Journal of Affective Disorders 232 (2018) 79–82

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Exploring alternative rTMS strategies in non-responders to standard high frequency left-sided treatment: A switching study

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ARTICLE INFO

Keywords:
Brain stimulation
Mood disorders
Treatment
Cognitive
Antidepressant
TMS
Switching

ABSTRACT

Background: High-frequency left-sided repetitive transcranial magnetic stimulation (rTMS) is now commonly used treatment for patients with depression. However, there are several other forms of rTMS (low-frequency right-sided and sequential bilateral rTMS) which have also been shown to be effective. No information has been systematically gathered on the likelihood of response to alternative forms of rTMS in patients who do not improve after an initial course of left-sided treatment.

Objective: To evaluate whether there are differences in antidepressant response between switching to either low-frequency right sided or sequential bilateral stimulation or continuing high-frequency left-sided TMS following non-response to an initial course of high-frequency left-sided rTMS.

Methods: 113 rTMS naïve patients were provided with an initial three-week course of high-frequency left-sided rTMS. Non-responders were then randomised to receive another three weeks of left-sided treatment (n = 21), right-sided low frequency stimulation (n = 18) or sequential bilateral rTMS (n = 20).

Results: Although there was an overall improvement in depressive symptoms in the randomised phase of the study, no significant differences in response was seen between the three treatment groups on Montgomery Asberg Depression Rating Scale or Hamilton Depression Rating Scale scores.

Limitations: The main limitation of the study was the duration of treatment provided in both the lead in and random treatment phases.

Conclusion: This study does not provide evidence for differences in response to different forms of rTMS in initial non-responders to left-sided stimulation. However, further studies with longer periods of treatment and a larger sample size are required to definitively establish or exclude between group differences in rTMS response in initial non-responders to treatment.

1. Introduction

Over recent decades, repetitive transcranial magnetic stimulation (rTMS) has been developed as an alternative intervention for the 30% of patients with major depressive disorder (MDD) who do not respond to standard interventions (Fava and Davidson, 1996), commonly referred to as treatment resistant depression (TRD). Although the majority of research evaluating the use of rTMS has focused on left-sided treatment (Schutter, 2009; Slotema et al., 2010), several alternative treatment models have also been evaluated including the application of low-frequency stimulation applied to the right DLPFC (for example (Bares et al., 2009; Fitzgerald et al., 2003; Fitzgerald et al., 2006b)) and sequential bilateral stimulation (Blumberger et al., 2016; Fitzgerald et al., 2006a, 2011, 2012) combining both high-frequency left and low-frequency right-sided treatment. Both of these have been shown to be effective in their own right and to a similar degree compared to left-sided treatment (Chen et al., 2013, 2014; Zhang et al., 2015).

Limited research has demonstrated that patients failing to respond to one form of TMS, may respond to an alternative treatment approach (Fitzgerald et al., 2009) but minimal research has explored whether patients who have failed to respond to high-frequency left-sided rTMS are likely to respond to right sided or bilateral rTMS and how this would compare with just continuing left-sided rTMS. Therefore, in the current study we aimed to obtain preliminary data on the differential efficacy between these alternate approaches. We randomized non-responders to left-sided high-frequency rTMS to continue treatment or

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https://doi.org/10.1016/j.jad.2018.02.016
Received 8 September 2017; Received in revised form 12 January 2018; Accepted 15 February 2018
Available online 17 February 2018

switch to either right-sided low-frequency rTMS or sequential bilateral rTMS. Our primary hypothesis for the study was that either switch approach would result in greater therapeutic response compared to continuing left sided high frequency rTMS.

2. Methods

2.1. Study design

Initially, all patients were provided with 15 sessions of open label high-frequency left-sided rTMS over three weeks. After this lead in, patients who had failed to achieve at least a 25% reduction in their Montgomery-Asberg Depression Rating Scale (MADRS) score (non-responders) were included in the switching study. Non-responders were randomised to one of three groups: A) continuation of left-sided high frequency rTMS, B) provision of right-sided low-frequency rTMS, or C) provision of sequential bilateral stimulation (i.e., right-sided low-frequency rTMS followed by left-sided high frequency rTMS). All treatment approaches were provided for an additional three weeks (i.e., 15 sessions). Randomization occurred using a single computer generated number sequence. The TMS operator was provided with the group prior to the commencement of the first phase 2 treatment session and raters were blind to treatment type.

After a complete description of the study to the subjects, written informed consent was obtained from all patients on a form approved by the Human Research Ethics Committees of the Alfred Hospital and Monash University. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12610001071011).

