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Strategies for augmentation of high-frequency left-sided repetitive transcranial magnetic stimulation treatment of major depressive disorder

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ABSTRACT

Background: Repetitive Transcranial Magnetic Stimulation (rTMS) is an effective intervention for treatment-resistant Major Depressive Disorder (MDD). Early improvement during high-frequency left-sided (HFL) stimulation of the dorsolateral prefrontal cortex (DLPFC) is an important predictor of longer-term outcome, but most patients benefit later in their treatment course. We examined patients without early improvement with HFL to determine whether augmentation with additional stimulation approaches improved treatment outcome.

Methods: 139 participants received HFL in a measurement-based care paradigm. Participants who achieved < 20% improvement by treatment 10 could continue with HFL (N = 17) or receive one of two augmentation strategies: bilateral stimulation (BL; HFL followed by low-frequency stimulation of right DLPFC) (N = 69) or intermittent theta-burst priming of left DLPFC (iTBS-P) (N = 17) for their remaining treatment sessions. The primary outcome was the percent reduction in depressive symptoms at treatment 30.

Results: Participants who achieved < 20% improvement by treatment 10 and continued with HFL showed limited benefit. iTBS-P participants had significantly greater improvement, while those receiving BL trended toward improved outcomes. Ten sessions of either augmentation strategy appeared necessary to determine the likelihood of benefit.

Conclusions: Augmentation of early non-response to HFL appears to improve rTMS outcomes, with a novel iTBS-P strategy surpassing both continued HFL or BL treatment in participants with < 20% improvement after 10 treatments. These findings suggest that measurement-based care with addition of augmented stimulation for those not showing early improvement may yield superior rTMS treatment outcomes.

1. Introduction

Repetitive Transcranial Magnetic Stimulation (rTMS) is an efficacious treatment of Major Depressive Disorder (MDD) that is unresponsive to antidepressant medication (so-called treatment-resistant depression, or TRD) (Mutz et al., 2019). The standard, "high-frequency left-sided" (HFL) treatment for TRD consists of trains of 10 Hz stimulation delivered to the left dorsolateral prefrontal cortex (DLPFC) on consecutive weekdays, over several weeks. While rTMS is effective for many patients, response and remission rates remain modest in controlled studies. Early benefit from HFL treatment is an important indicator of good outcome, with one study noting that patients with 20% improvement by 2 weeks are significantly more likely to respond by treatment 20 (Feffer et al., 2018).

In addition to HFL, other forms of rTMS may be effective. Low-frequency (1 Hz) stimulation administered to right DLPFC (LFR) appears comparable in efficacy to HFL (Chen et al., 2013). Intermittent theta-burst stimulation (iTBS), a patterned form of stimulation in which 50 Hz triplet pulses are administered on a 5 Hz carrier frequency (Huang et al., 2005), also has been shown to have comparable efficacy to HFL (Blumberger et al., 2018). It has not been established which patients may be most likely to benefit from each of these forms of rTMS, alone or in combination.

When a patient fails to benefit from a single antidepressant

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medication, augmentation by adding a second antidepressant medication is a well-accepted treatment strategy (Sinyor et al., 2010). An analogous approach could be applied to rTMS, in which HFL treatment could be augmented with additional forms of stimulation for individuals with limited response. Because early improvement is an important predictor of longer-term benefit, early augmentation in patients lacking improvement by 2 weeks could improve treatment outcomes. In addition, most patients are eligible to receive only a limited number of rTMS treatment sessions because of third-party payor restrictions (Voigt et al., 2019, 2017). Early augmentation during the course of a finite number of insurance-covered sessions could enhance both cost-effectiveness and overall clinical benefit. There has been minimal research, however, on whether, how, or when to augment HFL treatment.

