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ORIGINAL ARTICLE

A randomized trial of unilateral and bilateral prefrontal cortex transcranial magnetic stimulation in treatment-resistant major depression

P. B. Fitzgerald[1,2]*, K. Hoy[1], R. Gunewardene[3], C. Slack[4], S. Ibrahim[5], M. Bailey[6] and Z. J. Daskalakis[7]

[1] *Monash Alfred Psychiatry Research Centre, The Alfred and Monash University School of Psychology and Psychiatry, Melbourne, Victoria, Australia*
[2] *The Victoria Clinic, Prahran, Victoria, Australia*
[3] *Mosman Private Hospital, Mosman, New South Wales, Australia*
[4] *Pine Rivers Private Hospital, Strathpine, Queensland, Australia*
[5] *Northpark Private Hospital, Bundoora, Victoria, Australia*
[6] *Monash University Department of Epidemiology and Preventive Medicine, The Alfred Hospital, Melbourne, Victoria, Australia*
[7] *Centre for Addiction and Mental Health, Clarke Division, Toronto, Ontario, Canada*

Background. Although several studies have reported that repetitive transcranial magnetic stimulation (rTMS) treatment has demonstrable efficacy in patients with depression, the parameters needed to optimize therapeutic efficacy remain unclear. To this end we determined the efficacy of low-frequency right rTMS to the dorsolateral prefrontal cortex (DLPFC) compared to two forms of bilateral rTMS to the DLPFC: (1) sequential low-frequency right-sided followed by high-frequency left-sided rTMS and (2) sequential low-frequency rTMS to both hemispheres.

Method. A total of 219 patients with treatment-resistant depression (TRD) were randomized to a 4-week course of rTMS applied with one of the three treatment conditions. Outcomes were assessed with standard rating scales.

Results. Overall, slightly more than 50% of the patients achieved clinical response criteria. There was no substantial difference in response between the unilateral and bilateral treatment groups. Successful response to rTMS was predicted by a greater degree of baseline depression severity.

Conclusions. There is no substantial difference in efficacy between unilateral right-sided rTMS and the two forms of bilateral rTMS assessed in the study. Furthermore, our results call into question the specificity between frequency and laterality and rTMS response.

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Key words: Antidepressant, depression, prefrontal cortex, remission, repetitive transcranial magnetic stimulation, response.

Introduction

Major depressive disorder results in significant individual suffering, disability and social economic impact. Despite the availability of several different forms of treatment, about 30% of patients with depression fail to respond to standard therapies (Fava, 2003). Consequently, substantial research effort over the past 15 years has focused on the development of repetitive transcranial magnetic stimulation (rTMS) as a potential treatment alternative for patients with treatment-resistant depression (TRD). This has included the conduct of numerous clinical trials (e.g. George *et al*. 1995, 2000; Padberg *et al*. 1999; Berman *et al*. 2000; Grunhaus *et al*. 2003; Fitzgerald *et al*. 2006*a*, *c*). The vast majority of trials to date have evaluated high-frequency rTMS, usually between 5 and 20 Hz, applied to the left dorsolateral prefrontal cortex (DLPFC) (see review by Daskalakis *et al*. 2008). Most of these trials have shown greater antidepressant efficacy of active rTMS over sham stimulation, which has been confirmed in several positive meta-analyses (e.g. McNamara *et al*. 2001; Burt *et al*. 2002; Lam *et al*. 2008). However, the degree of the active treatment/sham differences in these trials has been limited.

Studies have also been conducted on several other rTMS paradigms, suggesting their efficacy. First, low-frequency stimulation applied to the right DLPFC was shown to be superior to sham stimulation (Klein *et al*. 1999) and to have similar efficacy to high-frequency left-sided stimulation (Fitzgerald *et al*. 2003, 2009;

* Address for correspondence: Professor P. B. Fitzgerald, M.B.B.S., M.P.M., Ph.D., F.R.A.N.Z.C.P., Monash Alfred Psychiatry Research Centre, First Floor, Old Baker Building, The Alfred, Commercial Rd, Melbourne, Victoria 3004, Australia.
(Email: paul.fitzgerald@med.monash.edu.au)

