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Accelerated Repetitive Transcranial Magnetic Stimulation to Treat Major Depression: The Past, Present and Future

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is an effective and evidence-based therapy for treatment-resistant major depressive disorder. A conventional course of rTMS applies 20–30 daily sessions over 4–6 weeks. The schedule of rTMS delivery can be accelerated by applying multiple stimulation sessions per day, which reduces the duration of a treatment course with a predefined number of sessions. Accelerated rTMS reduces time demands, improves clinical efficiency, and potentially induces faster onset of antidepressant effects. However, considerable heterogeneity exists across study designs. Stimulation protocols vary in parameters such as the stimulation target, frequency, intensity, the number of pulses applied per session/over a treatment course and the inter-session intervals. In this article, clinician-researchers and neuroscientists with extensive experience in accelerated rTMS research synthesize and form consensual perspective on two decades of investigations and development, from early studies (‘Past’) to contemporaneous theta burst stimulation, a time-efficient form of rTMS gaining acceptance and utility in current clinical TMS settings (‘Present’). Overall, empirical studies show that accelerated rTMS protocols are well-tolerated and not associated with serious adverse effects. Importantly, accelerated rTMS’s antidepressant efficacy appears comparable to conventional, once-daily rTMS protocols. It remains uncertain if accelerated rTMS induces faster antidepressant effects. In this regard, treatment protocols incorporating high pulse dose and multiple treatments each day show promise and improved efficacy, pending future replication. We offer perspectives for reaching consensus regarding nomenclature describing accelerated rTMS and make recommendations for avenues to optimize therapeutic and efficiency potential, as well as protocol individualization using neuroimaging and electrophysiological biomarkers (‘Future’).

Keywords

Accelerated; transcranial magnetic stimulation; TMS; rTMS; brain stimulation; depression; major depressive disorder

INTRODUCTION

Major depressive disorder (MDD) is a common disorder associated with significant mortality and morbidity,[1,2] which can be difficult to treat with conventional psychotherapeutic and pharmacological approaches.[3] Treatment-resistance rates of 30% have been reported,[4] resulting in disability and subjective distress for patients while adding to carer burden and health economic costs.[5] So called treatment-resistant depression (TRD) can be broadly defined as depression that has had an insufficient clinical response following adequate trials of antidepressant therapy.[6] The classification systems for TRD share common frameworks that evaluate treatment resistance by way of the number and classes of antidepressant medications trialed with adequate dosing, duration and adherence. The severity of treatment resistance is then stratified in sequential stages.[7–9] In clinical practice, treatment-refractoriness and illness persistence increase with patients’ stages of

treatment-resistance, as demonstrated in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.[3] The cost of healthcare provision in TRD is markedly higher than in treatment-responsive depression.[10–12] Compared to patients with treatment-responsive MDD, TRD patients are more likely to have protracted hospitalization and higher rates of re-admission for symptom stabilization and/or treatment of suicidal thinking, culminating in increased health economic costs.[13] The prevalence, morbidity, mortality and health economic burden of TRD highlight the scale and significance of this problem. The imperative exists for novel and effective treatments for this common, debilitating and costly illness.

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique described nearly four decades ago[14] and repetitive transcranial magnetic stimulation (rTMS) was first applied to treat depression ten years after.[15,16] rTMS involves the repeated application of electromagnetic pulses delivered by a magnetic coil placed on the scalp to depolarize cortical neurons and modulate neuronal activity.[17–21] Multiple randomized sham-controlled trials and meta-analyses have established rTMS as an evidence-based therapy for TRD.[22–25] In large, real-world studies, treatment response rates to rTMS of 50–80% have been reported.[26–29] The physiological and hence therapeutic effects of rTMS are determined by the stimulation protocol, consisting of the stimulation target, frequency/pattern and intensity of the stimulation pulses applied, the number of pulses applied per stimulation session and the number of sessions applied over a treatment course.[30] The most commonly applied stimulation protocol to treat depression has been 10 Hz stimulation applied to the left dorsolateral prefrontal cortex (DLPFC), with each stimulation session lasting 20–40 minutes. Clinical trial evidence also supports the antidepressant efficacy of 1 Hz rTMS applied to the right DLPFC and sequential bilateral rTMS applied to both left and right prefrontal cortices.[31–35] In a standard treatment course, stimulation sessions are applied once a day, five days a week, with 20–30 sessions delivered over 4–6 weeks.[20,23,36–38] This poses foreseeable time demands and logistical challenges for patients, carers and treatment services. Typically, patients whose depressive symptoms respond to rTMS therapy experience improvement 2–4 weeks into their courses of treatment, but this can also be as late as after course completion.[39,40] In the meantime, many patients continue to experience subject distress and functional impairment. The time required for antidepressant response also limits rTMS's applicability in acute depression and scenarios with clinical risks, such as suicidality and inadequate oral intake contributing to rapid physical decline. As there are few effective therapeutic alternatives where urgent antidepressant response is crucial, rapid acting rTMS therapy, if effective, could transform the treatment of psychiatric emergencies such as suicidal depression.

With the aim to improve antidepressant efficacy, the development of rTMS protocols over time have seen gradual increases in the stimulation dose, reflected by more pulses applied per session, more sessions applied per treatment course and increases in the stimulation intensity applied relative to the recipient's motor threshold.[41–44] The application of multiple stimulation sessions each day with break periods (inter-session intervals) in between have been investigated in clinical trials, which enable completion of a treatment course with a predetermined number of stimulation sessions within a shorter timeframe, thereby enabling clinical efficiency. Moreover, the primary aim was to induce faster antidepressant effects.

Accordingly, this approach is commonly referred to as accelerated rTMS.[39,45–47] It has also been described as intensive rTMS,[48–50] or with specification of the number of treatments applied per day, such as twice-daily rTMS.[51–55] This article provides a perspective and commentary on accelerated rTMS applied to treat depression, spanning the early studies ('Past') that saw accelerated rTMS's development into its current forms ('Present'), and offers a forecast of research directions and developments over the coming years ('Future').

METHODS

This is a collaborative perspective article, featuring narrative reviews of the literature, by clinician-researchers and neuroscientists with collective expertise and experience in rTMS amounting to several decades, notably with accelerated rTMS clinical trials in MDD. The objective is to offer a consensual, expert perspective on the past, present, and future of accelerated rTMS applied to treat MDD. In doing so, literature was identified on MEDLINE, PubMed and Google Scholar (including ePUB, ahead of print, in-process and other non-indexed citations up till November 2022). Databases were searched using combinations of the following search terms and keywords: accelerated, intensive, high-dose, TMS, rTMS, transcranial magnetic stimulation, neuromodulation, depression and treatment-resistant depression. All relevant studies were included, with no restrictions on study type, design or the year published.