In this retrospective chart review, we examined whether augmentation of HFL with a second form of stimulation before or after HFL could enhance response (i.e., sequential stimulation). First, we examined sequential BL treatment in which HFL was followed by LFR. While some studies suggest this method's superiority to HFL alone (Blumberger et al., 2016, 2012; Brunoni et al., 2017; Trevizol et al., 2019) others note comparable efficacy (Chen et al., 2014; Fitzgerald et al., 2011). Second, we examined TMS priming in which HFL was preceded by iTBS (iTBS-P). Priming generally involves delivering brief high-frequency stimulation (i.e., ≥5 Hz) prior to a longer period of high- (Lefaucheur et al., 2012) or low-frequency (<5 Hz) stimulation (Fitzgerald et al., 2008) to induce long-term potentiation (Todd et al., 2009) through meta-plastic effects (Bienenstock et al., 1982). Researchers have employed priming to augment rTMS effects in depression (Fitzgerald et al., 2008), pain (Lefaucheur et al., 2012), and tinnitus (Langguth et al., 2008). Fitzgerald et al. (2008) used a 6 Hz high-frequency priming stimulus before delivering low-frequency stimulation to the right-DLPFC for the treatment of depression. In contrast, Lefaucher et al. (2012) showed that iTBS enhanced analgesic effects of HFL, when used as a priming stimulus. We are unaware of any study, however, examining the use of iTBS as a priming stimulus for HFL treatment in MDD.

In a network meta-analysis, Brunoni et al. (2017) ranked BL and priming as the two rTMS strategies most likely to induce therapeutic response in MDD. Their study did not, however, address the possible efficacy of either method as an augmentation strategy for HFL non-responders. In this study, we examined both of these rTMS augmentation strategies (BL and iTBS-P) in a controlled measurement-based care setting in patients who demonstrated limited (<20%) improvement after 2 weeks of HFL treatments (Feffer et al., 2018). The objectives of this study were: 1) to examine whether novel iTBS-P or BL were effective augmentation strategies in participants who showed < 20% decrease in depression scores by the 10th HFL treatment, and 2) to determine the time course over which augmentation strategies yielded benefit in an open-label clinical sample.

2. Materials and methods

2.1. Participants

Participants were 139 patients referred to the TMS Clinical and Research Service at UCLA for treatment of MDD. They were 20–78 years old (mean 45.2 ± 15.7) with 71 females (51%), and had primary diagnoses of MDD confirmed by the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Participants presented with an average baseline depressive symptom rating of 41.8 ± 11.1 on the Inventory of Depressive Symptomatology Self-Report (IDS-SR) (Rush et al., 1986). The majority received concomitant medication with rTMS treatment. All underwent standard safety screening and medical clearance to receive rTMS (Rossi et al., 2011). The UCLA Institutional Review Board (IRB) approved this retrospective analysis of de-identified clinical data.

Patient groups consisted of: 1) *HFL responders* who received HFL for all 30 treatments, with ≥ 20% improvement in IDS-SR score at treatment 10; 2) *HFL non-responders* who had < 20% improvement at treatment 10 but continued to receive HFL for all 30 sessions; 3) *BL* patients, who were HFL non-responders who went on to receive BL treatment after 2 weeks; and 4) *iTBS-P* patients, who were HFL non-responders who received iTBS-P after 2 weeks.

The primary outcome measure was percent change in IDS-SR from baseline to treatment 30. A briefer version of the IDS-SR (the 16-item Quick IDS-SR) was the primary outcome in the STAR*D trial, the largest psychopharmacological effectiveness trial conducted in over 4000 patients with TRD (Rush et al., 2006). IDS-SR scores are highly correlated with other self-rated measures such as the Beck Depression Inventory (BDI-II) (Rush et al., 1986) and clinician-rated measures such as the Hamilton Rating Scale for Depression (HAMD-17) (Rush et al., 1996) and the Montgomery-Asberg Depression Rating Scale (Corruble et al., 1999). Secondary outcome measures included response and remission defined as a ≥50% decrease in baseline IDS-SR score, and a final IDS-SR score of ≤13, respectively, at final treatment, as well as percent improvement on the Patient Health Questionnaire (PHQ-9) (Spitzer et al., 1999) at treatment 30. For our second objective, we aimed to define the time needed to determine whether an augmentation strategy would be helpful by identifying the post-switch timepoint at which 80% of each group achieved an incremental improvement of 20% in IDS-SR score.

