that originated from indirect monosynaptic corticocortical connections projecting onto the PTN through direct excitation of the axons of the layer 2/3 pyramidal neurons (Di Lazzaro, Oliviero, et al., 1998; Di Lazzaro & Ziemann, 2013). In addition, at intensities below the active motor threshold (e.g., parameters used in the standard TBS protocols), TMS activated

FIGURE 2 Schematic epidural recording of descending volleys through transcranial magnetic stimulation at a high stimulation intensity and the resultant small D wave, followed by the I-1 wave and later I waves

I-wave-related corticocortical circuits (Di Lazzaro et al., 1998b). This result was not unexpected because the axons of the more superficial pyramidal neurons (layers 2 and 3) are located close to the stimulating coil and may be the neural elements that are most excitable by magnetic stimulation (Di Lazzaro & Ziemann, 2013). Spinal epidural recordings have demonstrated that cTBS reduces the amplitude of early I waves of the corticospinal volley, whereas iTBS increases the amplitude of later I waves (Di Lazzaro et al., 2008).

Similarly, based on an extensive review, Suppa et al. (2016) established that the cTBS protocols mainly suppress the I-1 wave, whereas later I waves and the D wave are much less affected. By contrast, the iTBS protocol enhances later I waves (e.g., I-3 and I-4) with no changes to the I-1 wave (Suppa et al., 2016). This phenomenon indicates that I-wave-related intracortical interneuron networks are critical for the after-effects of TBS. This notion is in accordance with the results reported by Hamada et al. (2013), which indicated that participants with favorable recruitment of later I waves exhibited the “expected” inhibition after cTBS and facilitation after iTBS. In light of the aforementioned results and the finding that cTBS mainly engages the early I-1 wave (Suppa et al., 2016), both early and later I waves are clearly involved in the physiological mechanisms of cTBS.

1.3 | Glutamatergic and GABAergic neurotransmissions and TBS effects

Both glutamatergic and GABAergic neurotransmissions are involved in the TBS mechanisms. Animal and human studies have determined that excitatory neurotransmitter glutamate (e.g., via the NMDA receptors) is critically involved in the TBS mechanisms (Huang et al., 2007; Ishikawa et al., 2007; Labedi, Benali, Mix, Neubacher, & Funke, 2014). For example, to study the effect of N-methyl-D-aspartate receptor antagonist memantine on the after-effects of TBS, Huang et al. (2007) performed a double-blind, placebo-controlled study of six healthy volunteers and found that memantine blocked the suppressive effect of cTBS and the facilitatory effect of iTBS without affecting the resting and active motor threshold. In a rat study with a sham-controlled design, a high dose of NMDA receptor antagonist ketamine almost completely abolished the iTBS effects, and the expression of GABA interneurons was reduced (Labedi et al., 2014). However, because standard TBS protocols use subthreshold stimulation (i.e., 70–80% active or resting motor thresholds), TBS may have an unsubstantial effect on layer-5 pyramidal neurons, which are the sources of D waves. Supporting evidence indicates that even during continuous TBS treatment, D waves do not change (Suppa et al., 2016). A study indicated that TBS does not exhibit the expected higher intensity that causes greater neuromodulatory effects (Chung et al., 2018). Specifically, the study reported that iTBS at 100% resting motor threshold yielded considerably less neurophysiological change than that at 75% resting motor threshold. In addition, cTBS at 100% active motor threshold did not result in the expected after effects of depressed MEPs (Sasaki et al., 2018); instead, cTBS protocols at this high stimulation strength partly induced MEP facilitation. Overall, glutamate-related neurotransmission is crucial in the mechanisms of standard subthreshold TBS protocols, and the effects are not associated with direct stimulation of layer-5 pyramidal neurons.

