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A pragmatic randomized controlled trial exploring the relationship between pulse number and response to repetitive transcranial magnetic stimulation treatment in depression

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation treatment (rTMS) is an effective treatment for depression but the optimal methods of administration have yet to be determined. In particular, it is unclear whether there is a relationship between elements of the dose of stimulation (i.e., number of pulses) and clinical response. To address one aspect of dose, we conducted a trial comparing standard and high dose versions of high frequency left sided and low frequency right sided rTMS protocols (left standard = 50 trains, left high = 125 trains, right standard = 20 min, right high = 60 min, all per day in a single session).

Method: 300 patients with treatment resistant depression were enrolled in a four arm randomized controlled trial across a four week time period. The primary outcome assessment was a comparison of response and remission rates on data from the 17-item Hamilton Rating Scale for Depression Rating Scale (HRSD-17).

Results: The rate of response exceeded 45% in all groups. There was no significant difference between groups on initial analysis of the primary or secondary outcome measures (response rates: standard left = 52.5%, high left = 47.3%, standard right = 49.1%, high right = 48.4%). There was a greater remission rate with high compared to moderate dose left sided treatment when controlling for illness duration. We also found significant improvements in quality of life across all treatment groups. Illness duration was weakly associated with response.

Conclusions: There was no consistent association between the antidepressant effect of rTMS and the number of TMS pulses provided across the ranges investigated in this study. Increasing TMS pulse number in individual sessions seems unlikely to be a method to substantially improve clinical outcomes, and future research should explore alternative means of improving clinical response.

The study was registered on the Australian and New Zealand Clinical Trials Register (ACTRN12612000321842) https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=362063&isReview=true.

Introduction

Major Depressive Disorder (MDD) is a common disorder that results in significant individual suffering, disability, and socioeconomic impact [1–3]. There are a range of established treatments for

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MDD, including antidepressant medications and psychotherapy. However, up to a third of patients fail to respond to initial treatments [4].

Repetitive transcranial magnetic stimulation (rTMS) is an established intervention for patients with treatment resistant depression (TRD), which is typically defined as a failure to respond to at least 2 trials of antidepressant medications. Its effectiveness is supported by multiple meta-analyses of randomised clinical trials (e.g. Refs. [5–7]). Several forms of rTMS have demonstrated efficacy in TRD including high frequency rTMS applied to left prefrontal cortex (HFL-rTMS) and low frequency rTMS applied to right prefrontal cortex (LFR-rTMS) [8–12] with both of these forms of treatment supported in a recent network meta-analysis [7].

Since rTMS trials were first conducted in the mid 1990's, there has been a progressive escalation in the dose of stimulation used in these trials, including in the intensity of stimulation relative to the motor threshold, and the total number of TMS pulses applied in each treatment session. For example, whereas early high frequency left sided rTMS trials applied 10 to 20 trains of 10 Hz stimulation [13,14], more recent studies have applied up to 75 on each treatment day [15,16] and the use of 75 trains of stimulation has become a defacto standard in many places. One meta-analysis has suggested that the overall response rate to rTMS has increased over time, and attributed this to the increase in dose in 'newer' trials. However, it was not possible for the authors to separate out whether this improvement might have been due to one, or more, of the other factors that have changed over this time period [17] and this analysis is also relatively out of date. Despite the large number of trials conducted evaluating rTMS, and the increase in doses used over time, there has been minimal systematic research evaluating whether the response to rTMS treatment, either left or right sided, is influenced by dose and no substantive head to head comparative trials of different treatment doses.

The primary goal of this study was to examine whether response to rTMS is greater when treatment is applied at a higher, compared to a lower dose: specifically the number of TMS pulses applied across a course of treatment. We aimed to explore whether there was a difference in response based on the number of pulses applied per treatment session, and to explore this for both left and right sided rTMS treatment paradigms. We hypothesised that high doses of stimulation would be more effective for both left and right sided rTMS: that high dose left sided treatment would produce greater response and remission rates than 'standard' dose left sided rTMS and that high dose right sided treatment would produce greater response and remission rates than 'standard' dose right sided rTMS. However, there would be no difference in clinical response between standard left and standard right-sided treatment arms, and high dose left and high dose right sided treatment arms. To vary the dose of left sided high frequency stimulation, we altered the number of stimulation trains – the number of bursts of 40 pulses applied over 4 s (comparing 50 to 125 trains per day/treatment session). For right sided 1 Hz stimulation, a continuous train of 20 min duration was compared to a train of 60 min duration.