2.2. TMS treatment

All TMS treatments were delivered with either a MagPro X100 (Magventure, Farnum, Denmark) Magstim (Magstim, Whitland, UK), or Neurostar (Neuronetics, Malvern, PA) device. Resting motor threshold (MT) was determined prior to the first treatment as the minimum % stimulator intensity necessary to elicit a visually detectable hand movement in 5 of 10 single pulse trials. All participants received 30 rTMS treatment sessions in total, beginning with at least five sessions of HFL.

HFL treatment began with 3000 pulses per session delivered at 10 Hz administered to the left DLPFC with the Beam F3 targeting method (Beam et al., 2009) with a 40-pulse train and intertrain interval (ITI) of 26 s (37.5 min duration). Treatment intensity was titrated to 120% MT as tolerated with parameters modified according to a measurement-based care paradigm. Participants completed IDS-SR ratings at weekly intervals (every five treatments) and HFL treatment could be modified after the fifth treatment to optimize tolerability or augment HFL response. A subset of participants also completed the Patient-Health Questionnaire (PHQ-9), an additional self-report measure of depression symptoms designed for use in clinical settings (Spitzer et al., 1999).

Augmentation was typically initiated with either BL or iTBS-P at treatment 11 if a subject did not achieve > 20% improvement in their IDS-SR score. HFL non-responders continued to receive HFL for the entire duration of their treatment course if they preferred not to change parameters and/or it was the clinical judgment of the treatment team that these participants showed some improvement and might eventually derive greater benefit. BL consisted of HFL treatment followed by 1200 pulses delivered to F4 at up to 120% MT. BL can be performed with HFL and LFR delivered in either order; it is unclear whether there is an effect of the order of administration. iTBS-P consisted of 600 pulses of iTBS, 2s pulse duration, 8s ITI at an intensity of up to 120% MT delivered to F3 followed immediately by HFL treatment.

BL was the sole augmentation strategy offered over the first 36 months of the study period, with iTBS-P offered as a preferred strategy over the next 12 months because of published data questioning the incremental benefit of BL treatment (Chen et al., 2014) and research demonstrating the clinical efficacy (Li et al., 2014) and non-inferiority (Blumberger et al., 2018) of iTBS compared to HFL treatment. Our iTBS-P intervention was distinct from that employed by

Fitzgerald et al. (2008) in that we used iTBS delivered to F3, not 6 Hz stimulation (delivered over F4), as the priming stimulus. Moreover, in our protocol, iTBS was used to prime HFL treatment, while Fitzgerald et al. (2008) used 6 Hz to prime LFR treatment.

2.3. Statistical analysis

We completed all statistical analyses using SPSS v 26.0 (Armonk, New York, IBM Corp) and MATLAB R2017b (Natick, MA, Mathworks).

We used repeated measures ANOVA with group (*HFL responders, HFL non-responders, BL*, and *iTBS-P*) and device-type (i.e. Neurostar, Magstim, Magventure) as fixed variables, comparing percent change in IDS-SR and PHQ-9 over the total treatment course. We then computed post-hoc, two-tailed t-tests with false discovery rate (FDR) correction to identify statistically significant group differences in percent improvement at treatment 30. We also computed effect sizes to compare HFL-non-responders and BL, and HFL-responders and iTBS-P groups at treatment 30. We used the Kruskal-Wallis test for non-parametric data to analyze patterns of response (defined as greater than 50% improvement from baseline) and remission (defined as a final score of $\leq$13) on the IDS-SR. We used an α level of $p \leq 0.05$ for all statistical testing.

We also conducted post-hoc testing to define the number of treatments required to determine if an augmentation strategy would be helpful, calculating the number of sessions post-augmentation required for 80% of participants who ultimately achieved at least 20% improvement in IDS-SR to attain this benefit. The 20% individual improvement threshold reflects the minimal clinically important difference (MCID) used in other studies (Button et al., 2015; Mancini, 2013), as well as the degree of improvement used to predict eventual response in Feffer et al. (2018). The 80% group threshold indicates a low likelihood of additional participants benefitting beyond this time point.