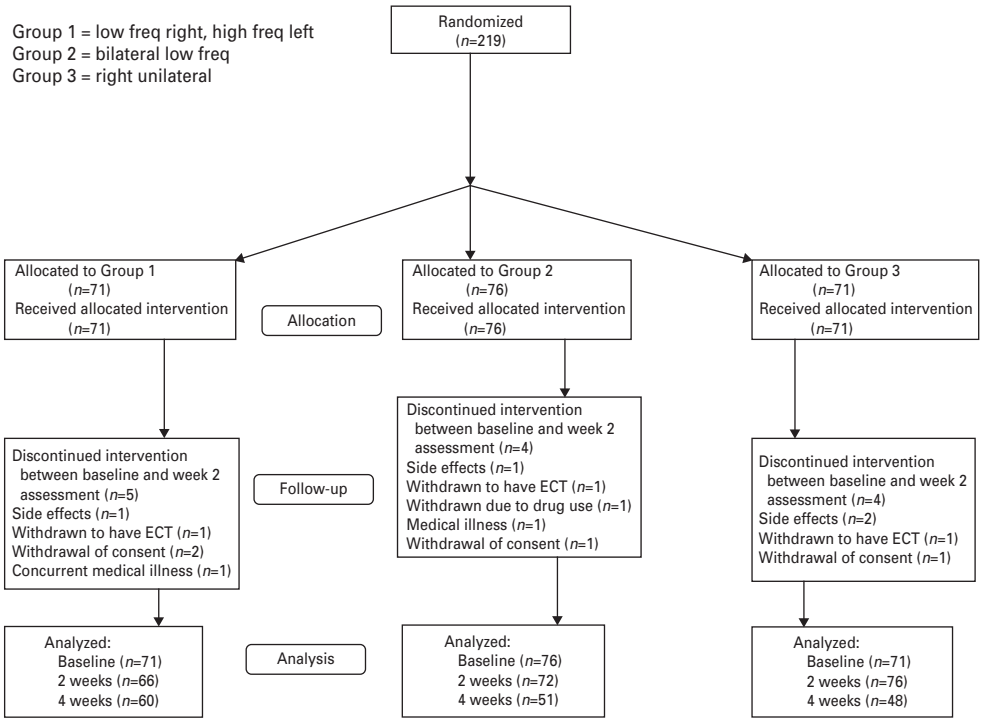

Fig. 1. Study participants.

Isenberg *et al*. 2005). Low-frequency stimulation applied to the right DLPFC has some advantages over high-frequency treatment in that is better tolerated and has a lower risk of seizure induction (Fitzgerald *et al*. 2003). Low- and high-frequency stimulation seem to have opposite effects on cortical excitability (Fitzgerald *et al*. 2003): in motor and prefrontal cortex, low-frequency stimulation reduces, and high-frequency stimulation increases, cortical excitability (Fitzgerald *et al*. 2006*b*, 2007). These disparate effects are thought to relate to antidepressant efficacy based on models that propose hypoactivity of the left PFC and/or hyperactivity of the right PFC in depression. One finding that is not consistent with these ideas is that low-frequency stimulation applied to the left PFC may also have antidepressant properties (Feinsod *et al*. 1998; Padberg *et al*. 1999; Speer *et al*. 2009).

Another novel approach has been the sequential combination of low-frequency stimulation applied to the right PFC followed by high-frequency stimulation applied to the left PFC. Similar effects to unilateral treatment have been reported in several small studies (e.g. Conca *et al*. 2002) and one larger study demonstrated that sequential bilateral rTMS produces considerable antidepressant effects with response rates considerably higher than in most of the studies of unilateral treatment (Fitzgerald *et al*. 2006*a*).

The current study was designed to compare the effectiveness of unilateral and bilateral rTMS. In particular, given its potential advantages over left-sided stimulation, we aimed to compare the efficacy of unilateral low-frequency right-sided rTMS to sequential bilateral rTMS using low frequency on the right and high frequency on the left. We hypothesized that bilateral treatment would be more effective than unilateral. In addition, we aimed to explore the potential efficacy of a novel form of bilateral rTMS: 1 Hz rTMS applied sequentially to the right and left PFC. To explore these questions, a large group of subjects with TRD were enrolled in a randomized, double-blind, three-arm, parallel group trial. We did not include a sham control because multiple trials, including our own (Fitzgerald *et al*. 2003, 2006*a*; Kauffmann *et al*. 2004), have shown superiority of both right-sided 1 Hz rTMS and sequential bilateral rTMS forms of stimulation over sham. In addition, we aimed to recruit a large enough sample to demonstrate differences between these active groups, an aim that would have been more difficult to achieve if the trial included a sham group. The unilateral right-sided treatment group did receive sham stimulation to the left hemisphere in addition to active stimulation to the right.