2.2. Subjects

113 rTMS naive patients with major depressive disorder completed at least the baseline assessment and were included in this report. This included 61 males and 52 females (mean age = 45.7 ± 13.5 years). Diagnosis was made by an experienced psychiatrist and confirmed using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). There were 65 patients with MDD – single episode and 52 patients with MDD – relapse.

Patients were recruited by referral from private and public psychiatrists between January 2008 and November 2010 and no patients were in hospital during the trial. The inclusion criteria included a diagnosis of moderate to severe depression (scoring greater than 20 (Bech et al., 1986) on the MADRS). All patients were required to have failed 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 (Thase and Rush, 1997)) (mean number of courses across episodes = 8.9 ± 16.9). Medications must not have been changed in the four weeks prior to commencement of the trial or during the trial itself. Exclusion criteria were a diagnosis of bipolar affective disorder, 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 or the presence of a pacemaker). Patients with other concurrent Axis 1 psychiatric disorders were not excluded, with the exception of schizophrenia spectrum disorders. In regards to concurrent medication treatment, 73.5% of patients were taking an antidepressant medication during the study, 15.0% were taking a mood stabilizer as adjuvant treatment, 41.6% a benzodiazepine and 31.9% were receiving concurrent treatment with an atypical antipsychotic.

2.3. TMS treatment

TMS was administered with a Medtronic Magpro30 magnetic stimulator using 70 mm figure-of-8 coils. Prior to the commencement of rTMS treatment, single pulse TMS was used to measure the resting motor threshold (RMT) for the abductor pollicis brevis (APB) muscle in the hand in all participants using standard published methods. All treatment was provided with the coil handle pointing back and away from the midline at 45 degrees and tangential to the scalp. All forms of stimulation were applied at 110% of the RMT. Stimulation was localised at the F3 or F4 10-20 EEG system points using the Beam-F3 method (Beam et al., 2009).

Left-sided rTMS was provided as follows: 4 s 10 Hz trains with a 26 s inter-train interval. 40 trains were applied daily. Right-sided stimulation was applied in a single train of 1200 pulses over 20 min. Sequential bilateral stimulation involved the application of 600 right-sided 1 Hz pulses in a single train followed by forty 10 Hz trains applied to 4 s each with a 26 s inter- train interval to the left side.

2.4. Clinical assessment

A diagnosis of MDD by DSM IV criteria was confirmed using the MINI Neuropsychiatric interview (Sheehan et al., 1998). Demographic variables and potential covariates were recorded at baseline including the duration of the current episode, years from first diagnosis, number of previous episodes and type and dose of current and previous treatment. Clinical measures were performed at baseline, 1, 4 (baseline for switching) and 7 weeks (3 week follow up for randomised treatment). The primary depression outcome variable was the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Patients were also assessed with the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory-II (BDI-II) (Beck et al., 1961). Ratings were conducted by trained raters who were not informed of treatment group when patients switched and patients were counselled to provide no details on their treatment group to the raters.

2.5. Data analysis

T tests and χ^2 -squared tests were used to investigate differences on demographic and baseline clinical variables. For the primary analysis we calculated a repeated measures ANOVA model (using last observation carried forward data) from the start of randomization to the week three follow-up using the MADRS data. The same approach was used to investigate differences in response between the groups on the HDRS and BDI scales. In addition, we calculated paired sample *t*-tests for each group on the MADRS and HDRS investigating changes across treatment times. All procedures were 2-tailed and significance was set at a α level of 0.05. All statistical analysis was conducted with SPSS 22.0 (SPSS for Windows. 10.0 Chicago: SPSS; 2013).

3. Results

3.1. Participants

113 patients were recruited and consented but 2 withdrew prior to the completion of the baseline assessment. 111 patients entered treatment in phase 1. Of these, 11 withdrew during phase 1 treatment: 3 due to side effects of TMS (pain and headache), 2 due to unrelated medical illness and 6 withdrew consent/decided not to continue treatment. A further 8 patients withdrew after the completion of the week 3 assessment: 2 due to physical health reasons, one due to a worsening of depression and 5 withdrew consent.

Of the remaining 92 patients there were 59 non responders who entered the switching study and were randomized: 21 to left sided treatment, 18 to right sided treatment and 20 to bilateral treatment. These 3 groups did not differ in age, sex, handedness, diagnosis (single or recurrent depression), duration of illness or duration of current episode, number of depressive episodes or number of past medications. They also showed no difference in MADRS, HDRS or BDI scores at the 3 week time point prior to randomization.

Of these 59 patients, 1 in the right-sided treatment group withdrew after 4 treatments and 58 completed 3 weeks of treatment.

