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A pilot investigation of an intensive theta burst stimulation protocol for patients with treatment resistant depression

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ABSTRACT

Introduction: Accelerated or intensive forms of repetitive transcranial magnetic stimulation (rTMS) are increasingly being explored for their potential to produce more efficient and rapid treatment benefits in major depressive disorder (MDD). However, accelerated or intensive protocols using standard forms of rTMS are still quite time-consuming to apply. Theta burst stimulation (TBS) is a novel form of magnetic stimulation with the potential to produce similar anti-depressant effects but in a much abbreviated period of time. The aim of this study was to investigate the comparative efficacy of an intensive TBS protocol compared to standard rTMS treatment.

Methods: 74 outpatients (36 female, mean age 44.36 ± 12.1 years) with MDD received either intensive TBS (3 intermittent TBS treatments per day for 3 days in week 1, 3 treatments a day for 2 days in week 2, and 3 treatments in 1 day in week 3 and in week 4, or standard rTMS (5 daily sessions per week for 4 weeks). Patients were assessed weekly throughout the treatment course, and at 4 weeks after treatment end.

Results: There were no significant differences in the degree of reduction in depressive symptoms, the rate of reduction in depressive symptoms, remission or response rates (response rates = 27.8% for intensive group, 26.3% for the standard group, $p > 0.05$ for all analyses) between the intensive TBS and standard rTMS treatment groups. However, the overall response and remission rates were limited in both groups. There was no difference in rates of side effects, no serious adverse events and no alterations in cognitive performance.

Conclusion: Intensively applied TBS appears to have similar efficacy to standard rTMS when these were applied as delivered in this study but does not produce more rapid clinical benefits. The overall response rates in both groups in this study were limited, most likely by the total doses provided in both study arms.

Clinical trials registration: Australian New Zealand Clinical Trials Registry: ACTRN12616000443493.

1. Introduction

Major depressive disorder is a severe illness of high prevalence [1–3]. Thirty percent of patients with depression fail to respond to standard treatments and continue to experience marked disability and high morbidity [4]. These patients are referred to as having treatment resistant depression (TRD). Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that has been subject to intensive evaluation as an antidepressant strategy, especially in patients with TRD. It has clear antidepressant efficacy and the response to rTMS has been shown to be clinically meaningful [5]. It is now being increasingly used in clinical practice around the world.

However, a barrier to the utilisation of rTMS is the relatively slow rate of response to treatment, often requiring daily treatments five days per week over four to six weeks. rTMS requires a considerable time commitment from both patients and clinicians and is of limited utility for patients who do not live within

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convenient traveling distance from treatment centres. The time needed before treatment response in some patients also makes rTMS unsuitable for some acutely suicidal patients. Instead, electroconvulsive therapy (ECT) is often considered for this subgroup of patients in whom rapid treatment response is sought, although possibly at the expense of cognitive side effects.

The treatment utility of rTMS could be substantially enhanced if the time course of treatment could be meaningfully compressed. Over recent years a number of studies have demonstrated the viability, and provided initial evidence for the efficacy, of "accelerated" rTMS treatment protocols – these usually apply a similar number of treatment sessions as standard rTMS courses but over a shorter period of time [6,7]. For example, we recently showed that a meaningful antidepressant response could be achieved with application of three rTMS sessions per day, over six days [8]. This accelerated regime showed no difference in efficacy from daily rTMS applied over 4 weeks.

Although this is a promising finding, and anecdotally accelerated treatment was popular with patients, the provision of three rTMS sessions per day was practically challenging from a treatment service perspective: in a busy TMS service where patients are scheduled on a daily basis, scheduling 3 treatment sessions is disruptive and often then leaves significant gaps on other days. An alternative approach to this would be to utilise theta burst stimulation (TBS) in a similar accelerated treatment protocol. TBS is a newer patterned form of rTMS which can be used to produce the same or greater physiological effects compared to standard rTMS but in a markedly reduced period of time (3 min compared to around 40 min for a standard session) [9,10]. Recent research shows that TBS applied on a daily basis may be as effective as standard daily rTMS, using intermittent TBS (iTBS) applied to the left dorsolateral prefrontal cortex (DLPFC) [11] although it is possible that these two interventions work through different mechanisms of action. Therefore, TBS would appear to be an ideal intervention to use in an intensive/accelerated format where multiple daily sessions could be applied but still in a reduced amount of time. To date only limited research has explored the potential application of accelerated forms of TBS. Duprat et al. randomised 50 patients to receive 20 iTBS sessions (or sham) over 4 days [12] although response duration was difficult to assess due to the trial's crossover design. We conducted a randomised controlled trial comparing an intensive TBS intervention to standard once daily rTMS to evaluate its relative effectiveness and rapidity of onset of antidepressant effects.

