

Subthreshold stimulation intensity is associated with greater clinical efficacy of intermittent theta-burst stimulation priming for Major Depressive Disorder

Jonathan C. Lee ^{a,*}, Juliana Corlier ^a, Andrew C. Wilson ^a, Reza Tadayonnejad ^{a, b}, Katharine G. Marder ^a, Doan Ngo ^a, David E. Krantz ^a, Scott A. Wilke ^a, Jennifer G. Levitt ^a, Nathaniel D. Ginder ^{a, c}, Andrew F. Leuchter ^a

^a TMS Clinical and Research Service, Neuromodulation Division, Semel Institute for Neuroscience and Human Behavior, And the Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, 760 Westwood Plaza, Los Angeles, CA, 90024, USA

^b California Institute of Technology, Division of the Humanities and Social Sciences, 1200 E California Blvd, Pasadena, CA, 91125, USA

^c VA Greater Los Angeles Healthcare System, 11301 Wilshire Blvd, Los Angeles, CA, 90073, USA

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ABSTRACT

Background: Intermittent theta-burst stimulation priming (iTBS-P) can improve clinical outcome of patients with Major Depressive Disorder (MDD) who do not show early benefit from 10 Hz stimulation of left dorsolateral prefrontal cortex (DLPFC), also known as high-frequency left-sided (HFL) stimulation. The intensity and pulse number for iTBS-P needed to induce clinical benefit have not been systematically examined.

Objective: To study the effect of intensity and pulse number on the clinical efficacy of iTBS-P.

Methods: We conducted a retrospective review of 71 participants who received at least five sessions of HFL with limited clinical benefit and received iTBS-P augmentation for between 5 and 25 sessions. Intensity of iTBS-P priming stimuli ranged from 75 to 120% of motor threshold (MT) and pulse number ranged from 600 to 1800. Associations among intensity, pulse number, and clinical outcome were analyzed using a mixed methods linear model with change in IDS-SR as the primary outcome variable, priming stimulation intensity (subthreshold or suprathreshold), pulse number (<1200 or >1200 pulses), and gender as fixed factors, and number of iTBS-P treatments and age as continuous covariates.

Results: Subjects who received subthreshold intensity iTBS-P experienced greater reduction in depressive symptoms than those who received suprathreshold iTBS-P ($p = 0.011$) with no effect of pulse number after controlling for stimulus intensity.

Conclusions: Subthreshold intensity iTBS-P was associated with greater clinical improvement than suprathreshold stimulation. This finding is consistent with iTBS-P acting through homeostatic plasticity mechanisms.

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Introduction

Repetitive Transcranial Magnetic Stimulation (rTMS) of the left dorsolateral prefrontal cortex (DLPFC) is an established non-invasive brain stimulation treatment for Major Depressive Disorder (MDD). Both 10 Hz (high-frequency left, or HFL rTMS) and intermittent theta burst stimulation (iTBS) are thought to induce

synaptic plasticity and long-term potentiation (LTP) [1]. These approaches yield response rates between 40 and 50% and remission rates of up to 30% [2–5], leaving room for improvement.

Few studies have examined methods to improve rTMS efficacy for patients who do not respond to HFL rTMS or iTBS. Traditional attempts to optimize rTMS outcomes in research contexts have focused on adjusting treatment parameters by enhancing accuracy

* Corresponding author. 760 Westwood Plaza, 57-464, Los Angeles, CA, 90024, USA.
E-mail address: jonchlee@gmail.com (J.C. Lee).

of targeting the left DLPFC [6–8], extending the number of pulses or treatment sessions [9,10], sequential bilateral (SBL rTMS) stimulation [11,12] or accelerated rTMS [13,14], putatively inducing neural plastic changes with each treatment [15].

Priming offers a potential alternative augmentation strategy [16]. Compared to SBL rTMS or accelerated rTMS, priming stimulation is a well-tolerated approach [5] that enhances rTMS-induced neural plasticity with little additional time, burden, and cost. Based upon results of preclinical studies of the motor system, priming uses a brief stimulus that is thought to lack independent therapeutic effects, and renders the cortex more receptive to the effects of a subsequent conditioning protocol [17,18].

Several different rTMS priming paradigms have been examined in clinical contexts. Fitzgerald et al. [19] first applied a priming approach to the treatment of depression over the right DLPFC. They found subjects receiving a brief, subthreshold 6 Hz priming stimulation prior to 1 Hz low-frequency stimulation of the right DLPFC (low-frequency right, or LFR rTMS) for four weeks experienced greater improvement in Montgomery-Asberg Depression Rating Scale scores compared to those receiving LFR rTMS alone. More recently, Lefaucheur et al. [20] applied subthreshold iTBS as a priming stimulus over the motor cortex prior to a HFL treatment protocol in patients with chronic pain. Subjects who received iTBS priming (iTBS-P) prior to their pain protocol experienced more analgesia than those who received continuous theta-burst priming or no priming at all. Our group first examined iTBS-P augmentation of HFL in 17 subjects with MDD, delivering 600 pulses of iTBS (2s duration, 8s intertrain interval at up to 120% MT) immediately before standard HFL rTMS [21]. We found that among patients who failed to achieve a 20% decrease in depressive symptoms after two weeks of HFL rTMS [21], those who switched to an iTBS-P paradigm showed significantly better treatment response than those who received HFL rTMS or SBL rTMS treatment for the remainder of their 30 treatment sessions. In the present study, we include data from these patients as well as an additional 54 patients who have since received iTBS-P in our clinic.