Compared with glutamatergic neurotransmission, modulation of GABAergic intracortical inhibition may play a more critical role in the TBS mechanism. The presynaptic changes in GABA release are involved in the TBS-induced potentiation of synaptic plasticity (Larson & Munkacsy, 2015). In a detailed review, Larson and Munkacsy (2015) indicated that a single burst is insufficient for LTP induction, but bursts repeated at the theta frequency induce maximal LTP, primarily because this frequency disables feedforward inhibition and allows sufficient postsynaptic depolarization. This disinhibitory process involves presynaptic GABA autoreceptors that inhibit GABA release. In fact, several animal studies have indicated that the blockade of GABAergic inhibition (e.g., via the GABA-A receptor or GABA-B receptor) plays a key role in LTP induction (Grover & Yan, 1999; Kotak, Mirallave, Mowery, & Sanes, 2017; Liu et al., 2014; Staubli, Scafidi, & Chun, 1999; Steward, Tomasulo, & Levy, 1990). For example, when GABA-A receptor and GABA-B receptor were both blocked, LTP in the perirhinal cortical neurons was reliably induced in rats through iTBS (Kotak et al., 2017). In addition, in brain circuits where strong inhibition occurs along with excitation (e.g., the dentate commissural pathway of the hippocampus), LTP is not expressed during high-frequency electrical stimulation (Steward et al., 1990). However, whether the induction of LTD in the pyramidal neurons depends on presynaptic GABAergic activities is not completely understood. However, Kotak, Mirallave, Mowery, and Sanes (2017) reported that, although cTBS induced LTD in pyramidal neurons, adding GABA-A and GABA-B antagonists reliably reversed LTD to LTP. Experiments on the GABAergic activities at the presynaptic and postsynaptic sites of hippocampal CA1 pyramidal cells have revealed that GABAergic interneuronal activities controlled the induction of certain excitatory LTD and that the timing-dependent LTD induced through theta frequency stimulation was regulated by both feedforward and feedback postsynaptic GABA-A receptor mediated inhibition (Nishiyama et al., 2010). In summary, animal studies have provided evidence that LTP induction depends on blocking GABAergic inhibition via the GABA receptors (Grover & Yan, 1999; Kotak et al., 2017; Liu et al., 2014; Staubli et al., 1999; Steward et al., 1990) and that of LTD may also depend on modulation of GABA interneuronal activities (Kotak et al., 2017; Nishiyama et al., 2010).

GABA-A- and GABA-B-receptor-mediated intracortical inhibition (ICI) contributes to later I waves; clear suppression of the later I-wave components of corticospinal volley was identified when a test magnetic stimulus was preceded by a conditioning stimulus at an 3-ms interstimulus interval (SICI) and at an 100-ms interstimulus interval (long interval intracortical inhibition, LICI) (Di Lazzaro & Ziemann, 2013). Although the conditioning magnetic stimulus is a subthreshold small stimulus, it may change the motor responses by activating the intracortical GABA interneurons before the activation of pyramidal neurons of the corticospinal tract. The standard bipulse paradigm commonly adopts the PA coil orientation, and the TMS pulse from this coil orientation elicits MEPs of the highest amplitude and shortest latency (I-1 wave) (Laakso, Hirata, & Ugawa, 2014). In one study, after GABAergic activity was enhanced through benzodiazepine (e.g., lorazepam) administration, pronounced suppression of later I waves was evident, but no change in the I-1 wave was observed (Di Lazzaro et al., 2000). These findings indicate that the GABAergic

neurons are more involved in the production of the later I waves than in the production of the I-1 wave. In addition, activating corticocortical projections onto the PTN plays a critical role in I-wave generation (Rusu, Murakami, Ziemann, & Triesch, 2014).

Additional evidence supports a role for inhibitory neurotransmitter-GABA in the effects of various TBS protocols: (i) the after-effects of iTBS included a lasting reduction in the expression of fast spiking (FS)-type PV+ GABAergic interneurons, and (ii) cTBS resulted in a decrease in CB+ GABAergic interneurons with no effects on PV+ cells in Dark Agouti rats (Suppa et al., 2016). The researchers who reported the aforementioned findings tested two additional rat strains, Sprague-Dawley (SD) and Long Evans (LE), and obtained different results. In SD rats, iTBS reduced PV and CB expression, whereas cTBS reduced only PV expression. LE rats exhibited an intermediate reaction (Mix, Benali, & Funke, 2014). Another study reported that cTBS and iTBS modulate the activity of cortical inhibitory interneurons (Labedi et al., 2014). Although the effects on subtypes of GABAergic interneurons seem to differ in different rat strains (Mix et al., 2014; Suppa et al., 2016), to date, studies have provided evidence that the modulation of GABAergic neurotransmission is critically involved in the mechanism regulating the effects of TBS.

