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rTMS of the Dorsomedial Prefrontal Cortex for Major Depression: Safety, Tolerability, Effectiveness, and Outcome Predictors for 10 Hz Versus Intermittent Theta-burst Stimulation

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ABSTRACT

Background: Conventional rTMS protocols for major depression commonly employ stimulation sessions lasting >30 min. However, recent studies have sought to improve costs, capacities, and outcomes by employing briefer protocols such as theta burst stimulation (iTBS).
Objective: To compare safety, effectiveness, and outcome predictors for DMPFC-rTMS with 10 Hz (30 min) versus iTBS (6 min) protocols, in a large, naturalistic, retrospective case series.
Methods: A chart review identified 185 patients with a medication-resistant major depressive episode who underwent 20-30 sessions of DMPFC-rTMS (10 Hz, $n = 98$; iTBS, $n = 87$) at a single Canadian clinic from 2011 to 2014.
Results: Clinical characteristics of 10 Hz and iTBS patients did not differ prior to treatment, aside from significantly higher age in iTBS patients. A total 7912 runs of DMPFC-rTMS (10 Hz, 4274; iTBS, 3638) were administered, without any seizures or other serious adverse events, and no significant differences in rates of premature discontinuation between groups. Dichotomous outcomes did not differ significantly between groups (Response/remission rates: Beck Depression Inventory-II: 10 Hz, 40.6%/29.2%; iTBS, 43.0%/31.0%. 17-item Hamilton Rating Scale for Depression: 10 Hz, 50.6%/38.5%; iTBS, 48.5%/27.9%). On continuous outcomes, there was no significant difference between groups in pre-treatment or post-treatment scores, or percent improvement on either measure. Mixed-effects modeling revealed no significant group-by-time interaction on either measure.
Conclusions: Both 10 Hz and iTBS DMPFC-rTMS appear safe and tolerable at 120% resting motor threshold. The effectiveness of 6 min iTBS and 30 min 10 Hz protocols appears comparable. Randomized trials comparing 10 Hz to iTBS may be warranted.
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Introduction

Repetitive transcranial magnetic stimulation (rTMS) is an emerging treatment for medication-resistant major depressive disorder (MDD), which affects approximately 2% of the population [1]. The most recent studies of rTMS in MDD have achieved fairly consistent response rates of 50–55% and remission rates of 30–35% in naturalistic case series and open-label trials [2–4]. However, although the first human studies of rTMS in MDD took place nearly 25 years ago [5,6], the optimal parameters of stimulation are still under investigation.

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; MDD, major depressive disorder; TRD, treatment-resistant depression; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; iTBS, intermittent theta burst stimulation; HamD17, 17-item Hamilton Depression Rating Scale; BDI-II, Beck Depression Inventory-II; MINI, Mini International Neuropsychiatric Interview; DSM, Diagnostic and Statistical Manual; FDR, false discovery rate.

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One key parameter is the stimulation target. The most widely used target for rTMS in MDD is the dorsolateral prefrontal cortex (DLPFC). However, convergent evidence from lesion, stimulation, neuroimaging, and connectivity studies also implicates a variety of other prefrontal regions in MDD [7,8]. Of these, the DMPFC has received the most attention to date. Recent case reports in MDD [9], case series in MDD and bipolar disorder [10,11], and studies in post-traumatic stress disorder [12] and eating disorders [13] have provided initial proof-of-concept evidence that DMPFC-rTMS may be safe, tolerable, and effective in MDD and other mood and anxiety disorders. However, as of this writing, it remains unclear whether DMPFC-rTMS matches or exceeds the effectiveness of conventional DLPFC stimulation overall, or indeed whether different sub-populations of MDD patients might respond preferentially to DMPFC- versus DLPFC-rTMS.

Another key parameter for optimization is the stimulation protocol itself. The most widely used protocol [14,15] applies 3000 pulses of 10 Hz stimulation to the left DLPFC over 37.5 min. However, lengthy protocols limit the number of patients who can be treated per day per device, which in turn obliges a high cost-per-session ($250–350 in many areas). A protocol with the same effectiveness but shorter duration (5–10 min) could permit up to five-fold increases in treatment capacity, which in turn would permit lower treatment charges. Such improvements would greatly facilitate wider affordability and adoption of rTMS as a mainstream treatment for MDD, as has been seen with other outpatient medical procedures (such as laser vision correction) where technical improvements allowed higher case volumes and lower per-procedure charges.

A promising form of patterned rTMS is theta-burst stimulation (TBS), which applies 50 Hz triplet bursts five times per second [16]. Intermittent theta burst stimulation (iTBS), on a 2 s on/8 s off cycle, delivers 600 pulses in just over 3 min. This pattern has been found to have an excitatory effect whose potency matches or exceeds much longer sessions of conventional rTMS [17]. If brief iTBS sessions could be shown to have equivalent antidepressant effectiveness to longer 10 Hz sessions, the translational implications for rTMS capacity and affordability would be tremendous.