3. Results

3.1. Participants

In total, 139 participants were included. Table 1 shows demographic and clinical characteristics of the study sample (*HFL responders* [$n = 36$], *HFL non-responders* [$n = 17$], *BL* [$n = 69$], and *iTBS-P* [$n = 17$]. Participants received 13 $\pm$ 3.4 and 12.9 $\pm$ 3.3 treatments, respectively, before switching to BL or iTBS-P augmentation strategies. The majority of participants ($n = 124$, 89%) were taking psychotropic medication during rTMS treatment. Participants tolerated both BL and iTBS-P treatments well, with none experiencing worsening suicidality, inpatient hospitalization, manic switch, or seizure.

IDS-SR scores were available for all 139 participants included in the analysis and are presented, according to group, in Fig. 1. PHQ-9 scores were available for baseline, treatment 15, and treatment 30 for a subset ($n = 129$) of the sample with clinical outcomes reported in Table 1.

3.2. Clinical outcomes

IDS-SR: Fig. 1 shows a boxplot of final median percent improvement in IDS-SR score by treatment group. Mauchly's test of sphericity indicated the assumption of sphericity was violated [$\chi^2(14) = 84.8$, $p < 0.001$]. Repeated measures ANOVA with Greenhouse-Geisser correction revealed a significant group by time interaction ($F(11.8) = 1.78$; $p = 0.05$) and main effect of group ($p < 0.001$), but no significant standalone or interaction effect of device-type on treatment outcome.

Post-hoc, pairwise, FDR corrected t-tests showed significant between-group differences in % improvement of IDS-SR scores at treatment 30 between HFL non-responders and HFL responders, [$p = 5.3 \times 10^{-8}$], and HFL non-responders and those who received iTBS-P [$p = 0.038$]. There was greater numerical benefit for those receiving BL, but no statistically significant difference in outcome between HFL non-responders and those who received BL treatment [$p = 0.26$]. The iTBS-P group was statistically significantly different from both HFL responders, and non-responders ($p = 0.0006$). Among HFL non-responders, those who switched to iTBS-P achieved the highest response and remission rates at treatment 30 (Table 1).

A Kruskal-Wallis test showed significant differences in response [$\chi^2(3) = 43.7$; $p < 0.001$] and remission [$\chi^2(3) = 29.5$; $p < 0.001$] among the four groups.

We found a large effect size of percent improvement in IDS-SR between iTBS-P and HFL non-responders ($d = 0.80$) and a small effect size between BL treatment and HFL non-responders ($d = 0.31$).

PHQ-9: Mauchly's test of sphericity indicated the assumption of sphericity was violated [$\chi^2(14) = 66.1$, $p < 0.001$]. Repeated measures ANOVA with Greenhouse-Geisser correction revealed a significant group by time interaction ($F(12.3) = 1.77$; $p = 0.049$), though none of the FDR post-hoc comparisons were significant (HFL non-responders v BL; HFL non-responders v iTBS-P).

Fig. 2 shows the results of post-hoc testing defining the number of treatment sessions needed to observe a 20% incremental benefit from baseline associated with each augmentation strategy. The 20% increment was chosen as a meaningful clinically important difference and was also the degree of improvement found to predict eventual treatment response (Feffer et al., 2018). As a group, 80% of those receiving either augmentation strategy achieved this MCID between 8–12 treatments post-switch.

4. Discussion

In this study, we compared the effects of two augmentation strategies (iTBS-P and BL) for individuals who did not improve with ten sessions of HFL treatment. Our findings indicate that iTBS-P achieved a significantly greater improvement at treatment endpoint in HFL non-responders than either continuing with HFL or switching to BL treatment. To our knowledge, this is the first study examining iTBS-P in depressed participants, and the first to examine it in the context of augmenting HFL treatment. The large effect size between treatment outcomes of those who received iTBS-P and those who continued to receive HFL despite limited improvement by treatment 10 indicate that iTBS-P, or "sequential *unilateral*" treatment, is a clinically beneficial augmentation strategy.

Our results also define the time, post-switch, required to assess the potential benefits of either augmentation strategy. Feffer et al. (2018) showed that HFL "early" response (i.e., >20% improvement by 2 weeks) was significantly associated with response after 20 sessions, defining this interval as a meaningful cut-off-point. Our work extends their finding by elucidating the time-course over which augmentation strategies demonstrate incremental beneficial effects. Notably, 80% of those who ultimately achieved 20% improvement with either augmentation strategy did so by approximately ten treatments post-augmentation. This finding suggests that clinicians electing to augment should deliver at least ten treatments of a new approach before considering additional major changes. In practice, this finding supports making major strategic changes in stimulation strategies no more than twice during a standard course of 30 treatments.

