



# 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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**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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## 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.

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 of 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

threshold for extensor hallucis longus. All patients initially received 20 sessions of treatment; those who achieved response but not remission criteria were offered an additional 10 sessions. rTMS was administered one session per day, 5 days per week, for a total of 4–6 weeks. Missed sessions were added to the end of the treatment course to achieve the target number of sessions per course; no patient missed more than 4 cumulative sessions per course.

Each session of 10 Hz stimulation applied 3000 pulses to the left hemisphere then again to the right hemisphere (6000 pulses total), with a duty cycle of 5 s on and 10 s off, for a total stimulation time ~30 min. Each session of iTBS applied 600 pulses per hemisphere (1200 pulses total), for a total stimulation time ~6 min. As these treatments were provided in a clinical context rather than a research trial, patients were not randomly allocated. Instead, since both treatments were permissible under Health Canada regulations, treatment selection followed an informed consent discussion with the patient, incorporating factors such as the extent of the evidence base for safety and efficacy, tolerability, and wait time to begin treatment (wait times for iTBS were shorter due to the briefer appointments required), as well as the availability of more conventional alternatives to DMPFC-rTMS at public and private clinics in the same downtown Toronto area. For consistency, a single investigator (JD) conducted all such discussions.

#### Clinical assessments

A standard clinical practice was instituted for monitoring progress in all patients undergoing rTMS for major depression. Patients received baseline clinical assessments one week before treatment, interim clinical assessments after each five sessions of treatment, and follow-up clinical assessments 2, 4, 6, and 12 weeks after treatment. Clinical assessments included the 17-item Hamilton Rating Scale for Depression-17 (HamD<sub>17</sub>) [23] and the Beck Depression Inventory-II (BDI-II) [24]. Response was defined as ≥50% symptom reduction from pre- to post-treatment; remission criteria were set at a post-treatment score ≤7 for HamD<sub>17</sub>, ≤12 for BDI-II. Responder counts include remitters. The post-treatment score was defined as the first available follow-up clinical assessment in the window from 2 to 6 weeks post-treatment. Patients with missing pre-treatment scores were excluded from calculating response but not remission rates.

#### Data analysis

Data analysis methods are described in detail in the [Supplementary Material](#). Mixed-effects modeling, and kernel density estimation of the response distributions were performed in Stata 13 (StataCorp, College Station, Texas, USA). False discovery rate (FDR) correction, cumulative distribution function plotting, and the Kolmogorov–Smirnov and Shapiro–Wilk testing of the response distributions (in cases of non-normality) were calculated in MATLAB (Mathworks, Natick, Massachusetts, USA). All data are presented as mean ± standard deviation.

## Results

#### Demographic and clinical characteristics

A total of 185 patients underwent DMPFC-rTMS during the defined period (10 Hz,  $n = 98$ ; iTBS,  $n = 87$ ). The groups showed no differences in proportion of males versus females, proportion of unipolar versus bipolar illness, pre-treatment severity of illness on HamD<sub>17</sub> or BDI-II, length of current episode, number of previous episodes, or number of previous medication trials (Table 1). However, iTBS patients were significantly older than 10 Hz patients

(10 Hz,  $38.4 \pm 12.6$ ; iTBS,  $45.9 \pm 13.2$ ;  $t_{183} = 3.99$ ,  $P = 0.001$ , FDR-corrected).

#### rTMS treatment parameters

Treatment parameters are summarized in Table 1. The total number of stimulation runs performed in this series was 7912, applied bilaterally during 3956 sessions, in 185 unique patients (10 Hz: 4274 runs, 2137 sessions, 98 patients; iTBS: 3638 runs, 1819 sessions, 87 patients). Overall mean course length was  $21.4 \pm 4.7$  sessions, with no significant difference between groups (10 Hz,  $21.8 \pm 4.3$ ; iTBS,  $20.9 \pm 5.1$ ;  $t_{183} = 1.33$ ,  $P = 0.183$ ). Expressed in terms of maximum stimulator output, the mean stimulation intensity (120% of resting motor threshold) did not differ significantly between groups for either left DMPFC (10 Hz,  $64.6\% \pm 11.2\%$ ; iTBS,  $65.1\% \pm 10.3\%$ ;  $t_{183} = 0.35$ ,  $P = 0.724$ ) or right DMPFC (10 Hz,  $64.5\% \pm 11.0\%$ ; iTBS  $65.0\% \pm 10.3\%$ ;  $t_{183} = 0.29$ ,  $P = 0.770$ ).