Method

Study design

The study involved a three-arm, double-blind, randomized controlled trial ($n=219$) (Fig. 1) conducted across four sites. Patients were randomized sequentially

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using a single computer-generated random number sequence (no stratification). 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 but specifics were not described. The duration of the trial was 20 sessions of treatment provided on 5 weekdays per week.

Subjects

A total of 219 patients, all naive to TMS, participated (71 males, 148 females, age range 19–88 years, mean age = 47.2 ± 13.8 years). Diagnosis was determined by a study psychiatrist using the Mini-International Neuropsychiatric Interview (MINI; Sheehan *et al*. 1998). There were 43 patients with major depressive disorder, single episode; 143 patients with major depressive disorder, relapse; 17 with bipolar I disorder, depressive episode; and 16 with bipolar II disorder, depressive episode. Co-morbid diagnoses were also recorded using the MINI. The presence of co-morbid borderline personality disorder was based on the clinical diagnosis of the referring psychiatrist confirmed by a study psychiatrist.

Patients were recruited by referral from private psychiatrists between January 2006 and May 2009. All patients were in-patients during the trial, which was conducted across four private psychiatric hospitals in the states of Victoria, New South Wales and Queensland. As for previous studies (Fitzgerald *et al*. 2006*c*), training in the TMS methods, trial management and ratings were conducted by the lead study site.

The study was powered (0.92) to show a five-point difference in the study end-point variable between any two of the groups ($\alpha < 0.05$, S.D. = 8), with a planned sample size of 80 per group. This difference is small but we considered that it was unlikely that a trial of active treatments in a treatment-resistant population would be likely to show greater differences. The variance data (8) were based as a relatively conservative estimate from Fitzgerald *et al*. (2006*c*).

The inclusion criteria included a diagnosis of moderate to severe depression [scoring > 13 (Bech *et al*. 1986) on the 17-item version of the Hamilton Depression Rating Scale (HAMD; Hamilton, 1967)]. We used the standard cut-off for moderate depression severity on this version of the HAMD; this meant we included a wide range of patients who were considered suitable, by referring psychiatrists, for rTMS treatment, rather than a more selective group of the severely depressed patients. Exclusion criteria were the presence of a significant currently 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 with a current DSM-IV diagnosis of alcohol or substance dependence were excluded because of concerns about seizure risk but patients with other concurrent axis 1 psychiatric disorders were not excluded.

All patients had failed to respond to a minimum of two courses of antidepressant medications for at least 6 weeks in the current episode [Stage II, Thase & Rush (1997) definition; mean number of courses across episodes = 5.40 ± 2.8]. Medications were not allowed to have changed in the 4 weeks prior to commencement of the trial or during the trial itself. A total of 186 patients were taking antidepressant medication during the study and 101 were receiving concurrent treatment with a mood stabilizer.

After complete description of the study to the subjects, written informed consent was obtained from all patients and the study received Human Research Ethics committee approval (at the Melbourne Clinic).

TMS treatment

rTMS was administered using Medtronic Magpro30 magnetic stimulators (Medtronic Inc., USA) with 70-mm figure-of-eight coils held in custom-made stands. The coils were held tangential to the scalp with the handle pointing back and away from the midline at 45°. The site of stimulation during the TMS treatment sessions was defined by 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 (Pridmore *et al*. 1998). Patients sat in a comfortable reclining chair during treatment.

The details of the TMS conditions are summarized in Table 1. The number of pulses was matched between the two bilateral groups and between each hemisphere. Bilateral stimulation was always applied to the right followed by the left hemisphere, in keeping with our previous study using bilateral stimulation (Fitzgerald *et al*. 2006*a*). Sham stimulation was applied on the left in the unilateral right-sided group with the coil angled at 45° off the scalp. The medial wing of the coil was resting on the scalp. This produced some scalp sensation and similar sound intensity to that of active stimulation. This method has been shown to produce a minimal degree of intracortical activity (Lisanby *et al*. 2001) and although we did not assess the beliefs of the participants about their treatment condition, this method has resulted in successful blinding in our previous studies (Fitzgerald *et al*. 2003, 2006*a*).

