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An Attempt to Increase the Rate and Magnitude of the Antidepressant Effect of Transcranial Magnetic Stimulation (TMS). A Pilot Study

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Abstract

Objective: An attempt to increase the rate and magnitude of the antidepressant effect of rTMS by providing fast frequency rTMS to the left prefrontal cortex (LPFC) followed by slow frequency TMS to the right (R)PFC at each treatment session.
Method: Eighteen adult patients with major depressive episode (15 unipolar and 3 bipolar) were randomly assigned into two treatment groups. The control group received 30 active trains (2s duration) of 20Hz rTMS to the LPFC followed by 200 1Hz placebo stimuli to the RPFC. The experimental group received 25 active trains (2s duration) of 20Hz rTMS to the LPFC followed by 200 active 1Hz stimuli to the RPFC. Stimulation was at 100% of motor threshold (MT). All patients received ten treatments over two weeks. Measurements were made using the Hamilton Depression Rating Scale, 17 item version (HDRS) and a range of self rated visual analogue scales (VASs) at baseline and after five and ten treatments. Response was defined as 50% reduction in HDRS rating and remission was defined as achieving an HDRS score of 8 or less.
Results: No significant differences were found between the groups overall (Pillai trace = 0.126, F (2,15) = 1.08, p = 0.37, power = 0.20). After ten treatments five of nine control group patients achieved response and all five had achieved remission, while six of nine experimental group patients achieved response and four of these achieved remission. These differences were not statistically significant. Both control and experimental TMS patients showed significant improvement in objective and subjective ratings of depression over the duration of treatment.
Conclusions: Ten treatments of 25 trains of 20Hz rTMS to the LPFC followed by 200 1Hz rTMS to the RPFC were not clinically superior to the 10 treatments of 30 trains of 20Hz rTMS to the LPFC followed by 200 placebo 1Hz to the RPFC with respect to the rate and magnitude of the antidepressant effect (German J Psychiatry 2005;8: 59-65).

Keywords: Transcranial magnetic stimulation, depression

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Introduction

Repeated Transcranial Magnetic Stimulation (rTMS) is a new technology in which electromagnetism is harnessed to deliver an electrical field to the cortex of the brain. It has been studied as a potential treatment of psychiatric disorders [1], particularly major depressive episode. There have been five meta-analyses of the studies comparing rTMS and placebo in the treatment of major depression [2-6]. All have found rTMS to have significantly greater antidepressant effect than placebo. With respect to the size of this antidepressant effect, there have been four studies in which TMS has been compared to ECT in major depression [7-9]. All have found rTMS to be as effective or almost as effective as ECT. One prominent double blind

study of rTMS in major depression [10] failed to find a significant difference in the response of active and placebo groups. However, both groups showed improvement, suggesting that the placebo may have been active. Subsequent work indicated that the placebo used may have reduced the induced voltage in the brain by only 24% [11]. There may also have been unspecified effects of clinical contact to explain this finding. Thus, there is evidence suggesting that rTMS has at least a modest antidepressant effect [12].

When stimulation is applied at 1Hz or lower and above 1Hz, the terms slow (SF-rTMS) and fast (FF-rTMS) have been used respectively [13]. Evidence indicates that SF-rTMS decreases [14] the excitability, while FF-rTMS increases [15] the excitability of the primary motor cortex. Whether these observations hold for all individuals and whether they hold for cortex other than the motor cortex is yet to be confirmed. Nevertheless, these findings have been used in devising therapeutic approaches.

Imaging studies have shown major depression to be associated with hypofunction of the left prefrontal cortex (LPFC) [16, 17]. These observations can be interpreted straightforwardly as indicating a decrease in function of the LPFC, or relatively, as indicating a decrease in function of the LPFC with respect to the RPFC [18]. The straightforward interpretation of these observations led to attempts to increase the activity of the LPFC using FF-rTMS [19]. Interpretation focusing on the relativity of the activity of the LPFC and the RPFC led to attempts to decrease the activity of the RPFC using SF-rTMS [20].