We hypothesised that treatment with an intensive form of TBS would be as effective as standard rTMS with no increase in treatment dropouts or serious adverse events. We chose to use once daily rTMS, rather than once daily iTBS, as the comparator group as daily iTBS was not considered an established treatment option at the time of study design. There are considerably variable accelerated or intensive protocols described in the literature to date (from 15 sessions in 2 days–20 session across 2 weeks [6,7,13]). In keeping with our previous study of accelerated TMS, we chose to provide an intensive series of treatments (three treatments per day over three days) in the first week followed by two treatment days in week two and then one treatment day in week three and week four in a consolidation phase. This was chosen to try and balance the number of treatment sessions with the standard group but also to address a problem we found with relapse rates when all treatment was provided in a single week in two initial small unpublished pilot studies. We are referring to our protocol as 'intensive' rather than 'accelerated' treatment as the primary intent was to produce the same clinical reponse in fewer treatment days with the rapidity of reponse only of secondary interest.

2. Methods

2.1. Study design

This study was a parallel design, two arm, single blind randomised controlled trial. Participants were randomised to either an intensive TBS or standard rTMS treatment schedule. Randomization occurred through the use of a single random number sequence. The clinician administering treatment was aware of the treatment group and the patient was aware of the treatment schedule. Symptom raters were blind to group. Patients were frequently counselled to avoid mentioning any information that would reveal the treatment schedule to the raters. We did not attempt to blind the patients: currently no sham coil system has been demonstrated to be effective in patients who are concurrently receiving both active TMS stimulation as well as sham. This would be required for us to fully blind this trial. However, considerable efforts were made to ensure that raters assessing patient's depression severity remained blinded: we used separate staff to schedule and administer the treatment from the raters and repeatedly reminded patients to be careful not to reveal details of their treatment during rating interviews. The conduct of the study was approved by the Alfred Hospital and Monash University Human Research and Ethics committees and the trial was registered on the Australian New Zealand Clinical Trials Registry (ACTRN12616000443493). All participants were required to give written informed consent in a form approved by the relevant human research and ethics committees.

2.2. Participants

Participants were recruited by referrals from both public and private psychiatrists. Participants in the study were diagnosed with MDD or Bipolar Disorder (depressive episode) by their referring doctor and by the study psychiatrist and diagnosis was confirmed through the use of the Mini International Neuropsychiatric Interview (MINI) [14]. Inclusion criteria included being between 18 and 70 years of age, moderate to severe depression as defined by a Montgomery Asberg Depression Rating Scale (MADRS) [15] score of >19, and TRD at Stage II of the Thase and Rush classification [16]. Stage II requires failure to respond to adequate courses of two different antidepressants. Patients were excluded if they had a contraindication to TMS (such as the presence of metallic implants in the head, cardiac pacemakers, cochlear implants or other implanted electronic devices), had initiated a new antidepressant treatment in the preceding 4 weeks (or changed medication dose), were found to have another Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-V) Axis I psychiatric disorder (except an anxiety disorder), had a history of substance abuse or dependence during the last six months, were pregnant, or had a past history of stroke, neurodegenerative disorder or other major neurological illness. Medication doses were kept unchanged during the trial. Of 75 patients assessed eligible and consented, 74 were randomised, see Consort Flowchart for details (Fig. 1).

2.3. Clinical assessment

Demographic variables and potential covariates were recorded at baseline following a clinical interview. To record depressive symptoms, we assessed patients with the MADRS [15] at baseline and at the end of weeks 1, 2, 3, 4 and 8. The schedule was the same for all patients so that the 8 week assessment fell 4 weeks after treatment for the standard group and ~4 ½ weeks after treatment end for the intensive group. Patients were assessed at the same time points with the Quick Inventory of Depressive Symptoms – subject rated (QIDS-SR) [17], the Columbia Suicide Severity Rating Scale (C-SSRS)

