Research Article

A RANDOMIZED TRIAL OF THE ANTI-DEPRESSANT EFFECTS OF LOW- AND HIGH-FREQUENCY TRANSCRANIAL MAGNETIC STIMULATION IN TREATMENT-RESISTANT DEPRESSION

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Background: *The majority of studies investigating the effectiveness of repetitive transcranial magnetic stimulation (rTMS) as a treatment for major depression have focused on high-frequency rTMS to the left prefrontal cortex (HFL-rTMS). In addition, low-frequency right prefrontal rTMS (LFR-rTMS) has also been shown to have antidepressant properties. To date only a small number of studies have directly compared the efficacy of these two approaches.* **Methods:** *The aim of this study, therefore, was to investigate further whether LFR-rTMS is as effective as HFL-rTMS in the treatment of major depression. Twenty-seven patients were randomized to one of two treatment arms (HFL-rTMS or LFR-rTMS) for 3 weeks with a possible 1-week extension. Non-responders were offered the opportunity of crossing over to the other treatment type. Stimulation parameters for HFL-rTMS were 30 stimulation trains of 5 s duration at 100% of the resting motor threshold (RMT); for LFR-rTMS, stimulation was applied in four trains of 180 s duration (30 s inter-train interval) at 110% of the RMT. Stimulation was provided 5-week days per week.* **Results:** *There were significant improvements seen from baseline to end point irrespective of group and on all clinical outcome measures. In addition, there was no deterioration in any of the measures used to assess cognitive change, and significant improvements were seen on measures of immediate verbal memory and verbal fluency.* **Conclusions:** *HFL-rTMS and LFR-rTMS appear to be equally efficacious in treating major depression. This study adds to the growing literature supporting LFR-rTMS as an additional viable method of rTMS delivery in the treatment of depression. Depression and Anxiety 26:229–234, 2009.*

Key words: *repetitive transcranial magnetic stimulation; depression; prefrontal cortex; response; remission; antidepressant*

INTRODUCTION

In the last decade repetitive transcranial magnetic stimulation (rTMS) has been extensively investigated as a novel treatment for psychiatric disorders with the majority of these investigations being into major depression [for example[1–4]]. Major depression results

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in substantial disability and morbidity, with a significant percentage of patients (30%) failing to respond to standard treatments.[5] As such, there is considerable impetus for the development of novel therapies, especially for treatment-resistant patients.

Most trials of rTMS in depression to date have used high-frequency (5–20 Hz) left-sided stimulation to the dorsolateral prefrontal cortex (DLPFC) (HFL-rTMS).[6] High-frequency rTMS is thought to increase cortical excitability,[7] which may alleviate depression by correcting an abnormally low level of cortical activity in the left DLPFC.[8] An alternative method of stimulation is low-frequency (~1.0 Hz) right DLPFC stimulation (LFR-rTMS).[1,9] Low-frequency rTMS appears to decrease cortical activity,[7] essentially producing the opposite effect to that seen after HFL-rTMS. To date only a limited number of studies have directly compared HFL-rTMS and LFR-rTMS in parallel trials. In each of the three direct comparisons published to date, no difference was reported between the two conditions in efficacy.[1,4,10] It has been suggested that LFR-rTMS is better tolerated than HFL-rTMS[1] making it a potential first-line approach. In this context it is important to confirm the therapeutic equivalence of the techniques. As such, the aim of this study was to investigate further whether LFR-rTMS is as effective as HFL-rTMS in the treatment of major depression. A smaller data set from this study will be reported separately in the context of a neuroimaging experiment that a subset of the patients in the study participated in.

METHODS

PATIENTS

Twenty-seven patients (15 male, 12 female) participated in the study. The patients were recruited from the outpatient department of Alfred Psychiatry, Alfred Hospital, Melbourne, Australia, and by referral from a number of private psychiatrists. Each patient had a DSM-IV diagnosis of major depressive episode (confirmed with the MINI neuropsychiatric interview) and scored greater than 20 on the Montgomery-Åsberg Depression Rating Scale (MADRS).[11] All patients had failed a minimum of two courses of antidepressant medications for at least 6 weeks in their current episode (mean number of lifetime courses = 6.1, *SD* = 2.6). Patients' doses of medication were not allowed to change in the 4 weeks before commencement of the study or during the trial and they could not commence or change medication during the time of the study. Five patients were not on medication and the others were on either a SSRI (9), TCA (2), MAOI (3), SNRI (3), or a combination of more than one antidepressant (5). Five patients had Electroconvulsive therapy (ECT) for previous depressive episodes (three were considered to have responded and two had not). There was no difference between groups at baseline with respect to medication status. Written informed consent was obtained from all patients and ethics approval was obtained from the Human Research Ethics committee of the Alfred Hospital, Melbourne.

