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ORIGINAL ARTICLE

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Effect of high frequency versus theta-burst repetitive transcranial magnetic stimulation on suicidality in patients with treatment-resistant depression

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Abstract

Objective: To investigate the effect of 10 Hz repetitive transcranial magnetic stimulation (rTMS) and intermittent theta-burst stimulation (iTBS) on suicidality in patients with treatment-resistant depression (TRD).

Methods: We used data from a three-site randomized clinical trial comparing 10 Hz rTMS and iTBS applied to the left dorsolateral prefrontal cortex (DLPFC) in patients with TRD. We compared the effect of 10Hz rTMS and iTBS on suicidality as measured by the suicide item of the Hamilton Depression Rating Scale 17-item (HDRS-17).

Results: Suicidality remitted in 71 (43.7%) participants randomized to 10Hz stimulation and 91 (49.1%) participants randomized to iTBS, without a significant difference between the proportions in the two groups ($X^2 = 0.674$, df = 1, $p = 0.4117$). There was a significant correlation between change in suicidality and change in depression severity for both modalities (10 Hz, Pearson's $r = 0.564$; iTBS, Pearson's $r = 0.502$), with a significantly larger decrease in depression severity for those in whom suicidality remitted compared to those in whom it did not ($t = 10.912$, df = 276.8, $p < 0.001$).

Conclusions: Both 10 Hz and iTBS rTMS were effective in reducing suicidality in TRD. Future trials of iTBS for depression should include discrete measures of suicidality.

KEYWORDS

brain stimulation, repetitive transcranial magnetic stimulation, suicidality, treatment-resistant depression

1 | INTRODUCTION

Major depressive disorder (MDD) is the leading cause of disability worldwide, affecting more than 322 million people.[1] More than half of MDD patients fail to remit after first-line therapy—which includes pharmacotherapy, psychotherapy or both[2]—with a progressively smaller proportion of patients remitting with each subsequent medication trial, and a remission rate of only 10–15% after a fourth antidepressant trial.[3-5] When patients with MDD do not achieve response to first-line antidepressants, they are considered to have a treatment-resistant depression (TRD).[6,7] In comparison with the general population, MDD is associated with a 2.3 fold increase in prevalence of suicidal ideation,[8] with a lifetime rate of death due to suicide of 15–20%.[9] Evidence suggests that 30% of patients with TRD will attempt suicide during their lifetime, which is a two-to-four times greater proportion than those patients with MDD responsive to treatment.[7,10]

Repetitive transcranial magnetic stimulation (rTMS) is an effective intervention for TRD, especially when applied over the prefrontal cortex.[11] It uses powerful, brief magnetic pulses to induce neuronal depolarization in the target cortical area, which alters cortical excitability in a lasting manner. It is usually applied over the dorsolateral prefrontal cortex (DLPFC), a brain region of interest in MDD, which is involved in regulating thoughts, emotions and behaviour.[12-14]

There are a wide variety of rTMS parameters both described in the literature and employed in clinical practice. The conventional, original FDA-approved rTMS modality is delivered to the left DLPFC at 10Hz for 37.5 min per session.[15,16] A newer rTMS modality, called intermittent theta-burst stimulation (iTBS), delivers 600 pulses in only 3 min; it has similar or more potent neurophysiological effects,[17] and has been shown to be superior to sham for TRD.[17-20] In a three-site non-inferiority randomized trial (THREE-D trial) directly comparing the efficacy of iTBS and 10 Hz rTMS in participants with TRD, iTBS was found to be non-inferior to 10 Hz for the treatment of depressive symptoms.[21] This finding contributed to the FDA approval of iTBS for the treatment of TRD.

With the increasing use of rTMS as a treatment for MDD, there is a need to better characterize its effects on suicidality. Participants with high baseline levels of suicidality may require more intensive or different forms of treatment. However, the potential for rTMS to provide relief to those patients with suicidality needs to be better understood.

1.1 | Aims of the study

The overall goal of this analysis was to compare the effect of 10 Hz rTMS and intermittent theta-burst stimulation on suicidality using data from the THREE-D trial. Given the previously reported effects of rTMS on depressive symptoms in general, we hypothesized that there would also be an effect on suicidality. We sought to explore the change in suicidality during treatment and the rates of remission of suicidality in those receiving 10 Hz rTMS and intermittent theta-burst stimulation.