THE PAST

Early Accelerated rTMS Studies in Depression

Loo et al. first reported the application of two sessions of 10 Hz rTMS per day separated by two-hour inter-session intervals (ISI), and found active treatment was superior to sham stimulation in treating depressive symptoms.[53] Holtzheimer et al.'s subsequent open-label trial found that 15 rTMS sessions applied over two days produced antidepressant effects lasting up to six weeks while being well-tolerated.[56] Additional studies added to the evidence base supporting twice-daily[57–59] and accelerated rTMS's antidepressant efficacy.[48,60] In addition to possibly achieving rapid antidepressant effects, it was anticipated at this time that these session-intensive rTMS protocols could achieve depression remission rates expected with electroconvulsive therapy (ECT). Although considered the gold standard therapy for TRD,[61] drawbacks of potential cognitive adverse effects and the enduring stigma associated with ECT[62,63] motivated early accelerated rTMS research in the hope that it could be an efficient, effective and viable alternative.[45] In a sham-controlled crossover trial featuring accelerated high-frequency rTMS (aHF-rTMS), Baeken et al. found approximately one-third of patients with TRD achieved depression response and remission criteria.[48,60] Serial resting state functional magnetic resonance imaging (rsfMRI) showed that the patients whose depression responded to aHF-rTMS demonstrated stronger functional connectivity anti-correlation between the subgenual anterior cingulate cortex (sgACC) and the dorsomedial prefrontal cortex (DMPFC) compared to non-responders.[64] Positron emission tomography (PET) showed significant decreases in sgACC metabolic activity were found in treatment responders,[60] suggesting baseline sgACC metabolic activity may hold predictive value for response to aHF-rTMS. A later study by the same group observed a

correlation between significant increases in γ-aminobutyric acid (GABA) concentration in the left DLPFC and clinical response to aHF-rTMS. Additionally, aHF-rTMS did not affect the measured ratio of N-acetylaspartate to creatinine (NAA/Cr) (a marker that reflects the functional status of brain tissue[65]), suggesting aHF-rTMS had no negative influence on neural integrity.[66]

Fitzgerald et al. were the first to prospectively and directly evaluate the antidepressant efficacy and tolerability of accelerated rTMS against a standard once-daily schedule.[67] Participants with TRD (n = 115) were randomized to 10 Hz rTMS applied in an accelerated schedule of three sessions per day and tapering treatment days over three weeks, or 20 sessions of daily rTMS over four weeks. All participants received a total of 63,000 rTMS pulses over their respective treatment courses. No significant differences in depression remission, response rates or rate of depression severity reduction over time were observed. No serious adverse effects were reported, although the accelerated rTMS group was associated with a higher rate of stimulation-associated scalp discomfort and transient, mild headaches. Apart from this trial, the early accelerated rTMS studies in depression were generally small in scale, especially if compared with the pivotal once-daily rTMS trials that established rTMS's evidence base in TRD.[37,68] These early accelerated rTMS studies in depression are summarized in Table 1, adapted from a recent systematic review. Study selection criteria and procedures are described in Chen et al. 2020.[39]

Review Articles of Accelerated rTMS Studies

Sverak and Ustohal and Caulfield et al. reported on the therapeutic efficacy and safety of accelerated rTMS applied to treat various psychiatric conditions.[50,69] When applied to treat depression, these reviews found accelerated rTMS (referred to as intensive rTMS in Sverak and Ustohal), to be efficacious. Tolerability and safety seemed comparable with standard, once-daily rTMS. Three systematic reviews specifically focusing on accelerated rTMS applied to treat depression shared the conclusion that it was effective in treating depressive symptoms in TRD,[39,46,47] although the modest number of sizeable, randomized, controlled trials were noted. Further, heterogeneity in the study designs, including stimulation parameters, scheduling of sessions and the outcomes measures used, made pooling of primary data for quantitative meta-analysis challenging. Nonetheless, preliminary meta-analyses reported antidepressant effect sizes favoring accelerated rTMS over sham stimulation,[39,47] but not over once-daily rTMS.[39] From a qualitative perspective, Caulfield et al. observed that depression response rates were higher with stimulation protocols that featured higher pulse counts, treatment sessions per day and courses with higher treatment sessions.[69] Some retrospective case series have suggested more rapid week-by-week improvement with twice-daily versus once-daily sessions.[54,55] Conversely, in a prospective study with arms matched for total pulse count, Fitzgerald et al.[67] reported similar week-by-week trajectories of improvement with once-daily treatment administered 5 days per week, versus thrice-daily treatment administered two to three days per week. A key issue to be clarified therefore concerns whether trajectories of improvement track the number of cumulative pulses, or the number of cumulative sessions, or some combination of the two.

Safety and Tolerability of Accelerated rTMS

Importantly, however, these early studies found that the side effects of accelerated protocols seemed similar to those of once-daily rTMS protocols, with accelerated rTMS being generally well-tolerated, not associated with serious adverse events[39,46,47,69] or negative cognitive effects.[67] A 2022 review by Caulfield et al.[69] addressed accelerated rTMS's safety and tolerability in detail, assessing these conventional rTMS studies as well as more recent studies featuring accelerated rTMS applied in theta-burst pattern. The authors arrived at the conclusion that the rates of rTMS-induced seizures, adverse events, discomfort, and study dropout with accelerated rTMS were comparable to once-daily scheduling. Accelerated rTMS also appeared to be safe in elderly populations, as reported in a feasibility study (n = 10)[70] and a retrospective review.[71]

THE PRESENT

Theta Burst Stimulation

Accelerated rTMS protocols enabled completion of a treatment course with a predefined number of stimulation sessions over fewer days, which translated to faster completion of rTMS courses consisting of 20–30 sessions. However, the scheduling of two or more rTMS sessions per day, each of approximately 30-minute duration, separated by one-hour (or more) ISIs presented a different kind of impracticality and clinical inefficiency.[67] These schedules required patients to attend treatment settings for long periods on each treatment day, limiting patient capacity at treatment clinics. This challenge was, at least in part, alleviated by the development and increasing acceptance of a novel and time-efficient form of rTMS called theta-burst stimulation (TBS). This patterned form of rTMS was derived from experimental studies applying triplets of electrical pulses in gamma frequency to neurons at theta frequency 'bursts.' Doing so induced observable and long-lasting strengthening and reduction of inter-synaptic transmission, known as long-term potentiation (LTP) and long-term depression (LTD),[72,73] which have been implicated in memory and learning.[74,75] Patterned bursts repeatedly delivered at theta frequency cycles were found to be more efficient at inducing LTP/LTD than stimulation applied at other frequencies.[76] The ability to induce transient states of increased and decreased synaptic transmission via direct electrical stimulation provided evidence of these interventions' potential to affect neuroplasticity.[77,78] In the TMS literature, TBS generally refers to three TMS pulses applied at 50 Hz (gamma frequency), repeated at 5 Hz (theta frequency) intervals. Two forms of TBS were introduced by Huang et al.: continuous (cTBS) and intermittent TBS (iTBS).[78] One cTBS session delivers 600 rTMS pulses and can be completed within 40 seconds. The iTBS protocol delivers 2 seconds of active stimulation followed by 8-seconds of rest. This cycle repeats for 192-seconds, delivering 600 rTMS pulses in this time. Hence, TBS sessions are briefer in duration relative to traditional rTMS approaches[79–81] and lends well to application in accelerated schedules. Two or more TBS sessions can be delivered within an hour, separated by ISIs. From both patients and clinicians' perspectives, this time-efficiency had foreseeable advantages and was welcomed. Despite its brevity, TBS demonstrated measurable and significant neuronal conditioning effects.[30,78,79,82] With regards to safety, a review by Oberman et al. found that TBS is well tolerated and not associated with serious adverse effects.[83]

Applying Theta Burst Stimulation in Accelerated Schedules to Treat Depression

Over recent years, cumulative clinical trial evidence has substantiated TBS's therapeutic efficacy in TRD[79,84–88] and saw to its increasing adoption in treatment services. Studies in TRD evaluated iTBS applied to the left DLPFC, cTBS to the right DLPFC or a bilateral approach, where left-sided iTBS and right-sided cTBS are applied sequentially.[89] A sham-controlled crossover study demonstrated that an accelerated iTBS (aiTBS) protocol applying five iTBS sessions per day, separated by 15 min ISIs, for courses of 20 treatments over four days was effective in treating TRD[80,90] and suicidal ideation.[91] Although response (38%) and remission rates (30%) were comparable with the depression treatment outcomes from the aforementioned aHF-rTMS protocol investigated by the same group,[48,60] the onset of the efficacy of the antidepressant action peaked two weeks after the completion of the aiTBS protocol.[80] It is uncertain if TBS's physiological mechanisms, such as its modulation of inter-synaptic transmission, might explain this delay in therapeutic effect. Case reports showed aiTBS could be an alternative to ECT for elderly depressed patients[92] and was effective in treating depression with psychotic features.[93] A case series found that five of nine TRD patients achieved antidepressant response to 20 aiTBS treatments over eight days.[94] A double-blinded, sham-controlled trial randomized 208 TRD patients to two sessions of iTBS (600 pulses per session) per day separated by a 60-minute ISI or one session of iTBS (1,200 pulses per session) per day over 30 days. Depression severity improved in both groups with no significant between-group differences.52

