Theoretical Review

THETA-BURST STIMULATION: A NEW FORM OF TMS TREATMENT FOR DEPRESSION?

Sung Wook Chung, B.Sc. (Hons.), Kate E. Hoy, B.B.N.Sc. (Hons.), D.Psych. (Clin. Neuro.), and Paul B. Fitzgerald, MBBS, Ph.D.*

Major depressive disorder (MDD) is a common debilitating condition where only one third of patients achieve remission after the first antidepressant treatment. Inadequate efficacy and adverse effects of current treatment strategies call for more effective and tolerable treatment options. Transcranial magnetic stimulation (TMS) is a noninvasive approach to manipulate brain activity and alter cortical excitability. There has been more than 15 years of research on the use of repetitive form of TMS (rTMS) for the treatment of patients with depression, which has shown it to be an effective antidepressant treatment. Even though rTMS treatment has shown efficacy in treating depression, there is a high degree of interindividual variability in response. A newer form of rTMS protocol, known as theta-burst stimulation (TBS), has been shown to produce similar if not greater effects on brain activity than standard rTMS. TBS protocols have a major advantage over standard rTMS approaches in their reduced administration duration. Conventional rTMS procedures last between 20 and 45 min, as compared to TBS paradigms that require 1 to 3 min of stimulation. Recently, a small number of studies have suggested that TBS has similar or better efficacy in treating depression compared to rTMS. Optimization, identification of response predictors, and clarification of neurobiological mechanisms of TBS is required if it is to be further developed as a less time intensive, safe, and effective treatment for MDD. Depression and Anxiety 00:1–11, 2014.

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DEPRESSION

Major depressive disorder (MDD) is one of the most common mental disabilities worldwide, with global point prevalence of 4.7%.[1] The World Health Organization predicts MDD to be the leading cause of disease burden by 2030.[2] Even with effective treatments available, only one third of MDD patients achieve remission after the first antidepressant treatment,[3] with failure to respond to two consecutive antidepressant trials leading to an even greater reduction in remission rates.[4,5] An analysis study of antidepressant response reported that as many as 34% of the depressed patients were treatment-resistant, whereas another 15% only responded partially, following standard doses of antidepressants for 6 weeks or more.[6] In addition, in a recent study, the recurrence rate of MDD despite specialized mental care 5 years after recovery was 60%, and up to 85% over 15 years.[7] These findings question the effectiveness of current treatment strategies. Apart from inadequate efficacy, side effects can occur frequently with antidepressant medication and

Monash Alfred Psychiatry Research Centre, Central Clinical School, The Alfred and Monash University, Melbourne, Australia

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*Correspondence to: Paul B. Fitzgerald, Monash Alfred Psychiatry Research Centre, Central Clinical School, The Alfred and Monash University, Level 4, 607 Saint Kilda Road, Melbourne, Victoria 3004, Australia. E-mail: paul.fitzgerald@monash.edu
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this can be a significant factor for discontinuation.[8] There is clearly a need for more effective and tolerable alternative treatment options.

ALTERNATIVE TREATMENT

One of the main alternatives for treatment-resistant depression (TRD) is electroconvulsive therapy (ECT), and even though the side-effect profile has improved over time, it is still associated with cognitive side-effects.[9] Adverse side effects (e.g., memory impairment), requirement to induce a seizure under general anesthesia and the stigma associated with ECT have led patients to seek a more noninvasive procedure with fewer side effects. One such alternative is "transcranial magnetic stimulation" (TMS).[10]

TMS

TMS is a widely used technique in the neurosciences and involves stimulating the brain through the intact scalp.[11] TMS produces a magnetic field that passes freely into the brain and induces electrical activity in underlying neurons, which results in their depolarization.[12] A single TMS pulse can produce the acute effect of neural circuit activation that is generally short-lived (up to hundreds of milliseconds).[13] By applying stimulation repetitively, however, TMS has been shown to alter the excitability of the stimulated area in the brain,[14] outlasting the period of the stimulation. This characteristic of repetitive TMS (rTMS) is particularly beneficial from a therapeutic perspective.[15] Depending on the frequency of stimulation, the effect on cortical excitability can generally be either excitatory or inhibitory.[16] Low-frequency rTMS (1 Hz) has been shown to reduce cortical excitability when applied for 15 min,[17] whereas high-frequency rTMS (5–20 Hz) has been observed to increase excitability.[18] However, there is no consistent evidence that low-frequency rTMS produces inhibitory effects, and even though most studies of high-frequency rTMS showed increased excitability, varying results were reported.[19] rTMS appears to mimic the effects of long-term depression (LTD) and long-term potentiation (LTP),[20] and it may exert its therapeutic effects in depression via modifying plasticity.