There are two mechanisms through which priming is hypothesized to occur: *neuronal gating* or *homeostatic plasticity* [18,22]. According to neuronal gating theory, the priming stimulus determines outcome of the conditioning protocol – whether long-term potentiation (LTP) or long-term depression (LTD) – by inducing an excitatory or inhibitory state in the post-synaptic neurons [23]. If the priming stimulus induces an excitatory state in the postsynaptic neurons, it is believed to remove voltage-gated magnesium blocks on NMDA receptors, leading to greater calcium influx, and, accordingly, greater LTP in response to the conditioning stimulus. If the priming stimulus is inhibitory, however, the voltage gated channels are thought to remain closed, and the same conditioning stimulus is thought to induce an LTD-like response. According to gating theory, one might anticipate a highly excitatory priming stimulus to be more effective at inducing LTP.

Homeostatic plasticity has been proposed as an alternative priming mechanism [23,24]. According to the Bienenstock-Cooper-Munro theorem [17], the threshold for LTP induction by a conditioning stimulus depends on the preceding level of activation of the postsynaptic neuron [23]. Therefore, a suprathreshold priming stimulus that activates postsynaptic neurons is thought to raise the threshold of activation required for subsequent conditioning stimulus to induce LTP. Conversely, a subthreshold priming stimulus that has temporarily lowered postsynaptic activity, lowers the threshold of activation required of a conditioning stimulus to induce LTP in the same postsynaptic neuron. According to this perspective, subthreshold iTBS priming may enhance the relative effect of a subsequent conditioning protocol (i.e. HFL rTMS) by lowering the threshold of LTP induction.

The optimal parameters for iTBS-P for MDD have not been systematically studied. It is unclear whether treatment outcome is impacted by the intensity of the priming stimulus or the number of priming pulses delivered. If iTBS-P efficacy is attributable simply to the addition of greater treatment time per day, as performed in an “accelerated” rTMS approach [13,14,25,26] – whereby multiple independently therapeutic treatment protocols are administered in succession – we might anticipate priming stimuli with greater intensity and pulse number to be more efficacious. If iTBS-P enhances efficacy through a true priming effect, it is unclear whether the gating or homeostatic plasticity models best explain outcomes. If iTBS-P acts through gating, we would anticipate that subjects who received both iTBS and HFL rTMS at suprathreshold intensity (i.e., 120% MT) would fare better than those receiving subthreshold iTBS-P. If homeostatic plasticity is responsible for iTBS-P's effects, those receiving subthreshold should fare better than those receiving suprathreshold iTBS-P.

In this study, we examined whether iTBS-P intensity or pulse number were associated with better clinical outcome in subjects who failed to show early benefit from HFL rTMS stimulation of left DLPFC.

Material and methods

Study design

This was a retrospective review of patients receiving measurement-based care (in which protocol changes are made according to improvement thresholds achieved on standardized assessments) in the UCLA TMS Research and Clinical Service, from November 2018 to January 2021. Weekly self-ratings of depression severity were collected using standardized questionnaires (i.e. IDS-SR). Treatment approaches are routinely assessed at treatment 10 and 20, with changes in treatment protocol made according to a predefined treatment algorithm. This study was approved by the UCLA IRB for use of retrospective, anonymized clinical data.

Study subjects

All subjects had a primary diagnosis of non-psychotic MDD confirmed on the MINI International Diagnostic Interview (MINI) at intake assessment [27]. All subjects had failed at least three antidepressant medication trials of adequate dose and duration, one augmentation strategy, and one evidence-based psychotherapy before initiating rTMS. Subjects were not offered rTMS if they had any history of cardiac pacemaker, cochlear implant, deep brain stimulator, unprovoked seizure, unstable neurological disorder, or uncontrolled substance use disorder. All subjects completed assessments using the Inventory of Depressive Symptomatology Self-Report (IDS-SR) at weekly intervals beginning at pre-treatment baseline until treatment 30 [28]. IDS-SR scores correlate highly with other self-rated measures of depression severity such as the Beck Depression Inventory (BDI-II) [29] and clinician-rated measures such as the Hamilton Rating Scale for Depression (HAM-D-17) [30] and the MADRS [31]. Subjects continued to take any medications as directed by their outpatient psychiatrist and were instructed to avoid starting, stopping, or adjusting the dosage of psychotropic medications during the course of rTMS treatment. The majority of patients maintained constant medication regimens during the course of treatment, but detailed week-by-week dosing data on all study subjects were not available. We included data from patients who received at least eight iTBS-P sessions during their treatment course as previous work has established that 80% of the maximal clinical benefit of iTBS-P occurs after a minimum of eight sessions [21].

rTMS treatment

All rTMS treatments were delivered with either a MagPro X100 (Magventure, Farnum, Denmark), Magstim Horizon (Magstim, Whitland, UK), or Magstim Super Rapid² (Magstim, Whitland, UK) device. We determined the resting motor threshold (RMT) – defined as the minimum stimulus intensity necessary to elicit an overt motor response in the right abductor pollicis brevis for $\geq 50\%$ of applied stimuli – for each subject before the first treatment. Subjects received 30 rTMS treatment sessions beginning with HFL rTMS, consisting of 10 Hz stimulation (4-s trains, 26-s intertrain intervals, 75 trains and 3000 pulses total) lasting 37.5 min daily to L-DLPFC using the Beam F3 localization method [6]. We increased HFL rTMS intensity to 120% RMT as tolerated over the first three treatments.