Participants who received BL treatment did not show significantly improved clinical outcomes as compared to those who continued receiving HFL. Nonetheless, these participants did show a numerically greater symptom improvement by treatment 30. It is possible that a more significant difference may have emerged with additional treatment sessions. Fitzgerald et al. (2018) recently conducted a controlled switching study in which they randomized non-responders to HFL at three weeks to receive three additional weeks of HFL, LFR, or BL treatment. They found no group differences in final outcome. The authors note that participants may have not received enough post-switch treatments to determine the subsequent efficacy of each strategy. They

Table 1
Demographic and clinical characteristics.

	HFL Early Responders (n = 36)	HFL Non-responders (n = 17)	BL (n = 69)	iTBS-P (n = 17)	Test Statistic	Significance
Age	48.3 ± 15.6	44.6 ± 15.4	42.8 ± 15.9	49.4 ± 14.3	F = 1.45	p = 0.23
Women	20 (56%)	11 (65%)	33 (48%)	7 (41%)	χ^2 = 2.49	p = 0.48
Baseline IDS-SR	41.6 ± 11.7	38.7 ± 12.5	41.8 ± 10.7	45.4 ± 10.0	F = 1.04	p = 0.375
Treatment 30 IDS-SR	13.8 ± 11.4	29.4 ± 12.7	28.3 ± 12.2	26.1 ± 13.0	F = 12.55	**p<0.001****
Response Rate[a]	29 (81%)	2 (12%)	13 (19%)	7 (41%)	χ^2 = 43.7	**p<0.001****
Remission Rate[b]	22 (61%)	2 (12%)	10 (15%)	3 (18%)	χ^2 = 29.5	**p<0.001****
Baseline PHQ-9	17.4 ± 5.9 (n = 31)	15.6 ± 5.5 (n = 16)	17.0 ± 5.4 (n = 65)	19.2 ± 4.5 (n = 17)	F = 1.28	*p = 0.29*
Treatment 30 PHQ-9	5.3 ± 5.2 (n = 31)	10.5 ± 5.6 (n = 16)	11.0 ± 6.0 (n = 65)	9.5 ± 6.1 (n = 17)	F = 6.88	**p<0.001****
Receiving psychotropic medications during rTMS	31 (86%)	15 (88%)	63 (91%)	15 (88%)		
SSRIs	15 (42%)	5 (29%)	24 (35%)	6 (35%)		
SNRIs	12 (33%)	4 (24%)	9 (13%)	3 (18%)		
TCAs	2 (6%)	2 (12%)	1 (1%)	0 (0%)		
MAOIs	0 (0%)	0 (0%)	5 (7%)	1 (6%)		
Atypical Antidepressants	16 (44%)	6 (35%)	42 (61%)	8 (47%)		
Atypical Antipsychotics	12 (33%)	6 (35%)	21 (30%)	7 (41%)		
Antiepileptics	14 (39%)	7 (41%)	28 (41%)	6 (35%)		
Benzodiazepines	15 (42%)	8 (47%)	26 (38%)	4 (24%)		
Stimulants	11 (31%)	5 (29%)	23 (33%)	4 (24%)		
Lithium	0 (0%)	0 (0%)	8 (12%)	2 (12%)		
Device Type	Neurostar 23 (64%) Magstim 7 (19%) Magventure 6 (17%)	Neurostar 14 (82%) Magstim 2 (12%) Magventure1 (6%)	Neurostar 49 (71%) Magstim 17 (25%) Magventure3 (4%)	Magstim 11 (65%) Magventure: 6 (35%)		

HFL: High-frequency, left-sided treatment; BL: Bilateral treatment; iTBS-P: intermittent theta-burst stimulation priming; IDS-SR: Inventory of Depressive Symptomatology (Self-Report); rTMS: Repetitive Transcranial Magnetic Stimulation; SSRIs: Selective Serotonin Reuptake Inhibitors; SNRIs: Serotonin and Norepinephrine Reuptake Inhibitors; TCAs: Tricyclic Antidepressants; MAOIs: Monoamine Oxidase Inhibitors. *HFL early Responders*: participants who obtained ≥20% improvement from baseline IDS-SR at treatment 10. *HFL non-responders*: participants who obtained <20% improvement from baseline IDS-SR at treatment 10. *BL:* participants who received sequential bilateral treatment, HFL followed by LFR after their switch. *iTBS-P:* Participants who received iTBS priming stimulation followed by HFL after their switch. Data expressed presented as mean ± standard deviation.