#### Safety and tolerability

No seizures or other serious adverse events occurred in any patient during the period reviewed. Confidence interval estimation (via the adjusted Wald method) yields an estimated incidence rate range for seizure or other serious adverse events at 0.0002 per stimulation run (95% confidence interval (CI), 0–0.0008), 0.0005 per session (95% CI, 0–0.0015), and 0.010 per patient (95% CI, 0–0.323) for 10 Hz DMPFC-rTMS. For iTBS, the corresponding estimates are 0.0003 per stimulation run (95% CI, 0–0.0009), 0.0005 per session (95% CI, 0–0.0018), and 0.011 per patient (95% CI, 0–0.362).

The all-causes premature discontinuation rate for 10 Hz stimulation was 6 of 98 patients (6.1%). 1 patient quit at 10 sessions due to intolerable headaches, 2 patients quit at 18 sessions and 2 at 19 sessions due to lack of response, and 1 at 14 sessions due to excessive commute time to the clinic. The all-causes premature discontinuation rate for iTBS was 12 of 87 patients (13.8%). 2 patients quit at 9 and 16 sessions for intolerable headache, 1 at 11 sessions for intolerable vertigo, 1 at 19 sessions due to mood improvement complicated by increasingly hostile thoughts toward co-workers (but no manic symptoms), 2 at 11 and 19 sessions for lack of response, 3 at 4, 10, and 11 sessions due to excessive commute time, 2 at 16 and 18 sessions after achieving satisfactory gains, and 1 for reasons unspecified. The proportion of patients discontinuing due to adverse symptoms, lack of response, or unspecified reasons did not differ significantly between groups (10 Hz, 5/98; iTBS, 7/87;  $P = 0.552$ , Fisher's exact test). The proportion of patients discontinuing due to any adverse symptom (headache/vertigo/hostility) also did not differ significantly between groups (10 Hz, 1/98; iTBS, 4/87;  $P = 0.189$ , Fisher's exact test).

#### Treatment efficacy – dichotomous outcomes

Among patients for whom HamD<sub>17</sub> data was available, in the 10 Hz group, 42/83 (50.6%) achieved response and 37/96 (38.5%) achieved remission. In the iTBS group, 32/66 (48.5%) achieved response and 24/86 patients (27.9%) achieved remission. Among patients with BDI-II data, in the 10 Hz group, 39/96 (40.6%) achieved response and 28/96 (29.2%) achieved remission. In the iTBS group, 37/86 (43.0%) achieved response and 27/87 patients (31.0%) achieved remission. There was no significant difference in rates of response or remission between groups on either measure (Table 2).

Combining available data from both groups, on the HamD<sub>17</sub>, 74/149 (49.7%) achieved response, and 61/182 (33.5%) achieved remission overall. On the BDI-II, 76/182 (41.8%) achieved response

**Table 1**  
Demographic and clinical characteristics and treatment parameters for patients undergoing 10 Hz and iTBS DMPFC-rTMS.

	Overall	10 Hz	iTBS	<i>t</i>	<i>P</i>	<i>P</i> (FDR)
Total sessions	3956	2137	1819	–	–	–
# patients	185	98	87	–	–	–
Female	127	70	57	–	0.429	0.770
Bipolar	29	17	12	–	0.549	0.770
Age	41.9 ± 13.4	38.4 ± 12.6	45.9 ± 13.2	3.99	>0.001	0.001
Pre-treatment HamD <sub>17</sub>	21.7 ± 6.2	22.1 ± 6.9	21.1 ± 5.1	1.03	0.303	0.770
Pre-treatment BDI-II	35.6 ± 10.4	35.4 ± 10.8	35.9 ± 9.9	0.34	0.733	0.770
Length of current episode (months)	41.4 ± 61.2	39.8 ± 53.1	42.9 ± 68.1	0.31	0.755	0.770
# previous episodes	4.6 ± 8.8	4.1 ± 8.3	4.9 ± 9.2	0.40	0.689	0.770
# previous medication trials	6.2 ± 3.9	5.9 ± 3.9	6.5 ± 3.9	0.89	0.375	0.770
# sessions/course	21.4 ± 4.7	21.8 ± 4.3	20.9 ± 5.1	1.33	0.184	0.770
Stimulation intensity (Left)	64.8% ± 10.8%	64.6% ± 11.2%	65.1% ± 10.3%	0.35	0.724	0.770
Stimulation intensity (Right)	64.8% ± 10.6%	64.5% ± 11.0%	65.0% ± 10.3%	0.29	0.770	0.770