rTMS was delivered using a measurement-based care paradigm described previously [21,32] in which change in depression severity scores obtained after every five treatments were used to modify treatment parameters. Feffer et al. [33] showed that patients who did not improve at least 20% by treatment 10 were very likely to be non-responders at the end of a six-week treatment course (negative predictive value [NPV] > 85%). iTBS-P augmentation was offered as a treatment option typically after ten sessions of HFL rTMS if subjects showed <20% decrease in symptoms from baseline by treatment, or earlier if in the clinical judgment of the treating psychiatrist a patient might benefit from such a change. Subjects treated during the initial 24 months of the study period generally received 600 iTBS-P pulses per Huang et al. [34] at subthreshold (80–90% MT) intensity, titrated (if at all) over the first week after initiating iTBS-P, immediately before HFL rTMS. Li et al. [35] subsequently found that up to 1800 pulses of iTBS delivered at 120% MT could be effective for MDD [35]. We also delivered higher iTBS pulse number (1200–1800) and suprathreshold intensities (110–120% MT) as tolerated, with intensity and pulse number titrated as tolerated over one week.

Data analysis

Data analyses were performed using SPSS, version 27 with two-tailed tests, and an alpha level of 0.05. Response was defined as a $\geq 50\%$ improvement in IDS-SR score from pretreatment baseline to final assessment. Remission was defined as a final IDS-SR score ≤ 13 .

The mean iTBS-P intensity and pulse number were calculated within subjects across all of their iTBS-P sessions. Subjects were categorized as receiving “subthreshold” (<100% MT treatment intensity) or “suprathreshold” ($\geq 100\%$ MT) priming stimulation based on their mean iTBS-P stimulus intensity. Subjects were also categorized by pulse number (i.e. <1200 pulses or >1200 pulses) based on the mean number of priming pulses they received over their treatment course. Potential baseline group differences in age at first HFL rTMS treatment, baseline IDS-SR score, and total number of iTBS-P sessions were tested with independent samples *t*-tests. Differences in gender, medications, and response and remission rates between groups were assessed with a chi-square analysis.

We fit a linear mixed methods (LMM) model with IDS-SR score as the primary outcome variable with fixed effects of intensity, pulse number, and gender. Number of iTBS-P sessions and age at first rTMS treatment were entered as covariates. Multiple imputation (with a linear regression approach) was employed to generate missing IDS-SR scores for the LMM analysis. All other means and standard deviations were calculated using available data from the original (non-imputed) data set.

We subsequently conducted a sensitivity analysis using the original (non-imputed) data set and a general linear model (GLM)

entering pulse number, intensity, and gender as between-subjects factors and number of iTBS-P treatments and age at first treatment as continuous covariates.

Results

71 patients (age 45.4 ± 16.4 , range 17–72) received HFL rTMS and at least eight subsequent sessions of iTBS-P for MDD. All patients offered iTBS-P elected to proceed with this augmentation strategy. Four patients (6%) were offered iTBS-P before session 8 based on the clinical judgment of the treating psychiatrist. Eight patients (11%) received between 8 and 9 HFL rTMS sessions before iTBS-P augmentation. The remaining 59 (83%) received 10 or more HFL rTMS sessions before iTBS-P was introduced. Mean baseline IDS-SR score of the total sample was 43.1 ± 10.4 . Subjects received a mean of 12.5 ± 4.2 (range 5–22) HFL rTMS treatment sessions before receiving a mean of 16.5 ± 4.7 (range 8–25) iTBS-P sessions during their treatment courses. There was no statistically significant difference in final IDS-SR score between those who received <10 or ≥ 10 HFL sessions before receiving iTBS-P. IDS-SR data were missing for 12 of a total 497 possible follow-up data points (2.4%). The overall group mean percent improvement in IDS-SR score from baseline to treatment 30 was 31.8 ± 23.7 (range –9.8 to 91.4).

iTBS-P was well-tolerated with no subjects discontinuing augmentation treatment. No patients were hospitalized, or experienced mania, attempted suicide, or seizures.

Demographic and baseline characteristics of study subjects in each group (i.e., subthreshold versus suprathreshold) are detailed in Table 1. A total of 27 subjects received subthreshold iTBS-P, while 44 received suprathreshold iTBS-P. No baseline group differences were found in age at first rTMS treatment, gender, baseline total IDS-SR score, number of HFL rTMS or iTBS-P sessions received, comorbid diagnoses, or medications. Subjects who received subthreshold iTBS-P showed greater symptom reduction than those receiving suprathreshold augmentation (Fig. 1), while those with greater or lesser numbers of pulses showed similar outcomes (Fig. 2). LMM analysis revealed a significant effect of stimulus intensity $F(1,65) = 8.41$, $p = 0.005$ on treatment 30 IDS-SR score, favoring subthreshold stimulation, but no other significant effects. Table 2 details parameter estimates gleaned from the LMM analysis. No group differences in response or remission were detected. Consistent with the LMM, a GLM using the non-imputed data set revealed a significant effect of iTBS-P intensity on final IDS-SR score ($F = 9.044$, $df = 1$, $p = 0.004$). No other factor (pulse number, age, gender, or number of iTBS-P treatments) achieved statistical significance in this model.

