

Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a new technology which holds promise as a treatment of psychiatric disorders. Most work to date has been on depression. Superiority to placebo has been indicated in three small blind studies. We compared the antidepressant effects of rTMS and ECT in 32 patients suffering major depressive episode (MDE) who had failed to respond to at least one course of medication. There was no limit to the number of treatment sessions which could be given and treatment was continued until remission occurred or response plateaued. A significant main effect for treatment type was found [Pillai trace = 0.248, $F(3,28) = 3.076$, $p = 0.044$; power = 0.656], reflecting an advantage for ECT patients on measures of depression overall, however, rTMS produced comparable results on a number of measures. Blind raters using the 17-item Hamilton Depression Rating Scale (HDRS) found the rate of remission (HDRS ≤ 8) was the same (68.8%), and the percentage improvement over the course of treatment of 55.6% (rTMS) and 66.4% (ECT), while favouring ECT, was not significantly different. Significant differences were shown ($p < 0.03$) in percentage improvement on Beck Depression Inventory ratings (rTMS, 45.5%; ECT, 69.1%), but not for improvement in Visual Analogue ratings of mood (rTMS 42.3%; ECT, 57%). rTMS has antidepressant effects of useful proportions and further studies are indicated.

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Introduction

Transcranial magnetic stimulation (TMS) is a new technology which has potential for investigation and treatment in neurology and psychiatry (Pridmore and Belmaker, 1999). The technique involves holding of an insulated coil in contact with the scalp over the region of interest. When a strong current is passed around the coil a magnetic field is created which passes through the scalp and skull and into the brain. Rapidly fluctuating the strength of that current produces fluctuations in the magnetic field, which in turn produces tiny secondary currents (Cadwell, 1989) in proximity to the junction of grey and white matter (Epstein et al., 1990).

In animal studies, rTMS has been found to have similar effects to ECT. Fujiki and Steward (1997) compared the effects of 25 Hz rTMS and electroconvulsive shock (ECS) in mice. They found similarities in expression of glia fibrillary acidic protein mRNA. Ji et al. (1998) compared 25 Hz rTMS and ECS in rats. They found both produced increased immediate early gene expression but in different patterns. ECS increased *c-fos* mRNA throughout the brain particularly in the hippocampus and neocortex. By contrast, rTMS increased *c-fos* mRNA more discretely particularly in the paraventricular nucleus of the thalamus. Fleischmann et al. (1999) applied 20 Hz rTMS to rats and found that chronic exposure produced increases in seizure threshold similar to those reported for ECS and ECT.

In both open (Epstein et al., 1998; George et al., 1995) and blind (Avery et al., 1999; George et al., 1997; Pascual-Leone et al., 1996) clinical trials, rTMS has demonstrated antidepressant effects. In the double-blind clinical trials, however, this effect had been disappointingly transient (Pascual-Leone et al., 1996) or

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small (George et al., 1997). At the time of designing the present study, all published study protocols had limited the number of rTMS treatment sessions to a maximum of 10.

In our clinical experience more than 10 sessions of rTMS treatment are usually necessary for optimum results. In a study of 12 dexamethasone suppression test (DST) non-suppressors suffering MDE who were treated with an average of 12 sessions of rTMS (Pridmore, 1999), 6 showed clinical improvement and normalization of the DST response. We also reported the case of a female DST non-suppressor with major depressive disorder who received three courses of rTMS (a total of 30 treatments) over a period of 3 months (Reid and Pridmore, 1999), ultimately with lasting remission. Established ECT practice is that different individuals with similar psychopathology may require a different number of treatments, and it can be anticipated that this will be the case with rTMS.

Andrews (1989) states that we can reasonably conclude that a treatment is responsible for observed improvement provided a dose-response relationship can be identified. We were interested in this concept as we would be unable to utilize a placebo stream.

The aims of the study were:

- (1) to compare the maximum antidepressant response to rTMS (using particular stimulation parameters) and ECT (using particular treatment parameters) achievable with courses of treatment of unlimited length;
- (2) to compare the side-effect profile of the two treatments;
- (3) to examine the evidence for dose-response relationships.

Method

This study was approved by the Ethics Committee of the Royal Hobart Hospital and all patients were fully informed and gave written consent.

Consecutive patients suffering DSM-IV (American Psychiatric Association, 1994) major depressive episode who scored 18 or above on the 17-item HDRS (Hamilton, 1960) and who had failed to respond to a 4-wk trial at maximum recommended doses of medication from at least one family of antidepressants and for whom, on clinical grounds, a physical treatment was considered to be the next appropriate step, were invited to participate. They were told the study was a comparison of ECT and rTMS, and that both were considered to be effective treatments of MDE. They were randomly assigned to groups according to order of presentation. They were free of serious medical illnesses and those who received rTMS were right handed and free of epilepsy and intracranial

metal objects. Details of age, sex, duration of the present episode, ECT history, and medication at entry to the study were tabulated. Medication was tapered and ceased where possible; no new medication was commenced in the 2 wk before entry into the study. Entry was considered to occur on the morning of the first day of treatment. Exit from the study was considered to occur on the afternoon of the last treatment.