To date, at least 2 case series have used some form of TBS in MDD, and each has demonstrated that TBS is safe, tolerable, and at least comparably effective to conventional stimulation [18,19]. More recently, 2 randomized controlled trials have demonstrated superior antidepressant efficacy of TBS over sham rTMS [20,21]. However, as of this writing, there has been no explicit comparison of the efficacy of iTBS versus conventional 10 Hz stimulation in MDD.

The definitive demonstration of non-inferiority for iTBS over 10 Hz rTMS will require a substantially larger patient sample and a randomized controlled design. However, in the interim, evidence from large-*N*, open-label case series may help to inform the design of future studies. As an example, several large open-label series have helped to establish the optimal course length for DLPFC-rTMS in the average range 26–28 sessions [2,22].

We have previously reported outcomes, and neuroimaging correlates of outcome, for two small case series of patients undergoing 10 Hz DMPFC-rTMS for a major depressive episode [10,11]. Here, we report data from a chart review of a larger series of 185 patients who received 20–30 sessions of open-label, add-on rTMS of the left and right DMPFC, delivered as either 10 Hz stimulation or iTBS, for treatment of a major depressive episode, over a 3-year period at a single high-volume clinic. Data from patients receiving DLPFC-rTMS will be reviewed in a subsequent work, due to an insufficient number of DLPFC cases available for analysis at present.

We hypothesized *a priori* based on previous observations [17] 1) that both 10 Hz and iTBS of the DMPFC would be safe, tolerable, and effective; 2) that iTBS would not differ significantly from 10 Hz DMPFC-rTMS in terms of effectiveness on self-reported or clinician-rated measures. In addition, based on previous observations [11], we hypothesized 3) that outcomes for DMPFC-rTMS would show a non-normal, bimodal distribution for both 10 Hz and iTBS; 4) that pre-treatment anhedonia symptoms would predict response to DMPFC-rTMS using either iTBS or 10 Hz stimulation.

Materials and methods

Chart review and patient population

This chart review encompassed data on stimulation parameters, tolerability, safety, and effectiveness on self- and clinician-rated symptom scales for every patient who received open-label, add-on rTMS of the bilateral DMPFC at the University Health Network's MRI-Guided rTMS Clinic between April 2011 and February 2014 for treatment of a major depressive episode, whether in the context or unipolar or bipolar illness. Throughout this period, this clinic accepted community referrals and offered treatment without charge to every referred patient free of pre-specified clinical contraindications to rTMS (active substance use disorders; psychotic disorders; neurological disorders; rTMS or MRI contraindications, including implanted devices, foreign ferromagnetic metal bodies, uncontrolled cardiac arrhythmias, unstable medical conditions, a history of epileptic seizures, traumatic brain injury or other central neurological abnormality, or pregnancy). The defined period for this retrospective case series ended with the onset of substantial recruitment volumes to a subsequent prospective randomized controlled trial, currently in progress.

Following referral, all patients completed the Mini International Neuropsychiatric Interview (MINI) 6.0 screen, and then underwent a full clinical psychiatric assessment (including multi-axial diagnosis) by a Canadian Royal College-certified psychiatrist (JD or PG) using DSM-IV criteria. Responses to the MINI screen were used to identify diagnostic categories for additional scrutiny during interview. All patients had a history of resistance to at least two adequate medication trials (including discontinuations due to adverse effects), and at least one trial in the current episode, based on clinical interview supplemented by medical and pharmacy records. To maximize the generalizability of the reported results to real-world practice, no co-morbidities were used as exclusion criteria in this chart review. Likewise, in order to better reflect clinical practice, treatment was offered to all patients with illness severe enough that they were willing to attend a course of at least 20 sessions of rTMS; thus, no *a priori* minimum threshold of symptom severity was applied. As a standard clinical practice, all patients were required to maintain a consistent regimen of medications for 4 weeks prior to treatment, and throughout the treatment course, to help disambiguate the source of any symptomatic improvement or decline. All patients provided informed consent for rTMS prior to initiating treatment, following UHN guidelines for clinical procedure consent. This chart review was approved by the Research Ethics Board of the University Health Network.

DMPFC-rTMS procedures

The neuronavigation, motor threshold, and coil placement procedures for DMPFC-rTMS, as practiced here, have been previously described in detail elsewhere [10,13]. rTMS was delivered using a MagPro R30 device equipped with a Cool D-B80 Coil (MagVenture, Farum, Denmark) and a Qooler high-performance cooling system, under MRI guidance using the Visor 2.0 system (Advanced Neuro Technologies, Enschede, Netherlands) in all cases. Stimulation targeted the left then right DMPFC at 120% of the resting motor

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