Discussion

We found that subthreshold priming intensity was associated with superior reduction in treatment-30 IDS-SR scores in those receiving iTBS-P for MDD when compared to suprathreshold priming. According to the BCM theorem [23], a subthreshold priming stimulus that activates postsynaptic neurons only weakly lowers the threshold of activation necessary for a subsequent conditioning stimulus to induce LTP. Our findings are consistent with this priming theory and the existing literature base suggesting rTMS priming effects occur through homeostatic mechanisms [17,18,36].

There was no statistical association between pulse number and final IDS-SR score though patients in the subthreshold group were significantly more likely to have received lower pulse number. Response (33% v 18%) and remission (19% and 5%) did not differ statistically between subthreshold and suprathreshold iTBS-P, respectively, however, the overall response and remission rates

Table 1

Demographic and clinical characteristics of study sample (n = 71). Baseline averages and analyses reported here were drawn from the original (non-imputed) data set. One of 44 (2%) treatment 30 IDS-SR scores was missing from the original data set. A significant effect of intensity on final score was found using both the linear mixed methods analysis (LMM) analysis of the imputed data set, and subsequent sensitivity analysis using a general linear model (GLM) and the original (non-imputed) data set. IDS-SR: Inventory of Depressive Symptomatology Self-Report, iTBS-P: intermittent theta burst priming, MT: Motor Threshold, SSRIs: Selective Serotonin Reuptake Inhibitors, NDRIs: Norepinephrine-dopamine reuptake inhibitors, SNRIs: serotonin-norepinephrine reuptake inhibitors, NaSSAs: Noradrenergic and specific serotonergic antidepressant, TCAs: tricyclic antidepressants, MAOIs: monoamine oxidase inhibitors.

	Primarily Subthreshold (n = 27)	Primarily Suprathreshold (n = 44)	Significance level
Age at first treatment	48.3 ± 19.2	42.9 ± 14.4	n.s.
Gender			
Female	12 (44%)	23 (52%)	n.s.
Male	15 (56%)	20 (45%)	n.s.
Transgender (F>M)	0 (0%)	1 (2%)	n.s.
Mean Baseline IDS-SR Score	40.5 ± 10.5	44.8 ± 10.1	n.s.
Mean Number of iTBS-P sessions	15.7 ± 4.6	16.9 ± 4.7	n.s.
Mean Intensity (%MT) used for priming stimulus	85.6 ± 5.2	113.9 ± 5.3	p = 5.5 × 10 ^{-33**}
Mean Number of Priming Pulses	774.7 ± 265.5	962.7 ± 412.3	p = 0.022
600–1200	22 (81.4%)	26 (59.1%)	
1200–1800	5 (18.5%)	18 (40.9%)	
Comorbid Psychiatric Diagnoses			
Anxiety Disorder	14 (22%)	15 (34%)	n.s.
Posttraumatic Stress Disorder	3 (11%)	6 (14%)	n.s.
Obsessive Compulsive Disorder	0 (0%)	1 (23%)	n.s.
Eating Disorder	1 (4%)	2 (5%)	n.s.
Substance use Disorder	2 (7%)	1 (2%)	n.s.
Personality Disorder	0 (0%)	3 (7%)	n.s.
ADHD	2 (7%)	5 (11%)	n.s.
Concurrent Daily Medications			
SSRIs	13 (48%)	17 (39%)	n.s.
SNRIs	5 (19%)	9 (20%)	n.s.
Atypical Antidepressants (NDRIs, NaSSAs)	6 (22%)	16 (36%)	n.s.
Atypical Antipsychotics	10 (37%)	21 (48%)	n.s.
Mood Stabilizers/Antiepileptics	9 (33%)	15 (34%)	n.s.
Stimulants	3 (11%)	12 (27%)	n.s.
Benzodiazepines	11 (41%)	14 (32%)	n.s.
Non-benzodiazepine anxiolytics	1 (4%)	3 (7%)	n.s.
TCAs	2 (7%)	1 (2%)	n.s.
MAOIs	1 (4%)	0 (0%)	n.s.
Alpha agonist	0 (0%)	3 (7%)	n.s.
Treatment 30 IDS-SR	24.6 ± 11.2	32.6 ± 13.1	p = 0.011*
Response	9 (33%)	8 (18%)	p = 0.253
Remission	5 (19%)	2 (5%)	p = 0.102

were low in both groups. It is possible that a larger sample with greater power could have revealed a statistically significant between-group difference. Feffer et al. [37] found that patients showing less than 20% improvement by treatment 10 had an NPV of 85% for non-response by treatment end. Since the patients

analyzed in this study all failed to show >20% improvement by week 2, it is perhaps surprising that response and remission both exceeded 15% in the subthreshold group. These findings suggest that the addition of subthreshold iTBS-P at treatment 11 was sufficient to augment the rate of response and remission (numerically) in patients drawn from a population otherwise unlikely to have