Co-morbidity or a past history of certain disorders in which symptomatic lowering of mood is a feature (dysthymia, cyclothymia, depression not otherwise specified, adjustment disorder with depressed mood or personality disorder) was allowed. Exclusion criteria included mood disorder due to a general medical condition or substance use, and co-morbidity for mental disorders other than those listed above.

It was not possible for patients to be blind to the form of treatment. Blind raters performed objective assessments of mood. They were not involved in the treatment of patients, nor were they members of the study team. They were instructed to avoid any discussion of treatment.

For both groups (i) the 17-item HDRS was scored by a blind rater at entry and exit, (ii) the BDI (Beck et al., 1961) was scored at entry, exit and at weekly intervals throughout treatment, (iii) a Side-effects scale was scored at entry, exit and at weekly intervals throughout treatment, and (iv) the Visual Analogue Scale (VAS) (a 100-mm horizontal line with the anchor points 'I feel the best/worst I have ever felt' at either end, as described by Ahearn, 1997) was scored at entry, exit and 3 times per week throughout the study. The Side-effects scale was especially developed for this study. It is a 7-item schedule which rates: 'headache', 'memory problems', 'muscle stiffness', 'dry mouth or blurred vision', 'nausea, abdominal discomfort or bowel problems', 'tremor' and 'weakness, tiredness or sleepiness' on a b-point severity scale.

To allow maximum possible response to these forms of treatment there was no upper limit on the number of treatment sessions which could be provided. Patients remained the responsibility of their treating psychiatrist who made the decision to cease or change treatment. The research team provided rTMS as a discrete service and arranged for the collection of assessment results.

rTMS was provided using a Magstim Super Rapid stimulator (Magstim Co.). Treatments were given 5d/wk, applied to the left prefrontal cortex (LPFC) at the following parameters: 100% of motor threshold (MT), 20 Hz, 2-s trains, 30–35 trains/d separated by 28-s rest periods. MT was determined as the minimal percentage of machine output which consistently resulted in contraction of thumb muscles when applied to the motor cortex (Pridmore et al., 1998)

Table 1. Summary of demographic variables for patients in rTMS and ECT treatment groups (standard deviations in parentheses)

	rTMS (n = 16)	ECT (n=16)	p value
Mean age	44.0 (11.9)	41.5 (12.9)	0.57, ns
Number of males	4	3	0.27, ns
Mean duration of episode (months)	7.6 (12.3)	6.4 (8.6)	0.74, ns
Years since initial episode	9.3 (9.2)	5.3 (7.8)	0.19, ns
Diagnosis (bipolar disorder)	5	1	0.17, ns
Co-morbid symptoms	9	6	0.48, ns
Concurrent medication	12	13	0.99, ns
Previous history of ECT	6	3	0.25, ns

ECT was provided using a Thymatron DGx and Thymapad electrodes (Somantics Inc.). Treatments were given 3 d/wk, applied to the non-dominant hemisphere using 100% of machine output (504 mC) with the stimulus width at 0.5 ms. All patients received a standard anaesthetic: pre-oxygenation, intravenous induction with 1–1.5 mg/kg methohexitone and partial paralysis with 0.5 mg/kg suxamethonium.

Results

Demographic and historical comparisons

At entry, there were no significant differences between the groups with respect to age, gender, duration of current episode, years since first episode, diagnosis, co-morbid symptoms, concurrent medication and history of ECT (for details see Table 1).

Data was analysed following a doubly multivariate design with the independent variables of time (entry, exit) and treatment (rTMS, ECT), and the dependent measures comprising the HDRS, BDI and VAS. Multivariate tests show a significant main effect for time [Pillai trace = 0.824, $F(3,28) = 43.749$, $p < 0.001$], reflecting the improvement in all measures of depression during the subject's hospital stay. A significant main effect for treatment type was also found [Pillai trace = 0.248, $F(3,28) = 3.076$, $p = 0.044$; power = 0.656], reflecting an advantage for ECT patients on measures of depression overall. There was no significant interaction between treatment and time [Pillai trace = 0.151, $F(3,28) = 1.663$, $p = 0.1981$, reflecting that the improvement in depression ratings over time was common for both ECT and rTMS treatment groups. Univariate analyses for individual depression rating scales are discussed separately below.

The mean number of treatments for the rTMS group was 12.2 (S.D. = 3.4) and for the ECT group, 6.2 (S.D. = 1.6).