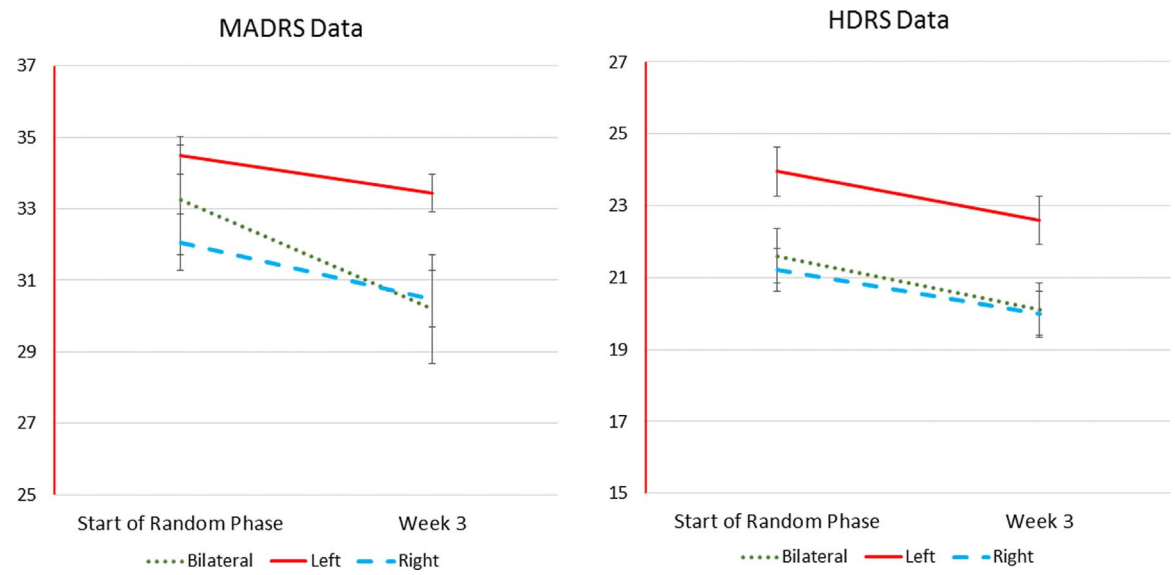

Fig. 1. Montgomery Asberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HDRS) scores (SE) across study time points.

3.2. Primary outcome

For the primary outcome, from week 3 to week 6 (i.e., the 3 weeks of randomized treatment), there was a significant effect of time ($F(1,56) = 5.7$, $p = .02$) but no effect of group ($F(2,56) = 0.63$, $p = .53$) and no group by time interaction ($F(2,56) = 0.65$, $p = .52$) (Fig. 1). Only 2 patients met response criteria at week 6, both of whom received bilateral treatment. On pairwise *t*-tests, there was a trend for a significant reduction in MADRS scores in the bilateral group ($p = .08$) but no difference in the other 2 groups (left: $p = .4$, right: $p = .2$) (Table 1).

3.3. Secondary outcomes

Similar results were seen for the secondary outcome measures. For both the HDRS and the BDI there were significant effects of time (HDRS: $p = .008$, BDI: $p = .02$) but no significant group by time interactions (HDRS: $p = .97$, BDI: $p = .75$). On pairwise *t*-tests, there was a trend for a significant reduction in HDRS scores in the 2 unilateral treatment groups (left: $p = .06$, right: $p = .08$) but no difference in the bilateral group ($p = .19$).

4. Discussion

The main objective of this study was to evaluate if there were significant differences between different types of rTMS treatment delivery in patients who had a minimal response to an initial course of high-frequency left-sided rTMS. We did not find this to be the case. However, we did find that an additional 3-week course of rTMS (i.e. 6 weeks in total) did result in significant therapeutic benefit in patients with TRD.

There are several features of our study that are worthy of note in interpretation of the results of this trial. First, we randomized patients who had not experienced any degree of clinical response following an initial course of high-frequency left-sided treatment using a stricter definition of non-response than normally adopted. We chose to time this randomization after three weeks of treatment to both restrict the overall length of the study and to inform decision-making at a point in time of treatment that would limit the overall course of treatment. However, the initial three weeks of treatment may well have been insufficient to truly identify non-responders to high-frequency left-sided treatment as patients may respond after a longer period of treatment (Yip et al., 2017). However, it is very unclear how long this optimal period of left-sided initial treatment should have been as no studies have definitively outlined guidance for the optimal duration of rTMS therapy. Our treatment parameters in the open label phase probably contributed to our overall response rate (~ 36%). This is higher than response rate seen in double-blind trials but significant we lower than we have seen across a range of other studies as described in (Fitzgerald et al., 2016). Although we provided fewer stimulation trains that has become a relatively standard approach (40 compared to 75), it is our view that the duration of treatment (only three weeks) was probably

Table 1
Demographic and outcome measures for patients in the cross over analysis.