In the first study to compare accelerated iTBS to daily rTMS, 74 TRD patients were randomized to an aiTBS schedule where three iTBS treatments were administered per day or standard, once-daily 10 Hz rTMS.[49] Similar to the same group's earlier aHF-rTMS schedule,[67] this study's aiTBS protocol applied more sessions per day in the first and second weeks of the four-week treatment course. There was no significant difference in depression symptom reduction between the aiTBS and once-daily 10 Hz rTMS treatment arms. This form of aiTBS did not induce faster reduction of depression severity compared with once-daily rTMS. No difference in rates of side effects were reported. Additionally, no serious adverse events and no alterations in cognitive performance were observed. This pilot led to the largest accelerated TBS trial in depression to date: a multi-site, three-arm, randomized, controlled trial comparing accelerated bilateral TBS applied at two stimulation intensities (120% or 80% of the resting motor threshold (RMT)) over 10-days against a standard 4-week course of 10 Hz rTMS as active control.[95] Both accelerated bilateral TBS and daily 10 Hz rTMS arms applied a total of 20 treatment sessions. In the accelerated TBS arms, two-to-three bilateral TBS sessions were applied on each treatment day, separated by 15-minute ISIs. cTBS and iTBS were applied, respectively, to the right then left DLPFC, while 10 Hz rTMS was applied to the left DLPFC. The decision to target bilateral prefrontal cortices was based on a preliminary systematic review and meta-analysis[84] and earlier study findings[87] (in the absence of sizeable randomized trials of TBS in depression at the time) suggesting superior antidepressant effects may be expected with bilateral TBS and left-sided iTBS. This study found overall comparable antidepressant efficacy between accelerated bilateral TBS and standard one-daily rTMS. While accelerated bilateral TBS did not induce antidepressant effects faster than daily 10 Hz rTMS, this accelerated protocol was popular with patients, improved clinical efficiency, and enabled the provision more

treatments in busy clinical settings.[95] There was also no significant difference in depression response and remission rates between accelerated bilateral TBS applied at sub- (80% RMT) or supra-threshold (120% RMT) intensities. Given that the earlier TBS in depression trials typically applied stimulation at sub- or at-threshold (80–100%) intensities[87,96–101] and standard practice applying 10 Hz or 1 Hz rTMS was at 120% RMT intensity,[25,32,35] this head-to-head comparison of the antidepressant effects of 80% and 120% RMT TBS was of scientific interest and possibly clinical relevance.[95] Lastly, the authors found that accelerated bilateral TBS was safe and not associated with serious adverse events, although a small number of participants reported difficulty tolerating the stimulation sensation of bilateral TBS applied at 120% RMT. These and other accelerated TBS studies are summarized in Table 2.

Neuroimaging Findings in Accelerated Theta Burst Stimulation for Depression Studies

Over a series of studies that combined neuroimaging with aiTBS applied to depressed participants, active but not sham aiTBS was found to result in rapid volumetric increases in the left hippocampus (dentate gyrus), not influenced by changes in local blood perfusion.[102] Accelerated iTBS's effects on brain graph and functional connectivity measures were observed to distribute beyond the stimulation site.[103] Further, depression improvement was associated with increased brain perfusion at the region of stimulation, as well as in distal regions that were structurally connected.[104] Utilizing diffusion MRI tractography, reduced modularity of brain network configurations was seen within days of commencing active aiTBS, but not sham stimulation.[105] Later studies by the same group indicated that the cortical thickness of the right anterior cingulate cortex (ACC)[106] and the indirect structural connections between the left DLPFC target site and the right caudal cingulate and left posterior cingulate cortex[107] could be predictive for depression treatment response with aiTBS. Additionally, the strengthening of functional connectivity between the sgACC and the ventromedial prefrontal cortex (VMPFC) was found to correlate with reductions in feelings of hopelessness.[90] Finally, a retrospective analysis found that individual baseline interregional perfusion and connectivity patterns could play a role in predicting antidepressant response to aiTBS.[108] Together, these brain imaging findings indicate that interregional connectivity and brain perfusion changes can be seen in depressed patients who respond to aiTBS therapy (or once-daily iTBS and rTMS). Although larger, prospective validation is warranted, these findings were in-keeping with earlier observations that functional connectivity between the prefrontal rTMS stimulation site and the sgACC correlated with and therefore had the potential to predict clinical response to rTMS/TBS therapy.[109] Although appreciation of these connectivity and perfusion changes with accelerated TBS/rTMS are only emerging, they present exciting avenues for individualization of stimulation protocols and cortical targets to possibly enhance accelerated (and conventional) rTMS's antidepressant efficacy.

Stanford Neuromodulation Therapy

Stanford Neuromodulation Therapy (SNT) is a rapid-acting stimulation protocol that can be applied with rTMS and, potentially, other neuromodulation devices. SNT was originally conceived as a reorganization of rTMS therapy for MDD where time (accelerated scheduling and inter-session intervals), space (cortical target), and dose (pulse dose per session/day/

course) are optimized. Using an rTMS device, SNT combines rsfMRI-guided prefrontal cortical coil localization, theta burst pattern stimulation and high pulse doses. To our knowledge, SNT is the most accelerated and dose-intensive TBS protocol for the treatment of depression published to date, delivering markedly more stimulation pulses than other rTMS and TBS protocols to treat depression. Ten sessions of iTBS are applied per day at 90% RMT (each delivering 1,800 pulses) over five consecutive days, amounting to 90,000 pulses over fifty sessions.[81,110,111] This is equivalent to the total pulse count of the FDA-approved 10 Hz rTMS protocol delivering thirty daily rTMS sessions over six weeks. The stimulation target is personalized based on the individual's pretreatment rsfMRI to a site over the DLPFC that is most anti-correlated to the sgACC. The first open-label SNT study treated individuals with severe TRD failing ECT and conventional rTMS.[81] The second open label trial reported a depression remission rate of 90.5% in 21 TRD participants and rapid reduction of depression severity, where participants met treatment response criteria after a mean of 2.3 days.[111] In the follow up double-blinded, randomized, sham-controlled trial, mean reduction in depression severity was 62.0% in the active SNT and 14.3% in the sham group from baseline to day 5 post-treatment.[110] At week 4, the mean reduction in depression severity from baseline was 52.5% in the active treatment group and 11.1% in the sham group. Categorization of treatment responders and remitters were based on achieving criteria at any point during the 4-week follow-up, which was discussed as a departure from the more common single-time-point criterion used in similar trials.[110] Whereas the former categorization yielded response and remission rates, respectively, of 85.7% and 78.6% for participants randomized to active SNT and 26.7% and 13.3% for those randomized to sham. Remission and response states were then monitored over the course of four weeks in one-week intervals. Immediate remission and response rates at the end of the treatment were, respectively, 57.1 and 71.4% for active and 0 and 13.3% for sham stimulation. After four weeks, the remission and response rates were, respectively, 46.2 and 69.2% for active and 0 and 7.1% for sham stimulation. Results from this study led to the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) Neuromodulation System to recently receive US FDA Breakthrough Device Designation, followed by FDA clearance for therapeutic use in adults experiencing TRD.[112]