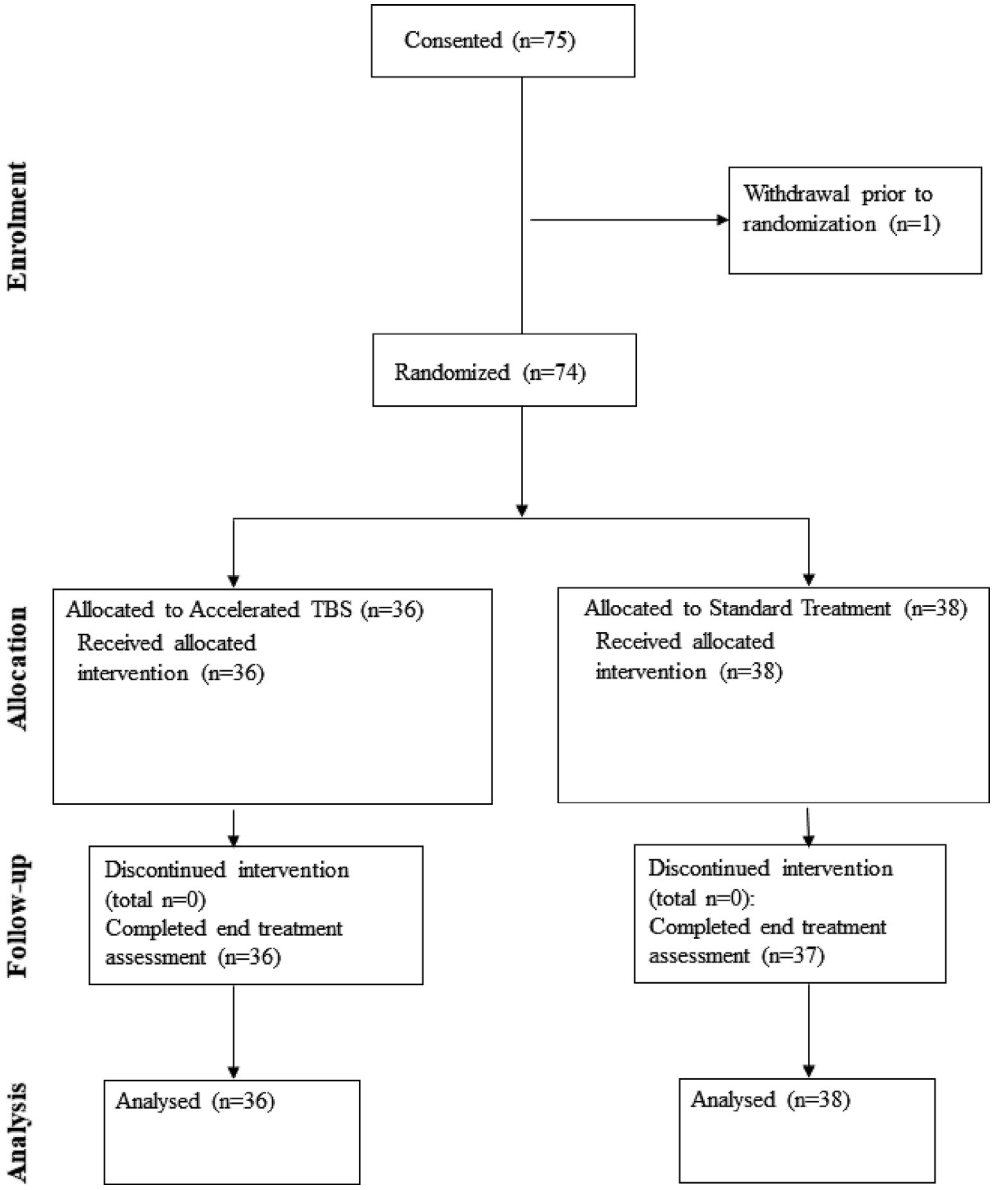

Fig. 1. CONSORT diagram for study. Note, accurate figures on the number of patients who did not progress following screening is not available.

[18] and the Clinical Global Impression Severity and Improvement scales (CGI-S). Response on the MADRS scales was defined as a greater than 50% reduction in scores. Remission was defined as a score of less than 10 on the MADRS [19]. The EuroQOL EQ-5D Quality of Life Questionnaire [20] was used to assess quality of life and functioning. In addition, we assessed performance across a number of cognitive domains, at baseline and week 4 (after the last treatment); including assessments of information processing and complex attention (Digit Span – WMS-III [21], Trail Making Test A & B [22]), verbal and visual memory (Brief Visuospatial Memory Test [23], Rey Auditory Verbal Learning Test [24]), and executive function (Stroop [25]). The Wechsler Test of Adult Reading was done at baseline as an estimate of premorbid ability [26].

2.4. Treatment

Prior to the commencement of rTMS or TBS treatment, single pulse TMS was used to measure the resting motor thresholds (RMT) for the abductor pollicis brevis (APB) on the left motor cortex in all subjects using standard published methods [27]. Patients received one of two treatment conditions with a Magpro device with figure of 8 coil (Magventure, Denmark):

1. *Intensive TBS treatment:* This used the following schedule to provide 21 iTBS sessions:
   Week 1: 3 treatment days, 3 sessions per day (9 total)
   Week 2: 2 treatment days, 3 sessions per day (6 total)
   Week 3: 1 treatment day, 3 sessions per day (3 total)
   Week 4: 1 treatment day, 3 sessions per day (3 total)

   Treatment sessions were separated by 15 min intervals.
   iTBS involved application of 3 TMS pulses at 50 Hz every 200 msec (5 Hz). This was delivered in 2 s trains and repeated every 10 s, ie., 2 s of TBS followed by 8 s of inactivity, for a total of 190s. Stimulation intensity was at 120% of the RMT. In this arm, 600 pulses were applied in each iTBS session, totalling 12,600 pulses over the course of 21 treatments.