STUDY DESIGN

This was a two-arm randomized double-blind study of HFL-rTMS and LFR-rTMS. Patients were randomized immediately before the commencement of treatment with the use of a randomization code generated by a computer sequence and stored in a sealed envelope. The patients and raters were blind to treatment, but the clinician administering rTMS was aware of the treatment group. Patients who were judged to have met "interim response criteria" after 3 weeks of treatment (reduction in MADRS scores of >30%) were offered a further week of treatment. Patients who did not meet the interim response criteria were offered the opportunity of crossing over to the other treatment type. During the cross-over phase of the study, raters remained blinded to treatment type. The study end point refers to the time point at which the patients received their final review and is inclusive of the cross-over phase.

rTMS

rTMS was administered with a Medtronic Magpro30 magnetic stimulator (Medtronic Inc, Minneapolis, USA) using a 70 mm figure of 8 coil, which was held in place with a stand. At all times the coil was held tangential to the scalp with the handle pointing back and away from the midline at 45° and the induced current flow was posterior to anterior in the cortex perpendicular to the central sulcus. The site of stimulation during the rTMS treatment sessions was defined by a point 5 cm anterior to that required for maximum stimulation of the Abductor Pollicis Brevis (APB). Single-pulse TMS was used to measure the resting motor threshold (RMT) for the APB muscle using electromyographic recording. The RMT was defined as the minimum stimulator intensity that evoked a peak–peak amplitude Motor Evoked Potential (MEP) of >50 μV in at least three out of five consecutive trials. For HFL-rTMS, 30 stimulation trains of 5 s duration at 100% of the RMT were given per session with an inter-train interval of 25 s. For LFR-rTMS, stimulation was applied in four trains of 180 s duration (30 s inter-train interval) at 110% of the RMT. The two conditions were designed to be of approximately equal administration time (rather than matched for pulse number) and the use of higher stimulation intensity with LFR-rTMS was based on the greater tolerability of this procedure.

Sixteen patients received HFL-rTMS, with the mean stimulation intensity being 62.75 ± 10.59, whereas 11 patients received LFR-rTMS at a mean stimulation intensity of 69.81 ± 17.75. Stimulation was provided 5-week days per week.

CLINICAL ASSESSMENT

At baseline, week 3 and week 4, patients were assessed with the MADRS,[11] the Beck Depression Inventory (BDI),[12] the Hamilton Depression Rating Scale (HAMD),[13]the Brief Psychiatric Rating Scale (BPRS),[14]the CORE rating of psychomotor disturbance,[15] and the Global Assessment of Function (GAF). In addition, cognitive assessments were undertaken at baseline, week 3, and week 4. The battery, designed primarily to measure memory and frontally mediated cognitive processes, included the Brief Visuospatial Memory Test (BVMT), the Hopkins Verbal Learning Test (HVLT), Controlled Oral Word Associated Test (COWAT),[16] and the digit span subtest from the Weschler Adult Intelligence Scale (WAIS).[17]

DATA ANALYSIS

T tests and χ^2-squared tests were used to investigate differences between the groups on demographic and baseline clinical variables. Data were included on an intention-to-treat basis for all patients with at least one post baseline evaluation. Therefore, repeated measures analysis of variance (ANOVAs) were used to analyze group differences on all clinical and cognitive scales at two time points (i.e., baseline and end point). The percentage of patients meeting response (>50% reduction in MADRS score) and remission (final MADRS score of <10) criteria were compared with χ^2-squared test

at study end point. Data were examined and all relevant assumptions were satisfied. All procedures were 2-tailed and significance was set at an α level of .05.

RESULTS

PATIENTS

As shown in Table 1, there were no statistically significant baseline differences between the groups.

EFFECTIVENESS OF rTMS

As shown in Table 2, there was a significant improvement in depressive symptomatology over time, as measured by scores on the MADRS, HAMD, BDI, BPRS, CORE, and GAF. Additionally, there was no significant group by time interactions, indicating improvements were irrespective of group (i.e., HFL-rTMS or LFR-rTMS).

Twelve patients (44%) met full response criteria (>50% reduction in MADRS scores) at study end point. There was no significant group difference in the proportion of patients meeting response criteria at study end point; a total of seven (44%) patients in the HFL-rTMS group and five (45%) in the LFR-rTMS group ($P = .62$, Fisher's exact test).

Seven (26%) patients achieved remission by study end. Again, there was no difference between the two groups ($P = .28$ Fisher's exact test), with a total of three (19%) patients in the HFL-rTMS group and four (36%) patients in the LFR-rTMS group achieving remission by study end (Table 3).