	Baseline						Baseline differences	3 Weeks						Change (*p* for effect of time)
	Left		Right		Bilateral			Left		Right		Bilateral		
	Mean	SD	Mean	SD	Mean	SD		Mean	SD	Mean	SD	Mean	SD	
Age	50.3	13.7	42.6	13.6	46.4	15.3	ns							
Sex (M/F)	11/10		10/8		10/10		ns							
Duration Of Illness	22.3	14.8	19.8	12.2	20.9	13.0	ns							
Duration of current episode	7.3	12.2	5.6	6.2	4.2	3.9	ns							
Number of episodes	6.3	4.3	2.8	1.0	5.8	2.9	ns							
Number of past medications	6.3	3.1	11.1	24.5	6.6	4.7	ns							
MADRS	34.2	5.6	32.4	6.4	33.3	7.3	ns	33.4	8.7	30.4	6.7	30.2	11.2	0.02
HAMD	24.0	5.3	21.1	5.1	21.6	5.3	ns	22.6	5.8	19.9	5.8	20.1	7.7	0.008
BDI	35.0	12.2	31.1	11.2	34.8	12.1	ns	33.2	14.6	28.2	12.4	31.0	14.2	0.02

Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory-II (BDI-II).

the main factor determining the limitations of this response rate. There is clearly more consistent trends in the literature for duration of treatment to be associated with improved outcomes than number of rTMS trains (Kedzior et al., 2014). The patients included in this study also had a relatively high degree of treatment resistance and chronicity.

Perhaps a greater limitation of our capacity to demonstrate differences between the active groups arose from the limited duration that we provided of treatment in the double-blind phase. This was restricted to 3 weeks for practical and resource related reasons. Clearly, if we were able to provide longer periods of treatment we may well have achieved greater responses, especially in the right-sided and bilateral treatment groups. The overall degree of response was also very low across all three groups. Although this was statistically significant, the mean changes in depression rating scores were very small in all likelihood reflecting some of these limitations in stimulation protocol delivery. It is worthy of note, however, that a recent study of dorsomedial TMS for depression found that partial symptom response/improvement by 2 weeks was quite predictive of ultimate improvement (Feffer et al., 2017). One further limitation arose from patients entering the randomized phase of treatment immediately after their initial course of left-sided treatment. This was necessary for patients having left-sided treatment to continue with that modality but understanding responses to the other forms of treatment is somewhat more complicated. It is certainly possible, as is seen occasionally clinically, that patients who were non-responders at the point of randomization, could have gone on to have had a delayed response to left-sided treatment confounding assessment if they were randomized to one of the other treatment groups. Our overall design did limit our final randomized study sample and this significantly compromised the power we had to show differences between the groups. However, the similarity of responses seen across all three arms of the study suggest that very large samples (in the hundreds per group) would be required to demonstrate any meaningful difference in response under the circumstances. Unfortunately, it is difficult to obtain funding for these forms of large pragmatic trials.

The one important conclusion that we can draw from the results of this study is that a failure to meet response, or even partial response, criteria after three weeks of rTMS treatment does not indicate that therapy should be stopped at that time. There was an overall improvement across the sample in depression scores from 3 to 6 weeks indicating that improvement was achieved regardless of the type of treatment administered. However, we are not really left with any capacity to draw conclusions as to whether therapeutic benefit is likely to be specifically related to a frequency laterality combination or just continuation of 'generic' rTMS stimulation. However, the overall limited degree of response seen in the crossover phase of treatment suggest that maybe a non-specific effect was at play here.

In summary, the study found no substantive differences between unilateral left, unilateral right or bilateral rTMS treatment in patients who had initially failed to respond to a three week course of high-frequency left-sided stimulation. Further more substantive studies, probably on a multi-site basis, are required to answer this increasingly commonly faced clinical question.

Acknowledgements

This study was supported by a grant from the Alfred Foundation.

PBF is supported by a Practitioner Fellowship grant from National Health and Medical Research Council (NHMRC) (1078567). KEH is supported by an NHMRC Career Development Fellowship (1082894). ZJD was supported by the Ontario Mental Health Foundation (OMHF), the Canadian Institutes of Health Research (CIHR), the Brain and Behaviour Research Foundation and the Temerty Family and Grant Family and through the Centre for Addiction and Mental Health (CAMH) Foundation and the Campbell Institute.

Clinical trials registration

Australian New Zealand Clinical Trials Registry: ACTRN12610001071011.

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