[a] Response defined as ≥50% improvement from baseline IDS-SR score at treatment 30.

[b] Remission defined as IDS-SR total score ≤13 at treatment 30.

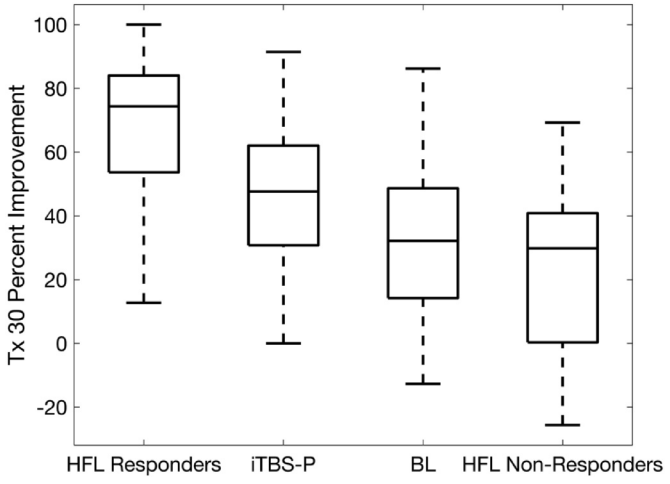

Fig. 1. Boxplot of percent improvement by group at treatment 30. Shows the final median percent improvement in each group. Apart from HFL responders, those who switched to iTBS-P had the greatest percent improvement. Patients who achieved <20% improvement by treatment 10 who continued receiving HFL fared the worst.

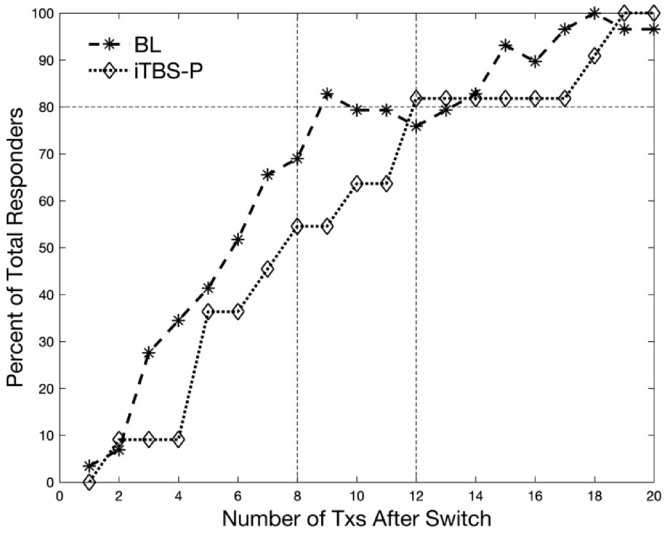

Fig. 2. Time-course over which patients gained an additional 20% improvement post-switch. The proportion of individuals ultimately achieving a 20% improvement in IDS-SR after switching to BL (n = 29, 42%) or iTBS-P (n = 11, 65%) treatments (at treatment 5 or beyond) compared to early HFL non-responders who improved at-least 20% on their IDS-SR in the first two weeks and continued with HFL. BL and iTBS-P augmentation necessitated 8 and 12 post-switch treatments, respectively, to achieve the predetermined threshold of 20% improvement in 80% of participants.

further suggest that additional treatments after switching could have uncovered statistically different outcomes.