Significant outcomes

- Intermittent theta-burst stimulation continues to be non-inferior to 10 Hz rTMS
- Both treatments resulted in a clinically meaningful reduction in suicidality symptoms
- Continued investigation of individual depressive symptoms will better inform clinical practice

Limitations

- Lack of a sham control arm limits our ability to draw definitive conclusions
- Assessment of suicidality was restricted to a single item of a larger depressive symptom scale
- Participants with severe baseline suicidality symptoms were excluded from the original trial

2 | MATERIAL AND METHODS

This is a secondary analysis of data from the THREE-D trial; full details of the protocol are reported elsewhere.[21] The analysis focused on the suicide item of three standardized assessment scales—the Hamilton Depression Rating Scale (HDRS-17),[22] the Inventory of Depressive Symptomatology (IDS-30)[23] and the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR16).[24]

2.1 | Participants

Participants were recruited to the original trial after referral to specialty neurostimulation centres at the Centre for Addiction and Mental Health (Toronto, Canada), Toronto Western Hospital (Toronto) and the University of British Columbia Hospital (Vancouver, Canada). Detailed inclusion and exclusion criteria are reported elsewhere; however, it is important to note that participants with active suicidal intent were excluded from the original trial. The study was approved by the research ethics boards of the three institutions, and written informed consent was obtained from all participants prior to study

participation.[21] The trial was registered on ClinicalTrials.gov (NCT01887782).

2.2 | Intervention

Each participant received a high-resolution anatomical MRI before treatment, and real-time MRI-guided neuronavigation (ANT Neuro, Enschede, Netherlands) was used in each treatment session to position the treatment coil.[21] The left DLPFC was localized in each participant by reverse co-registration from the MNI152 stereotaxic coordinate (x-38, y+44, z+26).[25] rTMS was delivered with a MagPro X100 or R30 stimulator, equipped with a B70 fluid-cooled coil and high-performance cooler (MagVenture, Farum, Denmark). Resting motor threshold (RMT) was determined for each participant using visual observation in accordance with standard clinical practice.[26] See Table 1 for detailed stimulation parameters.

2.3 | Clinical assessments

The GRID version of the HDRS-17[27] was administered by a trained rater at baseline, after every five treatments and following the completion of the acute intervention. At the same time points, the same rater administered the IDS-30, and the self-rated QIDS-SR16 was completed by each participant. Suicidality was measured using the suicide items of the HDRS-17 (item 3), IDS-30 (item 18) and QIDS-SR16 (item 12). See Appendix A for individual items and scoring anchors.

2.4 | Statistical analysis

2.4.1 | Primary analyses using the HDRS suicide item (#3)

Only participants with a non-zero baseline score on item 3 of the HDRS-17 were included in the analysis. The primary outcome was remission of suicidality, defined as a decrease from any non-zero score on the suicide item of the HDRS-17 before intervention to a score of zero at the end of acute intervention. A chi-squared test was performed to assess the difference in the proportion of remitters between the two treatment groups. A survival analysis was also performed to investigate differences in the time to reach remission in each treatment group. Additionally, a linear regression model was created to investigate whether baseline severity of suicidality affected the time to reach remission.

A Pearson correlation was performed to determine the correlation between overall change in HDRS-16 total score (not including item 3) and change in suicidality score at the end of the acute intervention. A Welch two-sample *t*-test was performed to determine whether there was a significant difference in the change in HDRS-16 total score when comparing those participants who achieved suicidality remission and those who did not.

Finally, a chi-squared test was performed to investigate any difference between treatment groups in the following subgroups: participants with a non-zero baseline suicidality score whose score improved but did not reach remission by the end of the acute intervention, and participants with a non-zero baseline suicidality score whose score worsened during the treatment course.

2.4.2 | Sensitivity analyses: Composite score

To account for any differences in reporting that may occur with different clinical assessments, the suicide item of each scale (HDRS-17, IDS-30 and QIDS-16) was used and their scores were averaged at each time point for each patient to create a composite suicidality score. Again, remission was defined as a combined score of zero by the end of the acute intervention. Participants missing any of the three suicidality measures at any time point were excluded from this sensitivity analysis so as not to bias scores in favour of reduced suicidality due to missing data. Chi-squared tests were performed as outlined above to assess differences between the two treatment groups.