rTMS IN DEPRESSION

Dysfunction of neural circuits is associated with the pathophysiology of many psychiatric disorders,[21] and the modulatory effects of rTMS in the stimulated area have allowed for treatment of mood disorders, particularly showing significant efficacy in depressed patients.[9] More than 15 years of research has been conducted on the use of rTMS for the treatment of patients with depression,[15] with a large number of rTMS treatment trials in MDD targeted to dorsolateral prefrontal cortex (DLPFC).[22] An early depression study using positron emission tomography (PET) showed reduction of glucose metabolism in prefrontal cortex (PFC) areas, including the DLPFC,[23] followed by a series of PET studies that demonstrated a correlation between the effects of antidepressant treatment and normalization of hypoactivity in the PFC.[24,25] Based in part on this research, rTMS targeting of DLPFC has become the conventional stimulation approach in depression treatment. However, a recent review explored alternative stimulation sites to improve rTMS efficacy, suggesting a range of other options such as dorsomedial PFC, frontopolar cortex, ventromedial PFC, and ventrolateral prefrontal cortex.[26]

In regard to targeting the DLPFC, the presence of interhemispheric asymmetry in prefrontal regions in clinically depressed patients has allowed for several therapeutic options.[27] There are two commonly used rTMS protocols in treating depression – high-frequency rTMS (5–20 Hz) targeting left DLPFC[28] and low-frequency rTMS (~1 Hz) over the right DLPFC.[29] The majority of depression studies have been conducted using high-frequency rTMS (at or above motor threshold) to the left DLPFC since its initial demonstration of antidepressant efficacy in an open study,[30] and subsequent randomized sham-controlled trials[31–34] and meta-analyses[35–37] support its effectiveness. On the other hand, there are now a growing number of studies suggesting that low-frequency rTMS is as effective as high-frequency rTMS in the treatment of depression.[38–43] Different parameters commonly used in treating depression are summarized in Table 1.

Even though many studies support the antidepressant effect of rTMS, varying outcomes have been reported among early studies, and some have shown no beneficial effects.[44–46] Early rTMS protocols have shown less antidepressant effect compared to more recent protocols,[47] which may explain such variability. Different frequencies ranging from 5 Hz to 20 Hz have been investigated,[30,48,49] with 10 Hz being most frequently used.[50,51] The largest multisite randomized controlled trial (301 medication-free patients) to date showed significant antidepressant results compared to sham using 10 Hz,[52] followed by a more recent sham-controlled randomized trial involving 190 intention-to-treat patients that reported clinically meaningful antidepressant effects compared to sham with 10 Hz rTMS.[33]

A recent meta-analysis on the clinical relevance of rTMS concluded unfavorably toward its antidepressant effect,[53] but it did not examine the treatment duration and cumulative dose as factors affecting the outcome. It is critical to note that fairly clear dose–response relationship has emerged in depression treatment with rTMS in the recent years,[54,55] and rTMS clinical trial reports reveal reasonably consistent efficacy signals.[33,55,56]

Recently, low-field magnetic stimulation inducing low, pulsed electric field (≤1 V/m, 1 kHz) has demonstrated rapidly acting antidepressant responses,[57] supporting the previous studies of antidepressant properties with low magnetic field.[58–60] The field strength

