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Accelerated theta burst stimulation for the treatment of depression: A randomised controlled trial

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ABSTRACT

Introduction: Theta burst pattern repetitive transcranial magnetic stimulation (TBS) is increasingly applied to treat depression. TBS's brevity is well-suited to application in accelerated schedules. Sizeable trials of accelerated TBS are lacking; and optimal TBS parameters such as stimulation intensity are not established.

Methods: We conducted a three arm, single blind, randomised, controlled, multi-site trial comparing accelerated bilateral TBS applied at 80 % or 120 % of the resting motor threshold and left unilateral 10 Hz rTMS. 300 patients with treatment-resistant depression (TRD) were recruited. TBS arms applied 20 bilateral prefrontal TBS sessions over 10 days, while the rTMS arm applied 20 daily sessions of 10 Hz rTMS to the left prefrontal cortex over 4 weeks. Primary outcome was depression treatment response at week 4.

Results: The overall treatment response rate was 43.7 % and the remission rate was 28.2 %. There were no significant differences for response ($p = 0.180$) or remission ($p = 0.316$) across the three groups. Response rates between accelerated bilateral TBS applied at sub- and supra-threshold intensities were not significantly different ($p = 0.319$). Linear mixed model analysis showed a significant effect of time ($p < 0.01$), but not rTMS type ($p = 0.680$).

Conclusion: This is the largest accelerated bilateral TBS study to date and provides evidence that it is effective and safe in treating TRD. The accelerated application of TBS was not associated with more rapid antidepressant effects. Bilateral sequential TBS did not have superior antidepressant effect to unilateral 10 Hz rTMS. There was no significant difference in antidepressant efficacy between sub- and supra-threshold accelerated bilateral TBS.

1. Introduction

Major depressive disorder (MDD) is a common psychiatric illness associated with high mortality and morbidity, which can be difficult to treat with conventional psychotherapeutic and pharmacological approaches [1]. Treatment resistance rates of up to

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30 % have been reported [2], resulting in distress and disability for those living with depression, along with carer burden and health economic costs. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that has been extensively investigated and established as an effective therapy for treatment-resistant depression (TRD) [3–6]. rTMS applies localised electromagnetic pulses to superficial neurons of the cerebral cortex, causing repeated neuronal depolarisation, in turn altering neuronal excitability [7–9]. Evidence from early neuroimaging studies of depressed patients identified aberrant blood flow/metabolic activity in the prefrontal cortices [10–12], hence its initial selection as a site to apply rTMS to treat this mood disorder. rTMS modulates prefrontal regional excitability and induces changes in functional connectivity and downstream electrophysiological effects along the frontostriatal and limbic brain networks that the prefrontal cortical neurons project to [13]. These changes are hypothesised to underpin rTMS's mechanisms of action [14–16].

A novel patterned form of rTMS, theta burst stimulation (TBS), applies triplet bursts of gamma frequency (50 Hz) pulses at theta frequency (5 Hz) intervals. TBS appears to induce similar effects as standard rTMS but with markedly less time demands [17–20]. Two forms of TBS have been described: intermittent TBS (iTBS), where 2 s of 50/5 Hz TBS are applied every 10 s over 192 s (600 total pulses) and continuous TBS (cTBS), where 50/5 Hz TBS is applied continuously for 40 s (600 total pulses). Whereas iTBS induces neuronal excitatory effects similar to high-frequency (10–20 Hz) rTMS and is typically applied to the left prefrontal cortex to treat depression, cTBS appears to have an opposite, suppressive effect on neuronal excitability akin to low-frequency (1 Hz) rTMS [18,21], typically applied to the right prefrontal cortex to treat depression. The definitive THREE-D study demonstrated once-daily left-sided iTBS's non-inferiority relative to 10 Hz rTMS [22], leading to its approval by the U.S. Food and Drug Administration (FDA) for the treatment of TRD [23]. With respect to tolerability, TBS has not been found to have poorer safety profile or higher rates of adverse events relative to standard rTMS approaches [24].

The antidepressant efficacy of iTBS [25,26], cTBS [27–29] and bilateral TBS, where cTBS and iTBS are applied sequentially to, respectively, the right and left prefrontal cortices [30–32], have been reported and summarised in recent reviews [33–35]. To date, the only randomised trial that evaluated all three TBS approaches head-to-head showed superior treatment response favouring bilateral TBS (66.7 %) over left-sided iTBS (40.0 %) and right-sided cTBS (25.0 %) [30], although this needs to be considered in the context of the study's small sample size. In a large network meta-analysis combining the results of 113 non-surgical brain stimulation trials in the treatment of acute depression, Mutz et al. suggested bilateral TBS's antidepressant potential (Odds ratio (OR) 4.44, 95 % CI 1.47–13.41) may be superior to high frequency left-sided rTMS (OR 3.17, 95 % CI 2.29–4.37) and left iTBS (OR 3.20, 95 % CI 1.45–7.08), relative to sham stimulation [36]. Given bilateral TBS's antidepressant potential and posited antidepressant superiority over unilateral, left-sided TBS and rTMS approaches, empirical validation by means of a prospective comparison was warranted.

In addition to stimulation site and TBS type, evaluation of TBS's stimulation parameters, such as the stimulation pulse count and intensity, may also improve its antidepressant efficacy and deserves systematic investigation. With respect to the latter, TBS studies in depression have tended to apply TBS at sub- or at-threshold intensities (80–100 %) relative to patients' resting motor thresholds (RMT) [34], while the THREE-D study applied iTBS at 120 % RMT [22]. In preclinical studies, Nettkoven et al. reported increased motor cortical conditioning effects of 90 % and 110% RMT iTBS in healthy controls relative to other stimulation intensities, particularly with progressively longer iTBS durations [37]. Chung et al. investigated iTBS's impact when applied at different intensities to the prefrontal cortex and found 75 % RMT iTBS yielded superior neuronal conditioning effects relative to 50 % and 100 % RMT iTBS [38]. In therapeutic applications, however, it remains undetermined whether supra- or sub-threshold TBS has superior antidepressant efficacy. This formed one of the key research questions for this study.