Regarding data from human experiments, Harrington and Hammond-Tooke (2015) researched the effects of iTBS and cTBS on the cerebellum in healthy individuals and found that iTBS increased the N100 amplitude of the TMS-evoked potential (i.e., a marker of intracortical GABA-mediated inhibition), whereas cTBS reduced the N100 amplitude. Furthermore, by directly measuring the GABA concentration in brain voxels through magnetic resonance spectroscopy (MRS), Stagg et al. (2009) found that cTBS over the motor cortex increases GABA concentrations without affecting the glutamate and glutamine levels, suggesting that the mechanisms of cTBS involve enhancement of the GABAergic interneuronal activities. The researchers suggested that cTBS may provoke activity in GABAergic and glutamatergic circuits and thus increase synthesis of both neurotransmitters. In turn, this effect would lead to increased presynaptic GABA levels and an increase of the MRS signal. Negative findings reported for glutamate and glutamine levels after cTBS have indicated that the presynaptic release of glutamate is unchanged and no glutamate accumulation occurs (Stagg et al., 2009).

However, Iwabuchi et al. (2017) recently reported that iTBS over the left DLPFC significantly reduced GABA/Glx levels in the regional DLPFC and a remote region of the anterior cingulate cortex (ACC). These findings suggest that the prefrontal iTBS results in the inverse involvement of both the GABAergic and glutamatergic systems in functionally connected brain regions. Similarly, by applying iTBS to the left inferior parietal lobe, Vidal-Pineiro et al. (2015) used MRS and found that GABA levels increased in a functionally connected region, the posterior cingulate cortex; this modulation of GABA can be used to predict intrinsic functional connectivity at baseline.

1.4 | Updating glutamatergic and GABAergic roles in the proposed simplified model

Regarding TBS's after effects, Huang et al. (2011) proposed a simplified model using the glutamatergic synapses in which postsynaptic

Ca^{2+} influx (i.e., the trigger factor in stage 1) initiates processes leading to a different amount of potentiation and depression of synaptic transmission (stage 2), and the final effect results from summation of the two effects (stage 3). The model provides a satisfactory basis for explaining the common “expected” after-effects of TBS (i.e., cTBS as inhibitory, iTBS as facilitatory, and a middle form, imTBS, as having no significant effect). Herein, we provide some potential explanations for the model on the basis of the aforementioned novel findings; these mechanisms may also explain individual variability. We used the basic functional microcircuit of the cerebral cortex previously proposed for modeling TMS effects (Di Lazzaro & Ziemann, 2013; Douglas & Martin, 1991; Esser, Hill, & Tononi, 2005). The model represents the minimum architecture necessary for the most essential cortical input–output operations. It includes the superficial population of the excitatory pyramidal neurons of layers 2 and 3 (layer 2/3), the large pyramidal tract neurons in layer 5 (PTN), and the inhibitory GABAergic interneurons (Figure 3). Layer 1 is not included in this model because of the sparseness of neurons, and layer 4 is not modeled because the motor cortex has a thin layer 4 (Esser et al., 2005).

As illustrated in Figure 3a for iTBS’s mechanisms, the sudden increases of trigger factor in stage 1 may occur because of the rapid activation of layer-2/3 pyramidal neurons in the target hand muscle region (the dashed circle) and the inhibition of GABAergic interneurons, which in turn lead to the disinhibition of more pyramidal neurons. As already stated, the most excitable neural elements under TMS are the axons of the more superficial layer-2/3 pyramidal neurons (Di Lazzaro & Ziemann, 2013). Another piece of supporting evidence is that the after-effects of iTBS and cTBS depend on the recruitment of later I waves, which are indicative of activating corticocortical inputs to the target region, and the layer-2/3 pyramidal neurons are the main

targets of corticocortical afferents (Hamada et al., 2013; Suppa et al., 2016). LTP is triggered only by a brief increase in postsynaptic Ca^{2+} influx (Yang, Tang, & Zucker, 1999). The sudden increases of Ca^{2+} influx, through activation of repeated bursts on the apical and basal dendrites of the layer-2/3 pyramidal neurons in the stimulated brain regions, enhance corticospinal tract excitability and increase facilitatory neurotransmission. The solid red circle in Figure 3a denotes the neurons with dendrites most vulnerable to iTBS bursts.