FDR, false discovery rate; iTBS, intermittent theta burst stimulation; HamD<sub>17</sub>, 17-item Hamilton Depression Rating Scale; BDI-II, Beck Depression Inventory-II. Values indicate mean ± standard deviation. *P*-values are for two-sample *t*-statistics for continuous variable comparisons and for Fisher's exact test for proportion comparisons.

and 55/183 (30.1%) achieved remission overall. Denominator variations above reflect missing values.

#### Treatment efficacy – continuous outcomes

On the HamD<sub>17</sub>, symptoms improved from 22.4 ± 6.5 to 12.3 ± 8.9 (decreasing 44.3% ± 35.5%) in the 10 Hz group and from 21.1 ± 5.1 to 12.7 ± 7.9 (decreasing 43.6% ± 35.6%) in the iTBS group (Fig. 1A). The mixed-effects model revealed a significant main effect of time ( $z = -5.90$ ,  $P < 0.001$ ) but not of group ( $z = -0.01$ ,  $P = 0.994$ ). Notably, the group by time interaction was non-significant ( $z = -0.72$ ,  $P = 0.473$ ). There was also no significant difference in pre-treatment, post-treatment scores or percent improvement between groups (Table 3).

Likewise, on the BDI-II, symptoms improved from 35.3 ± 10.8 to 22.4 ± 15.5 (decreasing 38.4% ± 36.6%) in the 10 Hz group and from 35.9 ± 9.9 to 20.2 ± 13.3 (decreasing 42.6% ± 32.2%) in the iTBS group (Fig. 1B). Here again, the mixed-effects model revealed a significant main effect of time ( $z = -9.02$ ,  $P < 0.001$ ) but not of group ( $z = 0.11$ ,  $P = 0.910$ ). The group by time interaction was also non-significant ( $z = 1.84$ ,  $P = 0.066$ ) and trending in favor of iTBS over 10 Hz stimulation. There was no significant difference in pre-treatment, post-treatment BDI-II scores or percent improvement between groups (Table 3).

On further examination, the Shapiro–Wilk test revealed a significantly non-normal distribution of outcomes in both the 10 Hz group (HamD<sub>17</sub>:  $W = 0.958$ ,  $P = 0.010$ ; BDI:  $W = 0.973$ ,  $P = 0.042$ ) and the iTBS group (HamD<sub>17</sub>:  $W = 0.969$ ,  $P = 0.093$ ; BDI:  $W = 0.957$ ,  $P = 0.007$ ); the HamD<sub>17</sub> distribution in the iTBS group trended toward non-normality without reaching significance. On inspection of the kernel density estimates for each group and each measure, the distribution appeared trimodal in most cases, with a distinct non-responder and responder subgroup as well as intermediate, partial responder subgroup (Fig. 2).

In light of the non-normal distributions of outcomes, we also performed a non-parametric (two-sample Kolmogorov–Smirnov) comparison of the cumulative distribution functions for the degree of improvement across all subjects in each group. Once again, there was no significant difference between 10 Hz and iTBS outcomes on either the HamD<sub>17</sub> ( $D = 0.07$ ,  $P = 0.991$ ) or BDI-II ( $D = 0.108$ ,  $P = 0.646$ ) (Fig. 3).

Finally, due to the non-normal distributions of outcomes, in order to rule out the possibility of subtle differences in the effectiveness of 10 Hz versus iTBS that might be apparent in responders alone, we separated the responder and non-responder individuals, then repeated the mixed-effects model analysis using only the responder patients (Fig. 4). Once again, on the HamD<sub>17</sub>, the

responder subgroup showed a significant main effect of time ( $z = -7.70$ ,  $P < 0.001$ ) but not of group ( $z = -1.00$ ,  $P = 0.316$ ), and the group by time interaction was also non-significant ( $z = -0.11$ ,  $P = 0.914$ ). On the BDI-II, the responder subgroup showed a significant main effect of time ( $z = -10.4$ ,  $P < 0.001$ ), and a significant main effect of group with the iTBS group showing slightly more severe illness in general ( $z = -2.05$ ,  $P = 0.041$ ). Here the group by time interaction showed a small but significant effect in favor of iTBS over 10 Hz stimulation ( $z = 2.35$ ,  $P = 0.019$ ).