TABLE 1. Commonly used rTMS and TBS parameters in treating depression

Parameters	rTMS		TBS	
	Low-frequency rTMS	High-frequency rTMS	cTBS	iTBS
Intensity (motor threshold)	110% rMT	120% rMT	80% aMT/rMT	80% aMT/rMT
Frequency of stimulation	1 Hz	10 Hz	50 Hz	50 Hz
Interstimulus interval (ISI)	1 s	100 ms	20 ms	20 ms
Train duration	20 min	4 s	20 or 40 s	2 s
Intertrain interval (ITI)	–	25 s	200 ms	200 ms
Interblock interval (IBI)	–	–	–	10 s
Number of trains	-	75 trains	-	10 trains each block
Total number of stimulus[a]	1,200	3,000	300 or 600	600
Administration site	Right DLPFC	Left DLPFC	Right DLPFC	Left DLPFC

[a]Total number of stimulus given per day may vary.
aMT/rMT, active/resting motor threshold; DFLPC, dorsolateral prefrontal cortex; cTBS/iTBS, continuous/intermittent theta-burst stimulation; rTMS, repetitive transcranial magnetic stimulation.

was significantly lower than rTMS for depression treatment (100 V/m, 10 Hz), and therefore, it is not clear whether high field strength is required to obtain the therapeutic effects of rTMS in depression treatment.

The differences in the possible methods of rTMS treatment delivery and the techniques involved can result in varying outcome, and a mixed combination of different variables used in rTMS parameters across studies (such as stimulus frequency, intensity, and number of stimuli) may limit systemic comparisons. Additionally, interpretation of the results in clinical trials may be affected by interindividual variability of response to rTMS,[61] and therefore, standardizing rTMS parameters and developing a better understanding of different rTMS applications would benefit future research and also provide more efficacious clinical outcome. There is also potential value in exploring rTMS-related stimulation options that may produce greater brain effects.

THETA-BURST STIMULATION (TBS)

In search for more effective ways of modifying brain activity, researchers have been investigating novel ways of applying rTMS. Several animal model studies have demonstrated effectiveness in inducing synaptic plasticity using bursts of high-frequency theta stimulations.[62–64] Mimicking LTP and LTD inducing paradigms in such animal models laid the basis for the development of patterned rTMS protocols known as TBS.[65]

TBS involves pulses being applied in bursts of three at high frequency (50 Hz) with an interburst interval of 200 ms (5 Hz, which is in the range of theta frequency). Based on animal experiments that showed powerful effects on synaptic plasticity using repeated short bursts of high-frequency stimulation at 50–100 Hz given three to five times per second (theta range),[66,67] a pilot study investigated the effect of a single short burst of 50 Hz rTMS at low intensity in human motor cortex, and reported TBS could safely be applied to human cortex to study long-term potentiation.[68] TBS requires less stimulation time and lower intensity (typically 80% of the active motor threshold (aMT)) to produce longer lasting effects in the human cerebral cortex compared to other known rTMS protocols.[65] There are two different patterns of TBS that are commonly used, continuous (cTBS) and intermittent (iTBS), which have opposite effects (Fig. 1). In cTBS, either 300 pulses (20 s) or 600 pulses (40 s) of TBS are delivered without any interruption. This paradigm reduces cortical excitability beyond its stimulation duration by approximately 20 min for 300 pulses of cTBS, and up to 1 hr for 600 pulses of cTBS. In iTBS, 2 s of TBS trains (30 pulses) are repeated every 10 s for 190 s, with a total number of 600 pulses. iTBS produces facilitatory effects on motor cortex excitability that outlast the stimulation time for at least 15 min.[65]

Similar protocols to above-mentioned TBS paradigms have been used in animal models to induce facilitation[62,69] or to produce suppression,[70] but it is unclear how the parameters were developed for human cortex. In an earlier study of rat hippocampus, variable amounts of LTP were observed depending on how many trains of TBS were delivered.[71] A recent study in human has demonstrated the importance of break during 5 Hz rTMS for facilitation, as the after-effects reversed into inhibition when 5 Hz was applied continuously[72], which may explain the rationale behind the development of different TBS protocols.