The rapid increases in facilitatory neurotransmission may accompany feedforward inhibition of GABAergic interneurons (e.g., PV or SST) in the target hand regions, which in turn result in the suppression of GABA interneurons (dotted red circles in Figure 3a). The supporting evidence includes that iTBS’s effects require disabling feedforward inhibition from the presynaptic GABA receptors; thus, the subsequent postsynaptic depolarization can be facilitated (Larson & Munkacsy, 2015). Other explanations for the critical role GABAergic interneuron inhibition in LTP production are detailed in earlier sections of this article. Additional supporting evidence for the notion of feedforward inhibition of GABAergic interneurons is that group I metabotropic glutamate receptors (mGluRs) are necessary for LTP induction and are expressed by numerous interneurons (Le Duigou, Holden, & Kullmann, 2011). The activation of group I mGluRs at synapses on interneurons, such as through high-frequency stimulation, may acutely depress transmission in the feedforward inhibitory pathway (Le Duigou et al., 2011). In addition, the findings of decreased GABAergic neurons (e.g., PV or SST) (Yang et al., 1999) and changed GABA levels in the target or functionally connected regions (Iwabuchi et al., 2017; Stagg et al., 2009; Vidal-Pineiro et al., 2015) support our notion. However, whether the after-effects of TBS in the human cortex depend on the feedforward inhibition of GABAergic interneurons through mGluR activation warrants further investigation.

FIGURE 3 Schematic depicting how the intermittent and continuous theta-burst stimulation (iTBS and cTBS, respectively) protocols produce the expected facilitatory and inhibitory after-effects on the hand region of the motor cortex, respectively. (a) Bursts from iTBS activate pathways contributing to later I waves (solid red circles), including apical and basal dendrites of layer-2/3 neurons in the target regions (i.e., the main targets of corticocortical inputs), to induce long-term potentiation. The rapidly induced activations may also lead to suppression of GABA interneurons (dotted red circles), potentially via a feedforward inhibitory pathway. The effects are summed to generate facilitatory after-effects. (b) Continuous bursts from cTBS could cause prolonged Ca^{2+} increases, leading to long-term depression of synaptic strength of the layer-2/3 neurons in the targeted regions (dotted green circle). In turn, the continuous bursts might slowly increase the inhibitory activities of the GABAergic interneurons (solid green circles). Most importantly, cTBS mainly activates the I-1 pathway (dashed green triangle). The contribution of the I-1 wave is plotted separately from the later I waves for clarity. The overall effects from cTBS, therefore, cause inhibitory after-effects [Color figure can be viewed at wileyonlinelibrary.com]

Regarding cTBS, because prolonged increases rather than rapid increases of Ca^{2+} influx reliably lead to LTD (Yang et al., 1999), prolonged activation from continuous burst stimulation through cTBS in stage 1 may eventually result in LTD in synaptic strength of the layer-2/3 pyramidal neurons in the target hand regions (green dashed circle in Figure 3b). This leads to a decrease in neuronal activities in later stages. The functional inhibition of layer-5 pyramidal neurons in the target hand region of the motor cortex (Figure 3b) seems not to be the main contributor to the expected inhibitory effects of cTBS because D waves do not change under cTBS treatment (Suppa et al., 2016). By contrast, because the recruitment of later I waves plays a critical role in the expected after-effects of cTBS (Hamada et al., 2013), the modulation of transsynaptic cortical inputs from functionally connected brain regions to layer-2/3 pyramidal neurons by cTBS could be the key. However, the amplitudes of later I waves are not significantly affected by cTBS; this may be because of the net effect of decreased activities of both the pyramidal neurons and GABAergic interneurons of the involved excitatory and inhibitory inputs. Low-intensity TMS was found to mainly engage the intracortical inhibitory circuits related to later I waves but not the I-1 wave (Di Lazzaro et al., 1998b). Furthermore, later I waves are more sensitive to GABAergic activities (Di Lazzaro et al., 2000; Laakso et al., 2014), as discussed earlier herein.

The slowly increased inhibition induced by cTBS, as introduced in Huang's simplified model, may result from increases in the inhibitory activities of the GABAergic inhibitory interneurons (via the PV or SSV interneurons; solid green circles in Figure 3b) through cTBS. The supporting evidence comes from recent human studies. For example, Stagg et al. (2009) observed through MRS that cTBS over the motor cortex increases GABA concentrations without affecting glutamine and glutamine levels, suggesting that the cTBS mechanism involves an enhancement of GABAergic interneuron activities. cTBS was found to increase GABAergic inhibitory neurotransmission such as SICI, which is mainly mediated by the GABA-A receptors (Hamada et al., 2013).