#### Predictors of outcome

Demographic, clinical, and rTMS parameter predictors of outcome are presented in Table 4. Neither the 10 Hz group, nor the iTBS group, nor the combined set of both groups showed any significant correlation (post-FDR-correction) between percent improvement on the HamD<sub>17</sub> and any of the following variables: age, sex, unipolar/bipolar illness, pre-treatment HamD<sub>17</sub> or BDI score, length of current episode, number of previous episodes, number of previous medication trials, number of treatment sessions, or stimulation intensity. We also examined each individual item on the pre-treatment HamD<sub>17</sub> and BDI-II scales for correlation to improvement on the HamD<sub>17</sub> post-treatment (Tables S1–S3, Supplementary Material). Across all patients, only BDI-Pessimism ( $P = 0.047$ ) and BDI-Indecisiveness (0.024) significantly correlated to HamD<sub>17</sub> outcome following FDR-correction.

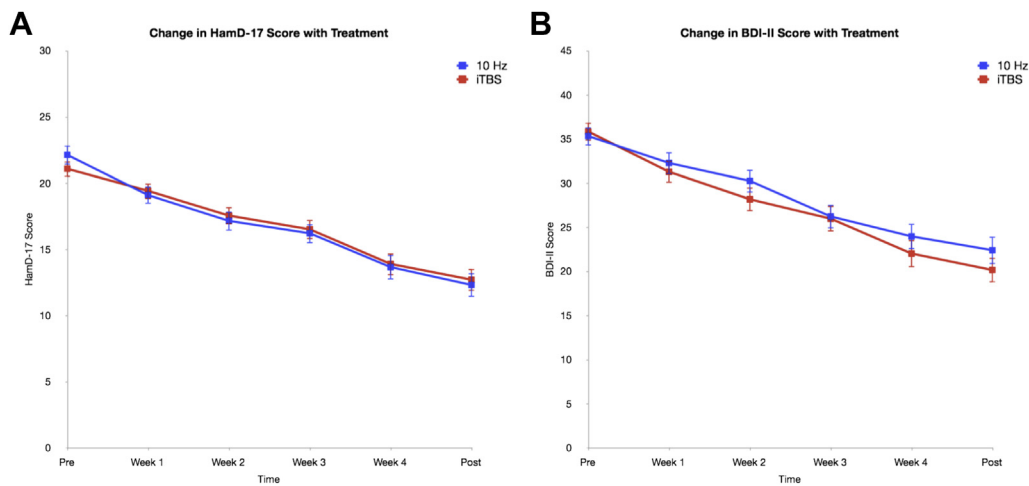
## Discussion

To our knowledge, this case series of 185 patients is the largest thus far reported for patients receiving DMPFC-rTMS for a major depressive episode. Consistent with our first hypothesis, both iTBS and 10 Hz stimulation appear to be safe and well tolerated, with no serious adverse events in >7900 stimulation runs, and no

**Table 2**  
Dichotomous outcomes for patients undergoing 10 Hz and iTBS DMPFC-rTMS.

	Overall	10 Hz	iTBS	<i>P</i>
HamD <sub>17</sub>				
Response	74/149 (49.7%)	42/83 (50.6%)	32/66 (48.5%)	0.869
Remission	61/182 (33.5%)	37/96 (38.5%)	24/86 (27.9%)	0.157
BDI-II				
Response	76/182 (41.8%)	39/96 (40.6%)	37/86 (43.0%)	0.765
Remission	55/183 (30.1%)	28/96 (29.2%)	27/87 (31.0%)	0.872

FDR, false discovery rate; iTBS, intermittent theta burst stimulation; HamD<sub>17</sub>, 17-item Hamilton Depression Rating Scale; BDI-II, Beck Depression Inventory-II. *P*-values are for Fisher's exact test comparing the 10 Hz and iTBS outcomes.