TABLE 1 Stimulation parameters used with 10 Hz rTMS and iTBS

	10 Hz	iTBS
Stimulation intensity	120% RMT	120% RMT
Frequency	10Hz	Triplet 50 Hz bursts, repeated at 5 Hz
Train duration	4 s on and 26 s off	2 s on and 8 s off
Total pulses per session	3000	600
Total treatment duration	37.5 min	3 min 9 s
Total number of treatments	20–30 (5 sessions per week)	20–30 (5 sessions per week)

Abbreviations: iTBS, intermittent theta-burst stimulation; RMT, resting motor threshold.

3 | RESULTS

3.1 | Primary analyses using the HDRS suicide item (#3)

After removing participants with a suicidality score of zero at baseline, 301 participants remained (10 Hz, n = 142; iTBS, n = 159). Suicidality remitted in 71 (43.7%) participants randomized to 10Hz stimulation and 91 (49.1%) participants randomized to iTBS, without a significant difference between the proportions in the two groups ($X^2 = 0.674$, df = 1, $p = 0.4117$) (Figure 1a). The survival analysis showed no significant difference in the mean (SD) number of weeks needed to reach suicidality remission: 3.23 (1.86) weeks for the 10 Hz group and 3.13 (1.62) weeks for the iTBS group ($X^2 = 1$, df = 1, $p = 0.30$) (Figure 2). A linear regression model was generated for those participants who reached remission, to determine whether baseline suicidality severity affected the time to reach remission and whether the treatment groups differed no significant effect was found ($R^2 = 0.0158$, $p = 0.54$). The frequency of raw scores on item 3 of the HDRS-17 over time can be viewed in Figure 3.

Changes in HDRS-16 total score and suicidality score before and after treatment significantly correlated in both treatment groups (10 Hz group: Pearson's $r = 0.564$, $n = 142$, $p < 0.001$; iTBS group: Pearson's $r = 0.502$, $n = 159$, $p < 0.001$). The mean (SD) HRSD-16 scores (Figure 1b) decreased 5.18 (6.22) points in the suicidality non-remitter group vs. 13.23 (6.10) points in the suicidality remitter group, a statistically significant difference (Welch 2-sample $t = 10.912$, df = 276.8, $p < 0.001$). To avoid the

