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Does switching between high frequency rTMS and theta burst stimulation improve depression outcomes?

To the editor,

We read with interest recent articles in *Brain Stimulation*, reporting on the antidepressant effects of theta burst stimulation (TBS) applied in accelerated schedules [1,2] and the efficacy comparison between unilateral and bilateral repetitive transcranial magnetic stimulation (rTMS) approaches [3]. We recently reported a multisite randomized controlled trial comparing the antidepressant efficacy of accelerated bilateral TBS applied at 80% or 120% of the resting motor threshold (RMT) and left-sided 10 Hz rTMS applied at 120% RMT [4]. The increasing evidence base supporting TBS's antidepressant effects has seen it gain acceptance as an alternative to standard left-sided 10 Hz rTMS in treatment-resistant depression (TRD). Little is known whether TRD patients who do not experience antidepressant benefits with a standard course of rTMS might do so with a subsequent course of TBS, or vice-versa. Given that approximately 60–80% of patients who undergo a course of left-sided 10 Hz rTMS can expect to experience depression treatment response [3,5], this is a clinically relevant knowledge gap for which minimal evidence-based guidance exists. One way to address this is to evaluate non-responders' treatment outcomes to a crossover course of the alternate stimulation protocol. To our knowledge, such a crossover study has not been reported.

We report the treatment outcomes of participants from our study [4] who did not achieve treatment response from an initial course of left-sided 10 Hz rTMS or accelerated bilateral TBS, who then underwent an elective crossover course of the other rTMS modality. Of 300 consenting participants, 299 were randomized to one of two accelerated bilateral TBS treatment arms (24,000 pulses over 20 sessions across 10 days) or to the 10 Hz rTMS arm (60,000 pulses over 20 sessions across 4 weeks). Details of the study protocol are previously described [4]. More than 80% (252/300) of participants completed the initial treatment course (rTMS or TBS) and week 4 assessment. Elective crossover to accelerated bilateral TBS applied at 120% RMT or left-sided 10 Hz rTMS were offered to 142 participants identified as non-responders (Supplementary Fig. S1). Treatment response was defined as a $\geq$50% reduction of Quick Inventory of Depressive Symptomatology – Clinician Rated Version (QIDS-C_{16}) score from baseline to week 4 assessment, while depression remission was defined by achieving a QIDS-C_{16} score of $\leq$5 [6]. The elective crossover phase was discussed with study participants at the time of obtaining informed consent and revisited with treatment non-responders at the week 8 review of the initial course. This gap of at least 4-weeks between completion of the initial rTMS/TBS course and the re-assessment of baseline depression severity prior to starting the crossover course sought to minimise carryover treatment effects from the initial to the crossover course.

To investigate antidepressant response to accelerated bilateral TBS following non-response to left-sided 10 Hz rTMS, the proportion of responders to crossover TBS was descriptively considered with reference to the initial rTMS responder proportion of 0%, and vice-versa for non-responders to TBS who underwent crossover 10 Hz rTMS. Mean, standard deviation, median and range of QIDS-C_{16} at baseline timepoints for the initial and crossover treatment courses within each sequence arm (rTMS to TBS and TBS to rTMS) were inspected for carryover effects. Continuous summary statistics were calculated using Stata 17.0 (StataCorp) to characterize depression symptom severity of sequence arms at baseline and week 4 timepoints and within-arm percentage change. The study was approved by the Monash Health Human Research Ethics Committee and registered on the Australian New Zealand Clinical Trials Registry, Trial ID: 12617001443381.

We found that three of eight (38%) non-responders to initial 10 Hz rTMS that crossed over to accelerated bilateral TBS treatment subsequently achieved response status. Two of eight (25%) achieved remission status. Two of ten (20%) non-responders to initial accelerated bilateral TBS achieved response and remission status to crossover 10 Hz rTMS (Supplementary Fig. S1). QIDS-C_{16} summary statistics for each arm are presented in Table 1.

Considering the posited distinctions by which TBS and standard rTMS influence neuronal excitability [7,8], it is reasonable to suggest there is difference in their antidepressant effects, although little is known whether 10 Hz rTMS and TBS non-responders might respond to the alternate rTMS approach. We believe this is the first report of depression treatment outcomes of crossover left-sided 10 Hz rTMS and bilateral TBS in TRD patients who did not respond to the other rTMS modality. We observed that depression treatment response can be achieved following crossover but only in a modest number of participants. This may be attributable to the chronicity and treatment-refractoriness of our participants [4], who have also not responded to an initial course of TBS or rTMS. The data suggests that response may be more likely when switching from 10 Hz rTMS to accelerated bilateral TBS rather than the opposite.