The SNT protocol featured 50-minute ISIs, which may be advantageous for the induction of neuroplasticity owing to the time-dependent cellular mechanisms outlined in a later section. Its personalized, neuronavigated targeting of the stimulation site may also contribute to its high response and remission rates. Notably, SNT's antidepressant efficacy may be enhanced by its high pulse dose count, namely pulses/session, sessions/day, and total pulses/course. While it may be argued that a dose-dependent relationship between rTMS antidepressant efficacy and the number of pulses applied per session has been inconsistently demonstrated with some negative[41,55] and positive[29] studies examining conventional rTMS, the contrast in study methodologies and stimulation protocols preclude transfer of these findings to hypothesis generation with respect to TBS's antidepressant efficacy. For one, Schulze et al.'s study, in which the rate of improvement in depression severity was reported to be associated with the number of cumulative sessions applied, not the cumulative number of pulses, was a retrospective chart review of open-label 20 Hz rTMS applied to the bilateral DMPFCs.[55] The potential biases inherit with this study methodology[113,114] and limitations

of the study were comprehensively discussed by the authors, as was the acknowledgement of heterogeneity in the interventions applied: 20 Hz rTMS in the twice-daily rTMS group versus 10 Hz rTMS in the once-daily rTMS group.[55] In contrast to retrospective reviews, prospective randomized trials minimize selection, reporting and other biases.[115–117] Whether the number of pulses applied with 10 or 20 Hz rTMS and its therapeutic potential is directly translatable to the current conceptualization of the optimal dose- and session-dosage of rTMS applied in theta burst pattern is unknown given iTBS's non-inferiority to 10 Hz rTMS despite its relatively fewer pulse count/session,[85] suggesting TBS pattern stimulation may have enhanced physiological potency. Further, other randomized sham-controlled trials have reported notable therapeutic benefits with once-daily iTBS applying 1,800, as opposed to 600, pulses per session.[87,118] In addition, a body of literature exists with a clear signal that increasing total pulses per treatment course appears to increase efficacy.[6] By plotting depression response rates against the total number of sessions and pulses applied over courses of accelerated rTMS, Caulfield et al. demonstrated a positive dose-response relationship.[69] This relationship is further supported by studies that reported depression treatment response in initial non-responders is possible with the provision of more treatment sessions.[119,120]

Does Accelerated rTMS/TBS Induce Antidepressant Effects Faster?

Except for SNT, other prospective accelerated rTMS/TBS studies demonstrate less certainty as to whether the acceleration of stimulation scheduling results in faster induction of antidepressant effects. Randomized parallel arm trials comparing accelerated left-sided 10 Hz rTMS,[67] left-sided iTBS[49] and bilateral sequential cTBS and iTBS[95] against once-daily 10 Hz rTMS did not find the accelerated protocols produced more rapid improvement of depressive symptoms. Using group-based trajectory modelling, four distinct depressive symptom response trajectories were identified with courses of iTBS and 10 Hz rTMS treatment.[40] The same model was applied to treatment data from aforementioned aHF-rTMS[67] and aiTBS[49] studies, which showed that these established response trajectories were not affected by accelerated scheduling,[121] thereby suggesting that these accelerated rTMS/TBS protocols were not faster to induce antidepressant effects relative to daily rTMS.

Conversely, other studies support the notion that accelerated rTMS can induce faster antidepressant effects. This perhaps makes intuitive sense, given that with most medical interventions, the onset of therapeutic effects is expected to occur proportionally to the rate at which the interventions are administered. Specifically, two retrospective chart reviews observed that twice-daily rTMS induced antidepressant effects faster than once-daily administration.[54,55] In particular, Modirrousta et al. observed a similar pattern of reduction in depression severity for every ten treatment sessions, so that patients receiving twice-daily rTMS experienced symptomatic improvement in half the time as patients receiving once-daily treatment.[54] Holtzheimer et al.'s accelerated protocol applying 15 rTMS sessions over two days observed rapid antidepressant effects by Day 3,[56] although the study's modest sample size, dropout rate and lack of sham-control are noteworthy limitations. Future research with sizeable samples that specifically examine the rate of onset of antidepressant effect are needed to elucidate if accelerated rTMS/TBS can rapidly induce these effects.

THE FUTURE

More than a decade of research has culminated in considerable insights and evidence base that supports the accelerated application of rTMS scheduling to treat MDD. Much remains to be investigated to achieve optimization of antidepressant efficacy and therapeutic efficiency. The scope for future research is diverse and extends beyond the crucial need for larger clinical trials featuring prospective, randomized, comparison or sham-controlled designs.[39,46,47,50] The heterogeneity of stimulation parameters, coil localization, illness/participant variables and other methodological factors and the array of permutations formed by the combination of these elements is an inherit and recognized challenge in this field of research.[82,88,89,122,123] At the same time, it also encourages diverse lines of scientific inquiry, such as those pertaining to safety and durability of treatment response.[69] Tolerability and safety concerns may be expected with more accelerated protocols delivering more pulses per session, more sessions per day (particularly with short ISIs) and at higher stimulation intensities relative to RMT. As such, the reporting of adverse effects with accelerated rTMS protocols in both research and clinical settings is strongly encouraged. The sharing of experiences with some of the practical aspects of accelerated rTMS, such as the logistical challenges associated with scheduling multiple sessions per day, if and when reviews of treatment plans are indicated in cases of inadequate therapeutic response, etc., can also promote peer review, learning and directions for future research. Here, we offer perspectives on the nomenclature used, the cellular mechanisms implicated in accelerated rTMS and how protocol optimization and neuroimaging- and electrophysiology-derived personalization measures could shape this field in the years to come.

Consensus of Nomenclature Describing rTMS Applied More Than Once a Day

As previously suggested by Chen et al. and Sverak and Ustohal, the nomenclature describing rTMS applied more than once a day deserves consensus regarding what should be considered accelerated rTMS.[39,50] Literature searches yield various descriptors for rTMS applied more than once a day, such as accelerated, intensive, high-dose. Numerical specifiers for the number of sessions applied each day have also been used, e.g., twice-daily rTMS. Standardization of this nomenclature is a critical first step to progress research of accelerated rTMS protocols. We suggest that the description ‘intensive’ does not clearly or sufficiently differentiate between rTMS applied more than once a day, rTMS applied at high stimulation intensity, high pulse doses or in high session numbers. Additionally, intensive rTMS may be open to interpretations other than the time-efficient scheduling of treatment sessions and convey meanings such as increased workload, demands placed on patients or even increased efficacy. We suggest the uniform adoption of accelerated rTMS protocols where two or more treatment sessions are applied per day, as this conveys the concept of stimulation applied in a time-efficient schedule and enables the faster completion of a course of treatment with a predetermined number of treatment sessions. This nomenclature is also in keeping with the description used in recent European guidelines.[23] The one limitation of describing an rTMS protocol as ‘accelerated,’ however, is that it does not sufficiently distinguish between accelerated treatment scheduling and the accelerated induction of therapeutic effects. In this regard, we propose accelerated rTMS to mean accelerated delivery, not necessarily accelerated response.