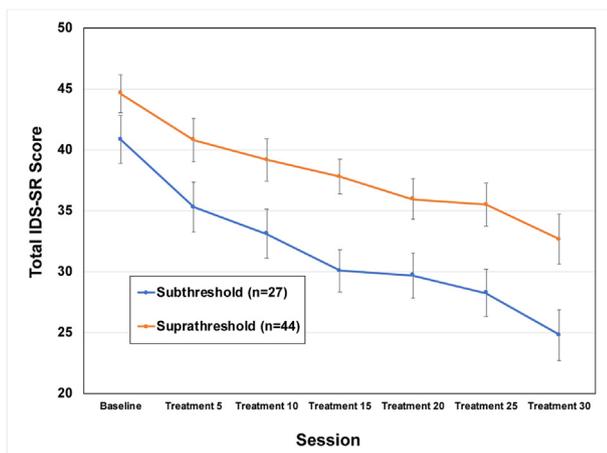


Fig. 1. Change in Absolute IDS-SR score by iTBS-P intensity (n = 71). The original (not imputed) data set was used to generate this figure. Twelve data points of a possible 497 were missing (2.4%). Error bars show standard error of the mean. IDS-SR = Inventory of Depressive Symptomatology Self Report.

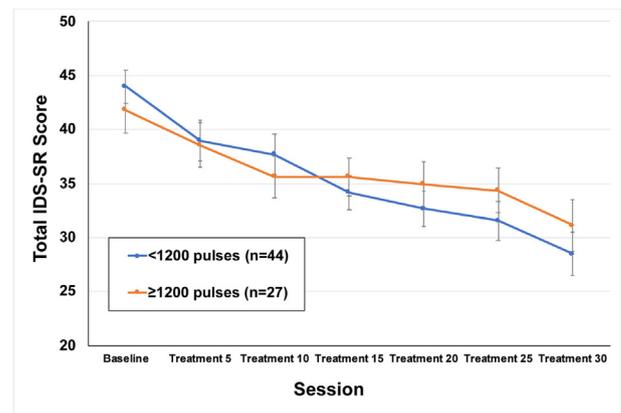


Fig. 2. Change in Absolute IDS-SR score by iTBS-P pulse number (n = 71). The original (not imputed) data set was used to generate this figure. Twelve data points of a possible 497 were missing (2.4%). Error bars show standard error of the mean. IDS-SR = Inventory of Depressive Symptomatology Self Report.

Table 2
Parameter table.

	<i>b</i>	<i>SE_b</i>	95% CI
Pulse Number	1.59	2.36	−3.12, 6.30
Intensity	−6.60	2.38	−11.35, −1.84
Gender	5.95	9.59	−13.20, 25.12
Number of iTBS-P treatments	−0.25	0.25	−0.74, 0.24
Age at first treatment	−0.03	0.07	−0.17, 0.11

responded. Brief subthreshold iTBS-P (i.e., 600 pulses delivered at <90% MT) may augment HFL rTMS as well or even better than longer, suprathreshold iTBS-P (i.e., >600 pulses delivered at ≥100% MT).

While SBL rTMS initially showed promise as an augmentation strategy [38], Fitzgerald et al. [16] subsequently found equivocal benefit with this strategy. A meta-analysis by Chen et al. [39] also showed that SBL rTMS conferred no marginal benefit in clinical outcome, tolerability, or acceptability above HFL or LFR rTMS [39], while lengthening treatment time. Mutz et al. [5] found in their comparative meta-analysis of non-invasive and invasive brain stimulation techniques that priming rTMS possessed the greatest odds of response compared to sham (6.02, 95% confidence interval [CI] 2.21 to 16.38) amongst all rTMS interventions, outstripping SBL rTMS (4.92, CI 2.93 to 8.25), LFR rTMS (3.65, CI 2.13 to 6.24) and HFL rTMS (3.17, CI 2.29 to 4.37). Priming TMS was second only to bitemporal ECT (8.91, 2.57 to 30.91) and high dose right unilateral ECT (7.27, 1.90 to 27.78) in summary odds of response. Notably, priming TMS was the most acceptable of rTMS approaches. Our recent retrospective analysis showed that those who did not experience early clinical response with HFL rTMS (defined as a >20% improvement from baseline depression by 10 treatments) experienced a significant improvement in final rate of clinical response with the addition of iTBS-P [21]. In contrast, those who switched to SBL rTMS did not show any statistically significant improvement beyond those who continued to receive HFL rTMS for the remainder of their 30 treatments. Taken together these findings provide real-world evidence of the value of iTBS-P as an augmentation strategy, suggesting that brief (600-pulse) subthreshold iTBS-P is a practical augmentation strategy for those failing to respond to HFL rTMS treatment in a time- and cost-sensitive clinical setting.

It is important to note that we calculated priming stimulus intensity based on a percentage of RMT, not *active* motor threshold (AMT). While Fitzgerald et al. [19] used 90% RMT for their 6 Hz priming stimulus intensity, Lefaucheur et al. [20] used 80% of AMT for their iTBS-P pain approach. Because AMT is known to be lower than RMT [40], using 80% of AMT for dosing intensity could further enhance the efficacy and tolerability of iTBS-P augmentation. The relatively greater effectiveness of a subthreshold priming intensity is consistent with a homeostatic model of priming plasticity, whereby a weak priming stimulus, too weak to independently activate a population of postsynaptic neurons, renders them more responsive to a subsequent treatment protocol [18].