Methods and materials

Study design

The study involved a four arm double blind randomised controlled trial (Fig. 1), conducted across five private hospital sites. Patients were randomized using a separate computer generated random number sequence at each site. The patients and raters were blind to treatment, but the clinician administering rTMS was aware of the treatment group. The patients and raters were advised that there was a difference in the stimulation parameters in the groups. The patients were aware of the laterality of treatment, but specifics of the differences between the treatment doses (how long treatment should take, number of pulses etc.) were not described in any detail. All patients were naive to rTMS treatment. For all treatment conditions, 20 sessions were provided over 5 days per week. Patients received treatment in a standard clinical service with the only study related constraint being on changes to medication dose. Decisions on the length of treatment were made by the patient's treating psychiatrist and as such patients could withdraw before 4 weeks if they had achieved an adequate clinical response.

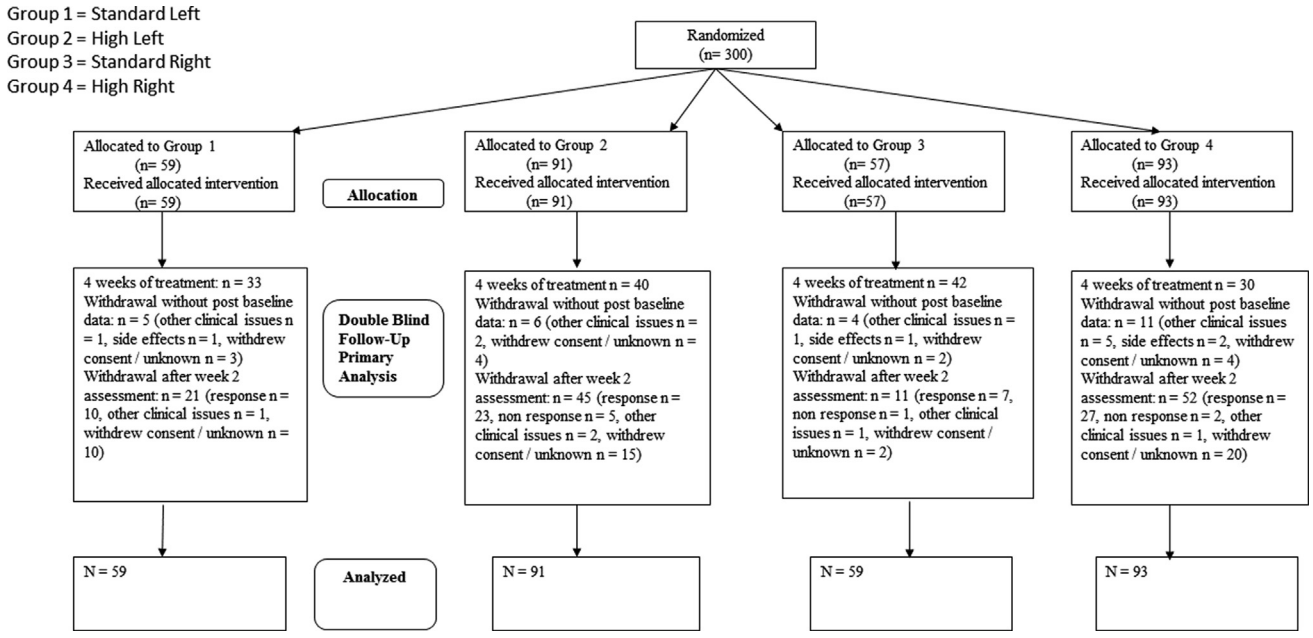

Fig. 1. Study Participants and flow through study.

Subjects

300 patients participated (87 male, 213 female, age range, mean age = 46.4 ± 13.8 years). Diagnosis was determined using the Mini-International Neuropsychiatric Interview (MINI) [18] by a study psychiatrist for each patient. Patients were included who had either major depressive disorder – single episode, major depressive disorder – relapse, bipolar I disorder - depressive episode and bipolar II disorder – depressive episode.

Comorbid diagnoses were also recorded using the MINI (Table 1). Patients were allowed to participate if they had the presence of a comorbid axis I or axis II disorder, other than a schizophrenia spectrum or dementia/organic disorder. The inclusion criteria was a diagnosis of moderate to severe depression (scoring greater than 17 [19] on the 17-item Hamilton Rating Scale for Depression (HRSD-17) [20]) and a failure to respond to a minimum of two courses of antidepressant medications, for at least six weeks in the current episode (Stage II, Thase and Rush Definition [21]) (mean number of courses across episodes = 4.2 ± 2.4) (data collected by a study psychiatrist at screening). Failure to respond to ECT in the past was not an exclusion criteria. Medications were not allowed to have changed in the four weeks prior to commencement of the trial, or during the trial itself. 249 patients were taking antidepressant medication during the study and 102 were receiving concurrent treatment with a mood stabilizer. Exclusion criteria included the presence of a current and significant active medical illness, current neurological disease, or a contraindication to rTMS (for example a history of a seizure disorder, the presence of a pacemaker or metal somewhere in the head other than the teeth).