**Figure 1.** Change in symptom severity over the course of treatment for patients receiving DMPFC-rTMS, using a 30-min 10 Hz ( $n = 98$ , blue) or a 6 min iTBS ( $n = 87$ , red) protocol, on the HamD17 (A) and the BDI-II (B) symptom scales. Mixed-effects modeling revealed a significant main effect of time ( $P < 0.001$ ) but not of group ( $P = 0.994$ ), and no significant group by time interaction (0.473) on the HamD17. The same was true for the main effect of time ( $P < 0.001$ ), group ( $P = 0.910$ ), and the group by time interaction ( $P = 0.066$ ) on the BDI-II. HamD17, 17-item Hamilton rating scale for depression; BDI-II, Beck Depression Inventory-II. iTBS, intermittent theta burst stimulation.

significant differences between groups in rates of discontinuation due to adverse effects. The safety profile of iTBS is particularly notable given that it was administered at the same stimulation intensity as 10 Hz rTMS: 120% of resting motor threshold for lower extremity movements. Not only is the motor threshold for the lower extremity approximately some 50% higher than for the upper extremity, but the multipliers commonly used for iTBS are also typically much lower: i.e., 80% of active (not resting) motor threshold [16,17,25,26]. This much lower intensity was also used in the most recent trials of TBS targeting DLPFC in major depression [20,21]. However, the absence of seizures or other adverse events, and equivalent tolerability across 3638 runs of stimulation in 87 individuals suggests that iTBS might be safely performed at the same intensity as 10 Hz stimulation, at least for the DMPFC target.

Regarding effectiveness, in keeping with our second hypothesis, iTBS matched or exceeded the effectiveness of 10 Hz stimulation on

both clinician and self-rated measures, despite requiring 5-fold fewer pulses and time to administer. The pace of improvement over time was also equal (or significantly better) for iTBS versus 10 Hz stimulation. Although patients were not prospectively randomized in this naturalistic series, there were no significant differences in demographic or clinical characteristics between groups, aside from higher age in the iTBS group. Thus, it is unlikely that the equivalent effectiveness of iTBS in this series can be accounted for solely in terms of less severe or less refractory illness in the iTBS versus the 10 Hz group.

As hypothesized, the distribution of outcomes was significantly non-normal on 3 out of the 4 plots and trending to non-normality on the fourth. Although our previous study of 10 Hz DMPFC-rTMS found a bimodal outcome distribution [11], the present series identified a more complex response distribution, appearing closer to trimodal across all 4 combinations of measures and interventions. In addition to responder and non-responder subgroups, each of the kernel density estimates revealed signs of an intermediate “partial responder” group, with a peak around 50–60% improvement, more apparent on self-report than clinician ratings (Fig. 2).

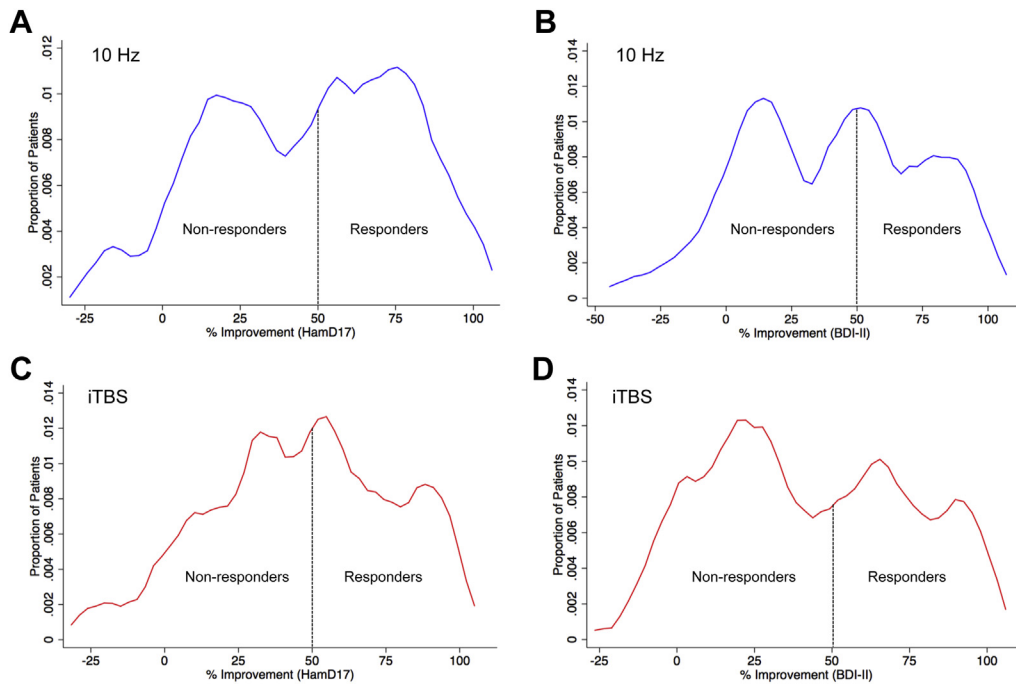
We have previously found that the response to 10 Hz DMPFC-rTMS could be predicted by anhedonia-related symptoms: pessimism, loss of pleasure, and loss of interest [11]. In this larger series, only BDI-Pessimism and BDI-Indecisiveness showed a significant correlation to HamD<sub>17</sub> outcome in the combined sample after correction for multiple comparisons (Supplementary Tables S1–S3). No single item, and no clinical or demographic feature, significantly predicted outcome in both groups independently. Thus, this larger sample did not confirm the utility of anhedonia symptoms, or any other clinical features, for predicting treatment outcome across 10 Hz or iTBS DMPFC-rTMS independently.