In its current form, a standard course of rTMS involves daily treatment sessions over 4–6 weeks. This limits its clinical applicability and presents logistical challenges. The application of rTMS may be accelerated with intensive treatment schedules applying multiple treatments per day. Whilst accelerated rTMS trials show therapeutic potential [39–42], the scheduling of multiple rTMS treatments, each lasting 30 min or more, can also be time consuming and practically cumbersome [43]. TBS's brevity of application suggests it could be conveniently applied in intensive/accelerated schedules, in turn reducing the duration of treatment courses. In our pilot study, we found accelerated iTBS to have similar antidepressant efficacy as 10 Hz rTMS applied daily over 4 weeks, but there was no shortening of the time to response [44]. Elsewhere, accelerated TBS's antidepressant potential have also been described [45–47]. A large, definitive trial evaluating accelerated TBS in depression, however, remains to be done.

There is clear merit in optimising rTMS's efficacy and efficiency to treat depression. We therefore sought to investigate the antidepressant and anxiolytic effects of accelerated bilateral TBS and the speed of response, compared with a standard, FDA-approved rTMS protocol that applied daily treatments [48]. To this end, we devised a trial protocol that combined accelerated TBS scheduling (deemed feasible by our pilot accelerated iTBS study [44]), and bilateral prefrontal stimulation, on the assumption that bilateral TBS might yield superior antidepressant efficacy over a standard left-sided 10 Hz rTMS protocol [30,36]. Our primary hypothesis was that accelerated bilateral TBS would have superior antidepressant efficacy over left-sided daily 10 Hz rTMS in TRD. Comparison of supra- (120 % RMT) and sub-threshold (80 % RMT) TBS's antidepressant efficacy was another key study aim. Based on findings from the aforementioned preclinical studies, we hypothesised 80 % RMT TBS would have superior antidepressant efficacy.

2. Methods

2.1. Study design

This was a parallel design, three arm, single blind, randomised, controlled trial conducted across three mental health services in three Australian states. Two sites were outpatient TMS services (The Adelaide Clinic, South Australia, and The Gold Coast University Hospital, Queensland) while the lead coordinating site provided TMS treatment in an inpatient setting (Epworth Camberwell, Victoria). Participants were randomised to one of three groups (Tables 1 and 2) using a computer-generated single random number sequence: 1) Daily 10 Hz rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) over 4 weeks to serve as an active control arm, 2) Low intensity (80 % RMT) sequential cTBS and iTBS applied to the right then left DLPFC in a 10-day accelerated schedule, which included a three-day break between the first and second weeks of treatment (24,000 pulses), or 3) High intensity (120 % RMT) sequential cTBS and iTBS applied to the right then left DLPFC in the same 10-day accelerated schedule (24,000 pulses). Daily 10 Hz rTMS adopted a standard, FDA-approved protocol: 75 × 4-s trains applied daily to the left DLPFC [48], delivering 20 daily treatments over 4-weeks (60,000 pulses). Twenty sessions of 10 Hz rTMS or bilateral TBS were administered across all treatment arms. TBS sessions were separated by 15-min inter-session gaps, measured

Table 1
Treatment parameters.

Treatment Group	Stimulation frequency	Stimulation train duration (s)	Number of trains per treatment session	Inter-train interval (s)	Stimulation intensity (% RMT)	Stimulation target	Pulses per treatment session	Sessions in treatment course	Total pulses in treatment course
1. Standard rTMS	10 Hz	4	75	26	120	Left DLPFC	3000	20	60,000
2. Accelerated BL TBS Low-Intensity	3 × 50 Hz pulses at 5 Hz bursts	40 for cTBS Followed by 192 for iTBS	1	n/a	80	Right DLPFC for cTBS followed by left DLPFC for iTBS	1200	20	24,000
3. Accelerated BL TBS High -Intensity	3 × 50 Hz pulses at 5 Hz bursts	40 for cTBS Followed by 192 for iTBS	1	n/a	120	Right DLPFC for cTBS followed by left DLPFC for iTBS	1200	20	24,000

BL = bilateral; cTBS = continuous theta burst stimulation; DLPFC = dorsolateral prefrontal cortex; Hz = Hertz; iTBS = intermittent theta burst stimulation; min = minute. RMT = resting motor threshold; rTMS = repetitive transcranial magnetic stimulation; s = seconds.
TBS = theta burst stimulation.

from completion of the preceding cTBS/iTBS session to ensure 15-min lapsed before the next cTBS/iTBS session was administered. Participants and clinicians administering the rTMS were aware of the treatment allocation, while the clinical raters remained blinded. Participants were informed at study commencement and reminded prior to each clinical assessment to not disclose their treatment schedule or type to the raters. This study was centrally approved by the Monash Health Human Research Ethics Committee and the Research Governance Offices at the study sites (Epworth HealthCare, Ramsay Health and Queensland Health). This study was registered on the Australian New Zealand Clinical Trials Registry (ANZCTR), Trial ID: 12617001443381.

2.2. Participants

Participants were recruited by referrals from treating clinicians or self-referrals in response to the trial's registration on ANZCTR. All participants were diagnosed with MDD or bipolar disorder (major depressive episode (MDE)) by their referring doctor and/or the study psychiatrist. Diagnoses were confirmed using the Mini International Neuropsychiatric Interview (MINI) [49]. Inclusion criteria for the study were: adults over the age of 18, confirmed diagnoses of MDE or MDD, score of ≥10 (moderate depression) on the Quick Inventory of Depressive Symptomatology – Clinician Rated Version (QIDS-C_{16}) [50,51], and at least Stage II TRD defined by the Thase and Rush classification [52]. Exclusion criteria included participants who had an absolute contraindication to rTMS, were pregnant or breastfeeding or had a clinically significant substance use disorder. All participants were on stable antidepressant regimes or no antidepressant therapy for at least 4 weeks prior to treatment commencement and until week 4 follow-up. For participants who had previously received rTMS or ECT, at least four weeks had lapsed since their last session of ECT or rTMS prior to recruitment. Participants who had previously received and not derived antidepressant benefit with left-sided 10 Hz rTMS were excluded.

Table 2
Schedule of rTMS/accelerated TBS treatments and clinical assessments.