Patients were recruited by referral from private psychiatrists and general practitioners between February 2012 and October 2015. All patients were inpatients during the trial, which was conducted across five private psychiatric hospitals in the Australian states of Victoria, New South Wales and Queensland. As for several previous studies (for example [22,23]), training in the TMS methods, trial management and ratings were conducted by the lead study site to assure the uniformity of delivery across sites.

After complete description of the study to the subjects, written informed consent was obtained from all patients. The study received Human Research Ethics committee approval (at the Melbourne Clinic) and all procedures were performed in accordance with relevant guidelines and regulations.

We aimed to recruit 300 patients, to provide at least an 80% chance of detecting a difference of 5 points on the HRSD-17 scale between doses in any of the two groups, assuming a standard deviation of 10 (differences approximated from our previous studies) (2-tailed analysis, $p < 0.05$). Given a baseline HRSD-17 level of approximately 25, this would mean a ~20% difference between the groups in final scores, which is likely to be of clinical significance.

TMS treatment

Across all study sites rTMS was administered using Medtronic Magpro30 magnetic stimulators (Medtronic Inc, Minneapolis, USA) using fluid filled 70 mm figure-of-8 coils held in stands. The coils were held tangential to the scalp at 45° to the midline. The location for stimulation was a point 6 cm anterior to that required for maximum stimulation of the Abductor Pollicis Brevis muscle. The resting motor threshold (RMT) was measured bilaterally using standard visual methods [24]. The mean RMT was 49.1 ± 14.8 on the left, and 49.8 ± 15.0 on the right. Patients sat in a comfortable reclining chair during treatment. Training in all treatment processes was provided across study sites by the lead site.

Treatment in the four groups was as follows:

1. Standard dose HFL-rTMS: This involved the application of 50 trains of 10 Hz rTMS on a daily basis. 4.5 s trains were applied at 120% of the resting motor threshold with a 20.5 s inter-train interval (2250 pulses per session)

Table 1
Demographic and baseline clinical variables.

		Left Standard		Left High		Right Standard		Right High		P value
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age		46.6	12.7	44.4	11.3	49.3	16.8	46.2	14.5	0.24
Sex (M/F)		11/48		34/57		14/43		28/65		0.09
Diagnosis (number of subjects)	MDD – single episode	23		25		18		22		0.31
	MDD – relapse	28		51		33		64		
	BPAD 1	4		2		4		5		
	BPAD 11	1		3		0		1		
Age of illness onset		29.9	15.1	27.5	13.0	29.3	15.8	28.7	15.2	0.80
Number of depressive episodes		3.9	6.0	5.1	7.5	4.2	3.6	3.6	4.1	0.48
Number of Failed Antidepressant Trials		4.5	2.9	4.3	2.6	3.9	2.0	4.1	2.2	0.62
HRSD		26.9	6.0	26.1	6.7	25.8	6.3	25.7	5.8	0.66
IDS		49.9	15.6	50.6	13.3	47.9	13.6	51.4	10.7	0.49
BAI		27.2	15.3	32.7	12.4	28.2	13.0	29.8	14.1	0.10
SHAP		15.5	13.4	20.7	14.8	14.4	12.9	23.2	13.6	0.001
Total QOL		25.7	12.8	24.7	12.4	27.0	11.9	28.4	13.6	0.30
Concurrently taking antidepressant medication (%)		86.4		88.8		80.0		88.9		0.42
Concurrently taking mood stabilizer medication (%)		37.3		31.9		36.8		32.3		0.85
Concurrently taking antipsychotic medication (%)		52.5		42.9		56.1		38.7		0.12
Past course of ECT (lifetime)		13		25		18		22		0.60
Self report ECT non responder (%)		65.2		62.1		42.3		48.1		0.39
Comorbid Diagnoses (%)	Panic	15.3		11.0		10.5		20.4		0.23
(number of subjects)	GAD	23.7		18.7		36.8		25.8		0.10
	OCD	13.6		8.8		8.8		5.4		0.38
	PTSD	10.2		12.1		7.0		6.5		0.54
	BPD	13.6		5.5		12.3		9.7		0.35

MDD = major depressive disorder, BPAD = bipolar affective disorder, OCD = obsessive compulsive disorder, GAD = Generalised Anxiety Disorder, PTSD = post traumatic stress disorder, BPD = borderline personality disorder, HRSD = Hamilton Depression Rating Scale, IBS = Inventory of Depressive Symptoms, BAI = Beck Anxiety Inventory, SHAP = Snaith Hamilton Pleasure Scale. Mood stabilizer = lithium, Sodium Valproate, Carbamazepine or Lamotrigine.