Inter-Session Interval (ISI) and the Implicated Cellular and Physiological Mechanisms

Depression of mood is associated with brain changes such as the loss of dendritic spines and synapses, glial cells and dendritic atrophy in areas such as the prefrontal cortex and the hippocampus,[124] while successful treatment with antidepressant medications has been found to produce opposing effects and can enhance neuroplasticity.[125] Indeed, TMS's effects on regional neuronal excitability,[18] synaptic plasticity[126,127] and downstream connectivity[128,129] may provide theoretical and empirical models for rTMS's mechanisms of action.[130–132] At the same time, these mechanisms may, at least in part, explain why accelerated rTMS scheduling does not result in faster antidepressant response. Specifically, it is possible that certain neurophysiological responses dependent on time-latency are needed before neuroplastic change is realised.[126,133]

A comprehensive review of the effects that ISIs have on TBS-induced neuroplastic changes found that repeated TBS applied at 10- or 40-minute intervals did not cumulatively strengthen inter-synaptic transmission (LTP), while longer ISIs of 60 or 90 minutes did.[127] Thus, the physiology of long-term plasticity may impose a limit on the ISI, below which additional stimulation sessions may fail to exert additional effect. At the cellular level, TBS administration leads to actin filament polymerization in the dendritic spines. Where spines were not affected by the first stimulus, the second TBS session, if applied 60 or 90 minutes later, induced polymerization in these spines. Interestingly, successive applications of TBS did not strengthen stimulation-induced changes in the same spines. Rather, the first stimulation appeared to prime certain spines and after an approximately 60-minute refractory period, the second stimulation induced polymerization in these primed spines.[127] A similar phenomenon was demonstrated in healthy controls where an initial session of iTBS produced the expected facilitation of the motor evoked potential (MEP), yet a second iTBS session 15 minutes later yielded no further increase in the MEP. Following this, a third iTBS session applied 30 minutes after the first session again produced additional MEP facilitation.[134] Successive runs of iTBS may thus require a minimum ISI to exert cumulative plasticity effects. These observations suggest that spaced ISIs of approximately one hour or more, as opposed to a mass or 'crammed' approach may be more effective in the reliable and persistent induction of LTP.[126,127] It is unclear, however, whether the optimal ISIs observed in animal and healthy human motor cortical conditioning models can be generalized to protocols stimulating the prefrontal cortical regions for therapeutic purposes.

Optimizing the Inter-Session Interval for Accelerated rTMS in Depression

When applying multiple daily sessions of rTMS, shorter ISIs are logistically favorable as they allow more sessions to be delivered in a briefer clinic appointment and are thus often preferred by patients and service providers. However, empirical research that can elucidate optimal ISIs are needed. Notwithstanding the differences in sample size, statistical power and other aspects of protocol design, more robust antidepressant efficacy have been reported in accelerated TBS trials incorporating 50-minute ISIs,[110,111] over those incorporating 15-minute ISIs.[49,80,95,102,105,107] However, the SNT protocol, with its 50-minute ISI design, differs from the above-cited trials by more ways than ISI alone. Variables such as the number of iTBS pulses per session, total number of sessions applied, rsfMRI-derived stimulation localization, etc. could individually and in their totality account for SNT's

antidepressant efficacy and efficiency. Bearing in mind the posited cellular mechanisms and effects of spaced learning,[126,127] discussed above, however, it is theoretically plausible to suggest that the 15-minute ISI in Fitzgerald et al. and Chen et al.,[49,95] may have been insufficient, and may in-part explain why these accelerated TBS protocols did not induce faster antidepressant effect, compared to daily 10 Hz rTMS. The counterargument to the relevance of ISI when using iTBS to treat depression can be found in a recent randomized trial that incorporated more robust blinding, and controlled for visit length and time spent in the treatment chair, in which no difference in response rates was found between two iTBS sessions (600 pulses) per day separated by a 60-minute ISI versus one iTBS session (1,200 pulses) per day with no ISI.[52] To optimize the ISI for accelerated rTMS in depression, future trials might therefore consider a direct comparison of depression symptom trajectories between briefer (10–20 min) and longer (50–90 min) ISIs. Comparison of varying ISIs in highly accelerated treatment protocols, such as the SNT, can similarly help to optimize this parameter of accelerated rTMS scheduling.

Alternatively, fMRI[129] and PET[135] studies suggest that rTMS applied to the DLPFC may engage less directly with the hippocampus, and more directly with cortico-striatal pathways via the head of the caudate nucleus, leading to localized dopamine release post-stimulation. In this light, it might be worthwhile to examine if dopaminergic augmentation using L-Dopa or psychostimulant medications[136] might further enhance and/or accelerate the response to rTMS applied multiple times per day, or perhaps reduce the minimum ISI required between stimulation sessions. If successful, such optimizations to the therapeutic regimen could be favorable for both clinic logistics and patient preference. Evaluations of the therapeutic impact of ISI and pharmacological augmentation strategies[137–140] create opportunities to better understand rTMS's mechanisms of action and indeed, the pathophysiology of depressive disorders.

How Might Neuroimaging Facilitate Individualization of Accelerated Theta Burst Stimulation Therapy in Depression?

The variability of inter- and intra-individual responses to rTMS[141–144] and TBS[145,146] are well-documented, opening the possibility of protocol personalization which may improve stimulation-induced neuromodulatory and therapeutic effects. In present day clinical practice, the stimulation intensity is typically the only personalized parameter in rTMS/TBS therapy,[123] derived from the individual's RMT, while the other stimulation parameters are predetermined and usually derived from clinical trial evidence. Personalization of rTMS parameters via modifications to, for example, the coil placement, orientation and stimulation intensity based on neuroimaging findings have been suggested.[147] Based on the knowledge that TMS effects propagate throughout the brain via functional and structural connections and that deeper brain structures such as the sgACC are implicated in mood regulation and hence clinical treatment response, a three-step approach to optimal coil positioning and orientation can be proposed. First, the indirect target should be defined based on *a priori* knowledge. Second, rsfMRI and diffusion weighted MRI data can be used to reconstruct individual connectomes. These can be used to derive a proxy stimulation target if the intended target identified in the previous step cannot be reached/stimulated directly with rTMS, e.g., if it lies too deep below the cortical surface. Third, simulation of

TMS-induced electric field distributions, based on anatomical MRI data potentially merged with diffusion weighted MRI data, may allow visualization of which brain regions are affected by the stimulation applied and the changes that occur with alterations to coil position and orientation. Combined, this approach may optimize stimulation localization and coil orientation to increase neuronal conditioning and, possibly, therapeutic efficacy. One example of a neuroimaging-derived target that is a potential alternative to the DLPFC is the VMPFC, which has been implicated in aiTBS-induced improvements in depression symptomatology and suicidality.[148] Furthermore, electric field simulation models may help define the stimulation intensity necessary to induce particular electric field strengths applied to the intended cortical target.[149] Alternatively, anatomical MRI data can be used to derive the distance between the coil and the cortical target, in order to account for the loss of stimulation intensity due to the scalp-to-cortex distance,[150] thereby ensuring the intended stimulation intensity is delivered to the cortex.

Whilst the added value of neurophysiology-derived personalization is logically reasoned, its clinic readiness is questionable. Modak and Fitzgerald's review of 30 studies that incorporated personalization of rTMS/TBS protocols using neuroimaging found a trend towards improved clinical outcomes with personalized stimulation parameters.[151] Validation of these approaches in future clinical trials would be worthwhile, although the statistical power required and the permutations of examinable personalization methods and parameters are foreseeable challenges.[123,147] It is also unclear at present how personalized parameters influence each other and whether attempts at personalization of multiple parameters might infer additional benefits over personalization of single parameters. Lastly, it is questionable if personalized stimulation parameters remain stable for the individual over time and if they are therapeutically advantageous. In the case of rTMS/accelerated rTMS applied over several days, it is unclear whether the network connectivity originally derived from neuroimaging and used to personalize stimulation target(s) might change over the treatment course, whether recalibration is necessary and when it is most appropriate to do so. Whether repeat neuroimaging and re-establishment of treatment parameters based on imaging markers over a course of rTMS/TBS therapy can improve antidepressant efficacy is a relevant question worth exploring. Taken together, these personalization approaches derived from neuroimaging and other potential biomarkers inform how accelerated rTMS/TBS protocols might develop into the future.