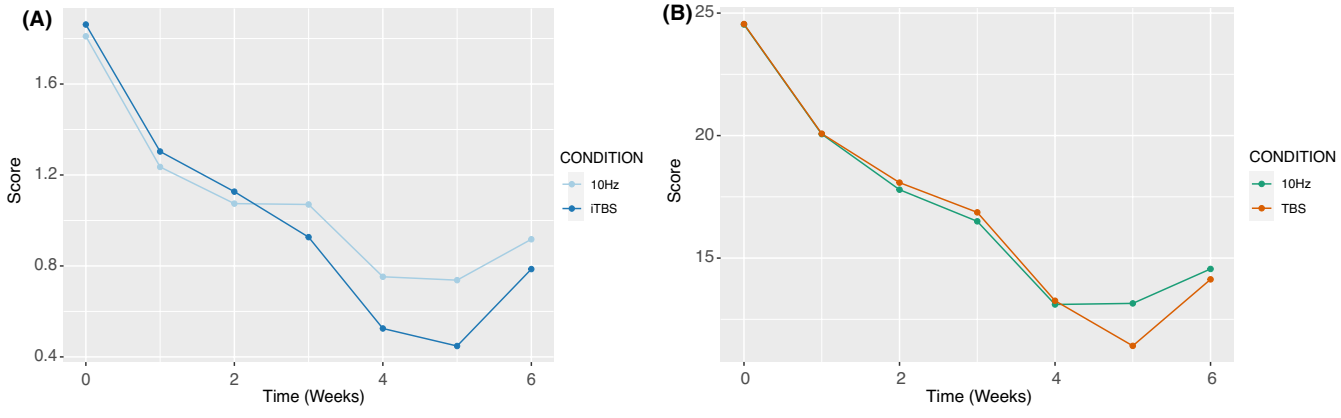

FIGURE 1 The trajectory of mean scores of HDRS-17 suicidality item (#3) over time for participants randomized to 10Hz rTMS or iTBS. Suicidality remitted in 71 (43.7%) participants randomized to 10Hz stimulation and 91 (49.1%) participants randomized to iTBS, without a significant difference between the proportions in the two groups ($X^2 = 0.674$, df = 1, $p = 0.4117$). HDRS-17, Hamilton Depression Rating Scale – 17 Item; iTBS, intermittent theta-burst stimulation; rTMS, repetitive transcranial magnetic stimulation. (A) HDRS-17 suicidality item (#3) Mean score over time in participants randomized to 10 Hz rTMS or iTBS. (B) HDRS-16 mean score over time in participants randomized to 10 Hz rTMS or iTBS

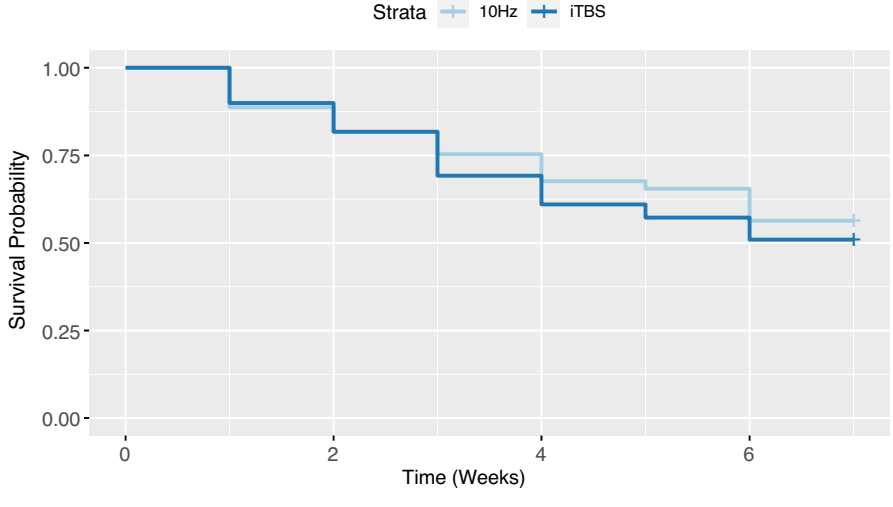

FIGURE 2 Survival analysis of suicidality remission in participants randomized to 10 Hz rTMS or iTBS. The survival analysis showed no significant difference in the mean (SD) number of weeks needed to reach suicidality remission: 3.23 (1.86) weeks for the 10Hz group and 3.13 (1.62) weeks for the iTBS group ($X^2 = 1$, df = 1, $p = 0.30$). HDRS-17, Hamilton Depression Rating Scale – 17 Item; iTBS, intermittent theta-burst stimulation; rTMS, repetitive transcranial magnetic stimulation