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8–10 follow-up
Treatment groups						
1. Standard rTMS		1 session per day over 5 days	1 session per day over 5 days	1 session per day over 5 days	1 session per day over 5 days	
2. Accelerated BL TBS Low-Intensity		11 sessions. 2 sessions applied on Day 1. 3 sessions applied on Days 2–4. Sessions separated by 15-min breaks.	9 sessions. 2 sessions applied on Day 1. 3 sessions applied on Days 2–4. Sessions separated by 15-min breaks.			
3. Accelerated BL TBS High -Intensity		11 sessions. 2 sessions applied on Day 1. 3 sessions applied on Days 2–4. Sessions separated by 15-min breaks.	9 sessions. 2 sessions applied on Day 1. 3 sessions applied on Days 2–4. Sessions separated by 15-min breaks.			
Clinical assessments						
MINI	X					
QIDS-C_{16}	X	X	X		X	X
QIDS-SR_{16}	X	X	X		X	X
BAI	X	X	X		X	X
SSI	X	X	X		X	X
EQ-5D-3L	X	X	X		X	X

BAI = Beck's Anxiety Inventory.
BL = bilateral.
EQ-5D-3L = EQ-5D Health Questionnaire.
MINI = Mini International Neuropsychiatric Interview.
QIDS-C_{16} = Quick Inventory of Depressive Symptomatology – Clinician Rated Version.
QIDS-SR_{16} = Quick Inventory of Depressive Symptomatology – Self Rated Version.
SSI = Scale for Suicidal Ideation; rTMS = repetitive transcranial magnetic stimulation; TBS = theta burst stimulation.

2.3. TMS treatment

rTMS was administered with figure-of-8 coils using the MagVenture MagPro R30 stimulator with the Cool-B65 coil (MagVenture Inc., Farum, Denmark) at the inpatient treatment site (Epworth Camberwell) and the Neurosoft MS/D stimulator with the AFEC-02-100-C coil (Neurosoft, Ivanovo, Russia) at the outpatient treatment sites (Adelaide Clinic and Gold Coast University Hospital). The coils were held by stands and tangentially placed over the participant's DLPFC, rotated at a 45° angle from the midline. Coil localisation was conducted using the algorithm developed by Beam et al. [53]. Treatment coils were placed over the F3 electrode when targeting the left DLPFC and the F4 electrode for the right DLPFC. Single pulse TMS was used to measure the RMT for the abductor pollicis brevis muscle (APB) using standard published methods and direct visualisation of APB movement [54]. Bilateral RMTs were measured for participants randomised to accelerated bilateral TBS. Training in all trial and treatment processes was provided by the lead site for the three study sites.

2.4. Clinical assessment

Demographic and illness variables and clinical ratings were recorded at baseline. Subsequent clinical assessments were conducted 1, 2, 4 and 8 weeks after treatment commencement for all participants (Table 2). This meant that for those randomised to standard 10 Hz rTMS treatment, the week 4 assessments took place on course completion and for those randomised to accelerated bilateral TBS protocols, 18-days after course completion, given the accelerated bilateral TBS courses were 10-days in duration. Depression severity was assessed using the QIDS-C_{16} and the Quick Inventory of Depressive Symptomatology – Self-Rated Version (QIDS-SR_{16}) [50]. Health-related quality of life was assessed using the EQ-5D Health Questionnaire [55] and single summary indices were calculated using the Australian value set [56]. Presence/severity of suicidal thinking was assessed using the Scale for Suicidal Ideation (SSI) [57]. A protocol amendment added the 21-item self-report Beck's Anxiety Inventory (BAI) [58] during the trial to measure anxiety severity.

2.5. Data analysis

Primary analysis was comparison of the proportion of treatment responders 4 weeks after treatment commencement using the X^2 test. Treatment response was defined as $\geq$ 50 % reduction in the QIDS-C_{16} from baseline while remission was defined as a QIDS-C_{16} score of $\leq$5 [50]. Seeing as end of treatment would be different for those who received accelerated bilateral TBS compared with once-daily 10 Hz rTMS, we conducted a sensitivity analysis at week 2 by comparison of response rates across the three treatment groups using the X^2 test (Supplementary). X^2 tests were also conducted to compare treatment response between the low- and high-intensity accelerated bilateral TBS groups and the proportion of treatment responders across the three groups at week 8 follow-up. Linear Mixed Model Analyses using restricted maximum likelihood (REML) were applied with Fixed Effects of Group and Time with the covariance structure treated as unstructured for all continuous outcome measures. This statistical method assesses changes over time and is robust to violations of normality [59]. It also handles missing values by treating them as missing at random, rather than listwise deletion. The F-test was used to evaluate if there were between-group differences and test for interactions by Time and by Treatment Group. The Bonferroni test was used for post-hoc comparisons between treatment groups at each time point. These utilise the predicted means and standard errors of difference that are recovered from the fitted mixed model. Diagnostic plots of residuals were assessed to ensure normal distribution criteria were met and variance stabilising transformations applied if not. All analyses were conducted using SPSS 25.0 (IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp; 2017).

3. Results

3.1. Patients

300 eligible participants were recruited and consented, as detailed in the CONSORT Flowchart (Fig. 1). There were no notable differences in demographic or clinical variables (Table 3), with specific comparisons between in- and outpatients included as supplementary material. 295 participants entered treatment and 252 participants completed treatment and week 4 assessment. Four participants allocated to the 120 % RMT accelerated bilateral TBS treatment group withdrew from the trial due to difficulty tolerating the stimulation sensation. It was not noted if the intolerance was specifically to cTBS or iTBS. Means of assessment variables across the three groups over each assessment timepoint are presented in Table 4. Sensitivity analysis at week 2 did not identify significant differences in response rates across the three groups.

3.2. Primary outcome – comparison of week 4 QIDS-C_{16} responders

We found an overall response rate of 43.7 % (110/252) and remission rate of 28.2 % (71/252). The proportion of patients who met QIDS-C_{16} response or remission criteria at week 4 did not differ to a statistically significant extent across the three groups (response: $X^2 = 3.429$, $p = 0.180$, remission: $X^2 = 2.303$, $p = 0.316$) (Table 5). Similarly, there were no statistically significant differences in response and remission rates between the inpatient and outpatient cohorts (response: $X^2 = 0.969$, $p = 0.325$, remission: $X^2 = 0.157$, $p = 0.692$) (Table 5). Findings in sensitivity analyses were largely consistent with the main X^2 tests, with no significant differences in response and remission rates between treatment groups at week 2 (Supplementary).

3.3. Low-intensity vs high-intensity TBS

Comparing low-intensity (80 % RMT) with high-intensity (120 % RMT) accelerated bilateral TBS, we found no significant difference in week 4 QIDS-C_{16} response ($X^2 = 0.995$, $p = 0.319$) or remission rates ($X^2 = 0.178$, $p = 0.673$).