2. High dose HFL-rTMS: This involved the application of 125 trains of 10 Hz rTMS. 4.5 s trains were applied at 120% of the resting motor threshold with a 15.5 s inter-train interval (5625 pulses per session).
3. Standard dose LFR-rTMS: This involved the application of 1 continuous train of 1 Hz rTMS of 20 min duration at 120% of the resting motor threshold (1200 pulses)
4. High dose LFR-rTMS: This involved the application of 2 trains of 1 Hz rTMS of 30 min duration at 120% of the resting motor threshold (3600 pulses per session total). The two trains were applied with just a brief break in between to allow the patient to move if required.

Each treatment was administered for four weeks, five days per week (total of 20 treatment sessions). The inter-train interval was kept shorter for the 125 train compared to the 50 train group to try and keep treatment times more closely equivalent. Alterations for 1 Hz stimulation were not possible.

Clinical assessment

Patients were assessed at baseline and after 1, 2, 3 and 4 weeks. The primary outcome for the study was scores on the HRSD-17 [20]. In addition, all patients completed the Inventory of Depressive Symptoms (IDS) – patient version, the Beck Anxiety Inventory, the Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form, the Snaith-Hamilton Pleasure scale (SHAP) [25,26] and the Scale of Suicidal Ideation (SSI).

Data analysis

The primary outcome analysis was made on response and remission rates for the HRSD-17 (co-primary outcomes), from baseline to end of treatment, with the last observation carried forward for missing data (intention to treat analysis). Response was defined as a greater than 50% reduction in HRSD-17, and remission as a final score on the HRSD-17 of less than 8. The primary analysis of response and remission rates was conducted with χ^2 tests.

A series of secondary analyses were then conducted. First, we conducted a regression analysis with both left and right sided treatment response and remission rates to explore whether illness duration (which was identified as a potential predictor of response to treatment) affected the primary outcome analysis. We conducted an additional regression to exclude an effect of study site as there was an imbalance of randomization resulting from a period of time when one site only recruited into the 2 high dose groups. Second, we examined whether there were differences between the groups on the various rating scales scored as continuous variables. To do this we conducted a mixed model analysis using the restricted maximum likelihood procedure (REML) in GenStat (Release 17.1, VSN International (2014). *Genstat for Windows* 17th Edition. VSN International, Hemel Hempstead, UK. Web page: Genstat.co.uk) with the covariance structure treated as unstructured. This approach does not delete missing values listwise, but rather handles missing values by treating them as being missing at random. The within-patient covariance structure was also investigated and Akaike's Information Criterion was used to select the most appropriate covariance structure for each outcome variable. Empirical studies have confirmed the advantages of mixed models over LOCF analysis [27,28]. We used this approach for HRSD-17, IDS, BAI, SSI, QOL and SHAP scores. Two QOL variables were included in the analysis: total QOL and the score on the QOL scale item 16 (overall sense of wellbeing).

In addition, we explored whether response and remission rates differed between the left and right sided treatment groups overall, or based on standard or high dose groupings (e.g. standard dose left versus standard dose right). In addition, as an exploratory investigation in relation to rate of response, we tested whether response and remission rates differed after 2 weeks of treatment (comparing the 2 left and 2 right sided groups separately).

Correlations (r) were then calculated to investigate potential predictors of response to treatment. Percentage change in HRSD-17 score was the dependent variable. Potential predictors included age, sex, illness and current episode duration, number of previous medications, baseline depression severity, diagnostic group and comorbid diagnosis. These potential predictors were entered into a linear (change in HAMD score from baseline to week 4 as the dependent variable) and binary regression (HAMD response baseline to week 4). We also analyzed the effect of baseline anxiety and suicidal ideation on response, as well as a past history of having received ECT, or reported ECT non-response. All procedures were 2-tailed and significance was set at an α level of 0.05. These analyses were conducted with SPSS 16.0 (SPSS for Windows 16.0, Chicago: SPSS; 2013).

The trial was registered on the Australian and new Zealand Clinical Trials Register (ACTRN12612000321842).

Results

Patients

Baseline clinical characteristics are summarized in Table 1. 300 patients met inclusion criteria and received a baseline assessment and at least one treatment session. There were no serious adverse events during the study. Patient flow is documented in Fig. 1. 9 patients withdrew before the week 2 assessment due to other clinical issues (medical comorbidity or hospitalization related) and 4 due to side effects/treatment intolerance. There was a high number of withdrawals between week 2 and week 4 due to clinical response (patients responding and no longer wanting to remain in hospital).