FF-rTMS to the LPFC has been the more extensively studied and in general, about 35-45% percent of depressed patients experience at least a 40% reduction in depression scores [21-23]. While significant with respect to placebo, this antidepressant effect is modest. Also, response may be slow and some studies have extended beyond two [8] and up to four weeks [9].

It is important to discover means to increase the rate and magnitude of the antidepressant response. Synergistic actions are activated when antidepressants from different families are combined in the treatment of resistant depression. It is reasonable to explore the possibility that FF-rTMS to the LPFC followed by SF-rTMS to the RPFC may have synergistic effects. In the present study an attempt was made to increase the rate and magnitude of the antidepressant effect of rTMS by providing FF-rTMS to the LPFC followed by SF-rTMS to the RPFC, at each treatment session.

Method

Subjects

This study was approved by the Ethics Committee of the Royal Hobart Hospital and all patients were fully informed and gave written consent. They were recruited from inpatients of the Royal Hobart Hospital and outpatients of private psychiatrists, and were referred specifically for the study. Patients were free to withdraw from the study as they desired, and could be withdrawn if clinical progress was not achieved. Clinical responsibility remained with the referring psychiatrist.

Inclusion criteria included, right handedness, 20-75 years of age, suffering DSM IV [24] major depressive episode (unipolar or bipolar) with a score 18 or above on the 17 item Hamilton Depression Rating Scale (HDRS) [25], failure to respond to at least a four week trial at maximum recommended doses of medication from at least one family of antidepressants, and clinical circumstances indicating that a physical treatment would be an appropriate next step. Exclusion criteria included a history of epilepsy, concurrent serious medical illness, alcohol or drug abuse, and presence of intracranial metal objects.

Eighteen patients participated in the study. Details of age, sex, duration of the present episode, ECT history and medication at entry to the study were tabulated. Medication was continued, no changes of medication were made for at least three weeks before entry or during the study.

Protocol

This was a randomized double blind controlled trial. Patients were assigned to treatment groups by the order of presentation. Neither patients nor objective assessors knew which treatment was provided. The persons providing the treatments were aware of the nature of the treatments, but refrained from discussing these details with patients or others.

There were two groups of nine patients. Both received 1200 stimuli at each treatment session. Group one received 25 trains of 20Hz stimulation (2s trains) applied to the LPFC, and 200 1Hz stimulations to the RPFC. This was considered the experimental group. This application of 200 1Hz stimuli to the RPFC was greater than the 120 stimuli which had been found to have antidepressant effects when applied to the RPFC in an earlier study [20].Group two received 30 trains of 20Hz stimulation (2s trains) to the LPFC followed by 200 1 Hz placebo to the RPFC. This was considered the control group. While there was the addition of a placebo, there was stimulation of the LPFC with 1200 active stimuli, which is similar to the total number of stimuli provided at each session in recently reviewed controlled trials [5].

rTMS was provided using a Magstim Super Rapid Stimulator (Magstim Co., Whitland, UK) via a figure of eight coil. Stimuli were provided at 100% of motor threshold (MT). MT was determined on the left hemisphere and was defined as the smallest machine output which consistently elicited a motor response [28]. Study stimulation on the left side was at the point 5cm anterior to that at which the MT was determined (LPFC), or at a corresponding point over on the right hemisphere (RPFC).

The placebo stimulation was provided using an electronic metronome set to click at 1Hz, taped to an inactive coil.

Stimulation was provided on ten days over two weeks.

Measurements

Objective assessments

The HDRS was scored by blind medical staff trained in the use of the scale. Scoring was performed at entry, and after five and ten treatments. Response was defined as 50% reduction in the HDRS score; remission was defined as achieving an HDRS score of 8 or less.

Subjective assessments

Six visual analogue scales (VASs) were completed by patients at entry, and after five and ten treatments. One measured depression using anchor points of "the worst I've ever felt" and "the best I've ever felt", as recommended [29]. The remaining five analogically measured the ability to experience pleasure (anhedonia), anxiety, sleep, concentration, and concern about physical health.