3.4. Responders at week 8 follow-up

Due to resource constraints, follow-up until week 8 was not possible for the majority of our outpatient participants. However, QIDS-C_{16} measures at week 8 assessment were available for analysis in 85 of the 116 participants who received rTMS/TBS as inpatients. For these, 43.5 % (37/85) remained in treatment response and 29.4 % (25/85) remained in remission (Table 6). There were no significant differences across the three treatment groups.

3.5. Change in depression severity over time

Applying the linear mixed model to the QIDS-C_{16} scores found a significant main effect of Time ($F(4, 200.65) = 136.92$, $p < 0.001$). There was no effect by Treatment Group ($F(2, 276.89) = 0.38$, $p =$

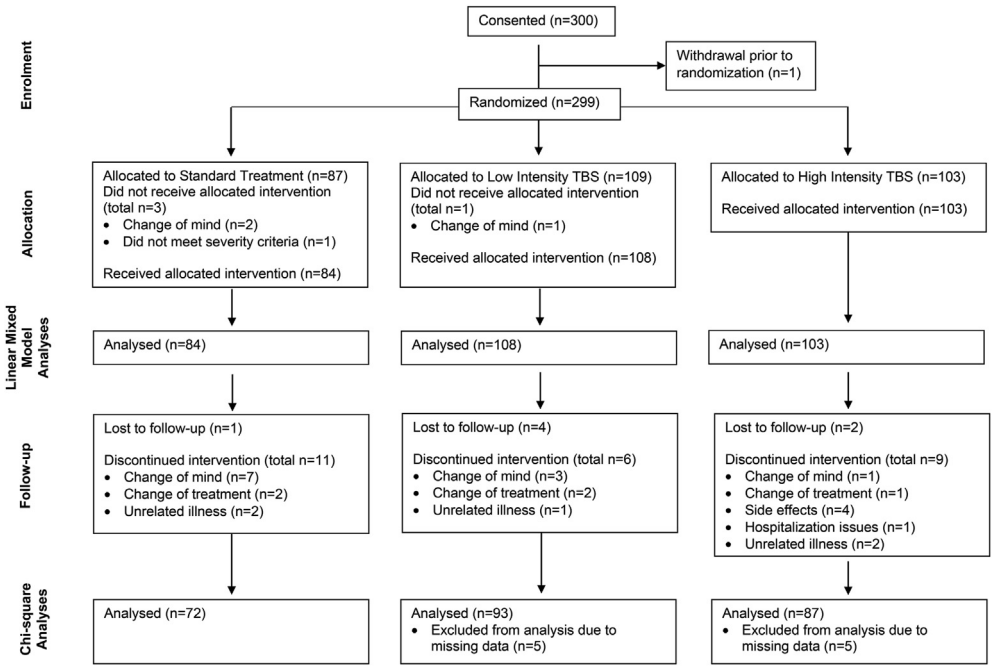

Fig. 1. CONSORT diagram.

0.680). However, there was a significant interaction between Time and Treatment Group (F (8, 200.61) = 2.78, $p = 0.006$). Post-hoc comparisons using the Bonferroni test indicated that the mean QIDS-C score at week 4 in the standard rTMS group was significantly lower compared to the low-intensity TBS; t (118.98) = 2.62, $p = 0.01$ and high-intensity TBS groups; t (118.61) = -3.65, $p < 0.001$. There were no significant differences between the treatment groups at any other time points. Fig. 2 shows reduction in the QIDS-C_{16} mean scores for the three treatment arms at each assessment timepoint. Fig. 3 delineates depression reduction trajectories by treatment groups and in-/out-patient settings.

3.6. Anxiety

There was no significant difference across the three rTMS approaches in reducing anxiety severity from baseline to week 4 and 8 (Fig. 4). Linear mixed model analysis found a significant effect on anxiety severity by Time (F (4, 87.45) = 25.11, $p < 0.001$), but not by Treatment Group (F (2, 109.59) = 0.01, $p = 1.00$).

3.7. QIDS-SR_{16}, suicidality and quality of life

The same linear mixed model was used to analyse the continuous variables of our secondary outcome measures. For the QIDS-

Table 3
Patient demographics, illness and treatment history.

	Standard		Low intensity		High intensity	
	Mean or Frequency	SD	Mean or Frequency	SD	Mean or Frequency	SD
Age	48.67	16.06	48.18	14.14	49.14	15.77
Sex (M/F)	35/49		35/73		33/70	
Diagnosis						
MDD single	37		43		39	
MDD relapse	38		53		47	
Bipolar I	7		6		10	
Bipolar II	2		5		6	
Melancholia (Y/N)	24/58		34/70		35/64	
Psychosis (Y/N)	10/73		10/95		10/90	
Duration of current episodes (months)	48.13	105.91	56.70	104.00	47.91	80.30
Number of depressive episodes	5.06	5.77	6.10	9.25	6.55	8.60
Age of illness onset	25.59	14.85	24.90	13.06	27.64	14.92
Number of antidepressants	8.15	5.65	8.15	5.12	8.68	6.15
Number of other drugs	1.68	2.23	1.77	2.12	1.41	1.80
Past ECT (Y/N)	26/58		39/65		34/66	
Responder to ECT (Y/N)	16/10		17/21		12/23	
Antidepressant (Y/N)	66/16		96/10		89/10	
Antipsychotic (Y/N)	30/51		47/56		30/63	
Mood stabiliser (Y/N)	20/58		33/67		27/66	
Stimulator allocation (MagVenture (Inpatients))/Neurosoft (Outpatients))	30/54		43/65		38/65	

Bipolar I = bipolar affective disorder – type 1; Bipolar II = bipolar affective disorder – type 2; ECT = electroconvulsive therapy; MDD = major depressive disorder.

Table 4
Mean scores of clinical assessments across the 3 treatment groups at each timepoint.