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Table 1. *Stimulation parameters for each condition*

				Train					
	Order	Hemisphere	Group	No.	Duration	No. of pulses	Inter-train interval	Total no. of pulses	Stimulation intensity (% RMT)
Unilateral right	1	Right	1 Hz	1	15 min	900	–	900	110
	2	Right	10 Hz Sham	18	5 s	50	25	900	110 (Sham)
Sequential bilateral	1	Right	1 Hz	1	15 min	900	–	900	110
	2	Left	10 Hz	18	5 s	50	25	900	110
Low-frequency sequential bilateral	1	Right	1 Hz	1	15 min	900	–	900	110
	2	Left	1 Hz	1	15 min	900	–	900	110

RMT, Resting motor threshold.

Clinical assessment

The primary outcome for the study was scores on the 17-item version of the HAMD (Hamilton, 1967). In addition, all patients completed the Beck Depression Inventory (BDI; Beck *et al*. 1961) and the Beck Anxiety Inventory (BAI; Beck *et al*. 1988).

Data analysis

For the primary analysis we conducted a mixed model analysis using the PROC MIXED procedure in SAS version 9.1 (SAS Institute Inc., USA) with the covariance structure treated as unstructured. The PROC MIXED procedure does not delete missing values listwise, but instead handles missing values by treating them as being missing at random. The PROC MIXED procedure uses a restricted maximum likelihood algorithm that enables specific modeling of the within-patient covariance structure. Using the lowest Akaike's Information Criteria (AIC) as a guide to goodness of fit enables the most appropriate covariance structure to then be evaluated for each situation. Empirical studies have confirmed the advantages of mixed models over last observation carry-forward (LOCF) analysis, with mixed effects (Mallinckrodt *et al*. 2001*a*, *b*). A secondary analysis used the same mixed model procedure to investigate the effect of covariates including the site of treatment. As a sensitivity analysis, an additional analysis was conducted using the mixed model procedure on change from baseline data.

χ^2 tests were used to investigate differences in the proportion of patients achieving response criteria (>50% reduction in HAMD, BDI and BAI scores) between the groups and to analyze differences in remission rates (defined as a HAMD score<8, a BDI score<10 or a BAI score<8). A linear regression analysis was undertaken to investigate potential predictors of response to treatment. All procedures were two-tailed and significance was set at an α level of <0.05, with a Bonferroni correction used for *post-hoc* comparisons. All statistical analysis was conducted with SPSS version 16.0 (SPSS Inc., USA) unless stated otherwise.

Results

Patients

Baseline clinical characteristics are summarized in Table 2. Of the total sample, 13 failed to complete 2 weeks of treatment and to have a single post-baseline assessment. Of these, four withdrew consent, three were withdrawn to have a course of electro-convulsive therapy (ECT), one was withdrawn due to the discovery of ongoing illicit drug use, one was withdrawn due to increased suicidal thoughts, four withdrew due to possible side-effects [one due to headaches (group 3), one due to treatment discomfort (group 1), one due to increased agitation (group 3), one due to an increase in severity of a pre-existing migraine condition (group 2)] and one was withdrawn due to a concurrent medical illness (pneumonia). Of the other 206 patients, 160 completed a full 4 weeks of treatment and 46 withdrew or were withdrawn after 2 weeks of treatment. Withdrawal occurred either because the patients felt they had achieved sufficient clinical response (nine met response and eight remission criteria at 2 weeks) or because they felt that they were not responding to rTMS and they wanted to pursue other treatment options. Withdrawal in some related to practical limitations on continuing treatment. There were no differences in withdrawal rates between the groups. In addition to the adverse events triggering early withdrawal, three patients developed hypomanic episodes towards the end of, or after the

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Table 2. *Demographic and baseline clinical variables*

	Bilateral 1 Hz/10 Hz		Bilateral 1 Hz/1 Hz		Right unilateral	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Age (years)	45.68	13.7	47.91	13.7	47.93	14.1
Sex (M/F)	9/52		28/48		24/47	
Diagnosis (no. of subjects)						
MDD, single episode	13		15		15	
MDD, relapse	45		47		50	
BPAD I	6		7		4	
BPAD II	7		7		2	
No. of failed antidepressant trials	5.5	3.0	5.5	2.8	5.2	2.6
HAMD score	21.2	5.6	20.9	5.3	21.8	4.7
BDI score	36.2	10.8	37.4	10.2	39.6	8.9
BAI score	25.6	11.5	25.1	12.3	26.6	12.4
Concurrently taking antidepressant medication (yes/no)	58/13		65/11		52/9	
Co-morbid diagnoses (no. of subjects)						
Panic disorder	3		1		4	
GAD	12		21		15	
OCD	4		3		8	
PTSD	3		3		3	
BPD	5		8		11	

M, Male; F, female; MDD, major depressive disorder; BPAD, bipolar affective disorder; OCD, obsessive–compulsive disorder; GAD, generalized anxiety disorder; PTSD, post-traumatic stress disorder; BPD, borderline personality disorder; HAMD, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; S.D., standard deviation.

conclusion of, treatment (two in group 1, one in group 2). All had a diagnosis of bipolar disorder.