2. *Standard rTMS treatment*: 20 rTMS sessions were applied daily, 5 days per week over 4 weeks. Stimulation was applied to the left

DLPFC. Stimulation frequency was set at 10 Hz, for 4.2 s trains with 25 s inter-train intervals. Intensity was applied at 120% of the RMT. In this arm, 3150 rTMS pulses were applied per day totalling 63,000 pulses over the course of 20 treatments.

One missed session was allowed per week and only one missed session in a row. Missed sessions were 'made up' with an extension of the treatment duration.

The treatment site was determined by the F3 beam method which has been demonstrated to accurately locate the dorsolateral prefrontal cortex (DLPFC) [28]. This site was marked on the scalp and used as the site of stimulation.

2.5. Data analysis

Student's t-tests and χ^2 tests were used to investigate differences between the groups on demographic and baseline clinical variables. Linear Mixed Model Analyses were conducted for dependent measures with Fixed Effects of Group and Time for all the rating scale data. An Autoregressive first order (AR(1)) covariance structure was determined to provide an appropriate fit for the data and Restricted Maximum Likelihood (REML) was used to estimate parameters. Secondary analysis of remission and response rates was conducted on MADRS data at week 4 and week 8 using χ^2 tests. To investigate cognitive outcomes of treatment, baseline to end of treatment change scores were calculated and compared between the two groups with independent samples *t*-test. Paired sample t-tests were used to look for changes in cognitive performance from baseline to end of treatment within the two treatment groups. All statistical analysis was conducted with SPSS 22.0 (SPSS for Windows. 10.0 Chicago: SPSS; 2013).

3. Results

3.1. Participants

75 patients were eligible and consented (Fig. 1). One patient withdrew prior to randomization and treatment due to severe anxiety and inability to tolerate the RMT process. Treatment outcomes for 74 patients were analysed. All patients completed the full course of treatment although one patient in the standard treatment group withdrew prior to the week 4 assessment. 20 patients did not complete the 4 week follow as they were either lost to follow up, withdrew consent or were withdrawn as they commenced other treatments in this time. The sample of 74 included 36 females and 38 males and had an average age of 44.36 ± 12.1 years. There were no differences in the baseline severity of scores on any of the rating scales or in any demographic or clinical variables between the groups (Table 1).

3.2. Primary outcome

For the MADRS, there was a significant main effect of Time ($F_{(5, 308.641)} = 14.236$, $p < 0.001$). There was no effect of treatment group ($F_{(1, 76.606)} = 1.621$, $p = 0.207$), nor a significant time by group interaction ($F_{(5, 308.641)} = 0.202$, $p = 0.961$) indicating no difference in the degree of response over time between the 2 groups (Fig. 2, Table 3). In regards to the pattern of response, the significant effect of time was determined by an overall reduction, irrespective of group, from baseline to week 1 ($p = 0.009$); week 1 to week 2 ($p = 0.012$); week 2 to week 3 ($p = 0.018$); and week 3 to week 4 ($p < 0.001$).

3.3. Secondary outcomes

For the QIDS, there was a significant main effect of Time ($F(5, 280.796) = 19.661$, $p < 0.001$) (Fig. 2). There was also no effect of treatment group ($F(1, 80.761) = 1.128$, $p = 0.291$), nor a significant time by group interaction ($F(5, 280.796) = 0.517$, $p = 0.763$). The effect of time was drive by an overall reduction, irrespective of group, from baseline to week 1 ($p < 0.001$).

There was also effects of time, but not a time × group interaction for the CGI severity (Time $= (F_{(5, 289.438)} = 9.674$, $p < 0.001$) interaction $= (F_{(5, 289.438)} = 0.586$, $p = 0.711$) and improvement measures (Time $= (F_{(4, 229.503)} = 6.027$, $p < 0.001$), interaction $= (F_{(4, 229.503)} = 0.307$, $p = 0.873$)).

Table 1
Patient Clinical and Demographic data.