Results

Demographic and historical comparisons

At entry there were no significant differences between the groups with respect to age, gender, duration of current episode, diagnosis, concurrent medication, or history of ECT (Table 1).

Treatment comparisons

Data was analyzed following a doubly multivariate design with the independent variables of time (entry, day 5, day 10) and treatment (control rTMS, experimental rTMS) and the dependent measures comprising the HDRS and VAS. Multivariate tests show a significant main effect for time (Pillai trace = 0.92, F (4,13) = 34.9, $p < 0.001$, power = 1.0) reflecting the improvement in both measures of depression during treatment (Table 2).

There was no significant difference between the groups overall (Pillai trace = 0.126, F (2,15) = 1.08, p = 0.365, power = 0.20). However, there was a trend toward an interaction between treatment and time (Pillai trace = 0.44, F(4,13) = 2.55, p = 0.09, power = 0.52), reflecting the finding that, while there was no overall differences between the treatment groups, the improvement in depression ratings over time may not have been uniform across both treatment groups. To clarify this finding, univariate analyses for individual depression rating scores are discussed separately below.

Table 1. Summary of Demographic Variables for Patients in Standard and Experimental rTMS Treatment Groups. Standard deviations in parentheses

	Experimental rTMS (n=9)	Standard rTMS (n=9)	p
Mean age (years)	47.0 (12.3)	53.4 (13.3)	0.30, ns
Number of males	3	3	1.00, ns
Mean duration of episode (months)	9.8 (6.3)	5.7 (5.1)	0.15, ns
Years since initial episode	13.1 (11.7)	12.5 (13.5)	0.92, ns
Diagnosis (bipolar disorder)	1	2	1.00, ns
Concurrent medication	9	9	1.00, ns
Previous history of ECT	4	7	0.33, ns

Table 2. Summary of treatment variables for patients in standard and experimental rTMS treatment groups (standard deviations in parentheses)

	Experimental rTMS	Standard rTMS	p value
	Hamilton Depression Rating Scale (HDRS-17)		
Entry (day 1)	23.8 (2.4)	23.0 (4.0)	0.62, ns
Day 5	10.9 (4.3)	17.0 (6.4)	0.03, ns*
Response (%) (50% reduction)	7/9	2/9	0.06, ns
Remission (%) (= ≤ 8)	2/9	1/9	1.00, ns
Day 10	10.2 (5.6)	9.8 (5.5)	0.87, ns
Response (%) (50% reduction)	6/9	5/9	1.00, ns
Remission (%) (= ≤ 8)	4/9	5/9	1.00, ns
	Visual Analogue Mood Rating Scale (VAS)†		
Entry (day 1)	2.2 (0.9)	2.5 (1.7)	0.70, ns
Day 5	5.0 (1.6)	4.2 (2.6)	0.43, ns
Day 10	5.7 (2.3)	6.3 (3.0)	0.65, ns

*Not significant at an alpha level of 0.05 for the group of HDRS post-hoc tests following Bonferroni adjustment for multiple hypothesis testing

†This VAS had anchor points of 0 = 'The worst I've ever felt' and 10 = 'The best I've ever felt'

HDRS comparisons

Repeated measures ANOVA on objective (HDRS) ratings of depression showed no significant main effect of treatment group [$F(1,16) = 0.95$, $p = 0.35$, power = 0.15]. However, a significant main effect of time [$F(1.7, 26.5) = 52.03$, $p < 0.001$, power = 1.00, following a Geisser-Greenhouse epsilon correction], and a significant time x treatment interaction [$F(1.7, 26.5) = 4.15$, $p = 0.034$, power = 0.63] indicate that the significant improvement in ratings of depression over the course of treatment did not progress at the same rate for both groups [Subsequent repeated measures ANOVA have had Geisser-Greenhouse epsilon corrections applied as appropriate].