Primary outcome

The percentage of patients who met response or remission criteria did not differ between the 4 treatment groups (Table 2). There were also no differences in response or remission rates comparing just the two left side treatment groups (response: $\chi^2 = 0.40$, $p = 0.53$, remission: $\chi^2 = 3.2$, $p = 0.07$), or the two right sided treatment groups (response: $\chi^2 = 0.01$, $p = 0.93$, remission: $\chi^2 = 0.82$, $p = 0.37$). There remained no significant effect of group on response when the number of failed medication trials and illness duration were included in a binary regression. However, when illness duration was entered into a regression with treatment group for left sided treatment, there was no effect for illness duration ($p = 0.10$) but the effect of treatment group was significant

Table 2
Treatment response and remission rates.

Group	Response	Remission
Standard Left	52.5%	18.6%
High Left	47.3%	31.9%
Standard Right	49.1%	26.3%
High Right	48.4%	33.3%
Chi-square	0.42, $p = 0.94$	4.5, $p = 0.21$

Response defined as a >50% reduction in Hamilton Depression Rating (HRSD) scale scores, Remission defined as an end of study HRSD score of <8.
The difference in remission rates for high left versus standard left did not reach significance (3.2, $p = 0.07$).

($p = 0.024$). This indicates that when controlling for illness duration, the high dose left sided group achieved greater remission rates than the moderate dose group. This effect remained significant ($p = 0.03$) when study site ($p = 0.64$) was entered into the regression model.

Secondary outcomes

There was a significant ($p < 0.001$) decline in HRSD-17 over time, and also significant differences between the treatment groups at some time points: there was a significant treatment by time interaction ($F_{12,318.1} = 2.19$; $P = 0.012$) (Table 3 and Fig. 2). Pairwise comparisons of the treatment means at each time indicated that there were no significant differences between the treatment groups at baseline, or at the end of treatment. There were, however, some differences at intermediate time points: scores were higher for patients in the high dose left group at week 1, compared to the standard dose left and high dose right groups.

($p = 0.038$ and $p = 0.024$ respectively). At week 2, scores in both left sided groups were significantly below the right standard group ($p = 0.018$ and $p = 0.040$ respectively). At week 3, scores in the right high dose group was significantly lower than in the standard right group ($p = 0.021$).

In regards to the IDS, BAI and SSI data, the unstructured within-patient covariance model provided the best fit to the data. There were significant declines over time in IDS ($p < 0.001$), BAI ($p < 0.001$), SSI ($p < 0.001$) and in SHAP scores ($p < 0.001$). There were no significant treatment by time interactions for IDS ($p = 0.78$), BAI ($p = 0.40$), SSI ($p = 0.13$) and SHAP ($p = 0.055$) mean scores.

There were significant increases over time in total QOL ($p < 0.001$) and QOL item 16 ($p = 0.009$) variables, but no significant treatment by time interactions for QOL ($p = 0.31$) or QOL item 16 ($p = 0.37$).

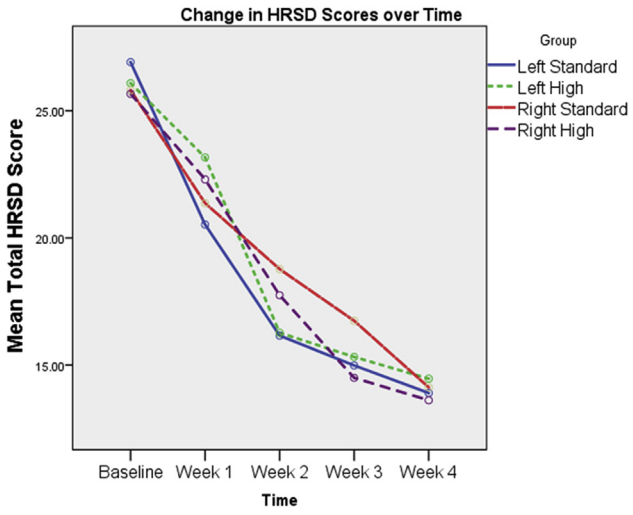

Fig. 2. Mean Hamilton Depression Rating Scale Scores at each study time point.

In comparing overall response and remission rates between patients who received left and right sided rTMS, there were no differences between the groups. Response rates overall were 49.3% for left-sided, and 48.7% for right-sided treatment ($p = 0.91$). Remission rates were 26.7% for left-sided treatment, and 30.7% for right-sided treatment ($p = 0.44$). There was also no difference in response or remission rates comparing left sided standard to right side standard dose groups, or left sided high to right sided high dose groups.