		Intensive TBS group		Standard Group		F/χ2	p
		Mean or Frequency	SD	Mean/Frequency	SD		
Age		44.0	12.2	44.7	12.2	−0.23	0.81
Sex (M/F)		17/19		21/17		0.48	0.50
Handedness (R/L/Ambidextrous)		35/0/1		29/4/5		9.7	0.02
Diagnosis	MDD – single episode	22		17		2.1	0.14
	MDD – relapse	14		21			
	Generalised anxiety disorder	21		22		0.08	0.78
	PTSD	3		6		1.09	0.30
	OCD	3		2		0.22	0.64
BPAD (Y/N)		3/33		3/35		2.0	0.37
Duration of Illness (years)		14.6	10.1	19.5	12.6		
Age of onset (years)		29.2	14.4	24.0	9.5	10.0	0.09
Number of depressive episodes		4.9	11.4	4.0	5.0	1.9	0.70
Length of Current Depressive Episode (years)		8.4	9.4	10.8	12.6	2.1	0.38
Number of Past medication trials		8.9	17.6	7.9	17.1	0.01	0.82
Previous ECT (Y/N)		3/33		4/34		5.6	0.13
ECT This episode		5/53		6/51		2.5	0.47
MADRS		33.6	5.2	31.9	6.7	2.0	0.21
QIDS		17.0	5.2	17.0	4.6	0.2	0.94
CSSR		1.8	1.5	1.4	1.3	2.5	0.27
EuroQol Index		0.41	0.27	0.48	0.21	2.7	0.19

MDD = major depressive disorder, BPAD = bipolar affective disorder, PTSD = Post Traumatic Stress Disorder, OCD = Obsessive compulsive disorder, MADRS = Montgomery Asberg Depression Rating Scale, QIDS = Quick Investory of Depressive Symptoms – subject rated, CSSR = Columbia Suicide Severity Rating Scale, CGI = and the Clinical Global Impression Severity Scale, EuroQol = The EuroQOL EQ-5D Quality of Life Questionnaire.

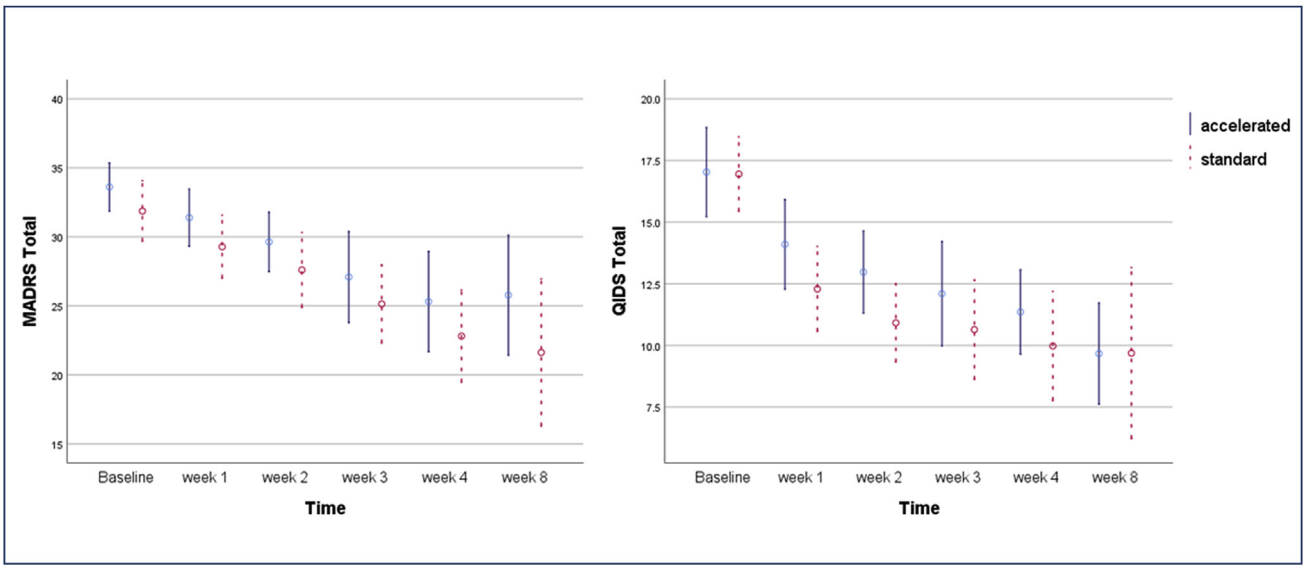

Fig. 2. Montgomery Asberg Depression Rating Scale (MADRS) and Quick Inventory of Depressive Symptoms – subject rated (QIDS-SR) scores across study timepoints.

Table 2
Treatment response and remission rates.