		Baseline			Week 1			Week 2			Week 4			Week 8		
		n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
QIDS-C_{16}	Standard rTMS	84	16.58	3.82	70	12.84	5.46	73	10.89	4.93	72	9.40	5.58	29	11.00	6.19
	Low intensity TBS	107	16.89	4.06	99	12.81	5.20	101	11.48	5.22	93	11.06	5.51	40	10.30	5.96
	High intensity TBS	101	17.40	3.68	93	13.22	4.77	90	11.38	5.64	88	11.80	5.73	39	10.21	5.20
QIDS-SR_{16}	Standard rTMS	83	16.43	4.85	73	11.97	5.72	76	10.41	5.60	70	9.79	6.31	28	10.86	6.50
	Low intensity TBS	103	16.97	5.10	100	12.38	5.53	97	11.10	5.70	88	10.72	6.32	38	11.08	5.99
	High intensity TBS	100	16.90	4.24	92	12.49	5.31	89	11.52	6.27	84	11.79	6.42	36	10.56	5.46
SSI	Standard rTMS	84	8.69	8.93	73	6.23	8.62	76	5.00	7.74	71	4.18	7.50	28	3.86	7.51
	Low intensity TBS	103	10.12	10.49	99	7.59	9.72	95	6.93	9.18	88	5.94	8.83	36	8.06	10.08
	High intensity TBS	99	8.26	9.10	88	5.18	7.30	87	4.79	6.89	83	4.87	7.19	35	3.83	5.86
EQ-5D	Standard rTMS	84	0.47	0.25	73	0.60	0.24	76	0.59	0.23	70	0.65	0.25	30	0.66	0.25
	Low intensity TBS	104	0.50	0.22	103	0.61	0.24	97	0.62	0.24	88	0.66	0.22	41	0.62	0.26
	High intensity TBS	99	0.50	0.22	93	0.59	0.20	89	0.62	0.21	84	0.61	0.23	35	0.66	0.75
Anxiety/Depression item	Standard rTMS	84	2.46	0.50	73	2.15	0.59	76	2.14	0.61	70	1.86	0.64	29	1.86	0.58
	Low intensity TBS	104	2.42	0.57	103	2.14	0.61	97	2.03	0.60	88	1.98	0.61	38	1.97	0.64
	High intensity TBS	100	2.46	0.50	93	2.15	0.53	89	2.08	0.59	84	2.13	0.66	35	2.09	0.56
Health today	Standard rTMS	83	42.94	19.01	72	48.53	20.30	76	51.76	21.02	69	58.83	22.47	29	54.34	22.61
	Low intensity TBS	102	43.55	18.43	101	50.82	19.60	96	54.32	18.46	88	56.59	20.72	37	57.16	19.39
	High intensity TBS	99	45.54	18.65	92	54.72	18.15	88	53.52	20.92	83	54.17	22.44	36	56.83	18.90
BAI	Standard rTMS	33	23.67	13.06	29	17.83	12.69	31	14.06	11.10	29	16.21	13.45	26	17.00	12.88
	Low intensity TBS	35	26.06	12.89	38	18.00	12.74	33	16.76	12.16	29	15.59	13.42	29	13.24	12.04
	High intensity TBS	39	23.95	11.95	36	18.06	12.82	33	14.09	10.80	30	18.20	11.02	29	13.72	11.38

Anxiety/depression item = anxiety/depression item of The EuroQoL EQ-5D Quality of Life Questionnaire; EQ-5D = Summary indices of The EuroQoL EQ-5D Quality of Life Questionnaire; QIDS-C_{16} = Quick Inventory of Depressive Symptomatology – Clinician Rated Version.
QIDS-SR_{16} = Quick Inventory of Depressive Symptomatology – Self Rated Version.
rTMS = repetitive transcranial magnetic stimulation; SSI = Scale for Suicidal Ideation; TBS = theta burst stimulation.

SR_{16}, SSI and the calculated EuroQoL EQ-5D indices, we found a significant effect by Time, but not by Treatment Group (Table 7).

3.8. Safety and tolerability

There were no serious adverse events across the treatment groups. Specifically, there was no induction of seizure or manic episodes in any participant. Gradual intensity titration to target suprathreshold intensities during initial stimulation trains/sessions were necessary in eight participants who received 120 % RMT TBS and five participants who received 10 Hz rTMS, due to initial stimulation-induced scalp discomfort. Overall, all three rTMS protocols were well-tolerated, although four participants allocated to the 120 % RMT TBS treatment group withdrew due to intolerance of the stimulation sensation (Fig. 1).

4. Discussion

This study is, to our knowledge, the first large trial of accelerated bilateral TBS to treat depression and the first to compare the antidepressant efficacy between 80 % and 120 % RMT TBS. As detailed in Tables 3 and 4, patient demographics, diagnoses and baseline illness severity were comparable across the three treatment groups, suggestive of minimal likelihood of sampling bias. Notably, the participants' psychiatric treatment history indicated particularly treatment-refractory depression, with multiple past trials of

Table 5
QIDS-C_{16} Treatment response and remission rates at week 4 endpoint.

Group	Response	Remission
Combined	43.7 % (110/252)	28.2 % (71/252)
L 10 Hz rTMS	51.4 % (37/72)	34.7 % (25/72)
BL TBS low intensity	44.1 % (41/93)	26.9 % (25/93)
BL TBS high intensity	36.8 % (32/87)	24.1 % (21/87)
Chi square statistic	3.429, $p = 0.180$	2.303, $p = 0.316$
Inpatients	**39.6 % (36/91)**	**29.7 % (27/91)**
L 10Hz rTMS	48.0 % (12/25)	36.0 % (9/25)
BL TBS low intensity	44.1 % (15/34)	35.3 % (12/34)
BL TBS high intensity	28.1 % (9/32)	18.8 % (6/32)
Chi square statistic	2.790, $p = 0.248$	2.824, $p = 0.244$
Outpatients	**46.0 % (74/161)**	**27.3 % (44/161)**
L 10Hz rTMS	53.2 % (25/47)	34.0 % (16/47)
BL TBS low intensity	44.1 % (26/59)	22.0 % (13/59)
BL TBS high intensity	41.8 % (23/55)	27.3 % (15/55)
Chi square statistic	1.455, $p = 0.483$	1.900, $p = 0.387$
Cohort comparison (Inpatients vs. Outpatients)		
Chi square statistic	0.969, $p = 0.325$	0.157, $p = 0.692$

BL = bilateral; Hz = Hertz; L = left-sided.
QIDS-C_{16} = Quick Inventory of Depressive Symptomatology – Clinician Rated Version.
TBS = theta burst stimulation.

Table 6
QIDS-C_{16} Treatment response and remission rates at week 8.