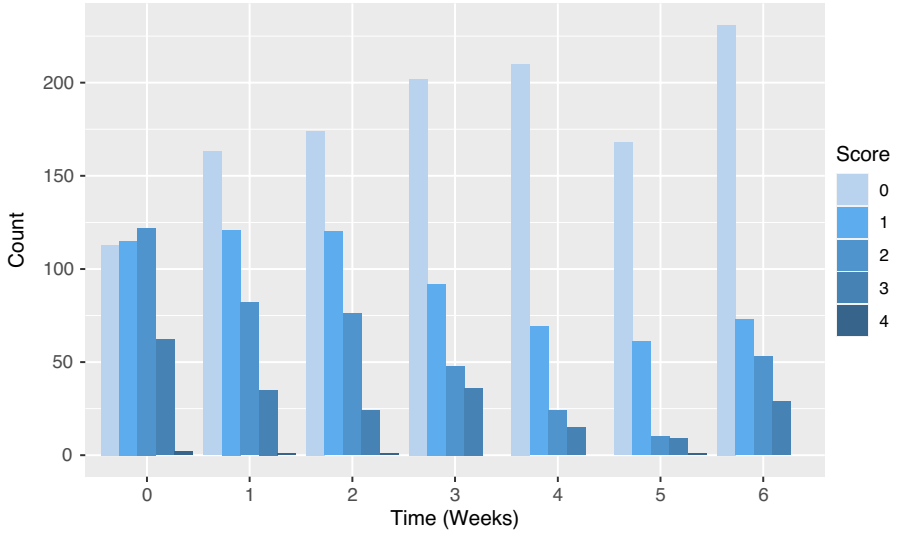

FIGURE 3 Raw HDRS-17 item 3 scores by frequency over time. Frequency of raw HDRS-17 Item 3 scores over time for all participants included in analysis. Patients can achieve scores ranging from Mild (0-1) in which the patient feels that life is not worth living, but has no wish to die, Moderate (1-3) in which the patient wishes to be dead but has no specific suicidal intent or plan, Severe (3-4) in which the patient has a clear suicidal intent or plan, and may have exhibited a suicidal gesture, to Very Severe (4) in which the patient has attempted suicide. HDRS-17, Hamilton Depression Rating Scale – 17 Item

potential confound of multiple comparisons, *p*-values for the above analyses were Bonferroni corrected, with the *p* value for significance set at 0.0125.

Of the 139 participants with a non-zero baseline suicidality score who did not achieve suicidality remission, 61 (43.9%) experienced a decrease in suicidality at the end of the acute intervention and there was no significant difference between the two treatment groups: 10 Hz: $n = 34$ (47.9%) vs. iTBS $n = 27$ (39.7%) ($X^2 = 0.641$, df = 1, $p = 42$). Also, 28 participants (9.3%) with a non-zero baseline suicidality score experienced a worsening in suicidality by the end of the acute intervention; again, there was no significant difference between the two treatment groups: 10 Hz: $n = 15$ (11.1%) vs. iTBS: $n = 13$ (8.78%) ($X^2 = 0.208$, df = 1, $p = 0.65$).

3.2 | Sensitivity analysis: Composite suicidality score

After excluding any participants missing one or more assessment, 315 participants (10 Hz, $n = 156$, iTBS, $n = 159$) were included in the sensitivity analysis using the composite suicidality score. The proportions of suicidality remitters did not differ between the two groups with 63 (40.9%) and 68 (43.3%) suicidality remitters in the 10 Hz and iTBS groups respectively ($X^2 = 0.0988$, df = 1, $p = 0.75$). Of the 184 participants whose suicidality did not remit, 35 (19.0%) saw improvement in their score after treatment; there was no significant difference between the two treatment groups: 10 Hz: 17 (68.0%) vs. iTBS: 18 (78.2%) ($X^2 = 0.225$, df = 1, $p = 0.64$). Only 6 participants experienced a worsening of their suicidality by the end of the acute intervention, and there was no significant difference between the two groups (10 Hz: $n = 3$ (12.0%) vs. iTBS: $n = 3$ (13.0%) ($X^2 = 0.183$, df = 1, $p = 0.67$).

4 | DISCUSSION

To our knowledge, this is the first report that compares the effects of 10 Hz and iTBS left DLPFC-rTMS on suicidality. There was no significant difference between 10 Hz rTMS and iTBS in suicidality remission rate or any of the additional measures we examined, either in the primary analysis based on the HDRS-17 suicide item, or in the sensitivity analysis combining all available suicidality measures. This overall finding is consistent with previous work investigating the efficacy of iTBS treatment on overall depressive symptoms[17-20,28] and adds further evidence on the clinical impact of iTBS in clinical practice.

Our analysis found that both 10 Hz and iTBS resulted in a clinically meaningful proportion of suicidality remitters (10 Hz: 43.7%, iTBS: 49.1%), and suicidality resolved within a few weeks of the initiation of treatment, with a mean time to suicidality remission of 3.2 and 3.1 weeks with 10 Hz rTMS and iTBS respectively. Previous studies that have examined the effect of rTMS on suicidality have reported mixed results. The number of randomized controlled trials in the literature that specifically address suicidality is small, and there is a high degree of heterogeneity in study designs, treatment modalities and outcome measures. A pilot study of accelerated rTMS on inpatients