		Group	Response	Remission
MADRS	Week 4	Intensive TBS	(7/36) 27.8%	(3/36) 8.3%
		Standard	(11/38) 26.3%	(5/38) 13.2%
		Chi-square	0.02, p = 0.89	0.45, p = 0.50
	Week 8	Intensive TBS	(10/36) 19.4%	(3/36) 8.3%
		Standard	(10/38) 28.9%	(5/38) 13.2%
		Chi-square	0.91, p = 0.34	0.45, p = 0.50

Response defined as a >50% reduction in Montgomery Asberg Depression Rating Scale (MADRS) scores. Remission defined as MADRS score of <11.

Table 3
Treatment data for all study time points.

		MADRS		QIDS	
Time	Group	Mean	Std. Deviation	Mean	Std. Deviation
Baseline	intensive	33.6	5.2	17.0	5.2
	standard	31.9	6.7	16.9	4.6
Week 1	intensive	31.4	5.8	14.1	5.1
	standard	29.3	6.6	12.3	5.0
Week 2	intensive	29.6	6.4	13.0	4.9
	standard	27.6	7.9	10.9	4.6
Week 3	intensive	27.1	9.3	12.1	5.8
	standard	25.1	8.3	10.6	5.7
Week 4	intensive	25.3	10.6	11.4	4.9
	standard	22.8	10.0	10.0	6.5
Week 8	intensive	25.8	11.0	9.7	3.7
	standard	21.6	12.6	9.7	7.2

3.4. Quality of life

For the EURO QOL total score, there was a significant main effect of Time ($F_{(5, 274.045)} = 4.170$, $p = 0.001$) but not a significant time by group interaction ($F_{(5, 274.045)} = 0.798$, $p = 0.552$). The greatest increase in quality of life occurred in the first week ($p = 0.007$).

3.5. Suicidality

Based on scores on the CSSR there was no difference in the 2 treatments on suicidal ideation intensity: for ideation there was the main effect of Time ($F_{(5, 275.851)} = 3.907$, $p < 0.001$) and no significant time by group interaction ($F_{(5, 275.851)} = 0.113$, $p = 0.989$). This was the same for intensity: Time ($F_{(5, 235.071)} = 6.189$, $p < 0.001$) and interaction ($F_{(5, 235.071)} = 1.219$, $p = 0.301$). There was also a significant overall group effect (and no interaction) for the MADRS suicidal ideation rating score.

3.6. Categorical outcomes

Response and remission rates at the end of the 4 and 8 week period on the MADRS are shown in Table 2. There was no significant difference in response rates or remission rates between the groups in any of the analyses.

3.7. Cognition

There were no between group differences in the change scores from baseline to end of treatment on any of the cognitive variables.

In the intensive TBS group there was significantly improved performance on the RAVLT recognition ($P < 0.01$), trail making B(($p = 0.001$) and the STROOP Word score ($P < 0.001$). For the standard rTMS group a significant improvement was found on the trail making A test ($p = 0.01$). No worsening of performance in either group was seen on any test. Interestingly, for all 4 of the improvements found in cognitive function, no correlation was found between improvements in cognitive performance and improvement in depression (MADRS scores) over the same time periods of assessment.

3.8. Safety and tolerability

There were no serious adverse events in either treatment group. 12 patients reported headache with TBS and 7 with standard TMS ($p > 0.05$.). 4 patients reported pain or discomfort at the scalp treatment site with TBS and 6 with standard rTMS. One patient in each group described the headaches with treatment as severe.

4. Discussion

Although there has been an increasing interest in exploring the use of accelerated rTMS treatment protocols in recent years, as well as an increase in studies exploring the therapeutic benefits of TBS, there remains a very limited number of randomised trials demonstrating the efficacy of accelerated TMS in general and accelerated or intensive TBS especially. This is the first published direct parallel groups comparison showing that an intensive TBS protocol may be used to achieve similar therapeutic benefits as those obtained with a standard daily rTMS treatment schedule. In our study, intensive TBS produced similar clinical benefits to standard rTMS on depression ratings, quality of life and assessments of suicidality without the occurrence of any serious adverse events. There was not an increased rate of treatment emergent side effects or observable cognitive impairment. The clinical benefits seen were similar to those achieved in our previous study of accelerated rTMS but in that study the lengthy administration of accelerated rTMS was associated with a slightly higher side-effect and dropout rate, neither of which were seen in the current study with intensive TBS [8].

Clearly there are substantial clinical and practical benefits with being able to achieve antidepressant responses more rapidly than what is achievable with standard rTMS treatment regimes. In this context, it is important to separate out two elements of response: 1) can a similar degree of clinical response be achieved (even if it takes the same amount of time) with far fewer treatment days, 2) can a more rapid improvement in symptoms be achieved. The former would make TMS treatment overall more practical and cheaper (especially where daily treatment provision over 4–6 weeks is too practically or logistically challenging for patients and clinical services) whilst the second element opens the possibility of the treatment of patients with acute risks, such as suicidal ideation. However, providing multiple lengthy rTMS sessions on a daily basis in an accelerated protocol is also logistically challenging [8]. Providing multiple TBS treatments, as done here, could be achieved in less than 1 h a day which is both convenient for patients and clinic scheduling.