Bonferroni-adjusted pairwise comparisons indicate that, while there were no significant differences between HDRS ratings for the two treatment groups at day 1 or day 10, there was a trend for those in the experimental treatment group to have lower HDRS rating scores at day 5 than standard rTMS patients (Table 2).

While there appeared to be a clinically encouraging difference in the numbers of patients achieving response (50% reduction from initial HDRS-17 rating) between the treatment groups at day 5, with seven of the nine experimental rTMS patients achieving response in comparison to two members of the standard rTMS group, this difference was not found to be significant (Table 2: $p = 0.06$). Similarly, there were no differences in the numbers of patients achieving response or remission between the groups at either the midpoint or completion of treatment.

Table 3. Summary of VAS ratings of individual symptoms for patients in standard and experimental rTMS treatment groups (standard deviations in parentheses)

	Experimental rTMS	Standard rTMS	p value
	Visual analogue rating of anhedonia†		
Entry (day 1)	1.5 (1.6)	1.6 (1.3)	0.85, ns
Day 5	3.7 (2.3)	4.7 (2.5)	0.41, ns
Day 10	4.2 (2.5)	6.3 (3.1)	0.13, ns
	Visual analogue rating of anxiety		
Entry (day 1)	3.0 (1.8)	3.4 (2.8)	0.73, ns
Day 5	5.5 (2.4)	4.6 (3.2)	0.52, ns
Day 10	4.9 (2.7)	6.2 (2.9)	0.35, ns
	Visual analogue rating of sleep problems		
Entry (day 1)	5.1 (3.0)	3.4 (2.9)	0.25, ns
Day 5	6.2 (2.2)	6.4 (3.0)	0.87, ns
Day 10	6.6 (2.5)	7.2 (3.4)	0.69, ns
	Visual analogue rating of concentration problems		
Entry (day 1)	3.2 (1.9)	4.3 (2.8)	0.33, ns
Day 5	4.5 (2.7)	3.9 (2.4)	0.59, ns
Day 10	5.5 (3.1)	6.7 (3.3)	0.42, ns
	Visual analogue rating of somatic concern		
Entry (day 1)	6.0 (3.2)	5.8 (3.4)	0.87, ns
Day 5	7.2 (2.3)	5.8 (3.3)	0.32, ns
Day 10	7.5 (2.4)	7.5 (2.2)	0.98, ns

†Each VAS scale had anchor points of 0 = "The most (symptom) possible" and 10 = "No (symptom)", for example 0="The most anxious possible" and 10="Not anxious". The only slight exception to this pattern was anhedonia, with anchor points of 0="Activities give normal pleasure" and 10= "No activities give pleasure".

VAS ratings of depression

Significant improvements in self-report VAS ratings of depression were seen for both groups over the course of treatment [$F (1.5, 24.5) = 19.39$, $p < 0.001$, power = 0.999]. No main effect of treatment group [$F (1,16) = 0.01$, $p = 0.99$, power = 0.050] or an interaction effect [$F(1.5, 24.5) = 0.77$, $p = 0.44$, power = 0.15] was shown, indicating that this improvement in VAS ratings over time was consistent across both patient groups.

VAS ratings of other individual symptoms

All VAS ratings of the individual symptoms of depression that were studied followed the same pattern (Table 3), showing a significant improvement over the course of

treatment [anhedonia: $F(1.3, 21.6) = 18.34$, $p < 0.001$, power = 0.99; anxiety: $F (1.9, 30.3) = 6.51$, $p = 0.005$, power = 0.86; sleep problems: $F(1.1, 18.1) = 8.97$, $p = 0.006$, power = 0.84; concentration problems: $F (1.9, 31.2) = 6.32$, $p = 0.005$, power = 0.87; and somatic concern: $F (1.5, 23.5) = 4.76$, $p = 0.027$, power = 0.65]. There were no main effects of treatment group or treatment x time interactions, indicating that these improvements for all symptoms were consistent across both treatment groups.