with suicidal ideation ($N = 41$) found a significant decrease in suicidality scores over nine treatments, but found no significant difference between active and sham treatments.[29] A similar trial investigating accelerated rTMS in antidepressant free outpatients ($N = 50$) found a similar significant decrease in suicidality scores but no difference between active and sham.[30] In a randomized controlled trial in a population of US veterans ($N = 164$), the effect of 10Hz rTMS on suicidality did not differ from the effect of the sham intervention.[31] In a randomized trial comparing the effects of rTMS and electroconvulsive therapy (ECT) on suicidality ($N = 73$), both treatments resulted in significant decreases in suicidality, although ECT had a stronger anti-suicidal effect than rTMS.[32] On the contrary, Pan et al.[33] ($N = 42$) found that active 10 Hz rTMS combined with escitalopram (10 mg/day) resulted in a significantly higher decrease in suicidality than sham rTMS plus escitalopram. A number of studies have endeavoured to systematically review the extant literature on the effect of rTMS on suicidality. Serafini et al. (2015)[34] conclude that rTMS has been found to attenuate multiple dimensions of suicidality, but that further sham-controlled studies were needed. Bozzay et al. (2020)[35] conclude that there is preliminary promise that rTMS can target SI, but called for further suicide-specific research, as well as the development of mechanistic targets for SI. A systematic review of the effect of all neuromodulation treatments on suicidality found that most studies resulted in a significant decrease in suicidality, and identify TMS as a promising therapeutic tool to directly address suicidal ideation in the context of mood disorders.[36] Godi et al. (2021) also identify rTMS delivered to the left DLPFC as a promising treatment in reducing suicidal behaviour in TRD, but highlight targeting of other cortical regions areas to mitigate suicide risk could not be established due to a scarcity of data.[37] Yet another review identified inconsistencies in results across rTMS studies for suicidality and called for further research into more naturalistic conditions with larger sample sizes to establish the superiority of active rTMS over sham.[38] With the lack of consistent findings in the literature as well as small sample sizes and diverse methodologies, dedicated large-scale sham-controlled trials are needed to further investigate the effect of rTMS on suicidality.

In our sample that excluded patients with the highest risk (i.e. those with suicidal ideation with plan and intent), baseline suicidality severity did not impact the time to reach suicidality remission in either treatment group. If this finding is replicated in a study using a suicide assessment scale as its outcome measure and including patients with higher level of suicidality, it would challenge the current clinical practice of referring patients who present with higher suicidality severity to inpatient treatment or to treatment with ECT. While further investigation is needed, our findings support the use of rTMS in patients with mild to moderate suicidality.

Our analysis found a significantly higher decrease in total HDRS-16 score in suicidality remitters than in non-remitters. While a correlation between change in overall depression score and suicidality score has been reported in previous analyses,[10,39-42] our analysis emphasizes the importance of assessing and analysing suicidality as a separate outcome in treatment studies of MDD. For example, Weissman et al.[39] found a significant decrease in suicidality score with bilateral rTMS treatment when compared to sham rTMS in an analysis of data from two randomized controlled rTMS trials, and a higher rate of remission of suicidality than overall depressive symptoms. A potential implication of these findings would be that suicidality response does not depend on overall depressive symptom response, and that targeting the right DLPFC and the left contributes to the decrease in suicidality scores. The majority of rTMS trials to date—including the THREE-D trial and the other rTMS RCTs outlined in this discussion—have targeted the left DLPFC for the treatment of depressive symptoms, leaving the effects of alternative rTMS coil placement on suicidality as an area that requires further investigation.

It is likely that unique biological mechanisms underly suicidality; for example, dysregulation of the hypothalamic–pituitary–adrenal axis and loss of neuroplasticity have been reported in suicide victims.[43] A recent electrophysiological study implicated the right DLPFC in the resolution of suicidality in patients undergoing a more powerful form of transcranial magnetic stimulation (TMS), magnetic seizure therapy (MST).[15,42] Another recent study found that baseline levels of left DLPFC activation were linked to resolution of suicidality after active rTMS but not after sham.[44] The treatment of suicidality as a separate entity that is not solely related to depressive symptoms is an area of active research, and further investigation is required to establish its underlying pathophysiology and to design specific therapeutic approaches.