Table 3
Treatment response.

	Treatment Group	Baseline				Week 1				Week 2				Week 3				Week 4			
		n	Mean	LL	UL	n	Mean	LL	UL	N	Mean	LL	UL	n	Mean	LL	UL	n	Mean	LL	UL
HRSD	Standard Left	59	27	25	29	30	16	14	19	48	14	12	16	43	14	11	16	33	12	10	15
	High Left	91	26	25	27	35	20	18	23	79	15	13	17	70	14	12	16	40	13	11	15
	Standard Right	57	26	24	27	37	19	16	21	48	18	16	20	42	16	13	18	42	13	11	16
	High Right	93	26	24	27	27	16	13	19	77	16	15	18	64	12	10	14	30	11	8	13
IDS	Standard Left	55	50	46	53	36	41	37	46	50	40	36	44	48	37	33	42	33	34	29	39
	High Left	83	50	48	53	36	43	39	47	78	40	37	43	69	35	31	39	43	31	26	35
	Standard Right	53	48	44	51	35	38	34	43	50	35	31	39	43	32	28	37	36	30	25	35
	High Right	87	52	49	54	29	44	39	48	75	41	38	44	65	34	30	38	29	32	27	38
BAI	Standard Left	57	27	24	31	36	22	18	26	50	21	18	25	46	19	15	23	32	18	14	22
	High Left	80	32	29	35	36	27	23	30	75	23	20	26	70	20	17	23	40	16	13	19
	Standard Right	51	28	24	32	36	24	20	28	49	20	16	24	42	19	15	22	36	16	12	20
	High Right	84	30	27	33	29	25	21	28	69	23	20	26	61	18	15	21	29	17	13	21
SSI	Standard Left	57	10	7	13	36	9	5	12	49	8	5	10	47	7	4	9	32	6	3	9
	High Left	89	13	11	15	36	11	8	14	77	8	6	10	71	7	5	9	40	6	3	8
	Standard Right	53	12	9	15	35	12	8	15	48	10	7	12	43	8	5	10	35	6	3	8
	High Right	87	14	12	16	29	12	9	15	72	9	7	11	61	6	4	8	27	5	3	8
SHAP	Standard Left	57	12	1	23													32	15	4	26
	High Left	81	10	−1	22													41	14	3	25
	Standard Right	52	12	1	23													33	14	2	25
	High Right	83	10	−1	22													28	11	0	23
QOL	Standard Left	56	25	21	30													31	37	32	43
	High Left	81	24	20	29													42	39	34	44
	Standard Right	54	27	22	31													33	36	31	41
	High Right	82	28	23	32													28	37	31	42
QOL Item 16	Standard Left	56	2	1	3													31	4	2	5
	High Left	81	3	2	4													42	4	3	5
	Standard Right	54	3	2	4													33	3	2	4
	High Right	82	2	1	3													28	2	1	4

Mean Hamilton Depression Rating (HRSD), Inventory of Depressive Symptoms (IDS), Beck Anxiety Inventory (BAI and the Scale of Suicidal Ideation (SSI) for each study visit. Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form (QOL) and the Snaith-Hamilton Pleasure scale (SHAP) scores at Baseline and end of treatment. LL = Lower Limit of the 95% CI for the mean, UL = Upper Limit of the 95% CI for the mean.

In regards to outcomes after 2 weeks, there was no difference in response or remission rates between the two left sided groups (response: standard: 39%, high: 37.4%, $p = 0.84$, remission: standard: 13.6%, high: 18.7%, $p = 0.41$). There was also no difference in either outcome for the two right sided groups (response: standard: 28.1%, high: 22.6%, $p = 0.45$, remission: standard: 5.3%, high: 6.5%, $p = 0.77$).

There was no difference in reduction in anxiety (BAI) between patients receiving left and right sided rTMS ($p = 0.93$).

Predictors of response

There was no relationship between response to treatment (change in HRSD-17) with age or other demographic/clinical variables, except for a weak negative correlation with illness duration ($r = -0.14$, $p = 0.03$). There was also no relationship between patient response and sex, or diagnosis. A higher level of baseline anxiety (BAI scores) was related to poorer response ($r = -0.14$, $p = 0.03$) as was higher suicidality scores (SSI scores) ($r = -0.23$, $p < 0.001$). There was no relationship between degree of response and baseline depression severity ($r = 0.04$, $p = 0.81$) and no relationship with anhedonia (SHAP scores) ($r = -0.05$, $p = 0.37$).

The overall linear regression model was significant ($p = 0.02$). The only significant predictor in the overall model was illness duration ($p = 0.047$).