This position is supported by Yip et al. (2017) who found that they could achieve a 61% response rate by delivering four additional weeks of twice weekly deep TMS in unmedicated participants who failed to respond after four-weeks of treatment This finding underscores the variability in time course of individual responses to acute rTMS treatment, and suggests that continuation treatment beyond six weeks, could yield greater overall response rates. Whether additional weeks of treatment would have widened the gap between HFL, LFR, and BL approaches in the study by Fitzgerald et al. (2018), or between HFL,

iTBS-P, and BL in ours, remains speculative. In view of our findings that incremental benefits associated with switching accrue over ten sessions, however, it seems plausible that additional treatments with BL or HFL would not accrue additional benefit.

In a time- and cost-sensitive healthcare environment (Voigt et al., 2017), the ideal augmentation strategy would maximize both efficacy and efficiency. In our study, iTBS-P was not only more efficacious but also required ~17 fewer minutes per day than BL treatment. iTBS-P also obviated the need to reposition the coil to F4 to deliver LFR stimulation associated with BL treatment. Our results suggest that electing to augment with iTBS-P instead of BL could result in roughly six hours of "found" time over a hypothetical course of 20 post-switch sessions at the individual patient level. This difference would not only lessen treatment-burden, but, multiplied over several patients' treatment courses, could render iTBS-P much more feasible than BL treatment in busy clinical contexts.

The results of this study should be interpreted in the context of three primary limitations. First, rTMS parameters were assigned by treating physicians based on weekly mood ratings using a measurement-based treatment algorithm in an unblinded fashion, limiting the causal inferences that can be drawn between changes in treatment strategy and outcome. While bias and placebo effects in patient self-reports cannot be excluded, this naturalistic approach arguably enhanced the study's ecological validity. Future studies should confirm these findings in a randomized, blinded trial comparing iTBS-P with other augmentation strategies, including BL treatment. Second, several different TMS devices were used to deliver treatment (i.e. Magventure, Magstim, and Neurostar). The impact of device-type on clinical effectiveness remains unclear, although our data did not reveal significant device differences. Finally, the great majority of participants received medications during their rTMS treatment courses. While these medications remained consistent for most patients, rare switches in concomitant medications could have affected clinical outcomes. The level of experimental control in our study, however, was comparable to that of other real-world studies of treatment-resistant depression such as the STAR*D trial (Wisniewski et al., 2009).

Decades after STAR*D underscored the value of switching and augmenting pharmacological treatment strategies (Sinyor et al., 2010), much remains unknown about effective rTMS augmentation strategies for TRD. Our results support previous findings suggesting the comparative value of priming stimulation (Mutz et al., 2019), and show for the first time that iTBS-P is an effective strategy for those participants lacking early response to HFL. Additionally, these findings suggest at least 10 treatments are needed to assess the clinical benefit of an rTMS augmentation strategy. Future controlled-trials could determine if iTBS-P could enhance overall rTMS response rates in all participants receiving HFL treatment and delineate the healthcare utilization and economic implications of this brief, effective augmentation strategy in comparison to its alternatives.

Author statement contributors

JCL – conceptualization, design, data curation, interpretation, drafting, revising manuscript, final approval

ACW – conceptualization, design, data curation, data analysis, interpretation, drafting, revising manuscript, final approval

JC – conceptualization, design, data curation, data analysis, interpretation, figures, drafting, revising manuscript, final approval

RT - conceptualization, design, data curation, data analysis, interpretation, figures, drafting, revising manuscript, final approval

KGM – data curation, interpretation, drafting, revising manuscript, final approval

CMP – data curation, interpretation, drafting, revising manuscript, final approval

DEK – interpretation, revising manuscript, final approval

SAW – data curation, interpretation, drafting, revising manuscript, final approval

JGL – data curation, interpretation, drafting, revising manuscript, final approval

NDG – data curation, interpretation, drafting, revising manuscript, final approval

AFL - conceptualization, design, data curation, data analysis, interpretation, figures, drafting, revising manuscript, final approval

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Declaration of Competing Interest

Jonathan Lee has received in-kind equipment support from Magventure Inc.

Andrew Wilson has served as a consultant to HeartCloud, Inc. within the past 36 months.

Juliana Corlier has no disclosures to report.

Reza Tadayon-Nejad has no disclosures to report.

Katharine Marder has no disclosures to report.

Christopher Pleman has no disclosures to report.

David Krantz has no disclosures to report.

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