It is believed that these after-effects of TBS originate from the cortex since spinal H-reflexes are unaffected by the intervention.[65] The cortical origin of the effects of TBS is also suggested by direct recordings of corticospinal activity. TMS can produce multiple descending corticospinal volleys containing a direct (D) wave followed by several indirect (I) waves, I1, I2, and I3, which can be recorded using electrodes inserted into the epidural space over the spinal cord.[73] The D-wave is thought to be caused by direct activation of corticospinal axons, and the I-waves by transsynaptic activation of the excited neurons.[74] TBS effects on cortical circuits showed

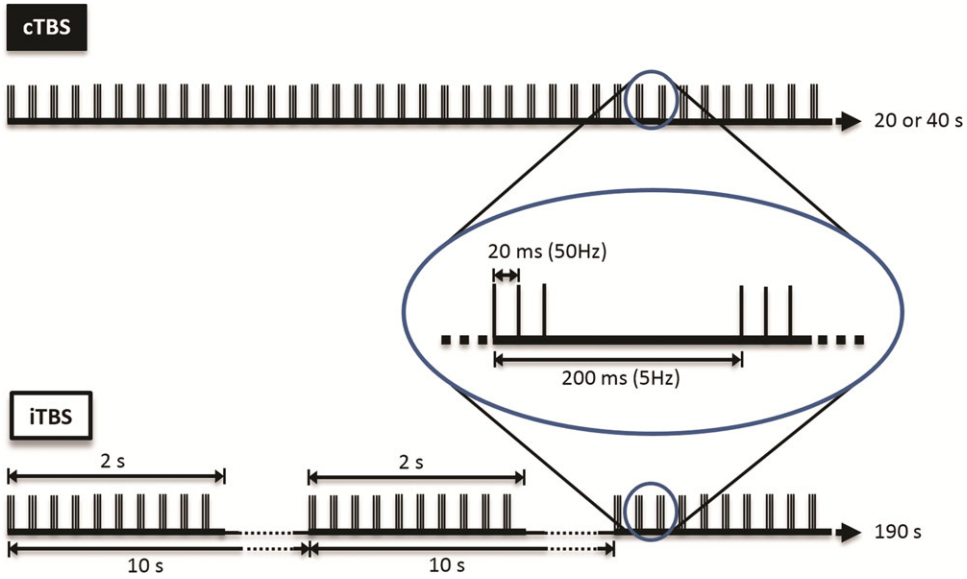

Figure 1. Different TBS protocols. TBS pattern consists of three bursts of pulses given at 50 Hz every 200 ms. When stimulated continuously (cTBS) for either 20 or 40 s, it induces LTD-like effect. However, when stimulated intermittently (iTBS) at 2 s every 10 s for 190 s, it induces LTP-like effect.

preferential decrease in the amplitude of I1 wave using cTBS,[75] whereas increase in the amplitude of later I-waves, but not the I1 wave, was observed with iTBS.[76] Such selective stimulation accommodates sophisticated investigation of facilitatory and inhibitory cortical interactions in humans. Furthermore, a recent study suggested that the after-effects of TBS protocols may be influenced by the recruitment of early and late I-waves, and optimizing the conditions for late I-wave recruitment would be necessary to improve TBS effects.[77]

MECHANISMS – ANIMAL MODELS

The neural mechanisms involved in the effects of TBS are inadequately understood in humans, though animal model studies aid in our understanding of this technique. A rat model study with cortical TBS stimulation demonstrated acute and long-term effects on the expression of glutamic acid isoforms in cortical inhibitory interneurons that are important for γ-aminobutyric acid (GABA) synthesis in neurotransmission.[78] Both cTBS and iTBS promoted GABAergic neurotransmission at the cellular level in the targeted rat cortex, whereas these parameters caused different effects on the cortical expression of calcium-binding proteins such as calbidin D-28k (CB) and parvalbumin (PV).[79] The latter study suggested that the iTBS may target the inhibition of pyramidal cell output by decreasing interneuronal PV expression, and cTBS influences the inhibitory activity of interneurons expressing CB that regulate the synaptic inputs to pyramidal cells. However, even though different inhibitory modulation was observed within the targeted cortex for different TBS patterns in the rat model, it may not necessarily translate into human studies of TBS.[79]