CROSS-OVER DATA

After the initial 3 weeks of treatment, eight patients were classified as not having met interim response criteria, and as such crossed over to the other active treatment (three patients crossed to LFR-rTMS and eight crossed to HFL-rTMS). MADRS scores for this group were analyzed using a repeated measures general linear model, which revealed a significant effect of time ($F(1, 6) = 7.22$, $P = .04$), but no effect of group × time ($F(1, 6) = 2.45$, $P = .16$). In terms of the response criteria, this effect was only seen in two of the cross-over patients, both of which were in the LFR-rTMS to HFL-rTMS group. There were no significant improvements in any of the other clinical measures.

COGNITIVE ASSESSMENTS

No deterioration was found in any cognitive measure over time, in either the overall sample or the individual

TABLE 1. Baseline differences

	Baseline		
	Left	Right	Significance
Gender (M/F)	7/8	8/3	>0.05
Age	42.12±9.32	46.54±11.43	>0.05
MADRS	33.68±3.97	34.27±4.98	>0.05
BDI	29.18±6.93	28.63±8.30	>0.05
HAMD	19.81±4.60	20.27±6.21	>0.05
BPRS	29.18±3.91	16.72±4.19	>0.05
CORE	7.00±3.52	8.00±2.82	>0.05
GAF	50.62±8.13	50.45±7.89	>0.05

MADRS, Montgomery-Åsberg Depression Rating Scale; BDI, Beck Depression Inventory; BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Function.

TABLE 3. Response and remission rates

	Response		Remission	
	No.	%	No.	%
Total participants	12/27	44	7/27	26
Participants receiving HFL-rTMS	7/16	44	3/16	19
Participants receiving LFR-rTMS	5/11	45	4/11	36
Participants who crossed from HFL to LFR	0/3	0	0/3	0
Participants who crossed from LFR to HFL	2/5	40	1/5	20

Figures indicate the number of patients who responded or remitted expressed in relation to the total number enrolled under each condition.
HFL-rTMS, high-frequency rTMS to the left prefrontal cortex; LFR-rTMS, low-frequency right prefrontal rTMS.

TABLE 2. Treatment response

	Baseline		Endpoint		Significance	
	Left	Right	Left	Right	Time effect	Group × time interaction
MADRS	33.68±3.97	34.27±4.98	18.31±11.48	19.90±14.52	<0.001	0.846
BDI	29.19±6.93	28.63±8.30	14.75±10.45	18.00±11.19	<0.001	0.333
HAMD	19.81±4.60	20.27±6.21	12.37±7.40	13.72±8.45	<0.001	0.735
BPRS	17.31±3.91	16.72±4.19	10.56±5.03	13.18±10.03	<0.005	0.231
CORE	7.00±3.52	8.00±2.82	3.75±3.43	5.18±3.73	<0.001	0.775
GAF	50.63±3.139	51.00±8.09	61.56±10.75	60.05±9.26	<0.001	0.743

MADRS, Montgomery-Åsberg Depression Rating Scale; BDI, Beck Depression Inventory; BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Function.

TABLE 4. Cognitive outcomes

	Baseline		Endpoint		Significance	
	Left	Right	Left	Right	Time effect	Group × time interaction
BVMT T1	6.25±2.40	5.54±2.87	6.50±2.60	6.00±1.73	0.095	0.232
BVMT T2	8.81±3.03	7.45±3.26	9.68±1.81	8.36±2.24	0.056	0.970
BVMT T3	9.93±2.79	9.09±2.80	11.06±1.12	9.72±1.55	0.084	0.622
BVMT delay	10.00±2.52	8.81±2.81	10.93±1.23	9.09±1.97	0.205	0.482
BVMT recognition	5.53±0.915	5.27±1.19	6.00±0.00	5.63±0.67	0.075	0.819
HVLT immediate	25.38±4.35	23.54±5.14	28.50±4.14	24.36±5.90	<0.050	0.125
HVLT delay	8.60±3.06	7.45±3.01	9.80±1.65	7.72±3.60	0.122	0.323
HVLT DI	10.93±1.62	9.90±1.70	10.93±1.09	10.36±1.62	0.528	0.528
Verbal fluency	39.93±14.09	40.54±13.05	47.18±16.13	44.54±13.87	< 0.050	0.417
Digits forward	11.31±1.85	11.72±2.10	11.75±1.88	11.45±2.25	0.870	0.483
Digits backwards	8.31±2.72	7.72±1.34	8.62±2.55	8.90±2.30	0.207	0.458

BVMT, Brief Visuospatial Memory Test; HVLT, The Hopkins Verbal Learning Test.

groups (Table 2). There were significant overall improvements exhibited in measures of immediate verbal memory ($F(1, 25) = 7.38$, $P = .01$) and verbal fluency ($F(1, 25) = 8.16$, $P = .01$). Improvements in these cognitive measures were not dependent on the type of rTMS received (Table 4).