Although there was no difference in response or remission rates between groups, the overall rate of remission and response in this sample was low and the analysis likely underpowered to detect such a difference. Study subjects were drawn from a highly treatment-resistant population that had failed to show improvement with HFL rTMS before starting iTBS-P. Whether a significant between-group difference in response or remission could be detected with a larger sample remains speculative.

It is not known whether iTBS-P would have clinical efficacy for augmenting treatments other than HFL rTMS. Fitzgerald et al. [19] used HFL rTMS to prime LFR rTMS of the right DLPFC in their

original study of priming rTMS for MDD. Lefaucheur used iTBS-P to augment 10 Hz stimulation at M1 [20]. Huang et al. [34] found that iTBS induced a longer period (60–90 min) of motor cortical facilitation (a measure of neural plasticity in the motor cortex) than HFL rTMS (30 min). It is unknown whether iTBS-P could keep different cortical areas in a primed state for other targets such as the supplementary motor area or dorsomedial prefrontal cortex. Future studies should examine such augmentation approaches systematically.

Limitations

The findings of this study should be interpreted in the context of several limitations. First, data were collected from patients seeking clinical treatment in a measurement-based care program rather than through a randomized controlled trial. The limitations of such a study design have been previously discussed and include the potential for selection bias and confounding effects [41]. The absence of patients in either group dropping out and inclusion of all subjects treated with iTBS-P lowers the potential contribution of sampling bias. Additionally, use of self-report questionnaires maximized accrual of data from all patients meeting inclusion criteria. Second, almost all subjects were receiving concomitant treatment with psychotropic medications during rTMS. Baseline differences in medications were not associated with outcome, but the presence of medications could have affected study results. Third, while the vast majority of subjects held medications constant, it is possible that uncontrolled factors such as medication changes could have affected outcome in some subjects. Because these patients were highly refractory to medication, however, it is unlikely that medication changes during the course of rTMS would be responsible for significant changes in symptoms. Finally, priming intensity and pulse number were not experimentally controlled for but instead were assigned based upon a clinical protocol. It is possible that uncontrolled factors in the clinical setting could have affected assignment of intensity and pulse number. Future prospective testing of intensity and pulse number in a randomized controlled trial is needed to confirm these results.

Conclusions

These results indicate that subthreshold priming was associated with clinical outcomes that were superior to those of supra-threshold priming in subjects who did not show early benefit from standard 10 Hz treatment. These findings provide evidence to support the use of subthreshold iTBS-P as an effective augmentation strategy. These results are consistent with the Bienenstock-Cooper-Munro theorem and suggest that homeostatic plasticity may account for benefits of subthreshold iTBS-P. Furthermore, these findings are of clinical significance as they demonstrate a briefer, less intense (and consequently more tolerable) priming stimulus was associated with better clinical response than a longer, more intense alternative. Clinicians aiming to improve outcomes could consider initiating subthreshold iTBS-P in those showing limited early response to HFL rTMS.

CRedit authorship contribution statement

Jonathan C. Lee: was involved in, Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, preparing, writing and editing the manuscript, Visualization, and project administration. **Juliana Corlier:** was involved in conceptualization, Methodology, and editing the manuscript. **Andrew C. Wilson:** was involved in conceptualization, Methodology, Validation, Formal analysis, Software, Visualization, review and editing,

and project administration. **Reza Tadayonnejad**: was involved in conceptualization, Methodology, and editing the manuscript. **Katharine G. Marder**: was involved in data curation and editing the manuscript. **Doan Ngo**: was involved in data curation and validation. **David E. Krantz**: was involved in data curation and editing the manuscript. **Scott A. Wilke**: was involved in data curation and editing the manuscript. **Jennifer G. Levitt**: was involved in data curation and editing the manuscript. **Nathaniel D. Ginder**: was involved in data curation and editing the manuscript. **Andrew F. Leuchter**: was involved in conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, preparing, writing and editing the manuscript, Resources, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

Drs. Corlier, Tadayonnejad, Marder, Krantz, Wilke, Levitt, and Ginder, along with Ms. Doan Ngo have no disclosures, Andrew Wilson has served as a consultant to HeartCloud, Inc within the past 36 months. Dr. Leuchter discloses that within the past 36 months he has received research support from the National Institutes of Health, Neuronetics, Department of Defense, CHDI Foundation, and NeuroSigma, Inc. He has served as a consultant to NeoSync, Inc., Ionis Pharmaceuticals, Inc., and EIMinda. He is Chief Scientific Officer of Brain Biomarker Analytics LLC (BBA). Dr. Leuchter has equity interest in BBA. Jonathan Lee has received in-kind equipment support from Magventure Inc. The authors report no other conflicts of interest in this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2021.06.008>.