MECHANISMS – HUMAN MODELS

Partially supporting these animal findings, a magnetic resonance spectroscopy study in humans revealed TBS modulation of GABA.[80] Increased GABA concentration was seen in primary motor cortex (M1) after cTBS stimulation with no significant changes in glutamate/glutamine levels. Furthermore, the involvement of the GABA receptor as a mediator for neuronal modulation was proposed.[81] The GABAergic inhibitory transmission between hippocampal interneurons and pyramidal neurons can be enhanced by activating the *N*-methyl-D-aspartate receptor (NMDA-R),[82] and the effects of cTBS-induced suppression and iTBS-induced facilitation were blocked by memantine, an NMDA-R antagonist, suggesting the after-effects might be mediated by LTD/LTP-like synaptic plasticity.[83] Additionally, TBS effects can also be modulated by dopamine as blocking D2 receptors impaired the effects of both cTBS and iTBS.[84] The activation of the D2 receptor suppresses NMDA-R activation,[85] as well as GABAergic inhibition,[86] indicating the existence of complexity involved in TBS-induced plasticity. Therefore, more studies are needed to enhance our understanding of its mechanism in humans.

MOTOR VERSUS NONMOTOR

The effects of TBS were first elucidated when it was applied to the motor cortex, and the majority of studies exploring the after-effects of TBS have studied this site.[65,83,87,88] This is, in part, because the modulatory effects on the motor cortical excitability can be assessed relatively directly[89] compared to nonmotor regions.

M1 excitability can be evaluated by measuring parameters such as motor-evoked potentials (MEPs), short-interval intracortical inhibition (SICI), and intracortical facilitation (ICF) using single-pulse (sp) TMS and paired-pulse (pp) TMS.[90] When applied over M1 in healthy individuals, cTBS showed reduction in MEPs and SICI, whereas iTBS had the opposite effect.[65] However, several studies did not find significant changes in SICI following both, or either one of TBS protocols.[91–94] One reason could be that the TBS effects on SICI are highly intensity dependent.[94] Different findings were observed in modulating ICF with TBS, where ICF remained unchanged with cTBS,[87,95] or showed decrease in ICF.[65,96] There was no effect in modulation of ICF with iTBS.[65,87] These varied results may be due to the opposite current direction used in two studies as responses in these paradigms are dependent on stimulation parameters.

Several attempts have been made to optimize the effects of TBS in motor cortex with modulation of variables such as frequency,[97–99] stimulation duration,[100] and a paired application,[101] but there is no consensus as to the optimal methods of applying TBS as yet. It is also unclear whether the optimized TBS parameters for motor cortex stimulation would result in similar effects in PFC, where only limited optimization effort has been made.

TBS influences on the modulation of corticocortical and intracortical circuits have been demonstrated in other brain regions with respect to M1. Remote suppression of M1 excitability can be caused by cTBS on premotor cortex,[102] and when cTBS was applied to the primary somatosensory cortex, an increase in MEPs was seen with no change in SICI or ICF on M1 circuitry.[96] In addition, the evidence of cerebellar efferent modulation to the motor cortex was observed when the induction of cTBS over lateral cerebellum caused a reduction in SICI within the contralateral M1.[103]

However, evaluation of TBS effects in other brain regions, such as parietal cortex and PFC, requires different approaches. The availability of neuroimaging techniques, such as PET, electroencephalography, functional MRI, and functional near-infrared spectroscopy, allows researchers to investigate the effects of TBS in nonmotor regions.[104–107] One recent study demonstrated hemodynamic change in prefrontal regions upon TBS stimulation, but this was an indirect measurement of prefrontal cortical activity.[108]

TBS stimulation over different brain regions has also been employed with therapeutic intent, such as in visual neglect,[109] tinnitus,[110,111] pain,[112] and depression.[113–115] However, despite the effectiveness of TBS in motor cortical modulation, its use has not yet substantially spread into clinical applications. This is likely due to this lack of investigation of the effects of TBS on more clinically relevant brain regions. In particular, the physiological effects of TBS in PFC, where abnormalities are prevalent for major depression[116] and schizophrenia[117], are not likely to be the same as in the motor cortex and require investigation.