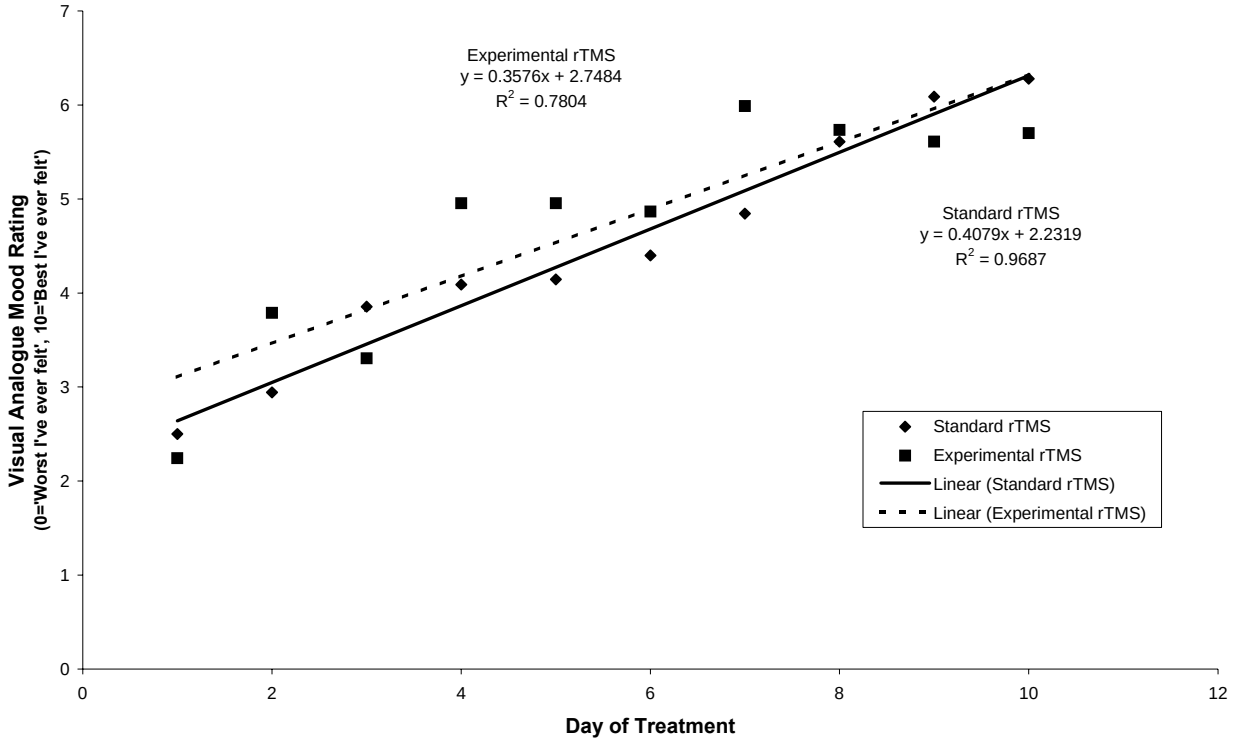
rTMS dose-response relationship

Significant linear trends showing continual improvement in VAS ratings of depression were shown for both control rTMS [$F (1,8) = 247.86$, $p < 0.001$] and experimental rTMS [$F (1,8) = 28.43$, $p < 0.001$] patient groups over the ten days of treatment (Figure 1). No higher-order trends were found to contribute significantly to these regression analyses. These findings suggest that both rTMS treatments obey a dose-response relationship over this period of treatment.

Discussion

rTMS treatment sessions of 1000 stimuli at 20Hz to the LPFC followed by 200 stimuli at 1Hz to the RPFC produced similar clinical outcomes to sessions of 1200 stimuli at 20Hz to the LPFC followed by 200 placebo stimuli at 1Hz. Thus, the experimental arrangement did not increase the rate and magnitude of the response after 10 treatments. There was a

Figure 1. Mean Visual Analogue Scale Ratings of Subjective Mood Over ten Days of Treatment for Patients with MDE who Were Treated with Standard rTMS or the Experimental rTMS Treatment.



trend for those in the experimental treatment group to have lower HDRS rating scores at day 5, but this had disappeared by day 10.