The exploratory nature of this study warrants caution in the interpretation of our findings. The sample size is small. Due to the elective basis on which non-responders proceeded to crossover treatment, results may be prone to volunteer bias. Similarly, treatment expectation bias may have been present in participants who did not achieve depression treatment response with the initial rTMS/TBS course and were keen to trial the alternative treatment. Conversely, few initial treatment non-responders elected to

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Table 1
Descriptive statistics and percentage change of QIDS-C_{16} scores over initial and crossover treatment courses.

Left-sided 10 Hz rTMS non-responders crossed over to accelerated bilateral TBS						
	Mean QIDS-C1$_6$ (SD)	Median QIDS-C_{16}	Range of QIDS-C_{16}	Mean % QIDS-C_{16} change (SD)	Median % QIDS-C_{16} change	Range of % QIDS-C_{16} change
Pre-rTMS baseline (n = 8)	16.38 (2.33)	16.0	[13, 20]	N/A	N/A	N/A
Post-rTMS week 4 (n = 8)	12.88 (5.11)	12.5	[8, 24]	−22.93 (22.00)	−27.21	[-40, 26]
Pre-crossover accelerated TBS baseline (n = 8)	15.13 (3.64)	14.0	[10, 21]	N/A	N/A	N/A
Post-crossover accelerated TBS week 4 (n = 8)	10.38 (6.14)	9.5	[3, 20]	−25.16 (56.00)	−32.05	[-84, 100]
Accelerated bilateral TBS non-responders crossed over to left-sided 10 Hz rTMS						
	Mean QIDS-C_{16} (SD)	Median QIDS-C_{16}	Range of QIDS-C_{16}	Mean % QIDS-C_{16} change (SD)	Median % QIDS-C_{16} change	Range of % QIDS-C_{16} change
Pre-accelerated TBS baseline (n = 10)	17.40 (2.46)	17.0	[12, 21]	N/A	N/A	N/A
Post-accelerated TBS week 4 (n = 10)	13.80 (2.66)	13.5	[11, 20]	−19.79 (15.10)	−20.59	[−45, 5]
Pre-crossover rTMS baseline (n = 10)	16.20 (3.46)	15.5	[12, 22]	N/A	N/A	N/A
Post-crossover rTMS week 4 (n = 10 with 1 LOCF)	12.6 (6.47)	12.5	[4, 21]	−22.95 (37.29)	−25.00	[−76, 54]

proceed to treatment crossover, resulting in reduced power in the crossover phase of the trial. Whilst most participants received concomitant antidepressant therapy, we ensured all participants' antidepressant regimes were unchanged for at least four weeks prior to and during their treatment courses. However, this also meant initial non-responders who underwent antidepressant changes and/or dose increases as part of their clinical treatment became ineligible for the crossover phase of the study. Additionally, it was possible for psychosocial circumstances to have changed for some participants, potentially confounding treatment outcomes. Lastly, although the minimum 4-week gap between the initial and crossover treatment courses was introduced to minimise carry-over treatment effects from the first to the second course of treatment, it is recognized that this delay in the provision of an alternate treatment approach may not reflect typical clinical management of TRD.

Notwithstanding, this study provides preliminary observation that depression treatment response to bilateral TBS or 10 Hz rTMS is possible following an unsuccessful initial course of the other. Future trial protocols that instigate crossover treatment for all non-responders (instead of elective crossover) can help increase study sample sizes and reduce the aforementioned limitations. Introducing an active control arm alongside the crossover arm in which participants receive a repeat course of the initial rTMS/TBS modality would allow more robust investigation into whether response to further treatment is attributable to the alternate modality or the reintroduction of the same treatment over a longer period, seeing as evidence supports the antidepressant efficacy of treatment continuation with both rTMS [9] and electroconvulsive therapy [10]. Identification of clinical factors and biomarkers that inform probability of treatment response to a crossover rTMS/TBS course can further inform the utility of this promising treatment strategy.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: In the last 3 years PBF has received equipment for research from Nexstim and Brainsway Ltd. He is a founder of TMS Clinics Australia and Resonance Therapeutics. KEH is a founder of Resonance Therapeutics. The other authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.brs.2022.06.005.

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Glossary

Hz = Hertz.:
LOCF = last observation carried forward.:
N/A = not applicable.:
rTMS = repetitive transcranial magnetic stimulation.:
TBS = theta burst stimulation.:
QIDS-C_{16} = Quick Inventory of Depressive Symptomatology – Clinician Rated Version.:
SD = standard deviation.:

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