STUDIES OF TBS IN DEPRESSION

TBS has been shown to be effective in modulating motor cortex physiology and behavior in healthy populations,[83,95] and has clear potential as a therapeutic tool in MDD.[114] As discussed above, an imbalance between left and right DLPFC activity has been proposed in MDD,[118] and different TBS paradigms could be applied to counter this interhemispheric asymmetry; iTBS to the left and cTBS to the right DLPFC. However, currently there are only a few studies investigating the antidepressant efficacy of TBS (summarized in Table 2).

Preliminary studies of antidepressant efficacy of TBS suggested its potential therapeutic applications in patients with major depression.[113,119] In one of the first studies, clinical improvement was observed after 2 weeks of treatment with, twice daily, iTBS (1,200 pulses/day) to the left DLPFC, as well as patients who received cTBS (1,200, 1,800, or 3,600 pulses/day) to the right DLPFC.[119] Different stimulation doses were used in four groups in the trial; three of the groups received cTBS after an initial comparison between iTBS and cTBS suggested greater efficacy with the latter. Antidepressant efficacy was lower for iTBS (28.6% improvement rate) than cTBS (50.0% improvement rate). Without significant adverse effects, dose-dependent efficacy was reported with more pulses of cTBS, suggesting that the extended number of TBS pulses may improve clinical outcome.

Similar TBS parameters (refer to Table 2) were used for a case series conducted by Holzer and Padberg (2010), which suggested antidepressant efficacy of iTBS. Significant reductions in Hamilton Rating Scale for Depression (HDRS, 43%) and Beck Depression Inventory (BDI, 49%) were seen after a 3-week course of treatment.[113] Longer treatment duration in this study may have resulted in better outcome as the treatment response to rTMS became clinically meaningful after 4 to 6 weeks of active treatment.[120] Even though there clearly was an antidepressant outcome in all groups, both studies were open with no sham control groups, and placebo effect needs to be considered.

A different approach has combined left-sided iTBS and right-sided cTBS successively. This randomized controlled pilot study investigated the efficacy of bilateral TBS to the DLPFC in 32 patients with MDD and found that antidepressant efficacy was significantly higher with bilateral TBS than sham TBS.[115] Treatment responses quantified by the Montgomery–Åsberg Depression Rating Scale (MADRS) showed nine responders (56%) and seven patients (44%) with remission in an active group, compared to sham group that had four responders (24%) and three patients (19%) with remission.

TABLE 2. TBS treatment trials in depression

Study	Subjects	TBS parameters	Significant difference (active vs. sham)	Results
Chistyakov *et al.*, 2010	33 medication-resistant MDD patients	10 sessions over 2 weeks, 50 Hz interstimulus interval repeated every 5 Hz. Group 1: 90% aMT, iTBS to left DLPFC, 600 stimuli repeated twice daily (1,200 stimuli) Group 2: 90% aMT, cTBS to right DLPFC, 600 stimuli repeated twice daily (1,200 stimuli) Group 3: 100% aMT, cTBS to right DLPFC, 900 stimuli repeated twice daily (1,800 stimuli) Group 4: 100% aMT, cTBS to right DLPFC, two consecutive trains of 900 stimuli each separated by a 30-min interval and repeated twice daily (3,600 stimuli)	n/a	18 of 32 (56.3%) patients reported improvement in depressive symptoms (50% decline on the HDRS). CTBS showed more effectiveness than iTBS. Dose-dependent improvement seen with cTBS (Group 2, 3, and 4). Improvement was seen in the following: Group 1: 2 of 7 (28.6%) Group 2: 3 of 6 (50.0%) Group 3: 3 of 5 (60.0%) Group 4: 10 of 14 (71.4%)
Holzer and Padberg., 2010	Seven medication-resistant MDD patients	Three-week course, 50 Hz interstimulus interval repeated every 5 Hz. 80% rMT, iTBS to left DLPFC, 600 stimuli repeated twice (10-min interval) daily (1,200 stimuli)	n/a	43 and 49% decline on HDRS and BDI, respectively. 70% (five of seven) response rate and 42% (three of seven) remission rate.
Li *et al.*, 2014	60 patients with TRD	10 sessions over 2 weeks, 50 Hz interstimulus interval repeated every 5 Hz at 80% aMT. Group 1: cTBS to right DLPFC, 1,800 stimuli daily Group 2: iTBS to left DLPFC, 1,800 stimuli daily Group 3: Combination of cTBS to right DLFPC (1,800 stimuli) and iTBS to left DLPFC (1,800 stimuli) successively (3,600 stimuli per day) Group 4: Sham TBS (either iTBS or cTBS) with 90° coil set	Yes	Significant decrease in HDRS scores in active TBS groups (especially with paradigms involving iTBS to the left DLPFC) compared to sham group. Group 1: 3 of 15 responders (−22.5% decrease in HDRS) Group 2: 6 of 15 responders(−42.3% decrease in HDRS) Group 3: 10 of 15 responders (−52.5% decrease in HDRS) Group 4: 2 of 15 responders (−17.4% decrease in HDRS)
Plewnia *et al.*, 2014	32 patients with MDD	30 sessions over 6 weeks, 50Hz interstimulus interval repeated every 5 Hz. 80% rMT, combination of 600 stimuli of iTBS to left DLPFC and 600 stimuli of cTBS to right DLPFC successively (1,200 stimuli per day) Sham with 45° coil set	Yes	Significantly superior effect in the active group (9 of 16 [56%] response, 7 of 16 [44%] remission) compared to sham group (4 of 16 [25%] response, 3 of 16 [19%] remission) quantified by MADRS scores.