In addition, because cTBS mainly reduces the strength of the I-1 wave (Suppa et al., 2016), cTBS clearly results in deactivation of the pyramidal neurons contributing to the I-1 waves of the corticospinal volley (the dotted green triangle in Figure 3b). Although the underlying mechanisms remain undetermined, we speculate that LTD induced by prolonged Ca^{2+} increases or "hyperpolarization" in the pyramidal neurons contributing to I-1 waves is critically involved. The I-1 waves originating from monosynaptic activation of the PTN also derive from the layer-2/3 pyramidal neurons in the target hand regions and are targets of low-intensity TMS (Di Lazzaro, Oliviero, et al., 1998; Di Lazzaro & Ziemann, 2013). However, whether the cTBS-induced I-1-wave inhibition resulted from LTD or hyperpolarization requires future studies to investigate. Prolonged high-frequency stimulation, such as tetanic stimulation of white matter, could lead to so-called activity-dependent slow hyperpolarization of cortical neurons (Kitagawa, Nishimura, Kumazawa, Akamine, & Yamamoto, 2000). That is, through prolonged high-frequency stimulation, hyperpolarization of the pyramidal neurons may slowly develop following initial membrane depolarization. Increased GABAergic inhibition at the synapses of the hyperpolarized pyramidal neurons is plausible because when high-frequency activation of interneurons is paired with postsynaptic

hyperpolarization, the high-frequency stimulation may eventually elicit delayed, long-lasting potentiation of the interneurons (Le Duigou & Kullmann, 2011) rather than depression of interneuronal activities (Le Duigou et al., 2011). Eventually, the activities of the GABAergic interneurons are potentiated.

As for a possible explanation for the variations in after-effects across individuals, the proportion of inhibitory and excitatory neurons in the brain volume activated by TBS plays a role. In addition, because the expected cTBS and iTBS effects derive from successful recruitment of later I waves (Hamada et al., 2013; Suppa et al., 2016), people with decreased amounts of cortical inputs to the target region exhibit unexpected after effects.

1.5 | Rhythm of brain stimulation as a main factor for the after-effects?

Evidence increasingly indicates that specific effects of brain stimulation derive from tuning the frequency of noninvasive brain stimulation techniques, including TMS, to target underlying oscillatory brain activity (for details, please refer to Romei, Thut, & Silvanto, 2016). The evidence suggests that the entrainment (i.e., induction of a distinct entrainment signature and progressive enhancement of the target oscillation during TMS) of electromagnetic forces through rhythmic stimulation interacts with endogenous oscillatory neural activity and modifies activity in the rhythm-specific functionally connected brain regions. For example, through TMS with concurrent EEG, Thut et al. (2011) found that alpha oscillations were induced during alpha-TMS over the parietal area and that progressive enhancement of alpha activity occurred in the functionally connected brain regions. Additionally, the entrainment depended on the background alpha rhythm. These results provide direct evidence that rhythmic TMS drive underlying brain rhythm. As already stated, the recruitment of later I waves, indicative of corticocortical inputs to the target region, plays a key role in the mechanisms of TBS (Suppa et al., 2016). Brain neurons communicate and synchronize using various oscillatory rhythms for coherent behavior and cognition in humans (Varela, Lachaux, Rodriguez, & Martinerie, 2001). Because TBS's effects may be more dependent on activation of functionally connected cortical regions, the rhythm of brain stimulation may be a key factor in the after-effects of TBS. Recently, we compared brain glucose metabolism before and after 2-week prefrontal TBS protocols to treat refractory depression (Li et al., 2018). We found that the TBS protocols primarily modulated the frontocingulate circuits, and most of the stimulated regions (e.g., the medial prefrontal cortex and ACC) exhibited prominent theta signals during a resting state. These results suggest that TBS is effective because it increases entrainment of the theta-prominent brain regions.