Group	Response	Remission
Total	43.5 % (37/85)	29.4 % (25/85)
L 10 Hz rTMS	31.8 % (7/22)	31.8 % (7/22)
BL TBS low intensity	57.6 % (19/33)	27.3 % (9/33)
BL TBS high intensity	36.7 % (11/30)	30.0 % (9/30)
Chi square statistic	4.451, $p = 0.108$	0.139, $p = 0.933$

BL = bilateral; Hz = Hertz; L = left-sided.
QIDS-C_{16} = Quick Inventory of Depressive Symptomatology – Clinician Rated Version.
TBS = theta burst stimulation.

antidepressant medications, and/or mood stabiliser or antipsychotic medication augmentation. Approximately half of our participants had previously been treated with electroconvulsive therapy (ECT). Despite the severity, refractoriness and chronicity of our TRD participants, we found an overall treatment response rate of 43.7 % (110/252) and remission rate of 28.2 % (71/252).

Our primary outcome was comparison of response and remission rates across the standard 10 Hz rTMS, accelerated 80 % RMT bilateral TBS and accelerated 120 % RMT bilateral TBS groups at the week 4 timepoint. We found no clinically or statistically significant differences, which suggests overall equivalent rates of categorical depression response and remission across the three groups, using pre-defined QIDS-C_{16} response and remission criteria [50]. In contrast, post-hoc comparison testing in linear mixed model analysis of the continuous variables found significantly greater reduction in QIDS-C_{16} scores at week 4 in the standard rTMS group compared with the accelerated bilateral TBS groups. This could reflect the discrepancies inherent in the categorical and continuous approaches to measuring depression severity. Whether differences in treatment completion owing to accelerated and once-daily TBS/rTMS scheduling introduced a potential confound is discussed below. Comparing our results with earlier trials, in our pilot study we similarly found no significant differences in antidepressant efficacy or rates of adverse effects between accelerated iTBS and once-daily rTMS [44]. Interestingly, the week 4 response and remission rates across all three treatment arms in the present study (36.8–51.4 % response and 24.1–34.7 % remission) were considerably higher than our pilot investigation (26.3–27.8 % response and 8.3–13.2 % remission), despite equivalent coil localisation techniques and 10 Hz rTMS parameters. These differences could be attributable to the present study's larger sample size and therefore statistical power, the different depression rating scales employed (QIDS-C_{16} versus the Montgomery Åsberg Depression Rating Scale) and, possibly, the additional therapeutic efficacy of bilateral TBS over unilateral iTBS, although this remains to be validated. With respect to other trials evaluating bilateral TBS's antidepressant

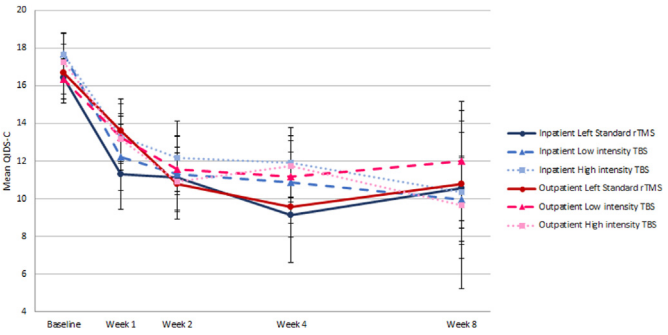

Fig. 3. QIDS-C16 mean scores: in- and out-patients.

efficacy in TRD, Li et al. reported 66.7 % responders (10/15), which was higher than the 40.0 % (6/15) of responders who received iTBS alone [60]. Bröker et al.'s case series of accelerated iTBS reported depression response in 55.6 % (5/9) of participants. However, both studies featured considerably smaller sample sizes, precluding like-for-like comparison. Indeed, comparing our results with published accelerated TBS trials has proven challenging given the paucity of comparable trials and, perhaps more importantly, variability in TBS scheduling and dosing parameters [45,46,61]. To this end, our overall response and remission rates of 43.7 % and 28.2 % respectively, were arguably most comparable with those reported in the THREE-D study: 47.4 % (91/192) responders and 26.6 % (51/192) remitters in the 10 Hz rTMS group, and 49.2 % (95/193) responders and 31.6 % (61/193) remitters in the iTBS group using the 17-item Hamilton Depression Rating Scale [22].

The brevity of TBS paradigms over conventional 37.5-min 10 Hz rTMS protocols confer clear efficiency and health economic advantages [62]. Applying TBS in our accelerated schedule saw to additional time efficiency and markedly reduced the number of occasions patients needed to attend our treatment centres. However, we did not find faster reduction of depression severity with the accelerated application of bilateral TBS compared to a conventional 4-week rTMS approach. This could be explained by Kaster et al.'s depressive symptom trajectory modelling in rTMS [63]. The same four distinct symptom response trajectories were observed when the model was applied to outcomes from our pilot accelerated iTBS versus once-daily rTMS trial, suggesting that rate of antidepressant response was not associated with accelerated treatment scheduling [64]. Nonetheless, the delivery of 20 TBS sessions in a more time-efficient manner offers appreciable convenience and practical advantages for patients and TMS services.

The inter-session interval specified in our accelerated bilateral TBS protocol warrants discussion, given its relevance when scheduling more than one TBS session per day and how different

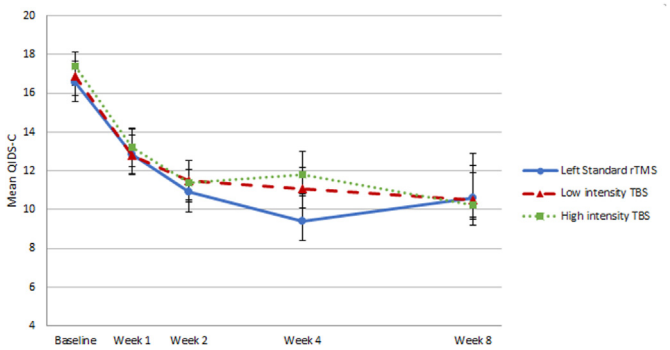

Fig. 2. QIDS-C16 mean scores over time.

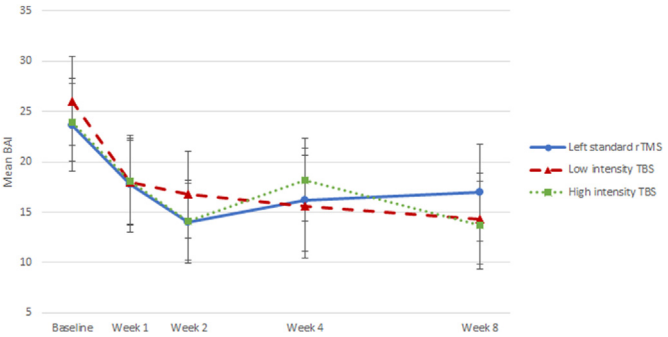

Fig. 4. BAI mean scores over time.