The study compares one group that receives active stimulation at a single frequency [20Hz] with a second group, which receives active stimulation at two frequencies [20Hz and 1Hz], one applied at one site [LPFC] and the other at another [RPFC]. The question being addressed was whether stimulation at two sites [with site specific frequencies] would give a better result than stimulation at one site [with a site specific frequency]. But there are other complications, as there are suggestions that the frequency of stimulation may not be crucial, and that the total number of stimuli provided may be influential. A recent study found that stimulation at both five and 10Hz applied to the LPFC produced antidepressant effects [30]. This is consistent with the findings of Dr W Lyndon of Sydney who has conduced an open study comparing three and 20Hz to the LPFC [personal communication]. In an attempt to improve outcomes, studies have been conducted with up to 4800 stimuli per session [31]. In the current study we decided to keep the total number of stimuli provided constant at 1200 per day; this meant that the number of stimuli applied to the LPFC varied [1200 in the control group and 1000 in the experimental group]. It would be interesting to repeat the study keeping the number of stimuli to the LPFC constant, in which case detected differences may be due to differences in the total number of stimuli provided.

The limitations of the study include the small sample size. The current study had power sufficient to detect a 50% difference in HDRS scores between the groups at day 5, with a beta of 0.20 and a two-tailed alpha of 0.05. Such a proportionate difference between treatments is the minimum considered clinically significant by the authors given the time-consuming nature of the experimental treatment. From an academic perspective it would be interesting to repeating the study with larger numbers. In such an endeavor, it would be important to examine for differences between groups at day 5.

A third group receiving placebo only was not employed. These patients were suffering moderate to severe major depressive episode. In our hands, FF-rTMS to the LPFC has a useful antidepressant effect [8,32-35]. The aim was to examine an arrangement, which may have increased the rate and magnitude of the antidepressant response to rTMS beyond that of our routine treatment. For this purpose, a placebo only group was unnecessary, and given our positive experience with FF-rTMS, a placebo group could be considered ethically questionable.

In rTMS there is always concern about the quality of the placebo treatment. In spite of extensive work, a perfect placebo has not been identified [38]. Even with what has been considered the "least active" placebo, that is, with one coil touching and the long axis of the coils at 90 degrees to the scalp, direct examination of the primate brain has reveal measurable voltage changes [11]. Also, the touch (pressure) of the edge of one wing on the scalp is a different tactile experience to the touch of the greater flat area of the junction region of the two wings as occurs under standard stimulation conditions. The placebo as provided here (electronic

metronome set to 1Hz, taped to the top of an inactive figure of eight coil) gave the same touch (pressure) and a very similar auditory stimulus. It was plausible and can be considered a satisfactory placebo. Patients were advised that they could be treated on the right side with a placebo or rTMS different to that which they experienced on the left. An electronic metronome generates a tiny magnetic field.

It would be preferable to be able to compare two groups of drug free patients. However, due to the realities of clinical life, rTMS is frequently used as "an add on therapy", both in research and routine therapeutic settings [32,36,37]. In the study reported here, all patients in both groups were taking medication.

This was a moderately to severely depressed group of people, all of whom had failed an adequate trial of at least one antidepressant medication. Eleven of 18 had previously received ECT. The current episode had commenced 9.8 months previously for the experimental group and 5.7 months previously for the control group. This introduces the confound that the control group may have been closer to remission at entry, due to the natural course of the disorder. Interestingly, after 10 rTMS treatments, four of the experimental and five of the control group (total, 9) achieved remission, findings consistent with recent work in the field (39).

Further studies are required to find clinically useful ways of increasing the rate and magnitude of the antidepressant effect of TMS. It will be important to discover whether increasing the strength of the stimulus or increasing the total number of stimuli will have the desired effect.

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