Can Electrophysiological Biomarkers Optimize Accelerated Theta Burst Stimulation in Depression?

Separate to neuroimaging-informed optimization, the electroencephalogram (EEG) presents as a potential means to optimize rTMS and accelerated rTMS therapy. Real-time EEG-triggered rTMS assumes that brain oscillations represent various states of brain excitability, which can be measured by EEG. This method has been used to confirm that MEPs induced by motor cortex stimulation during the presumably high excitability state (i.e., negative peak of the mu-oscillation) were higher compared to random stimulation or stimulation during the low excitability states (i.e., positive peak of the mu-oscillation).[152] This has been translated to EEG-triggered TMS applied to the DLPFC to treat depression.[150] In this study, bursts of three TMS pulses (100 Hz) were synchronized to alpha oscillations derived from the F5

electrode channel in depression patients. Besides successful alpha-band synchronization of rTMS pulse delivery, this study showed that alpha-synchronized rTMS but not static rTMS (modified iTBS, with bursts at 100 Hz) reduced left frontal resting-state alpha power and increased TMS-induced beta oscillations over mesial frontocentral channels. The therapeutic potential of alpha-synchronized rTMS in depression was separately demonstrated in a recent study.[153] The inter-trial phase coherence (a measure used to quantify event-related phase modulations) was different after alpha-synchronized rTMS compared to unsynchronized stimulation. Specifically, EEG-synchronized rTMS was associated with greater entrainment of post-stimulation quasi-alpha (8–13 Hz range) entrainment. rTMS pulse trains were synchronized to the phase that maximally engaged the deep brain target in the ACC using an integrated fMRI-EEG-TMS setup. Still in its early stages of development, questions abound for this novel rTMS approach. With ongoing validation and replication studies, however, EEG-triggered rTMS or TBS might present as an effective form of personalized rTMS therapy that can be applied in accelerated schedules and/or induce faster antidepressant effects than conventional schedules.

In addition to the synchrony and trigger of rTMS with EEG, the dominant individual frequencies of brain oscillations can also be used to adapt the stimulation frequency to. In this sense, individualized frequency rTMS can be conceptualized for both once-daily and accelerated rTMS protocols. Previous work comparing standard 10 Hz rTMS to rTMS applied with alpha frequency individualization showed that smaller deviations between the individualized and standard frequencies were related to better responses in depressed patients.[154,155] When comparing 30-Hz bursts repeated at 6 Hz, 50-Hz bursts at 5 Hz, or individualized frequency in healthy volunteers, individual iTBS has been shown to significantly increase the amplitude of the TMS-evoked potentials at specific latencies compared to standard protocols.[156] Endogenous brain oscillation-derived, individualized frequency rTMS/TBS therapies may be novel variations of conventional approaches that can inform accelerated treatment protocols. To the best of our knowledge, however, no iTBS trials in depression utilizing individualized stimulation frequencies have been published.

Translational research and clinical trial efforts to date and over coming years have the potential to inform the utility of neuroimaging-[157] and electrophysiology-derived[158–160] techniques to personalize and optimize accelerated rTMS therapy in depression and possibly other neuropsychiatric disorders. The journeys of their development and clinical translation share one common challenge: that of the considerable heterogeneity in methodology, parameters, measurement, interpretation, software and equipment requirements,[151] in addition to the array of intrapersonal, interpersonal, diagnostic and illness-related variables.[161] In clinical practice, the potential time demands, technical expertise and advanced investigations for establishment of the necessary physiological biomarkers[162] at the front end (and possibly over the course of one’s accelerated rTMS course) is likely to come at a considerable cost. Into the future, cost-benefit analyses may help inform the role of these advanced, personalized stimulation therapies,[161] balanced against their generalizability, efficacy and the cost of functional impairment because of protracted illness and/or the need to effectively treat clinical risks arising in psychiatric emergencies.

Future Utilities for Stanford Neuromodulation Therapy and Similar High-Dose, Accelerated Theta Burst Stimulation Protocols

The most recent SNT trial featuring randomized, sham-controlled methodology has been described to represent "a significant therapeutic innovation for the use of rTMS as a treatment for MDD."[163] Notwithstanding the limitations discussed in the studies,[81,110,111] further research is needed to elucidate how the stimulation parameters, accelerated schedule and neuronavigated coil localization collectively contribute to its antidepressant efficacy. Additionally, the scope exists to optimize SNT's antidepressant efficacy and its duration. Beyond the acute course of SNT treatment, there is value in developing a longer term SNT protocol that can assist maintenance of the depression remission achieved following the acute course. The rationale for doing so with SNT (and other accelerated rTMS protocols) stem from the possibility that depression relapse shortly following successful treatment may be more likely in accelerated rTMS protocols, relative to longer, once-daily rTMS treatment schedules,[69] and that applying tapering/maintenance rTMS sessions after the initial accelerated course may prevent this.[92,93,164] Indeed, in the most recent SNT randomized trial, several participants experienced sufficient reduction of MADRS severity to meet remission criteria, but this did not maintain over time.[110] A non-invasive closed loop framework to stimulation application[165,166] may inform development of an SNT protocol to maintain its antidepressant effects. This can help establish SNT as a clinically feasible and durable treatment for a greater majority of depressed patients.

For years to come, the SNT protocol will likely remain an area of ongoing research and potential clinical use, not just for MDD but possibly for other neuropsychiatric conditions and applications in neurophysiology studies. While the original SNT trials' data was compelling, several parameters require further exploration, including individualization in the time domain (burst frequency, inter-burst frequency, inter-train interval), space domain (further optimization of the anticorrelated prefrontal cortical target to the sgACC, expansion to possible biotypes of MDD and other psychiatric conditions) and dose domain (maintenance SNT, individualized pulse dosage and potential characterization of patient and illness profiles that stand to benefit from this therapy). Application of SNT through an rTMS device is the first application of this platform technology but not the only possible hardware interface to apply this stimulation protocol. In the future, high dose accelerated, functional connectivity targeted neurostimulation strategies for therapeutic purposes may be realized with other electrical or non-electrical stimulation devices, such as low intensity focused ultrasound.

CONCLUSION

Like conventional once-daily stimulation, accelerated rTMS is an effective treatment for major depressive disorder, particularly for treatment-resistant patients. We highlight the advancement of accelerated approaches spanning more than a decade, from early findings to the more time-efficient TBS used in current treatment settings. The literature shows accelerated rTMS's antidepressant efficacy and side effect profiles are comparable with once-daily rTMS. This is supported by evidence derived from large, prospective clinical trials with parallel arm design allowing direct comparison of outcomes.[52,67,95] Accelerated

rTMS's time-efficiency seems popular with patients, practitioners and clinical services. In view of the evidence supporting its efficacy and safety, we form the consensual perspective that accelerated rTMS/iTBS can be offered to patients experiencing MDD following detailed discussion and consenting process about it being an alternate form of rTMS scheduling. As with all therapies, the efficacy, safety and tolerability of protocols that deviate from those investigated in clinical trials are unknown and should be cautioned against. The durability and depression relapse patterns following accelerated rTMS remain a recognized knowledge gap. There is clear merit in the ongoing research and development of accelerated rTMS protocols for depression and other neuropsychiatric conditions. To this end, we provide suggestions to work towards consensus of nomenclature and the systematic investigation of protocol parameters and treatment outcomes. Future neuroimaging and electrophysiology research may see translation to protocol individualization and optimization, in turn improve accelerated rTMS's therapeutic efficacy and efficiency.