Our data suggests that we may be able to address one of these two clinical problems. Intensive TBS appeared to have similar clinical efficacy to standard rTMS and as such could potentially be utilized in a relatively standard clinical protocol to achieve similar treatment response. However, we did not necessarily see any evidence that the clinical benefits seen with the intensive TBS regime occurred earlier or more rapidly. As seen in Fig. 2, the greatest degree of therapeutic change occurred relatively early in the course of treatment on the QIDS but this was the case in both treatment arms, and the pattern of symptom reduction was almost identical on the MADRS. There was no suggestion that the TBS group achieved clinical response substantially more rapidly than the group receiving standard rTMS. This was true for both the MADRS and the QIDS, as well as for the measures of suicidality. Even though almost all of the TBS treatment protocol was administered in the first two weeks, this did not appear to result in a more rapid reduction in the severity of depressive symptoms. In addition, although the patients in the TBS group received almost the equivalent of two weeks of sessions in the first week, they had not achieved a similar clinical response to that seen in the standard group after two weeks of therapy. This suggests that it may take neural circuits some time to adjust to the administration of magnetic stimulation protocols regardless of how these are applied or that an even greater dose application, which is likely to be impractical, might be required to try to achieve an earlier clinical response.

As seen in Table 2, there was no trend towards greater rates of response or remission in either group. In contrast, findings from our previous study [8] suggested greater rates of response and remission with standard over accelerated rTMS. It is notable, however, that the overall response and remission rates in this study were relatively modest. It is quite possible that this was related to the overall dose of treatment provided. Our standard rTMS treatment group only received 20 sessions over four weeks which is a modest dose compared to the 30 sessions/6 weeks of treatment that is commonly used in clinical practice [29]. We do not yet have a comprehensive understanding of what is the optimally effective dose of TBS in standard, or intensive format, but it would be reasonable to assume that is likely to be greater than the relatively modest doses provided here. Given the ease of provision of TBS sessions, it would not be difficult to increase TBS duration and hence, dose, beyond what our protocol provided while still enabling overall briefer treatment sessions for patients, over what a standard rTMS course allows.

The safety and tolerability of the intensive TBS condition in this study is worthy of note. rTMS is generally safe and its associated adverse effects well-tolerated. Serious adverse effects, such as seizure induction, are rare [30,31]. Seizure induction is associated with high-frequency sitmulation [32] and in this context it would be reasonable to assume that TBS protocols may be associated with greater rates of seizure (or other unidentified issues). Fortunately, this does not appear to have been the case when TBS has been used in standard once daily treatment schedules. So far the intensive use of TBS also appears to be well tolerated and without common serious adverse events [33,34]. It is worth noting that across both our accelerated rTMS study [8] and this study, anecdotally accelerated/intensive protocols were favored by patients. Any additional burden of treatment on the day of therapy was considered minor relative to the savings in time and clinic attendance requirements that accelerated/intensive treatment protocols allowed.

The most uncertain element in the intensive TBS parameters we developed was the choice of the duration patients would wait between stimulation trains in each treatment session, in this case 15 min. Although it would be convenient to assume that the dose of a TBS session could be increased by simply lengthening the duration of the application of stimulation (for example, doubling the number of pulses in a treatment session by increasing iTBS duration from 190s to 380s), preclinical studies exploring the effects of TBS on motor cortical excitability have demonstrated that longer durations of stimulation may have less or even opposite effects on

cortical excitability [35,36]. A limited number of studies, again focusing on the effects of TBS on motor cortical excitability, have demonstrated that greater effects are produced when two TBS sessions are applied some time apart, rather than continuously, although there are fairly inconsistent results in this literature (see Table 1 in Ref. [37]). For example, Tse et al. found a significant increase in motor cortical excitability when two iTBS blocks were applied at a 15 min interval (and a reduction in excitability when they were applied at a 5 min interval) [37]. The only study to date applying three iTBS trains using a 15 min inter train interval found a significant increase in motor cortical excitability with three trains compared to 2 trains or a single train of iTBS [38].