Table 7
Linear mixed model analysis of secondary outcome measures.

Assessment	Effect over time	*P* value	Effect by treatment group	*P* value
QIDS-SR_{16}	F (4, 194.37) = 105.91	<0.001	F (2, 275.25) = 0.35	0.71
BAI	F (4, 87.45) = 25.11	<0.001	F (2, 109.59) = 0.01	1.00
SSI	F (4189.29) = 31.56	<0.001	F (2, 279.41) = 1.41	0.25
EQ-5D	F (4, 191.87) = 40.51	<0.001	F (2, 279.64) = 0.18	0.83

BAI = Beck's Anxiety Inventory (21-item self-report).
EQ-5D = Summary indices of The EuroQoL EQ-5D Quality of Life Questionnaire; QIDS-SR_{16} = Quick Inventory of Depressive Symptomatology – Self Rated Version.
SSI = Scale for Suicidal Ideation.

interval durations could potentially influence TBS's neuronal conditioning and thereby, therapeutic effects. Animal models have shown 1-h intervals between iTBS sessions were necessary for the induction of neuroplastic changes [65], while a study in healthy adults found single- or double-session iTBS applied at 8- or 15-min intervals had no motor cortical excitatory effects [66]. In their review, Smolen et al. suggested 40-60-min intervals are needed between successive theta-burst stimuli to increase neuronal long-term potentiation (LTP) effects and that this may be explained by the initial stimulus's priming effects on dendritic spines before the subsequent stimulus is applied [67]. It is worth considering, however, that findings from experiments evaluating rTMS/TBS's effects on motor cortical excitability may not be extrapolatable to effects on the prefrontal cortex. Likewise, how TMS-induced changes in synaptic plasticity implicate treatment of depressive symptoms remains an area of ongoing investigation. Few depression studies have specifically investigated this aspect of TBS/rTMS's stimulation parameters. As such, the optimal TBS inter-session or rTMS intra-session/inter-train intervals for the purpose of induction of therapeutic effects remain undetermined [68]. With respect to inter-train interval's effects on antidepressant efficacy in 10 Hz rTMS, Carpenter et al. recently reported minimal differences in depression response and remission rates from a large multi-site registry between patients who received standard and a 'Dash' rTMS protocol that featured shorter inter-train intervals [69]. Our study's 15-min TBS inter-session interval mirrored the protocol of our pilot trial [44] and our earlier motor cortical conditioning studies [70,71]. In designing this study, the 15-min interval between three successive bilateral TBS sessions was also in-part chosen with the aim of developing a treatment schedule that could be implemented within an hour and hence align with schedules in a clinical TMS service. Administering three bilateral TBS treatments 45- to 60-min apart could have been practically challenging and inefficient in such settings, particularly for outpatient clinical services. Nonetheless, it remains unclear if longer inter-session intervals, a la the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) protocol [45,61], might have yielded different treatment outcomes for our trial participants.

Prior to the present study, little was known about the optimal TBS intensity relative to RMT for the treatment of depression. Preclinical studies investigating the neuronal conditioning effects of various TBS stimulation intensities on the prefrontal [38] and motor [37] cortices suggested sub- or near-threshold stimulation intensities were associated with significant neuronal conditional effects. The putative physiological basis for this is beyond the scope of this discussion, but was explored by Di Lazarro et al. [72,73] and postulated to be due to near-threshold TMS's preferential activation of interneurons via axonal projections. In our comparison of antidepressant efficacy between sub- and supra-threshold TBS, we did not find clinically or statistically significant differences between the 80 % RMT and 120 % RMT TBS arms. However, we observed that participants were more likely to find the scalp sensation associated with 120 % RMT TBS pulses difficult to tolerate. Given the comparable therapeutic efficacy observed here, sub-threshold TBS may be considered a viable TBS alternative to 120 % RMT TBS, especially for those patients unable to tolerate supra-threshold TBS.

Evaluation of the QIDS-C_{16} and QIDS-SR_{16} measures at week 4 suggest 10 Hz rTMS had superior antidepressant efficacy over the accelerated bilateral TBS approaches (Table 4, Figs. 2 and 3.), although the magnitude of depression symptom amelioration was less noticeable by week 8 follow-up. This observation might be explained by the earlier course discontinuation for patients receiving accelerated bilateral TBS, whereas patients who received the standard 4-week rTMS course benefitted from continuation of trial participation, clinic attendances and rTMS sessions. Discharge of inpatient participants after completion of accelerated bilateral TBS courses may also have seen to earlier relapse of depression in some susceptible patients relative to those continuing with 4 weeks of 10 Hz rTMS therapy, particularly as our trial protocol did not offer completed participants any form of tapering or maintenance rTMS/TBS. Alternatively, it is possible that 20 sessions of bilateral TBS delivered over 10 days was an insufficient dose, in view of the notion that TRD non-responsive to rTMS may be attributable to under-dosing [61] and that patients with highly refractory depression may benefit from more TMS pulses per day [30] and/or more total pulses per course [74]. In contrast to the bilateral cTBS600 and iTBS600 we applied over 20 sessions (equating to a total of 24,000 TBS pulses), Williams et al. reported favourable treatment response rates in both TRD [45,61] and obsessive-compulsive disorder [75] when 50 sessions of iTBS1800 were applied (totalling 90,000 pulses). Further, Nettekoven et al. found increased motor cortical excitability of iTBS1800 over iTBS600 and iTBS1200 protocols in healthy controls [37]. A more recent study evaluating various pulse counts of iTBS and cTBS found the higher pulse count iTBS1200 and cTBS3600 protocols were more effective in modulating motor cortical excitability, although high within and between subject variability were reported [76]. It is also unclear how pulse counts affecting TBS or rTMS's motor cortical conditioning effects in healthy controls relate to its antidepressant efficacy when applied to the prefrontal cortices to treat TRD. The counterargument to a pulse count-dependent response relationship applying rTMS to treat TRD is the finding of no consistent association between antidepressant response and the number of rTMS pulses applied over courses of high-/standard-dose 10 Hz rTMS and high-/standard-dose 1 Hz rTMS in a recent multi-site trial [77].