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Table 1

Characteristics of Accelerated rTMS in Depression Studies*

Study	Study Design	Acceleration schedule	Patient Sample Accelerated rTMS			Patient Sample Standard rTMS or Sham rTMS			rTMS Parameters				Main diagnosis	Treatment outcome measure	Treatment response rates	Comments
			N	Age	F/M	N	Age	F/M	Stimulation site (Localisation method)	% MT	Total pulses	Inter-session interval (mins)				
Szuba et al. (2001)[58]	Randomized sham-controlled	2 weeks 2 sessions/day vs. 1 session /day vs. 'low dose' vs sham rTMS	9	39.7	5/4	5	33.4	3/2	L-DLPFC (5cm)	100	TD: 20,000 OD: 10,000	10	MDD	HDRS6	Not reported.	Active rTMS more effective at treating depression than sham. Active rTMS elevated TSH levels.
			Which of the 9 patients receiving active rTMS received accelerated, standard or low dose rTMS were not specified.													
Loo et al. (2007)[53]	Randomized sham-controlled	2 sessions/day over 14 days	19	49.8	10/9	21	45.7	8/11	L-DLPFC (5cm)	110	30,000	120	MDD	HDRS MADRS	MADRS response: aTMS: 6/19 (31.6%) Sham: 3/19 (15.8%)	Significant MADRS but not HDRS response.
Holtzheimer et al. (2010)[56]	Open label	15 sessions over 2 days	14	51	5/9	n/a	n/a	n/a	L-DLPFC (5.5cm)	100	15,000	43	MDD	HDRS24 BDI	Week 6 Response = 5/14 (36%) Week 6 Remission = 4/14 (29%)	Small sample size and study drop out reduced statistical significance.
Baeken et al. (2013)[48]	Randomized sham-controlled crossover	5 sessions/day × 4 days	21	49.3	13/8	Same patient sample crossed over			L-DLPFC (Neuronav)	110	31,200	15–20	Treatment-resistant MDD	HDRS	7/20 (35%)	Pre-trial medication washout for all patients. Studies that report on the same patient sample: Baeken et al. 2014;[64] Baeken et al. 2015;[60] Baeken et al. 2017.[66]

Study	Study Design	Acceleration schedule	Patient Sample Accelerated rTMS			Patient Sample Standard rTMS or Sham rTMS			rTMS Parameters				Main diagnosis	Treatment outcome measure	Treatment response rates	Comments
			N	Age	F/M	N	Age	F/M	Stimulation site (Localisation method)	% MT	Total pulses	Inter-session interval (mins)				
McGirr et al. (2015)[57]	Open label	2 sessions/day over 14 days	28	47.7	21/7	n/a	n/a	n/a	L-DLPFC (10/20 EEG)	120	60,000	60	Treatment-resistant MDD	QIDS-C-16	15/27 (56%) Remission = 10/27 (37%)	Well-tolerated. Comorbid anxiety improved in depression responders.
Theleritis et al. (2017)[59]	Randomized sham-controlled	15 once daily vs. 30 twice daily sessions × 15 days vs. once daily sham rTMS vs. twice daily sham rTMS	26	38.9	11/15	26	39.1	15/11	L-DLPFC (neuronav)	100% MT	TD: 48,000 OD: 24,000	Not specified	Treatment-resistant MDD	HDRS CGI	Active rTMS: 59.2% Sham: 2.5%	Improved efficacy with TD could be due to a greater number of pulses. No therapeutic efficacy with sham.
Dardenne et al. (2018)[69]	Open-label	5 sessions/day × 4 days	10	73.9	10/0	n/a	n/a	n/a	L-DLPFC (6cm)	110	31,200	Not specified	Treatment-resistant MDD	HDRS BDI	4/10 (40%)	Feasibility study in elderly females.
Fitzgerald et al. (2018)[66]	Randomized single blind	3 sessions/day × 6 days OR 1 session/day × 20 days	58	48.2	33/25	57	49.9	33/24	L-DLPFC (6cm)	120	63,000	15–30	Treatment-resistant MDD	HDRS MADRS	HDRS Acc 20.3% Std 29.8% MADRSaTMS 23.7% Std 33.3%	More treatment discomfort with aTMS. Therapeutic equivalence between daily and accelerated rTMS. The two courses had equal total pulse counts.
Modirrousta et al. (2018)[54]	Retrospective chart review of open label treatment	1 vs. 2 sessions/day × 30 sessions	17	45.4	9/8	19	50.6	10/9	L-DLPFC (neuronav and 5cm)	110	90,000	15	MDD	HDRS	aTMS = 82.4% std = 52.6% Remission: aTMS =	Faster treatment response in aTMS group.

Study	Study Design	Acceleration schedule	Patient Sample Accelerated rTMS			Patient Sample Standard rTMS or Sham rTMS			rTMS Parameters				Main diagnosis	Treatment outcome measure	Treatment response rates	Comments
			N	Age	F/M	N	Age	F/M	Stimulation site (Localisation method)	% MT	Total pulses	Inter-session interval (mins)				
															64.7% std = 36.8%	
Schulze et al. (2018)[55]	Retrospective chart review of open label treatment	1 (10Hz) vs. 2 (20Hz) sessions/day × 20–30 sessions	65	39.7	49/16	65	35.5	53/12	Bilateral DMPFC	120	aTMS: 60,000–90,000 std: 120,000–180,000	10	Treatment-resistant MDD	BDI	aTMS = 41.5% std = 35.4% Remission: aTMS = 35.4% std = 33.8%	Faster treatment response in twice-daily group. DMPFC stimulation site. Variable time points for end outcome.
Desbeaumes et al. (2019)[70]	Open label retrospective	2 sessions/day × 20–30 days	73	50.9	37/36	n/a	n/a	n/a	L-DLPFC (10/20 EEG)	110	60,000–90,000	90	Treatment-resistant MDD	MADRS	33/73 (45%)	Elderly depressed patients.

*Adapted from “Efficacy, efficiency and safety of high-frequency repetitive transcranial magnetic stimulation applied more than once a day in depression: a systematic review,” by Chen L, et al. J Affect Disord 2020;277:986–96. Used with permission.

5–6 cm, stimulation localisation by placing stimulation coil 5–6 cm anterior to motor hotspot; 10/20 EEG, stimulation localization using the 10/20 EEG coordination system; aHF-rTMS, accelerated high frequency repetitive transcranial magnetic stimulation; aiTBS, accelerated intermittent theta burst stimulation; arTMS, accelerated repetitive transcranial magnetic stimulation; BDI, Beck Depression Inventory; BPAD, bipolar affective disorder; CGI, Clinical Global Impression Scale; DMPFC, dorsomedial prefrontal cortex; GABA = γ-aminobutyric acid; HDRS, 17-item Hamilton Depression Rating Scale; HDRS24, 24-item Hamilton Depression Rating Scale; HDRS6 = 6-item Hamilton Depression Rating Scale; L-DLPFC, left dorsolateral prefrontal cortex; MADRS, Montgomery Åsberg Depression Rating Scale; MDD = major depressive disorder; MT, motor threshold; n/a, not applicable; Neuronav, stimulation localization using neuronavigation technique; QIDS-C-16, 16-item Quick Inventory of Depression Inventory–Clinician Version; R-DLPFC, right dorsolateral prefrontal cortex; sgACC, subgenual anterior cingulate cortex; rTMS, repetitive transcranial magnetic stimulation; std, standard, once daily rTMS; TSH, thyroid stimulating hormone.