The original rationale for pursuing rTMS of the DMPFC rather than the conventional DLPFC was to achieve better outcomes by targeting a region potentially more central to depression pathophysiology [7,27–29]. However, the present case series yielded overall response and remission rates of 49.7% and 33.5% (HamD<sub>17</sub>), and 41.8% and 30.0% (BDI-II). These rates are not, in fact, superior to rates reported in other open-label series using DLPFC-rTMS: 41.2% and 35.3% in  $n = 85$  [4], 51.6% and 34.4% in  $n = 93$  [3], 41.0% and 30.5% in  $n = 141$  [22], and 58.0% and 37.1% in  $n = 307$  [2]. This may indicate that DMPFC-rTMS offers no efficacy advantages over

**Table 3**  
Continuous outcomes for patients undergoing 10 Hz and iTBS DMPFC-rTMS.

	10 Hz	iTBS	<i>t</i>	<i>P</i>
All patients				
Pre-treatment				
HamD17	22.1 ± 6.9	21.1 ± 5.1	1.03	0.303
BDI-II	35.4 ± 10.8	35.9 ± 9.9	0.34	0.733
Post-treatment				
HamD17	12.3 ± 8.9	12.7 ± 7.9	0.32	0.750
BDI-II	22.4 ± 15.5	20.2 ± 13.3	1.03	0.307
% improvement				
HamD17	44.3% ± 35.5%	43.6% ± 35.6%	0.12	0.905
BDI-II	38.4% ± 36.6%	42.6% ± 32.2%	0.82	0.415
Responders only				
Pre-treatment				
HamD17	20.8 ± 6.9	21.3 ± 4.9	0.35	0.729
BDI-II	32.0 ± 11.2	36.5 ± 8.0	2.01	0.049
Post-treatment				
HamD17	5.7 ± 3.8	6.0 ± 3.9	0.33	0.740
BDI-II	14.1 ± 10.9	11.3 ± 7.6	1.29	0.200
% improvement				
HamD17	71.4% ± 18.2%	72.4% ± 16.2%	0.25	0.807
BDI-II	55.4% ± 29.3%	67.9% ± 22.3%	2.08	0.041

FDR, false discovery rate; iTBS, intermittent theta burst stimulation; HamD<sub>17</sub>, 17-item Hamilton Depression Rating Scale; BDI-II, Beck Depression Inventory-II. Values indicate mean ± standard deviation.