34.5% of non-responders had previously had ECT, compared to 21.4% of responders ($p = 0.02$), but there was no relationship between response to TMS and having failed or responded to ECT in the past ($p = 0.70$).

Discussion

The results of this study provided very limited evidence of differences in efficacy between standard and high doses of rTMS stimulation based upon pulse number, but provided supportive evidence that high frequency left sided rTMS and low-frequency right sided rTMS are therapeutically equivalent. There was no consistent pattern of a difference in response rates between the groups but there was an advantage of the higher dose versus moderate dose left sided group when controlling for illness duration. There were no differences in clinical response seen across all of the secondary outcome measures. There were no strong predictors of response to treatment, although there was a statistically significant relationship between overall response and illness duration. In addition, it is worthy of note that the high dose stimulation protocols were not associated with any serious adverse events. Reducing the inter stimulus interval to apply 125 10 Hz trains per day in a reasonable time span did not result in the induction of any seizures.

In regards to the primary outcomes, there was no difference, or trend towards a difference, in response rates. However, he observed remission rate in the high dose left-sided treatment group was greater than the rate in the standard dose left-sided treatment group and this difference was significant when controlling for illness duration. Notably, the high dose left-sided group did not produce a substantially higher remission rate than either of the right-sided groups, and there was a far smaller difference in remission rates between the two right-sided groups. Importantly, there were also no significant trends in any direction for differences in response rates between the groups: in fact, the observed response rate was higher in the standard left compared to the high dose left group questioning the overall significance of the differences in remission rates. Overall, the most sensible way to interpret these findings is an overall nil effect. Dose, referring to overall pulse number in the range in which we investigated it and within the limitations discussed below, does not have a strong relationship with overall therapeutic efficacy, when rTMS treatment is used in patients with depression.

During the development of rTMS treatment for depression there has been a progressive increase in the overall dose of stimulation provided. Initial studies using high frequency left sided stimulation used doses markedly lower than the pivotal study that was used to achieve FDA approval of rTMS in the US, and studies done in recent years. For example, the study of George et al., in 1995 applied 20 trains of 10 Hz stimulation [14] whereas the pivotal FDA trial [15] used 75 trains per day. It appears that there has been an assumption that increasing pulse number will result in improved clinical outcomes, but limited data to support this. Clearly our data does not support a strong dose response relationship within the range (albeit limited) that we have explored, although there was an indication that more left sided trains may provide some benefits given the remission rate difference we saw following correction for illness duration. Our results suggest that significantly escalating the number of trains applied per treatment session beyond the numbers that are commonly used today, is unlikely to markedly improve clinical outcomes. Other strategies, especially ensuring longer courses of treatment or improved targeting may be more fruitful.

It is important to note that the results of our study do not directly apply to dosing considerations related to new 'accelerated' treatment schedules [29–31]. The major difference is that in these accelerated protocols, treatment is typically applied across multiple sessions per day, rather than in one long high dose session. Recent physiological experiments exploring the effects of non-invasive brain stimulation on cortical excitability have suggested that there are significantly different brain effects produced when the dose of stimulation applied is split over multiple sessions, rather than in one continuous train (for example [32]).

It is important to note that two left sided treatment groups differed in a second variable other the pulse number – the inter-train interval (ITI). This was shorter (15.5 versus 20.5 s) in the high dose compared to the low dose group which could possibly have mitigated efficacy. To date there has been no published trials directly examining the effect of ITI on response rates in depression treatment. However, a systematic analysis has been published in abstract form supporting a view that a shorted ITI is not associated with poorer outcomes [33] and this has been sufficient for the FDA in the US to approve the clinical use of an ITI (11 s) considerably shorter than the ITI used in the high dose group here. The difference in ITI between the groups could have potentially influenced the outcomes, however.

As a secondary analysis, we also explored whether there was a difference in overall response and remission rates between high frequency left sided treatment, and low-frequency right sided treatment. A number of previous trials (summarized in a meta-analysis [11]) have found no differences in response rates between these two forms of treatment. However, all of the clinical trials included in this meta-analysis were published prior to 2010, and all used 'older' stimulation parameters: e.g. none of the trials used a stimulation intensity greater than 100% of the RMT. Therefore, our current report is the first to demonstrate the likely therapeutic equivalence of right and left sided rTMS at higher intensities of stimulation and a greater stimulation doses. We also analyzed the relative therapeutic efficacy of right versus left sided rTMS on anxiety symptoms. The preferential use of right sided 1 Hz rTMS in patients with anxious depression could potentially be justified on the small number of clinical trials demonstrating potential value of low-frequency right sided rTMS in the treatment of anxiety disorders (for example [34]). A therapeutic advantage of right sided treatment in treating anxiety symptoms was clearly not supported by our data.