Overall outcome/effectiveness

By study end, 117 patients from the total sample (53.4%) achieved response criteria and 69 (31.5%) achieved remission criteria.

Primary outcome analysis: continuous data

For the mixed model analysis of the HAMD data, there was a significant overall improvement (effect of time: $p<0.001$) but no difference in response over time between the groups (group × time interaction: $p=0.64$) (Fig. 2). There was a similar finding in the change from baseline analysis (effect of time: $p<0.001$, effect of group: $p=0.68$) (data in Table 3).

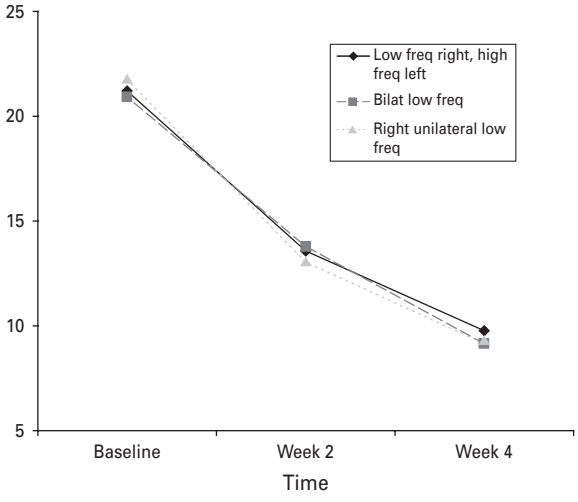

Fig. 2. Mean Hamilton Depression Rating Scale (HAMD) scores.

Secondary variables

For BDI scores, there was a significant overall improvement (effect of time: $p<0.001$) and a significant difference in response over time between the groups (group × time interaction: $p<0.01$). There was also a significant effect of time ($p<0.001$) and group ($p<0.05$) in the change from baseline analysis. A greater response was seen in groups 2 and 3 compared to group 1 but there were no significant differences between the groups in week 2 and week 4 scores in *post-hoc* tests.

For BAI scores, there was a significant overall improvement (effect of time: $p<0.001$) and a suggestion

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Table 3. *Treatment response*

		Baseline			Week 2 (all)			Week 4 (all)		
		n	Mean	S.D.	*n*	Mean	S.D.	*n*	Mean	S.D.
HAMD	Bilateral 1 Hz/10 Hz	71	21.24	5.64	66	13.61	6.08	60	9.93	5.94
	Bilateral 1 Hz/1 Hz	76	20.95	5.32	72	13.81	6.36	51	9.22	5.27
	Right unilateral	71	21.79	4.74	67	13.10	5.42	48	9.02	4.86
BDI	Bilateral 1 Hz/10 Hz	71	36.24	10.76	66	25.92	12.64	60	20.65	13.44
	Bilateral 1 Hz/1 Hz	76	37.37	10.24	72	25.53	13.84	51	16.84	12.36
	Right unilateral	71	39.63	8.93	67	23.73	12.39	48	16.52	12.15
BAI	Bilateral 1 Hz/10 Hz	71	25.58	11.49	66	16.73	11.24	60	13.30	10.25
	Bilateral 1 Hz/1 Hz	76	25.13	12.28	72	18.76	12.34	51	13.49	12.89
	Right unilateral	70	26.61	12.42	67	15.73	11.25	48	10.19	8.63

HAMD, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; S.D., standard deviation.

that the groups behaved differently over time (group × time interaction: $p = 0.07$). In the change from baseline analysis there was a significant effect of time ($p < 0.001$) and of group ($p < 0.05$). A greater response was seen in group 3 compared to groups 1 and 2 but there were no significant differences between the groups in week 2 and week 4 scores in *post-hoc* tests.