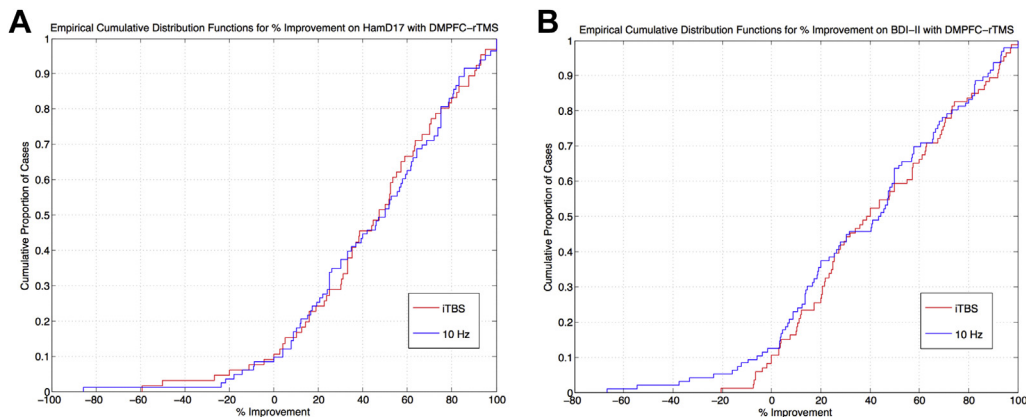


**Figure 2.** Kernel density estimates of the distributions of outcomes (expressed as percentage improvement from pre-treatment to first post-treatment follow-up) in patients receiving 10 Hz stimulation on HamD17 (A) and BDI-II (B) measures, and in patients receiving iTBS on HamD17 (C) and BDI-II (D) measures. HamD17, 17-item Hamilton rating scale for depression; BDI-II, Beck Depression Inventory-II. iTBS, intermittent theta burst stimulation.

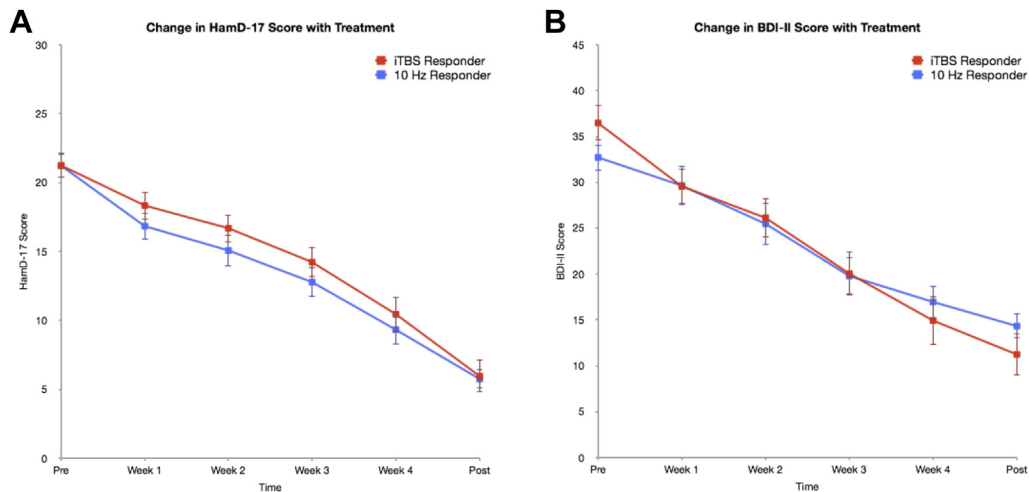
DLPFC-rTMS. Alternatively, broad access to treatment in this series may have allowed inclusion of patients with more refractory illness. It is also possible that DMPFC-rTMS and DLPFC-rTMS treat two different but roughly equal-sized subpopulations of MDD patients. Resolution of these issues must await a randomized trial comparing the two techniques directly.

The present report carried several important limitations. First, patients were not allocated randomly or prospectively, leaving open the possibility that some systematic allocation bias may have made the treatments appear more similar in efficacy than they are in reality. Second, the target of stimulation was the DMPFC rather than the standard DLPFC, leaving open the possibility that the findings may not generalize to the much more widely used DLPFC target. Likewise, because of the insufficient number of patients receiving

DLPFC stimulation at the clinic during the reviewed period, the present study does not allow for a comparison of outcomes for DLPFC- versus DMPFC-rTMS, whether unilateral or bilateral. Finally, the patient sample in this study was more broadly inclusive than in most randomized controlled trials of rTMS. Although the broad inclusion criteria were intended to make the findings more generalizable to real-world practice, the resultant heterogeneity may have obscured some potentially relevant predictors of outcome. Thus, in a more clinically homogenous sample, several of the clinical, demographic, and symptom items surveyed in this study could prove to be more reliable outcomes predictors. In particular, the lack of a structured assessment of medication resistance (e.g., the Antidepressant Treatment History Form) in the available clinical data may have obscured the role of medication resistance in



**Figure 3.** Empirical cumulative distribution function plots comparing the outcomes (expressed as percentage improvement from pre-treatment to first post-treatment follow-up) in patients receiving 10 Hz stimulation versus iTBS on HamD17 (A) and BDI-II (B) measures. Kolmogorov–Smirnov test revealed no significant differences in these distributions on either the HamD17 ( $P = 0.991$ ) or the BDI-II ( $P = 0.646$ ). HamD17, 17-item Hamilton rating scale for depression; BDI-II, Beck Depression Inventory-II. iTBS, intermittent theta burst stimulation.