A variety of rTMS modalities (i.e. 10Hz, iTBS and DTMS) will likely persist both in clinical practice and in research settings. The investigation of the effect of rTMS on individual symptom domains can provide insight to inform clinical practice regarding which rTMS modality and treatment configuration is best suited to each individual patient and their symptom presentation. This variety of treatment approaches also aligns with broader efforts in health care to personalize treatments to individual patients, and having a breadth of treatment options will maximize the utility of rTMS as a treatment for refractory mental illness.

The number of RCTs investigating the effects of rTMS on suicidality is limited, in part due to the majority of

acutely suicidal patients with MDD being hospitalized or given ECT. However, rTMS has been established as an effective treatment for TRD, and its effects on suicidality specifically are an area of active research. Efforts to conduct future large sham-controlled trials using dedicated suicide scales are needed to further understand the role of this intervention for patients with a broad range of suicidality. Our findings support that 10Hz rTMS and iTBS have very similar and clinically meaningful effects on suicidality. Due to the brief nature of iTBS, multiple groups are exploring the use of multiple sessions of iTBS per day to accelerate resolution of depressive symptoms.[29,30,45,46] Those trials should include more comprehensive measures of suicidality to inform whether such accelerated approaches can rapidly ameliorate suicidality.

5 | LIMITATIONS

This analysis has several limitations. The RCT that provided data for our analysis was not designed to assess our specific hypothesis of the effect of rTMS on suicidality, nor was it powered a-priori to do so. The lack of a sham control arm in the original trial limits our ability to make conclusions with respect to the specific effects of rTMS on suicidality. Also, both 10Hz and iTBS rTMS were delivered unilaterally to the left DLPFC, and as such, this analysis cannot address the effects on suicidality of other potential treatment targets. Additionally, suicidality was measured with the suicide item of the HDRS-17 instead of a dedicated suicide scale such as the Beck Scale for Suicidal Ideation (BSI) or the Columbia Suicide Severity Rating Scale (C-SSRS). This approach has been adopted by previous studies to measure treatment response,[10,39,47-49] and Szanto et al. (2003)[48] were able to successfully stratify suicide risk at baseline and predict response of suicidality to antidepressant treatment using the suicide item of the HDRS-17. In addition, item 3 of the HDRS-17 has been shown to be sensitive to change.[50-52] However, there are dimension of suicidality that are not captured by this item, including key indicators of risk such as previous suicide attempts, hopelessness and locus of control. Finally, the majority of participants included in the analysis did not present with severe suicidality, and as such, our ability to generalize our findings to that population is limited.

CONFLICT OF INTEREST

SM and CRW report no financial disclosures.

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

Research data are available upon request.

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APPENDIX A

A1 | HDRS-17 GRID SUICIDE ITEM (#3) SCORING ANCHORS

3. Suicide	Absent or clinically insignificant	Occasional	Much of the time	Almost all the time
Symptom Intensity				
Absent	☐ 0			
Mild (Feels life is not worth living, but expresses no wish to die e.g., "I don't care if I live or die")	☐ 0	☐ 1	☐ 1	☐ 2
Moderate (Wishes to be dead; thoughts of dying, but no specific plan or intent, e.g., "If i got hit by a bus, I wouldn't care," "I'd like to go to sleep and never wake up")		☐ 1	☐ 2	☐ 3
Severe (Clear suicidal plan or intent; suicidal gesture, e. g. taking a few sleeping pills)		☐ 3	☐ 3	☐ 4
Very severe (Attempts at suicide)		☐ 4	☐ 4	☐ 4

A2 | IDS-30 SUICIDE ITEM (#19) SCORING ANCHORS

0—Does not think of suicide of death.
1—Feels life is empty or not worth living.
2—Thinks of suicide/death several times a week for several minutes.
3—Thinks of suicide/death several times a day in depth, or has made or attempted suicide.

A3 | QIDS-SR16 SUICIDE ITEM (#12) SCORING ANCHORS

0—I do not think of suicide or death.
1—I feel that life is empty or wonder if it's worth living.
2—I think of suicide or death several times a week for several minutes.
3—I think of suicide or death several times a day in some details, or I have made specific plans for suicide of have actually tried to take my life.