Covariate and secondary analysis

Based on three regression analyses including all demographic and treatment variables (with outcome on each of the three rating scales), several factors were identified for analysis as covariates in the overall outcome analysis. These were age, presence of an anxiety disorder, current treatment with a mood stabilizer, current treatment with an antipsychotic, and diagnosis. Inclusion of these in the mixed model analysis did not change the results to any substantial degree. There was no effect of site on treatment outcome.

Categorical analysis

On the HAMD, 56.3, 48.7 and 54.9% of patients in groups 1, 2 and 3 respectively met response criteria by study end ($\chi^2 = 0.99$, $p = 0.61$); the corresponding figures are 35.2, 28.9 and 31.0% for patients who met remission criteria by study end ($\chi^2 = 0.69$, $p = 0.71$). On the BDI, 46.5, 51.3 and 46.4% of patients in groups 1, 2 and 3 respectively met response criteria by study end ($\chi^2 = 0.46$, $p = 0.79$); the corresponding figures are 21.1, 27.6 and 22.5% for patients who met remission criteria by study end ($\chi^2 = 0.97$, $p = 0.62$). On the BAI, 54.9, 39.5 and 57.1% of patients in groups 1, 2 and 3 respectively met response criteria by study end ($\chi^2 = 5.5$, $p = 0.06$); the corresponding figures are 44.9, 49.0 and 42.2% for patients who met remission criteria by study end ($\chi^2 = 2.3$, $p = 0.32$).

Predictors of response

The model from the linear regression analysis is presented in Table 4. There was a relationship between baseline depression severity and response such that greater baseline symptoms were associated with greater clinical response. There were also relationships between diagnosis, age and the number of past antidepressants and response that were significant at a trend level. For diagnosis, a single episode of unipolar depression was associated with a poorer outcome than the other groups (recurrent unipolar depression: $p < 0.01$, bipolar disorder type I: $p < 0.05$, bipolar disorder type II: $p = 0.09$).

Discussion

There are several findings of this study that are worthy of note. First, approximately 50% of patients achieved clinical response to any single course of rTMS and approximately one-third of patients ended the trial with depression scores in the remission range. Second, although we recruited a very large sample of patients, we were unable to establish significant clinical differences in response between low-frequency right-sided rTMS and the two forms of bilateral stimulation. There was clearly no advantage in bilateral stimulation despite patients in both bilateral groups receiving considerably more rTMS pulses overall. In fact, any trends were towards favoring the unilateral group, especially on the BAI and to a lesser degree the BDI data. Additionally, significant antidepressant responses were seen for patients both with unipolar and bipolar depression. The best predictor of response to rTMS was to have greater baseline depression severity. Having recurrent depression, having fewer failed antidepressant medication trials and being of old age were also weakly associated with clinical response.

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Table 4. *Variables predicting clinical response*

Variable	β	t	p
Age	0.29	1.7	0.09
Sex	−2.96	−0.60	0.55
Diagnosis	5.70	1.85	0.07
Anxiety disorder	−0.07	−0.05	0.56
Personality disorder	10.2	1.40	0.16
Number of past antidepressant medication trials	−1.63	−1.97	0.05
Receiving current antidepressant medication	−6.08	−0.98	0.33
Receiving current mood stabilizer medication	2.45	0.51	0.61
Receiving current antipsychotic medication	5.8	1.21	0.23
Baseline HAMD score	1.55	3.36	0.001
Baseline BAI score	−0.22	−1.06	0.29

HAMD, Hamilton Depression Rating Scale; BAI, Beck Anxiety Inventory.
Overall model $r = 0.38$, $p = 0.01$.

The most important finding of this study was that no substantial advantage was seen with bilateral over unilateral stimulation. Although several small studies have compared unilateral and bilateral rTMS, the sample sizes in these studies have generally been very small and the unilateral rTMS approach has always been high-frequency left-sided stimulation. For example, Hausmann *et al*. (2004) found no difference between response to bilateral and left-sided high-frequency rTMS (group sizes of 12 and 13), although their study was confounded by concurrent commencement of antidepressant medication. Conca *et al*. (2002) also found no difference in response between left-sided and bilateral rTMS (group sizes of 12). By contrast, Daskalakis *et al*. (personal communication) have recently found an advantage of sequential bilateral rTMS (low-frequency right followed by high-frequency left) over high-frequency left unilateral stimulation in a study with sample sizes of 20 per group. Our current data suggest that there is no substantial advantage in bilateral stimulation over right-sided unilateral rTMS. This does not imply that bilateral stimulation is not superior to unilateral left-sided high-frequency rTMS but the lack of differences between right and left unilateral approaches in previous research (Fitzgerald *et al*. 2003) argue against this possibility.