**Figure 4.** Change in symptom severity over the course of treatment for responder patients only ( $\geq 50\%$  improvement), using a 30-min 10 Hz ( $n = 98$ , blue) or a 6 min iTBS ( $n = 87$ , red) protocol, on the HamD17 (A) and the BDI-II (B) symptom scales. Mixed-effects modeling revealed a significant main effect of time but not of group, and no significant group by time interaction, on the HamD17. On the BDI-II, there was a significant effect of time ( $P < 0.001$ ), and of group ( $P = 0.041$ ) with more severe illness in the iTBS group, and a significant group by time interaction favoring iTBS over 10 Hz rTMS ( $P = 0.019$ ). HamD17, 17-item Hamilton rating scale for depression; BDI-II, Beck Depression Inventory-II. iTBS, intermittent theta burst stimulation.

predicting outcome. Previous authors have identified a variety of DLPFC-rTMS outcome predictors: age and number of previous failed medication trials [30], episode duration [31], extraversion [32], sleep disturbance [33], apathy symptomatology [34], and HamD<sub>17</sub> items for depressed mood and guilt [35]. A prospective study with more rigidly defined inclusion criteria, and more structured assessment of medication resistance, could reveal whether these predictors apply to DMPFC-rTMS as well.

Regarding future directions, the present findings are supportive for proceeding to a randomized trial comparing 3 min iTBS to the standard 37.5 min 10 Hz protocol [14,15] at the conventional left DLPFC target. Even if iTBS proved merely non-inferior to conventional stimulation, this would still allow up to a five-fold increase in capacity and decrease in cost-per-session, on existing infrastructure. iTBS could potentially reduce the cost of rTMS to under \$1000 for 20 sessions, while expanding the capacity of each clinic to >25 patients/device/day. Less expensive, higher-throughput protocols would constitute a major step forward toward widespread adoption of rTMS as a mainstream alternative/adjunct to medications and psychotherapy in MDD patients.

Another important follow-up study would involve a randomized comparison of DMPFC and DLPFC stimulation. Ideally, such a study would characterize individual patients as comprehensively as

possible prior to treatment, using clinical and behavioral measures as well as biological markers such as neuroimaging, electrophysiological, and genomic studies. These data would be essential for addressing whether DLPFC- and DMPFC-rTMS treat similar or distinct subpopulations of MDD patients. If the latter case, these data could also prove useful in identifying predictive biomarkers to guide the choice of stimulation target in individual patients presenting for rTMS treatment.

## Conclusions

The parameters of rTMS are still being optimized, nearly 20 years after the first use of the technique. The present study suggests that DMPFC-rTMS can be performed safely and tolerably at high stimulation intensities, and that 3 min iTBS protocols may match the efficacy of much longer 10 Hz protocols. The overall effectiveness of DMPFC-rTMS appears comparable to, but not markedly superior to, standard DLPFC-rTMS. Randomized trials comparing iTBS versus 10 Hz stimulation, and DMPFC- versus DLPFC-rTMS, will provide a more rigorous test of which techniques can achieve optimal outcomes, both in MDD in general, and in individual patients.

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## Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.brs.2014.11.002>.

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**Table 4**  
Demographic, clinical and treatment parameter predictors of outcome.

	10 Hz		iTBS		All patients	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Age	>0.001	0.998	0.223	0.072	0.091	0.272
Female	−0.008	0.946	0.160	0.199	0.069	0.405
Bipolar	0.083	0.456	−0.028	0.821	0.039	0.633
Pre-treatment HamD <sub>17</sub>	−0.089	0.426	0.030	0.811	−0.042	0.612
Pre-treatment BDI-II	−0.275	0.012	−0.038	0.763	−0.176	0.032
Length of current episode	−0.199	0.118	0.050	0.705	−0.062	0.500
# previous episodes	−0.210	0.233	0.154	0.314	0.082	0.474
# previous medication trials	−0.082	0.483	0.044	0.752	−0.038	0.670
# sessions	0.113	0.310	0.156	0.212	0.133	0.106
Stimulation intensity (left)	−0.023	0.837	−0.042	0.737	−0.031	0.709
Stimulation intensity (right)	−0.019	0.867	−0.085	0.496	−0.048	0.568

FDR, false discovery rate; iTBS, intermittent theta burst stimulation; HamD<sub>17</sub>, 17-item Hamilton Depression Rating Scale; BDI-II, Beck Depression Inventory-II.

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