Theta oscillations as the main frequency of TBS are believed to originate from deep neurons (levels IV–VI) in the cingulate cortex and can be detected in the posterior cingulate cortex (PCC) (Talk, Kang, & Gabriel, 2004) and frontal midline regions, including the ACC and prefrontal cortex (Asada, Fukuda, Tsunoda, Yamaguchi, & Tonoike, 1999), although the theta rhythms may originate independently from those in the hippocampus (Talk et al., 2004). Repeatedly applying theta waves through TBS to the inferior parietal lobe or prefrontal cortex may modulate the brain activities in the nearly theta-specific

functionally connected brain regions. Consistent with our speculation, Vidal-Pineiro et al. (2015) applied iTBS to the left inferior parietal cortex and determined that the GABA levels significantly increased, mainly in the PCC. Similarly, Iwabuchi et al. (2017) applied iTBS to the left prefrontal cortex and observed significantly reduced GABA/Glx levels in the regional prefrontal cortex and ACC. Although the exact mechanisms remain unclear, changes in activities in the remote regions functionally connected via theta waves can be achieved and entrained through repeated application of theta waves from the local target region.

1.6 | Other factors potentially influencing the TBS's after-effects

In addition to variations in the recruitment of later I waves in the target region across individuals, many other factors may bias the final TBS protocol results (e.g., brain region, physical activity around the time of TBS, stimulation strength, and genetic factors) (for details, please refer to Huang et al., 2017) and may be explained using the proposed updated mechanisms for TBS. For example, Martin, Gandevia, and Taylor (2006) compared the MEPs in response to TBS for a hand muscle and proximal arm muscle and established that the MEPs were not significantly depressed when the proximal arm-muscle biceps were targeted. The researchers emphasized that results obtained from the hand muscle should not be considered indicative of changes that will occur in other brain cortical regions. Many factors, including the degree of practice or exercise, could mediate the differences between brain regions. Motor practice increases practice-dependent plasticity by expanding trained representations of the motor cortex. As already stated, GABAergic inhibition plays a critical role in the after-effects of TBS. Ziemann, Muellbacher, Hallett, and Cohen (2001) indicated that a decrease in GABA-related inhibition facilitates practice-dependent plasticity in the motor cortex.

In addition, the muscle activity around the time of TBS may alter its after-effects. Such metaplastic effects of voluntary contraction significantly influence the responses to TBS (Huang et al., 2011; Suppa et al., 2016). Even the temporary muscle contraction used to measure active motor threshold prior to TBS application may block the after-effects of TBS on hand muscles (Goldsworthy, Pitcher, & Ridding, 2012). This effect is not unexpected because voluntary muscle contraction can increase the amplitude and number of the I waves, including the I-1 and later I waves (Di Lazzaro et al., 1998a). In fact, cortical activity of the human motor cortex depends on the balance of and complex interactions between inhibitory and excitatory neurotransmissions (Chen, 2004), both of which are crucial in the aforementioned mechanisms of TBS.

Furthermore, to determine whether the intensity of TBS influenced the plasticity response of the human motor cortex, Goldsworthy et al. (2016) recorded MEP input/output curves following cTBS and iTBS. Although standard TBS adopts subthreshold stimulation, the investigators found that the magnitude and consistency of cTBS-induced MEP suppression was greatest when using stimulus intensities at or above 150% of RMT, whereas facilitation of MEPs following iTBS was most consistent at 110% of RMT (Goldsworthy et al., 2016). In addition, genetic factors may also play a role. Jannati et al. (2017)

studied 21 healthy subjects through cTBS over the left motor cortex and identified two clusters exhibiting opposite responses, one with significant MEP facilitation and one with MEP suppression. They determined that subjects carrying BDNF Val66Met exhibited greater facilitation 10 min after cTBS than those carrying Val66Val, whereas apolipoprotein E genetic polymorphism seemed less involved (Jannati et al., 2017). Additional studies with larger sample sizes are required to determine the role of genetic effects on TBS responses.

2 | CONCLUSION

TBS is a patterned and powerful form of rTMS and stimulates unique mechanisms in human cortices. The latest findings on TBS from animal and human studies suggest that glutamatergic and GABAergic neurotransmissions are critically involved in these mechanisms. Herein, we proposed an updated model by integrating the glutamatergic and GABAergic neurotransmissions into different stages of Huang's simplified theoretical model. The updated model highlights critical components of the expected facilitatory effects for iTBS and inhibitory effects for cTBS and can be used to explain variability across individuals.

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