The response seen with bilateral low-frequency stimulation in this study is also of interest. This condition produced similar effects to right unilateral stimulation: left-sided stimulation was clearly not pro-depressive. However, adding left- to right-sided treatment also did not enhance efficacy, suggesting that its effects were neutral or that there was an overall ceiling to rTMS response. This approach clearly does not fit within a model of left frontal and/or right frontal hypoactivity. No substantial studies have investigated bilateral low-frequency stimulation previously, although its benefit was suggested in a small pilot study conducted in patients with depression in Parkinson's disease (Dragasevic *et al*. 2002). The antidepressant properties of low-frequency left-sided stimulation have also been suggested by several previous reports (Feinsod *et al*. 1998; Padberg *et al*. 1999; Speer *et al*. 2009), which throws considerable doubt on the model that the therapeutic effects of rTMS result from the propensity of high-frequency stimulation to increased activity in left DLPFC. It is possible that the antidepressant affects of the rTMS are not dependent on frequency and laterality. An alternative model is that repetitively stimulating frontal cortex at any frequency results in the strengthening of cortical subcortical/limbic connectivity, somehow restoring normal network function, perhaps through increasing the capacity of cognitive frontal regions to exert control over the emotive limbic subcortical areas of the brain involved in depression.

The overall response rates seen with rTMS treatment in this study are worthy of note. More than 50% of patients responded to rTMS which is a relatively high rate compared to other studies, although an important distinction is that many studies with lower response rates are sham controlled. It is certainly possible that non-specific treatment factors may have contributed to the overall rate of clinical response. However, the patients included in the current study had chronic depressive illnesses with high rates of comorbidity, which might be likely to reduce response rates overall.

Despite a sample size larger than most rTMS studies published previously, we did not detect strong predictors of response to treatment other than baseline depression severity. The finding of a weak relationship between age and response is in the opposite

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direction to that found in some previous analyses (Fregni *et al*. 2006). Previous studies that have directly explored the use of rTMS in elderly subjects have reported negative findings (e.g. Manes *et al*. 2001; Mosimann *et al*. 2004), but it is important to note that the majority of these have used relatively low stimulation intensities (80–100% of the RMT) and that more recent studies using higher intensities have suggested that depression in the elderly may well respond to rTMS treatment (Jorge *et al*. 2008). Of note, all of these studies, and most focusing on the prediction of antidepressant response, have studied high-frequency left DLPFC rTMS only. In a previous study exploring the relationship between response and right-sided rTMS we saw no deleterious effect of age (Fitzgerald *et al*. 2006*c*).

With regard to limitations, the fact that the study was not sham controlled is of significance. It is possible that a large placebo effect across the three groups acted to obscure any between-group differences. However, our main focus was on exploring differences between active treatment groups, not establishing treatment efficacy, and so a sham group was not included in a trade-off with the likelihood of enhancing recruitment. The possibility of a sham response related to non-specific effects is increased by the in-patient setting of treatment so this impacts on our capacity to generalize from the overall response rates seen in the study. It is also noteworthy that the treatment duration in our study was 4 weeks, which is shorter than in some studies published (e.g. Fitzgerald *et al*. 2006*a*; O'Reardon *et al*. 2007). However, we consider 4 weeks to be a sensible treatment duration to study as longer periods of time may prove to be impractical in clinical practice and 4 weeks seems to be sufficient to achieve a substantive clinical response. Further studies are required to establish whether there is a group of patients who respond only after a more prolonged period of rTMS treatment. Finally, as we were unable to follow up the patients, we have no information on the durability of response, which would help in understanding the value of these benefits.

In conclusion, this study found no substantial differences in response between low-frequency right-sided rTMS and two forms of sequential bilateral rTMS. Low-frequency right-sided rTMS is a simple, well-tolerated treatment paradigm that can be administered fairly quickly on a daily basis and with fewer issues regarding coil overheating than with high-frequency alternatives. It should be considered a viable first-line rTMS treatment option in all patients receiving rTMS treatment. An approximately 50% response rate with treatment was seen overall, although this may be confounded by placebo and non-specific treatment effects.

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Declaration of Interest

P.B.F. has received equipment for research from MagVenture A/S and Brainsway Ltd.

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