In regards to the relationship of clinical and demographic variables to therapeutic response, our findings are only partially consistent with what has previously been reported. We did not find a relationship between age, the number of failed medication trials, or age of illness onset, but did find a weak relationship with illness duration as previously reported [35,36]). Our finding that higher baseline levels of anxiety and suicidal ideation were related to poor response (in the basic correlation analysis but not regression) is a novel one, possibly because these factors have not been systematically investigated in many studies exploring predictors of treatment previously. In regards to anxiety, it is possible that patients with a mixed anxious depressive illness subgroup are less likely to respond to rTMS treatment than patients with other depressive subtypes. It is interesting that there was also a weak relationship with the degree of suicidal ideation, especially given that there was no relationship whatsoever with overall illness severity. It is possible that the presence of significant suicidal ideation somehow defines a more poorly responsive group, but is worthy of note that this relationship was weak and unlikely to have any clinical application.

There are a number of limitations worthy of consideration in interpretation of the results of this study. First, we explored the effect of pulse number as one critical element of dose but there are a number of other dose parameters that require separate exploration. Clearly, for practical reasons, we were unable to test response across a wide range of dose levels to establish what a dose response curve, in regards to TMS pulse numbers, might look like. We chose 50 trains of 10 Hz stimulation. This sat somewhat between the 75 train dose, which has become a somewhat de facto standard in clinical practice since the pivotal FDA trial, and the dosage levels that were commonly used in earlier clinical trials, which often ranged from 20 to 40 trains per day and which are still used in some places around the world where clinical uptake of rTMS has been driven by factors other than FDA approval. We chose 125 trains per day, as this seemed a substantial increase above the 50 trains (and the 75 trains) used in widespread clinical care. Therefore, we cannot definitively confirm that both the 50 and 125 train protocols were not inferior to providing stimulation at 75 trains. We can more confidently infer, however, that a marked escalation of dose was not associated with a clear improvement in outcomes making dose escalation an unlikely way to improve clinical outcomes with rTMS treatment. The choice of the standard treatment for right-sided stimulation was more straightforward. 15–20 min of 1 Hz stimulation is very much the commonly used clinical paradigm when using low frequency stimulation based on published 1 Hz studies and clinical practice, certainly as we are aware of it. 60 min as the high dose group was the longest that we thought was practically applicable.

The overall sample size and dropout rates is also of considerable relevance. The study was conducted across a number of busy real world clinical services with treatment decisions often leading to patient withdrawal. There were also difficulties at one site with obtaining week 1 assessments and in another with challenges having all baseline assessment measures obtained before treatment commencement. These factors have limited numbers across various study points substantially undermining power both for the primary analyses and analysis of changes over time. The dropout rate to final assessment will also have limited the power of the analysis of predictors.

We clearly did not have a sham/placebo-controlled group, but do not feel that this was warranted given the well-established clinical efficacy of both of these forms of rTMS. If possible, it would have been desirable to provide treatment for an identical period of time (for example applying 50 trains of standard treatment, and another 75 trains of sham stimulation in the modest dose left-sided group) to completely ensure that subjects were not biased by a belief that they were getting a higher dose or more optimal form of stimulation. The study results do not appear to have been affected by this form of bias though, as the high dose group did not achieve consistently better clinical outcomes. Another relevant issue concerns the overall duration of treatment – 20 sessions. We would have been more likely to achieve a greater overall clinical response with a longer (30 + session) treatment course and dose differences may have become apparent in this context. However, our response rates (~50%) were not markedly lower than those seen in some open label studies using 30 sessions (58% in Ref. [38]) especially given the degree of treatment resistance and comorbidity of our patients. The study may also have had greater capacity to demonstrate group differences if we had assessed outcomes across a follow up period. In addition, treatment was not applied with more recently developed neuro-navigational methods used to optimize coil placement. If overall response rates were improved with neuro-navigational placement, this may have provided more capacity for true differences to emerge between the groups. However, almost all clinical TMS is still done with methods like those applied in this study and so this doesn't necessarily fully mitigate the relevance of the current results. Finally, the results of this study do not inform the choice of dose for more recently developed theta burst stimulation protocols.

In summary, the results of our study indicate that although high dose left and right sided rTMS protocols can be safely applied, there is only weak evidence that there is a substantial therapeutic advantage of the high dose over more 'moderate' or standard doses and only for left sided high frequency stimulation. The study also indicates that low frequency right sided rTMS is as effective as high frequency left sided rTMS when applied at supra threshold stimulation intensities. Finally, there are no clinical or demographic variables that we have assessed that are strong predictors of successful clinical outcome.

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