aMT/rMT, active/resting motor threshold; BDI, Beck Depression Inventory; cTBS/iTBS, continuous/intermittent theta-burst stimulation; DLPFC, dorsolateral prefrontal cortex; HDRS, Hamilton Rating Scale for Depression; MDD, major depressive disorder; n/a, not applicable; TRD, treatment-resistant depression.

A more recent study compared antidepressant efficacy of different TBS paradigms in 60 patients with TRD. Fifteen patients were assigned to each group; right-sided cTBS (1,800 stimuli), left-sided iTBS (1,800 stimuli), bilateral TBS (3,600 stimuli), and a sham.[114] This randomized sham-controlled 2-week trial demonstrated a greater response rate (66.7%) in a group with bilateral stimulation (successive stimulation in a randomly assigned order), and iTBS on the left DLPFC (40%) compared to cTBS (20%) and sham group (13.3%).

Moreover, TBS treatment outcomes were associated with different refractoriness levels. Treatment resistance (i.e., antidepressant treatment failures), severity of symptoms, and duration of presenting episode were measured prior to randomization in terms of refractoriness scores, and categorized into three levels – low, moderate, and high refractoriness. Patients with lower refractoriness scores were also responsive to sham stimulation, but the sham responses gradually decreased as the treatment refractoriness level increased. Bilateral stimulation and iTBS were statistically more effective in patients with moderate to high refractoriness level, and cTBS showed antidepressant efficacy in treatment of patients with moderate refractoriness. The best response was seen in moderate refractoriness group, and it was suggested that patients in this group may have an underlying brain dysfunction that is more treatable by TBS.[114] This indicates that lower refractoriness scores are predictors for better TBS responses.

Twelve-week followup of the TBS data revealed 57.9% response rate in total,[114] which is similar to the response rate of acute-phase treatment with rTMS (58%) measured by the Clinical Global Impression – Severity (CGI-S).[56] It is worth noting that the change in mean HDRS of bilateral TBS treatment was 52.5% after 2 weeks,[114] a rate higher than most rTMS trials.[22]

TBS has shown a promising future in depression treatment. However, it is important to note that larger randomized controlled trials are required before the jury is out, since the studies that have been published so far are preliminary, mostly open, uncontrolled, and underpowered.

These studies of TBS have used mostly similar parameters, with some variation in stimulation intensity. The main difference can be seen in the stimulation duration (Table 2). Similar to recent rTMS trials, there appears to be a likelihood of dose dependence of antidepressant efficacy. However, this requires further investigation as simply prolonging the stimulation duration has resulted in reversed effects with motor cortex TBS.[100] Repeated stimulation at an interval of 10 to 15 min may produce increased antidepressant efficacy as a paired application of cTBS at 10-min intervals prolonged neuroplastic changes in M1 excitability,[101] and repeated trains of right parietal cTBS (up to four trains with 15-min interval) induced long-lasting improvement of visual neglect.[109] The latter study used a modified TBS paradigm with 30 Hz interstimulus interval and repeated every 6 Hz that was found to induce a superior neuroplastic response within M1 than standard cTBS paradigm.[99]