References

- Huang YZ, Lu MK, Antal A, Classen J, Nitsche M, Ziemann U, et al. Plasticity induced by non-invasive transcranial brain stimulation: a position paper. *Clin Neurophysiol* 2017;128:2318–29. <https://doi.org/10.1016/j.clinph.2017.09.007>.
- Brunoni AR, Chaimani A, Moffa AH, Razza LB, Gattaz WF, Daskalakis ZJ, et al. Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes. *JAMA Psychiatr*. 2017;74:143. <https://doi.org/10.1001/jamapsychiatry.2016.3644>.
- Berlim MT, Van Den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Psychol Med* 2014;44:225–39. <https://doi.org/10.1017/S0033291713000512>.
- Berlim MT, McGirr A, Rodrigues dos Santos N, Tremblay S, Martins R. Efficacy of theta burst stimulation (TBS) for major depression: an exploratory meta-analysis of randomized and sham-controlled trials. *J Psychiatr Res* 2017;90:102–9. <https://doi.org/10.1016/j.jpsychires.2017.02.015>.
- Mutz J, Vipulanathan V, Carter B, Hurlmann R, Fu CHY, Young AH. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. *BMJ* 2019;11079. <https://doi.org/10.1136/bmj.11079>.
- Beam W, Borckardt 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. <https://doi.org/10.1016/j.brs.2008.09.006>.
- Mir-Moghtadaei A, Caballero R, Fried P, Fox MD, Lee K, Giacobbe P, et al. Concordance between BeamF3 and MRI-neuronavigated target sites for repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex. *Brain Stimul* 2015;8:965–73. <https://doi.org/10.1016/j.brs.2015.05.008>.
- Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. *Biol Psychiatr* 2012;72:595–603. <https://doi.org/10.1016/j.biopsych.2012.04.028>.
- Schulze L, Feffer K, Lozano C, Giacobbe P, Daskalakis ZJ, Blumberger DM, et al. Number of pulses or number of sessions? An open-label study of trajectories of improvement for once-vs. twice-daily dorsomedial prefrontal rTMS in major depression. 2018. <https://doi.org/10.1016/j.brs.2017.11.002>.
- Yip AG, George MS, Tendler A, Roth Y, Zangen A, Carpenter LL. 61% of unmedicated treatment resistant depression patients who did not respond to acute TMS treatment responded after four weeks of twice weekly deep TMS in the Brainsway pivotal trial. *Brain Stimul* 2017;10:847–9. <https://doi.org/10.1016/j.brs.2017.02.013>.
- Fitzgerald PB, Benitez J, De Castella A, Daskalakis ZJ, Brown TL, Kulkarni J. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatr* 2006;163:88–94. <https://doi.org/10.1176/appi.ajp.163.1.88>.
- Blumberger DM, Mulsant BH, Fitzgerald PB, Rajji TK, Ravindran AV, Young LT, et al. A randomized double-blind sham-controlled comparison of unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant major depression. *World J Biol Psychiatr* 2012;13:423–35. <https://doi.org/10.3109/15622975.2011.579163>.
- Cole EJ, Stimpson KH, Bentzley BS, Gulser M, Cherian K, Tischler C, et al. Stanford accelerated intelligent neuromodulation therapy for treatment-resistant depression. *Am J Psychiatr* 2020. <https://doi.org/10.1176/appi.ajp.2019.19070720>.
- Holtzheimer PE, McDonald WM, Mufti M, Kelley ME, Quinn S, Corso G, et al. Accelerated repetitive transcranial magnetic stimulation for treatment-resistant depression. *Depress Anxiety* 2010;27:960–3. <https://doi.org/10.1002/da.20731>.
- Cirillo G, Di Pino G, Capone F, Ranieri F, Florio L, Todisco V, et al. Neurobiological after-effects of non-invasive brain stimulation. *Brain Stimul* 2017;10:1–18. <https://doi.org/10.1016/j.brs.2016.11.009>.
- Fitzgerald PB, Hoy KE, Singh A, Gunewardene R, Slack C, Ibrahim S, et al. Equivalent beneficial effects of unilateral and bilateral prefrontal cortex transcranial magnetic stimulation in a large randomized trial in treatment-resistant major depression. *Int J Neuropsychopharmacol* 2013;16:1975. <https://doi.org/10.1017/S1461145713000369>.
- Bienenstock EL, Cooper LN, Munro PW. Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex. *J Neurosci* 1982;2:32–48. <https://doi.org/10.1523/jneurosci.02-01-00032.1982>.
- Siebner HR. A primer on priming the human motor cortex. *Clin Neurophysiol* 2010;121:461–3. <https://doi.org/10.1016/j.clinph.2009.12.009>.
- Fitzgerald PB, Hoy K, McQueen S, Herring S, Segrave R, Been G, et al. Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. *J Clin Psychopharmacol* 2008;28:52–8. <https://doi.org/10.1097/jcp.0b013e3181603f7c>.
- Lefaucheur JP, Ayache SS, Sorel M, Farhat WH, Zouari HG, Ciampi De Andrade D, et al. Analgesic effects of repetitive transcranial magnetic stimulation of the motor cortex in neuropathic pain: influence of theta burst stimulation priming. *Eur J Pain* 2012;16:1403–13. <https://doi.org/10.1002/j.1532-2149.2012.00150.x>.
- Lee JC, Wilson AC, Corlier J, Tadayonnejad R, Marder KG, Pleman CM, et al. Strategies for augmentation of high-frequency left-sided repetitive transcranial magnetic stimulation treatment of major depressive disorder. *J Affect Disord* 2020;277:964–9. <https://doi.org/10.1016/j.jad.2020.09.011>.
- Stoykov ME, Madhavan S. Motor priming in neurorehabilitation. *J Neurol Phys Ther* 2015;39:33–42. <https://doi.org/10.1097/NPT.0000000000000065>.
- Ziemann U, Siebner HR. Modifying motor learning through gating and homeostatic metaplasticity. *Brain Stimul* 2008;1:60–6. <https://doi.org/10.1016/j.brs.2007.08.003>.
- Murakami T, Müller-Dahlhaus F, Lu MK, Ziemann U. Homeostatic metaplasticity of corticospinal excitatory and intracortical inhibitory neural circuits in human motor cortex. *J Physiol* 2012;590:5765–81. <https://doi.org/10.1113/jphysiol.2012.238519>.
- Desmyter S, Duprat R, Baeken C, Van Autreve S, Audenaert K, van Heeringh K. Accelerated intermittent theta burst stimulation for suicide risk in therapy-resistant depressed patients: a randomized, sham-controlled trial. *Front Hum Neurosci* 2016;10:480. <https://doi.org/10.3389/fnhum.2016.00480>.