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

	rTMS	ECT	p value
	Hamilton Depression Rating Scale		
Entry	25.3 (4.1)	25.8 (3.6)	0.7
Exit	11.3 (8.5)	8.3 (7.5)	0.3
Improvement (%)	55.6 (30.2)	66.4 (33.6)	0.4
Remission (%) (= ≤ 8)	11/16	11/16	0.9
	Beck Depression Inventory		
Entry	33.9 (6.8)	31.8 (6.6)	0.4
Exit	19.2 (11.8)	9.6 (8.9)	0.01*
Improvement (%)	45.5 (28.9)	69.14 (28.4)	0.03*
Remission (%) (= ≤ 15)	7/16	12/16	0.2
	Visual Analogue mood rating scales		
Entry	8.4 (1.2)	7.9 (1.9)	0.4
Exit	4.9 (2.8)	2.9 (1.7)	0.02*
Improvement (%)	42.3 (28.4)	57.0 (37.0)	0.2
	Side-effect rating scores		
Entry	8.1 (3.2)	6.1 (3.6)	0.1
Exit	3.9 (2.9)	5.3 (4.3)	0.3

* Significant at an alpha level of 0.05

HDRS comparisons

Repeated-measure ANOVAs for the effect of time and treatment type showed a significant main effect of time [$F(1,30) = 102.066$, $p < 0.001$], referring to the improvement in HDRS scores over the course of treatment for both groups. No significant main effect of treatment type [$F(1,30) = 0.579$, $p = 0.452$] or treatment x time interaction [$F(1,30) = 1.220$, $p = 0.278$] was found. This reflects the fact that, as shown in Table 2, no differences between the rTMS and ECT groups in HDRS scores were found at entry or exit to the study. Additionally, no

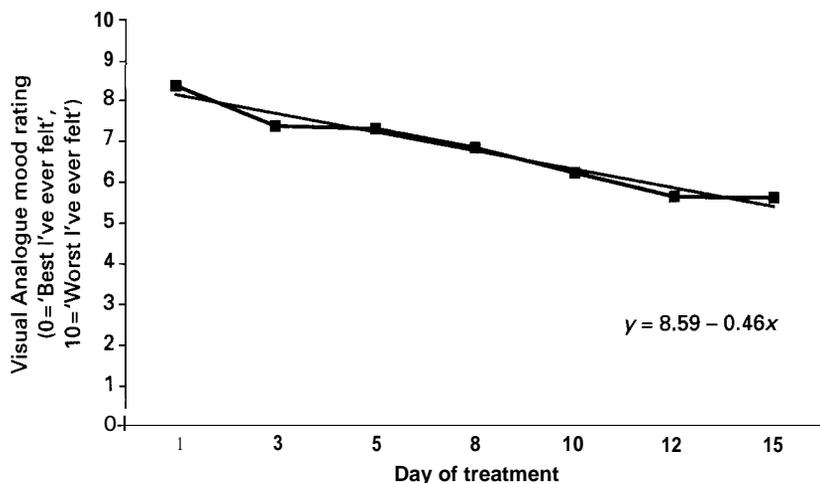


Figure 1. Mean Visual Analogue Scale ratings of subjective mood over the first 15 d treatment for patients with MDE who were treated with rTMS.

significant differences between the groups in percentage HDRS improvement or remission rates were shown.

BDI comparisons

Repeated-measure ANOVAs showed a significant main effect of time [$F(1,30) = 103.413$, $p < 0.001$], reflecting the improvement in BDI ratings for both groups over the course of treatment. A significant effect of treatment type was shown [$F(1,30) = 5.400$, $p = 0.0271$, indicating that the ECT group had lower BDI ratings overall. However, a statistically significant time \times treatment interaction [$F(1,30) = 4.335$, $p = 0.0461$] appeared, reflecting the fact that, while the groups did not differ in BDI ratings at intake, the ECT group reported significantly better BDI depression ratings than rTMS patients at discharge (as shown in Table 2). In concert with these findings, a significant difference between the groups was shown in the percentage improvement on the BDI [$F(1,30) = 5.537$, $p = 0.025$]; however, χ^2 did not detect significant differences in remission rates ($p = 0.2$).

VAS comparisons

Significant improvements in VAS ratings for both groups over the course of treatment [$F(1,30) = 76.418$, $p < 0.001$] was shown by repeated-measure ANOVAs. A significant main effect of treatment type also appeared [$F(1,30) = 5.701$, $p = 0.0231$, indicating that the VAS rating scores for patients treated with ECT were lower than rTMS clients overall. No interaction effect was shown [$F(1,30) = 2.628$, $p = 0.115$]. However, no significant difference was shown in VAS improvement ratings for the two groups [$F(1,30) = 1.587$, $p = 0.218$]. Descriptive statistics and results of follow-up tests of simple effects are shown in Table 2.