Table 2

Characteristics of Accelerated Theta Burst Stimulation in Depression Studies

Study	Study Design	Acceleration schedule	Patient Sample Accelerated iTBS			Patient Sample Once-daily rTMS or Sham TBS			TBS Parameters					Main diagnosis	Treatment outcome measure	Treatment response rates	Comments
			N	Age	F/M	N	Age	F/M	Stimulation site (Localisation method)	% MT	TBS type (no. of pulses/ session)	Total pulses	Inter-session interval (mins)				
Duprat et al. (2016)[79]	Randomized sham-controlled crossover	5 sessions/day × 4 days	50	42	35/15	Same patient sample crossed over			L-DLPFC (Neuronav)	110	iTBS (1620)	32,400	15	Treatment-resistant MDD	HDRS	18/47 (38%)	Rates of response = 38% and remission = 30%. aiTBS found to be safe. Studies that reported on same patient sample: Desmyter et al. 2016;[91] Baeken et al. 2017;[90] Baeken et al. 2019;[148] Caeyenberghs et al. 2019;[105] Klooster et al. 2019;[103] Baeken et al. 2020;[102] Baeken et al. 2020;[106] Klooster et al. 2020;[107] Wu et al. 2022;[104] Wu et al. 2022.108
Williams et al. (2018)[80]	Open label	10 sessions/day × 5 days	6	56	4/2	n/a			L-DLPFC (Neuronav)	90	iTBS (1800)	90,000	50	Treatment-resistant MDD	HDRS	Response = 5/6 (83.3%), Remission = 4/6 (66.7%)	Initial open-label trial of SNT protocol.
Brocker et al. (2019)[93]	Open label	8 treatment days Day 1: 1/day	9	40.67	7/2	n/a			L-DLPFC (5.5cm)	80	iTBS (1782)	35,640	20	Treatment-resistant	CES-D	5/9 (56%)	Open-label case series.

Study	Study Design	Acceleration schedule	Patient Sample Accelerated iTBS			Patient Sample Once-daily rTMS or Sham TBS			TBS Parameters					Main diagnosis	Treatment outcome measure	Treatment response rates	Comments
			N	Age	F/M	N	Age	F/M	Stimulation site (Localisation method)	% MT	TBS type (no. of pulses/ session)	Total pulses	Inter-session interval (mins)				
		Day 2–3: 2/day Day 4–8: 3/day												MDD and BPAD			
Cole et al. (2020)[11]	Open label	10 sessions/day × 5 days	22	44.86	12/10	n/a			L-DLPFC (Neuronav)	90	iTBS (1800)	90,000	50	Treatment-resistant MDD	MADRS	90.48%	SNT protocol, with MRI-guided targeting, was well tolerated and safe.
Fitzgerald et al. (2020)[41]	Open label prospective	3 sessions/day Week 1: 3 days Week 2: 2 days Week 3 and 4: 1 day	36	44	19/17	38	45	17/21	L-DLPFC (Beam F3)	120	iTBS (600)	12,600	15	Treatment-resistant MDD	MADRS	aiTBS (week 4) = 27.8% 10 Hz rTMS (week 4) = 26.3%	First parallel group comparison between intensive iTBS vs daily 10 Hz rTMS. Similar therapeutic benefits were found.
Konstantinou et al. (2020)[91]	Case report	8 sessions/day × 5 days then tapering regime	1	66	F	n/a	n/a	n/a	(Beam F3)	110	iTBS (1800)	72,000	Not specified	Treatment-resistant MDD	PHQ-9 BDI	Achieved depression remission (PHQ-9 = 3, BDI = 18)	Case report of aiTBS in late-life depression in place of ECT during Covid-19 Pandemic.
Blumberger et al. (2021)[52]	Randomized double-blind and sham-controlled	2 sessions (iTBS 600)/day OR 1 session (iTBS 1200)/day over 30 days	103	41	68/35	105	42	63/42	L-DLPFC (Neuronav)	120	iTBS (600 OR 1200)	36,000	60 (iTBS600) OR 0 (iTBS1200	Treatment-resistant MDD	HDRS	Day 30 Twice-daily iTBS 600 = 44.3% Once-daily iTBS 1200 = 41.1%	No difference in depression outcomes between once daily iTBS 1200 (no ISI) vs twice daily iTBS 600 (60-min ISI) after 6 weeks.
Chen et al. (2021)[94]	Randomized, single blind	Accelerated bilateral TBS = 20 sessions, 2–3 sessions/day	211	80% RMT: 48.2, 120%	80% RMT: 70/33 120%	84	48.67	49/35	Bilateral DLPFC (Beam F3)	80 OR 120	Sequential cTBS and iTBS	60,000	15	MDD or BPAD	QIDS	Overall = 43.7% 80% RMT TBS: 44.1%	Largest accelerated bilateral TBS study to date. No difference

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Study	Study Design	Acceleration schedule	Patient Sample Accelerated iTBS			Patient Sample Once-daily rTMS or Sham TBS			TBS Parameters					Main diagnosis	Treatment outcome measure	Treatment response rates	Comments
			N	Age	F/M	N	Age	F/M	Stimulation site (Localisation method)	% MT	TBS type (no. of pulses/ session)	Total pulses	Inter-session interval (mins)				
		over 10 days. L-DLPFC 10 Hz rTMS = 20 sessions, 1 session/day over 26 days.		RMT: 49.1	RMT: 73/35											120% RMT TBS: 36.8% rTMS: 51.4%	in outcomes across the three groups.
Konstantinou et al. (2021)[92]	Case report	8 sessions/day × 5 days then tapering regime	1	44	F	n/a	n/a	n/a	(Beam F3)	110	iTBS (1800)	72,000	Not specified	Treatment-resistant MDD	PHQ-9 BDI	Achieved depression response, remission and resolution of psychotic symptoms.	Case report of aiTBS in depression with psychotic features (nihilistic delusions).
Cole et al. (2022)[10]	Randomized, double-blind and sham-controlled	10 sessions/day × 5 days	14	49	5/9	15	52	5/10	L-DLPFC (Neuronav)	90	iTBS (1800)	90,000	50	Treatment-resistant MDD	MADRS	Active = 12/14 (85.7%) Sham = 4/15 (26.7%)	Active SNT protocol was more effective than sham stimulation.

ACC, Anterior cingulate cortex; Beam F3, F3 stimulation localization using the 10/20 EEG coordination system (as described," by Beam W, Brockardt JJ, Reeves ST, George MS. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications Brain Stimul 2009;2:50–4); aiTBS, accelerated intermittent theta burst stimulation; BPAD, bipolar affective disorder; BSI, Beck Scale for Suicidal Ideation; BDI, Beck Depression Inventory; cTBS, continuous theta burst stimulation; CES-D, Center for Epidemiological Studies–Depression Rating Scale; DLPFC, dorsolateral prefrontal cortex; ECT, electroconvulsive therapy;EEG, electroencephalogram; HDRS, 17-item Hamilton Depression Rating Scale; Hz, Hertz; ISI, intersession interval; iTBS, intermittent theta burst stimulation; L-DLPFC, left dorsolateral prefrontal cortex; MADRS, Montgomery Åsberg Depression Rating Scale; MDD = major depressive disorder; MRI, magnetic resonance imaging; MT, motor threshold; n/a, not applicable; Neuronav, stimulation localization using neuronavigation technique; QIDS, Quick inventory of depressive symptomatology; PHQ-9, Patient Health Quiestionnaire-9; RMT, resting motor threshold; sgACC, subgenual anterior cingulate cortex; SNT, Stanford Neuromodulation Therapy; TBS, theta burst stimulation; rTMS, repetitive transcranial magnetic stimulation; VMPFC, ventromedial prefrontal cortex.