- [26] Duprat R, Desmyter S, Rudi DR, van Heeringen K, Van den Abbeele D, Tandt H, et al. Accelerated intermittent theta burst stimulation treatment in medication-resistant major depression: a fast road to remission? *J Affect Disord* 2016;200:6–14. <https://doi.org/10.1016/j.jad.2016.04.015>.
- [27] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatr* 1998;59(20):22–33. quiz 34–57.
- [28] Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one. *Am J Psychiatr* 2006;163:1905–17.
- [29] John Rush A, Giles DE, Schlessler MA, Fulton CL, Weissenburger J, Burns C. The inventory for depressive symptomatology (IDS): preliminary findings. *Psychiatr Res* 1986;18:65–87. [https://doi.org/10.1016/0165-1781\(86\)90060-0](https://doi.org/10.1016/0165-1781(86)90060-0).
- [30] Rush AJ, Bernstein IH, Trivedi MH, Carmody TJ, Wisniewski S, Mundt JC, et al. An evaluation of the quick inventory of depressive symptomatology and the Hamilton rating Scale for depression: a sequenced treatment alternatives to relieve depression trial report. *Biol Psychiatr* 2006;59:493–501. <https://doi.org/10.1016/j.biopsych.2005.08.022>.
- [31] Corruble E, Legrand JM, Duret C, Charles G, Guelfi JD. IDS-C and IDS-sr: psychometric properties in depressed in-patients. *J Affect Disord* 1999;56:95–101.
- [32] Corlier J, Wilson A, Hunter AM, Vince-Cruz N, Krantz D, Levitt J, et al. Changes in functional connectivity predict outcome of repetitive transcranial magnetic stimulation treatment of major depressive disorder. *Cerebr Cortex* 2019. <https://doi.org/10.1093/cercor/bhz035>.
- [33] Feffer K, Lee HH, Mansouri F, Giacobbe P, Vila-Rodriguez F, Kennedy SH, et al. Early symptom improvement at 10 sessions as a predictor of rTMS treatment outcome in major depression. *Brain Stimul* 2018;11:181–9. <https://doi.org/10.1016/j.brs.2017.10.010>.
- [34] Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron* 2005;45:201–6. <https://doi.org/10.1016/j.neuron.2004.12.033>.
- [35] Li CT, Cheng CM, Chen MH, Juan CH, Tu PC, Bai YM, et al. Antidepressant efficacy of prolonged intermittent theta burst stimulation monotherapy for recurrent depression and comparison of methods for coil positioning: a randomized, double-blind, sham-controlled study. *Biol Psychiatr* 2020;87:443–50. <https://doi.org/10.1016/j.biopsych.2019.07.031>.
- [36] Fitzgerald PB, Hoy K, McQueen S, Herring S, Segrave R, Been G, et al. Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. *J Clin Psychopharmacol* 2008;28:52–8. <https://doi.org/10.1097/jcp.0b013e3181603f7c>.
- [37] Feffer K, Lee HH, Mansouri F, Giacobbe P, Vila-Rodriguez F, Kennedy SH, et al. Early symptom improvement at 10 sessions as a predictor of rTMS treatment outcome in major depression. *Brain Stimul* 2018;11:181–9. <https://doi.org/10.1016/j.brs.2017.10.010>.
- [38] Fitzgerald PB, Benitez J, de Castella A, Daskalakis ZJ, Brown TL, Kulkarni J. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatr* 2006;163:88–94. <https://doi.org/10.1176/appi.ajp.163.1.88>.
- [39] Chen J jun, Liu Z, Zhu D, Li Q, Zhang H, Huang H, et al. Bilateral vs. unilateral repetitive transcranial magnetic stimulation in treating major depression: a meta-analysis of randomized controlled trials. *Psychiatr Res* 2014. <https://doi.org/10.1016/j.psychres.2014.05.010>.
- [40] Ah Sen CB, Fassett HJ, El-Sayes J, Turco CV, Hameer MM, Nelson AJ. Active and resting motor threshold are efficiently obtained with adaptive threshold hunting. *PloS One* 2017;12. <https://doi.org/10.1371/journal.pone.0186007>.
- [41] Vassar M, Matthew H. The retrospective chart review: important methodological considerations. *J Educ Eval Health Prof* 2013;10:12. <https://doi.org/10.3352/jeehp.2013.10.12>.