SAFETY OF TBS

TMS is generally well-tolerated with a few mild side effects such as headache and neck pain. However, it poses a risk of seizure, and extensive safety guidelines for TMS have been established.[121] Theoretically, TBS has the potential of having a higher risk of seizure induction than rTMS due to its high-frequency bursts (50Hz), but it can also be viewed as a safer protocol as it uses less pulses in a shorter duration and at lower intensity. Due to lack of safety studies of TBS, current TMS safety guidelines do not include recommended procedures for minimizing adverse effects of TBS.[121] However, the application of TBS in research and clinical fields has increased since its introduction, and its safety has been investigated.[122] A recent meta-analysis reported that seizure has only occurred once with TBS to date, and it accounts for the crude risk of seizure per session of 0.02%. The overall crude risk of mild adverse events was estimated to be 1.1%, and these findings were comparable with high-frequency rTMS protocols. It should be noted that the seizure occurred at an intensity of 100% resting motor threshold (rMT) on M1,[123] while most studies followed original TBS paradigm at 80% aMT.[65] In addition, TBS safety study in children less than 18 years of age showed no serious adverse events.[124]

Safety of TBS was assessed in the studies of antidepressant efficacy, and it was found to be safe with no seizure occurrence.[114,115,119] Common side effects included headache and dizziness in a few patients in both active and sham group. Notably, dizziness was more prevalent in active group, especially with bilateral stimulation.[114] The author also reported a correlation between sequence of stimulation and dizziness ratio. It was found that most patients with dizziness received cTBS first followed by iTBS (four of seven), whereas only a small number of patients suffered from dizziness with the opposite sequence (one of eight). Increased intensity from 80 to 100% aMT and the number of stimuli from 1,200 to 3,600 each day did not cause any significant adverse effects,[119] which would allow for wider range of stimulation parameters to devise optimal efficacy. Despite the safe and efficacious application of TBS, a careful examination is required prior to and during the TBS stimulation.

CONCLUSIONS AND FUTURE DIRECTIONS

Studies of the modulation of plasticity in human motor cortices with TBS suggest that it is one of the most powerful tools for therapeutic noninvasive brain stimulation. Current research efforts are in progress to improve clinical efficacy of depression treatment, however, widespread clinical use of TBS is yet to emerge. TBS protocols have a major advantage over standard rTMS approaches in its administration duration. This, together with the fact that TBS uses a lower stimulation intensity of 80% instead of 120% used in rTMS, may allow for more comfortable treatment conditions in a therapeutic setting. However, the variety of parameters such as frequency, duration, total number of pulses, or total number of treatment sessions needs further investigation in order to optimize TBS efficacy.[88] It would also be worth looking at the effects of lower intensity TBS in depression. Long-lasting alterations in cortical excitability are

desirable for clinical applications, and therefore, a wider range of stimulation parameters deserve a closer look.

It must be noted that TBS protocols use very high-frequency stimulation, which may pose a higher risk of adverse events such as seizure.[122] Because TMS is known to carry a risk of seizures, safety guidelines for use of TMS have been established.[121] The lack of safety studies for TBS stresses the necessity to explore its equivalent guidelines. At this time, given the limited safety data, TBS protocols for depression or other psychiatric disorders should only be delivered in the context of a research study with special informed consent procedures. Currently, there is no FDA-cleared device for the delivery of TBS to patients for clinical care.

It is critical to develop more effective stimulation paradigms before larger studies can be conducted. In order to develop better forms of TBS, a further research is required to better understand the neurophysiological and clinical features of depressed patients who respond to TBS. The identification of reliable predictors for better TBS responses is another important future research area. Elucidation on the neurobiological mechanisms of the effect of TBS treatment in depression will contribute to identifying optimal forms of TBS, which can lead to personalized medicine with better clinical results. Finally, large treatment studies are required to better understand the mechanisms of treatment response, and these approaches will help establish TBS as a safe and effective treatment option for patients with MDD.

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