DISCUSSION

The results of this study suggest that HFL-rTMS and LFR-rTMS are effective in treating major depression, and there appears to be no significant difference in efficacy between the two methods. Significant improvements from baseline to end point were seen with all of the clinical outcome measures used. In addition, there was no deterioration in any of the measures used to assess cognitive change during the trial; in fact there were significant improvements on measures of immediate verbal memory and verbal fluency. Although these findings are somewhat limited because of the relatively small sample size, they add to the growing literature supporting LFR-rTMS as an additional viable method of rTMS delivery in the treatment of major depression. Such findings provide considerable impetus for replication studies on a larger scale.

To date there have only been three studies comparing the efficacy of HFL-rTMS to LFR-rTMS. Two of these involved the randomization of patients to HFL-rTMS, LFR-rTMS or sham. The smaller study included 30 patients treated over 2 weeks.[10] A moderate response rate after rTMS was reported across all three groups with no differences between the groups in depression.[10] The authors suggested that their results may have been limited by the small sample size; however, the duration of the trial may have also been a contributing factor as illustrated in a subsequent study.[1] In this, Fitzgerald et al.[1] randomized sixty patients for 2 weeks of double-blind treatment. At the 2-week point patients who had received some benefit continued for an additional 2 weeks. HFL-rTMS and LFR-rTMS were found to have treatment efficacy superior to sham, but no difference was found between the active groups.[1] In addition, there was also evidence that treatment for at least 4 weeks was required for clinically meaningful benefits.[1] These results have since been replicated in a study of 28 depressed medication free adults. Isenberg et al.[4] directly compared HFL-rTMS to LFR-rTMS over 4 weeks (with initial assessments made at 2 weeks) and found no differences between the groups, concluding that both appear to be effective treatments of refractory depression.[4] This study provides further support of these findings with an extended 3-week fully blinded period before initial assessment.

With growing evidence that LFR-rTMS has efficacious antidepressant effects, there are a number of potential advantages that have implications for the development of clinical rTMS protocols. The potential for seizure induction with rTMS administration is directly related to increasing frequency; therefore, LFR-rTMS should have a considerably lower seizure risk.[1] In fact, low-frequency stimulation itself may have some anticonvulsant effects.[18,19]

As such, LFR-rTMS provides a potential option for patients with risk factors for seizure induction or with substantial medical co-morbidity; patients who are traditionally excluded from HFL-rTMS trials and may be excluded from future treatment protocols. Additionally, although we did not collect data in this study to address this question, patients appear to better tolerate LFR-rTMS than HFR-rTMS[1] which produces more site discomfort during stimulation. These factors suggest that LFR-rTMS may not only have a specific role in certain patient subgroups but also may prove to be a sensible first-line treatment approach.

This study also provides a limited capacity to examine the efficacy of "cross-over" treatment (i.e., swapping between treatments in patients who did not respond to one stimulation type). Past research has suggested that there is potential value in a trial of HFL-rTMS after failed LFR-rTMS, but there is less evidence for the effectiveness of the opposite.[1] These findings are consistent with this study, which also suggested that crossing from LFR-rTMS to HFL-rTMS is a more efficacious switch. It is important to note that these observations are based on a very small number of patients and that a larger-scale replication of such results is required.

There are some limits of the study worthy of consideration. First, we have not included a sham control group in the study and as such cannot rule out non-specific effects that may have resulted in improvements on the clinical measures. However, as existing reports have established the differences between both LFR-rTMS[1,20] and HFL-rTMS[1] and sham it was felt that the inclusion of an additional study group would have diluted our power to detect between group differences on the question of interest. Also, most of the patients were taking antidepressant medication throughout the trial. However, as patients were quite treatment resistant and were not allowed to have increased medication doses or commenced new medications for at least 4 weeks before the commencement of the study, it is unlikely that the change in depression severity was attributable to medication effects alone. Finally, the sample size of the study was relatively small. However, the absence of a difference between HFL-rTMS and LFR-rTMS does not appear to be an issue of sample size, as a post hoc power analysis indicated that to obtain a significant result with the current effect size a sample of at least 548 would be required. This reflects the lack of a substantial trend toward a between group difference which would be representative of clinically meaningful results. Another potential confound concerns the possibility that, as there was not a "TMS-free" period at the time of crossing over, the two rTMS treatments may "combine" to form a sequential bilateral rTMS paradigm. Although there is some evidence that combining high-frequency left-sided stimulation with low-frequency right-sided stimulation has some therapeutic efficacy,[2,7] such bilateral treatments occur during the same treatment session and are not sequential over time.

Despite the promising findings in rTMS studies of both right- and left-sided stimulation, concerns continue to be raised as to whether the effects seen with rTMS are clinically relevant and applicable to practice; therefore, it is critical to increase the body of research around the efficacy of rTMS delivery methods. This study provides confirmatory evidence that LFR-rTMS and HFL-rTMS have equivalent clinical efficacy; however, further research on a larger scale is still required.

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