However, it is difficult to know how applicable these motor cortical studies are to the application of TBS applied to the prefrontal cortex in a condition such as depression. In a recent study, we explored the application of prefrontal TBS, using TMS evoked potentials measured with EEG as an outcome measure [39]. In this study we compared the application of one or two blocks of iTBS applied 15 min apart (to a sham stimulation condition). Both the single and repeated blocks of TBS increased markers of cortical excitability (increasing the amplitude of the TMS evoked N100 and P200 components). However, a greater effect of stimulation was not seen when the TBS condition was repeated compared to when it was applied in a single block. Even though this study investigated TBS applied to a brain region more relevant to depression than the motor cortex, the results were derived from healthy controls over one session of testing. As such, the clinical translatability of these findings remain uncertain. The fact that two blocks of iTBS applied 15 min apart did not show greater cortical conditioning effects, however, suggested 15 min was probably not the optimal time interval needed to produce maximal changes in cortical excitability. The design of future intensive TBS trials could well be informed by further preclinical studies of this sort.

It is interesting that we found improvements in cognitive performance in both groups but that these improvements were found on a wider variety of tasks in the iTBS compared to the standard rTMS group. It was also notable that improvements in cognition in both groups did not correlate with improvements in mood as would most typically be expected. Multiple lines of evidence have supported the notion that rTMS has the capacity to improve cognition across different neuropsychiatric disorders (for example [40,41]) and our data here in a very preliminary way suggest that potentially iTBS may have more of a pro-cognitive effect than standard TMS approaches.

There are several significant limitations affecting our ability to interpret the results of this study. First, it was not possible to keep patients blinded to treatment group. Second, we could not match both the number of treatment sessions and pulse number at the same time. We chose to approximate the session numbers although for practical reasons these were not exactly equivalent (20 and 21), a difference unlikely to make a meaningful difference to the outcomes. Third, it is possible that a larger study may reveal trends towards treatment effects that we did not find with our sample size. However, we saw no meaningful trend to a difference in mean reductions in MADRS scores or on any of the other outcome variables, and no trend towards differences in response and remission rates. Although our results do not hold the weight of a large multisite randomised trial, they certainly do provide a strong indication that intensive TBS treatment may have the capacity to produce the same clinical effects as standard courses of rTMS therapy.

Related to this concern, given the pilot study stage of this research, we did not power and design the study as a true test of non-inferiority. It is also important to note that our design, which entailed an unequal number of treatment session per week across the groups, makes direct comparison of the rate of symptom change problematic. However, our overall intent, to assess the overall clinical value of this form of protocol, versus standard TMS, required a direct comparison and we accepted a compromise in this regard. In addition, we did not include the collection of biomarkers that may have been utilized to examine whether there were determinants of response to either of the forms of treatment. It is also possible that we would have seen a greater antidepressant effect with iTBS provided at subthreshold intensity given that preliminary research suggests that the intensity of iTBS stimulation is likely to be relevant to its clinical effects [42]. However, we chose suprathreshold intensity as this had been used in a several depression iTBS studies and we did not have the benefit of knowledge of the Chung et al. outcomes at the time of designing this trial - systematic research in clinical populations is required to understand whether low intensities of stimulation will produce greater clinical effects. Our recent data, and data from other groups, also suggest that longer durations between iTBS stimulation sessions may produce greater results [39,43]. However, it is problematic to assume that we can directly infer optimal treatment variables from single session studies conducted in healthy control subjects. The overall dose (e.g. 4 weeks of standard treatment) is also likely to have contributed to the relatively limited response and remission rates although we chose this design deliberately to provide relative group treatment equality and maximize the success of rater blinding. We also included both uni and bipolar patients and a quite heterogenous and unwell population of patients, which may have affected outcomes although both groups have showed response in previous mixed samples. Finally, we did not systematically collect data on the preference of patients for one or other of forms of treatment. As with our previous trial of accelerated standard TMS, anecdotally patients certainly expressed preference for the shorted accelerated/intensive group but we did not establish this with systematic data collection.

In conclusion, the use of iTBS appears to be a very promising TMS protocol to apply in intensive treatment protocols. Intensive TBS appears to be well tolerated and produced clinical effects similar to those seen with a standard course of rTMS treatment. Notably, iTBS seemed safe even at 120% of the RMT and in the intensive schedule. However, the intensive TBS protocol we applied did not produce a more rapid onset of antidepressant effects. Further research, especially a large multisite trial with longer follow up, is required to validate the use of intensive TBS.

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Statement of interest

In the last 3 years PBF has received equipment for research from Magventure A/S, Medtronic Ltd, Neurosoft and Brainsway Ltd. He has served on a scientific advisory board for Bionomics Ltd and LivaNova and acted as a founder for TMS Australia. In the last 3 years, ZJD has received research and equipment in-kind support for an investigator-initiated study through Brainsway Inc and

Magventure Inc. For the remaining authors no conflicts of interest were declared.

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