Despite high rates of comorbidity between anxiety and depression [78] and the overlap in implicated brain regions in the two conditions [79,80], studies specifically addressing rTMS's therapeutic efficacy in primary anxiety disorders have reported equivocal results [81–84]. Limited research exists describing rTMS's efficacy in treating comorbid anxiety in depression, although recent analyses report comparable anxiolytic efficacy across the commonly applied rTMS protocols [85,86]. Less is known about TBS's anxiolytic potential in MDD, although a sub-analysis of anxiety outcomes from THREE-D point to therapeutic equivalence

between iTBS and 10 Hz rTMS [87]. Our study built on this and provided preliminary evaluation of accelerated bilateral TBS's effects on anxiety symptoms occurring in depression. To this end, we found no significant difference across the 10 Hz rTMS and bilateral TBS approaches ($p = 1.00$) (Table 7).

There are several limitations to the interpretation of our study results. First, we compared bilateral TBS with unilateral 10 Hz rTMS. In the interest of controlling for heterogeneity in the interventions applied, comparisons of accelerated bilateral TBS with once-daily bilateral rTMS or accelerated unilateral iTBS with once-daily unilateral 10 Hz rTMS could have been preferred alternatives. However, literature available at the time of study conceptualisation suggested that bilateral cTBS/iTBS may be more effective than unilateral iTBS alone [30]. Our intention was to design a definitive depression treatment trial comparing what was then-thought to be a potentially superior TBS protocol against a standard, 'treatment as usual' 10 Hz rTMS protocol as the active control. From this perspective, a comparison of bilateral TBS and unilateral rTMS was conceived. Due to the scheduling differences between the accelerated bilateral TBS and once-daily rTMS protocols, the week 4 endpoint assessment for participants allocated to the former treatment took place 18-days after course completion and, for those allocated to once-daily rTMS, at course completion, thereby introducing the confound associated with treatment/clinic attendance to the interpretation of our results. A second issue arising from scheduling differences was our inability to blind participants to their treatment allocations thereby possibly introducing expectation bias. Although we endeavoured to keep the assessors blinded by repeatedly reminding participants not to disclose their treatment group, systematic assessment of blinding was not carried out. Our trial did not feature a sham control arm, although this would not have been feasible or ethically justifiable given the study was conducted at busy clinical centres and participants were pragmatically recruited from moderate-to-severe TRD patients presenting for treatment, many with associated clinical risks. Given our primary outcome was the comparison of depression treatment response across the three TBS/rTMS protocols, the lack of sham control could still be considered an appropriate design for the purpose of our investigation. Whilst the participants' past antidepressant trials were recorded as numerical measures (Table 3), we did not curate the names and classes of antidepressants trialled, eg. through use of the Antidepressant Treatment History Form (ATHF) or similar instrument, thereby precluding correlation analysis of treatment response and the types of antidepressants tried. Further, although non-antidepressant concomitant medications were noted in a binary fashion (Table 3), we did not collate more detailed data such as the type of mood stabiliser medication (lithium or anticonvulsant mood stabilisers), concomitant benzodiazepine administration or the doses and treatment durations of these medications. This omission may be of relevance given these medications' possible influences on cortical excitability and therefore rTMS response [88,89], and in view of the literature that emerged since this study's conceptualisation that discuss the impact concomitant benzodiazepines might have on antidepressant response to rTMS [90–92]. Additionally, we did not systematically record tolerability issues expected with rTMS therapy, eg. headaches, head/facial muscle twitches, tiredness, etc., precluding quantitative comparison of these side effects across the three rTMS approaches. Lastly, being a multi-centre study, we were unable to control for potential variations in performance of the stimulators and coils used, which may be particularly relevant for rTMS applied at theta-burst frequency on the basis of power roll-off with rapid (50 Hz) sequential pulse discharges. This is a potential confound for all rTMS studies where 2 or more rTMS systems are used. To this end, we clarified with the respective stimulator manufacturers that both systems share comparable power roll-off properties at triplet/50 Hz stimulation when applied at 50–55 % power intensity or more. Further, we mitigated this potential confound by standardizing coil localisation and RMT measurement methods and stimulation protocols.

In conclusion, this study provides evidence that accelerated bilateral TBS is effective and safe in the treatment of TRD. Bilateral sequential cTBS/iTBS did not infer superior antidepressant effect over left unilateral 10 Hz rTMS. The brevity of TBS was well-suited to application in accelerated schedules. Despite the clinical efficiency of our 10-day accelerated bilateral TBS protocol and its popularity with patients, there was no convincing evidence it resulted in more rapid amelioration of depression severity compared to a conventional 4-week rTMS course. We found no significant difference in anxiolytic efficacy across the accelerated bilateral TBS and daily unilateral 10 Hz rTMS groups. As a preliminary attempt to compare the antidepressant efficacy of 80 % and 120 % RMT TBS, the therapeutic equivalence we observed suggest further research is needed to elucidate what effects TBS intensity has on antidepressant efficacy. In the meantime, subthreshold TBS may be an alternative to suprathreshold TBS for patients unable to tolerate the cutaneous sensations associated with the latter, although this warrants prospective validation. Future accelerated TBS trials adopting large, double-blind, sham-controlled study design can consolidate its antidepressant potential and define its role in the limited armamentarium of effective therapies for TRD.

CRediT authorship contribution statement

Leo Chen: Conceptualization, Methodology, Funding acquisition, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Elizabeth H.X. Thomas:** Data curation, Formal analysis, Writing – review & editing, Project administration. **Pakin Kaewpijit:** Data curation, Writing – review & editing. **Aleksandra Miljevic:** Data curation, Writing – review & editing. **Rachel Hughes:** Data curation, Writing – review & editing. **Lisa Hahn:** Data curation, Writing – review & editing, Project administration. **Yuko Kato:** Investigation, Writing – review & editing. **Shane Gill:** Investigation, Writing – review & editing. **Patrick Clarke:** Investigation, Writing – review & editing. **Felicity Ng:** Investigation, Writing – review & editing. **Tom Paterson:** Investigation, Writing – review & editing. **Andrew Giam:** Investigation, Writing – review & editing. **Shanthi Sarma:** Investigation, Data curation, Writing – review & editing. **Kate E. Hoy:** Writing – review & editing, Supervision. **Cherrie Galletly:** Investigation, Writing – review & editing, Supervision. **Paul B. Fitzgerald:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision.

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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.2021.07.018.

Statement of interest

PBF has received equipment for research from Medtronic, MagVenture A/S and Brainsway Ltd. He is on the scientific advisory boards for Bionomics Ltd and LivaNova and is a founder of TMS Clinics Australia. The other authors have no conflicts of interest to declare.

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