Side-effect comparisons

Repeated-measure ANOVAs for side-effect ratings shows a significant main effect of time [$F(1,30) = 9.190$, $p = 0.005$], indicating that, overall, reported side-effects reduced over time in treatment. There was no difference in side-effect ratings for the marginal means of the two groups [$F(1,30) = 0.111$, $p = 0.742$]. Additionally, a significant time \times treatment interaction appeared [$F(1,30) = 4.187$, $p = 0.0501$, reflecting the 'crossover' in the side-effect data, in that TMS patients started the study with non-significantly higher side-effect ratings than ECT patients, and exited with slightly lower ratings, as shown in Table 2.

rTMS dose-response relationship

Significant linear trends indicating continual improvement in VAS ratings were shown both for recovered patients alone and the rTMS group as a whole [$F(1,105) = 27.01$, $p < 0.001$]. No higher-order trends were found to contribute significantly to these regression analyses. Mean VAS scores over time for the rTMS group are shown in Figure 1. These findings indicate that rTMS treatment and response obeys a dose-response relationship.

Discussion

This was a comparison study of an experimental treatment (rTMS) and the most effective treatment of depression (ECT). That we did not have a placebo group may be deemed a design fault, however, these were suffering patients and we did not wish for, nor could we have obtained permission for a placebo stream. The objective (HDRS) raters were blind to the administered treatment.

One potential problem of this study is that during the exit interview, raters could have become aware of the nature of the administered treatment. To minimize bias these raters were not involved with the treatment of the patients or with the research project (other than as objective raters) and they were requested not to discuss the mode of treatment. In subsequent studies we will have raters give their best guess as to what form of treatment the patients received to document any bias. At this stage it is also impossible to give a course of rTMS without prolonged contact with the rTMS staff. Our rTMS staff were instructed to maintain a reserved demeanour and not to discuss psychopathology, aetiology or progress issues. Nevertheless, rTMS treatment was also a time of human contact. In the future a means of securing the coil may become available which will enable reduction of this contact.

The subjective measures of BDI and VAS both showed an advantage for ECT. For the BDI the percentage improvement (TMS, 42.3%; ECT, 69.1%) was significantly different ($p < 0.03$). The numbers achieving remission on the BDI (TMS, 43%; ECT, 75%) and the percentage improvement on the VAS (TMS 42.2 %; ECT, 57.0%) although favouring ECT, were not significantly different. Subjective assessments may be biased. While a case can be made that TMS may introduce bias through its novelty status, ECT involves the pre-anaesthetic electrocardiogram, induction of general anaesthesia and associated recovery-room procedures, which may also strongly bias responses.

With respect to the better response of the ECT group on BDI and VAS, the effect of that treatment on memory deserves consideration. Our impression was that in many instances ECT patients experienced temporary impairment of memory, and are unable to remember all the difficulties and conflicts which had played an aetiological or compounding role in their disorder. rTMS is not associated with such cognitive effects (Grafman and Wassermann, 1999) and the treated rTMS patients remained fully aware of the circumstances (difficulties and conflicts) of their lives.

We are reporting a 55.6 % improvement in HDRS with rTMS. This result is slightly higher than those reported previously. There are many variables, not only in the parameters applied, but also in information provided in the various reports. In two important open studies, Epstein et al. (1998) reported a 51% reduction in the HDRS of 32 individuals and Triggs et al. (1999) reported a 41% reduction in HDRS of 10 individuals with drug-resistant major depression. In double-blind studies Pascual-Leone et al. (1996) reported a 50% reduction in HDRS of 17 individuals and George et al. (1997) reported an 18% reduction in HDRS of 12 individuals with drug-

resistant major depression. From a table in the report of a double-blind study by Avery et al. (1999) there was a 50% reduction in the HDRS of 4 individuals. The dose and number of treatments we provided may have given a better response. George et al. (1997), Avery et al. (1999), and Triggs et al. (1999) used an intensity of only 80% MT, whereas we used 100% MT. All the above studies provided 5–10 treatment sessions. The mean number of treatments in the present study was 12.2.

Our study design allowed continuation of rTMS while improvement continued. Those who went on to remission received a mean number of 13.1 (s.d. = 3.1) treatments while those who did not achieve remission received a mean number of 10.6 (s.d. = 3.8) treatments. This flexibility is unique among the studies and may have contributed to the high remission rate. This arrangement led, of course, to greater quantities not only of rTMS, but also staff contact and it is probable that the reported improvements were influenced by these factors.

This study suggests that rTMS can achieve results approaching ECT, if stimulation is at 100% MT and the length of the course can be flexible, with no imposed upper limit to the number of treatments. This is important as ECT is regarded as the most powerful antidepressant available (Abrams, 1997). Further studies are required to characterize the antidepressant capacity of rTMS.

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