

Transcranial Magnetic Stimulation in Depression: an Overview

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Abstract

Objective: To examine the evidence for therapeutic effect of fast frequency repeated transcranial magnetic stimulation (stimulation at >1 Hz; FF-rTMS) on depression.

Method: All available information published in English was considered.

Results: A large body of animal studies indicates that FF-rTMS has the capacity to influence behaviour and biochemical actions, including the regulation of gene expression, in a manner similar to that of electroconvulsive shock (ECS) and antidepressant medication. There have been eight blind sham controlled studies. In one, the active stimulus may have been inadequate. In another, the sham may have been active. The remaining six studies all showed a significant antidepressant action for the active treatment. Two blind comparisons of FF-rTMS and ECT also indicate a useful antidepressant action for TMS.

Conclusion: The evidence strongly supports an antidepressant effect for FF-rTMS. The next step is to increase the efficacy of this treatment. That may involve increasing the dose (number of pulses and/or intensity) and number of treatment sessions (German J. Psychiatry 2001; 4:43-50).

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Introduction

Transcranial magnetic stimulation (TMS) is a new technology which applies the principles of electromagnetism to deliver an electrical field to the cortex of the brain. It is in regular use as an investigational tool in basic and clinical neurophysiology. The aim of this paper, however, is to examine some of the evidence suggesting that TMS has potential as an antidepressant.

By convention, repetitive stimulation at a particular site may be designated rTMS, but this is not mandatory. Additionally, when the repetitive stimulus is applied at 1 Hz or slower, the term slow frequency (SF-rTMS) may be used [1], and when the stimulus is applied at greater than 1 Hz, the term fast frequency (FF-rTMS) may be used [1]. SF-

rTMS applied to the right prefrontal appeared to have an antidepressant effect in an open study [1] and a 70 patient placebo controlled [2]. FF-rTMS, however, has been more extensively examined, and this review will focus on that type.

FF-rTMS has been suggested as a potential treatment for a range of neuropsychiatric disorders, but the large majority of research energy has been focused on the effect of this technique on major depression.

Animal Studies

In 1995, Fleischmann et al.[3] compared the effects of FF-rTMS and electroconvulsive shock (ECS) on animal models of depression in rats. They found that FF-rTMS and ECS had

similar effects on the characteristic behaviour of apomorphine-treated animals, the immobility time in the Porsolt swim test and the seizure threshold. The Porsolt swim test results and the anticonvulsant effects have been confirmed [4,5]. FF-rTMS and ECS have also been shown to have similar effects on brain monoamines [6], beta-adrenergic receptors [7], cyclic AMP [4] and gene expression in supportive [8] and neuronal tissue [9] of rodents. In comparison to sham treated and control rats, FF-rTMS was associated with a significant increase in serotonin 1A and N-methyl-D-aspartate (NMDA) receptors [10].

More recently, a German group [11] found that FF-rTMS mediated a neuroprotective effect against oxidative neuronal cell death in rats. They [12] then found that FF-rTMS increased both brain derived neurotrophic factor (BDNF) protein and mRNA and cholecystokinin (CCK) mRNA in rodent brain, in the manner of antidepressant medication and ECS. Most recently [13] they developed a method of providing FF-rTMS such that the resultant current density in rat brain is comparable to that which occurs with this treatment in the human brain. Applying this technology, they found that FF-rTMS produced behavioral and neuroendocrine changes in a rat line bred for high anxiety-related behaviour which are comparable to those induced by antidepressant drug treatment. Finally, others [14] have recently found that TMS has similar effects on the function of the hippocampal cells of the rat, as do the antidepressants mianserin and desipramine.

Thus, animal studies indicate that TMS has the capacity to influence behaviour and biochemical actions, including the regulation of gene expression, in a manner similar to that of ECS and antidepressant medication. For reviews see Belmaker and Grisaru [15] and Lisanby and Belmaker [16].

Introductory Clinical Evidence

FF-rTMS delays the onset of rapid eye sleep (REM) in normal subjects [17]; this is encouraging, as reduced REM latency is one of the most robust markers of depression [18]. FF-rTMS significantly increases the regional cerebral blood flow (rCBF) of the left anterior cingulate in depressed individuals, when the coil is placed over the left prefrontal cortex [19]; this is encouraging, as reduced rCBF in the cingulate and associated limbic structures is a feature of depression [20].

FF-rTMS at greater than motor threshold intensity elevated plasma thyroid-stimulating hormone (TSH) in healthy males in a placebo controlled trial [21]. This is of interest as TSH is elevated by sleep deprivation, which has an antidepressant effect. More recently, in a placebo controlled study of patients with major depression, a single session of FF-rTMS produced a significant elevation of TSH and mood [22].

FF-rTMS to the left prefrontal cortex increases the release of endogenous dopamine in the ipsilateral caudate nucleus [23]. This [¹¹C]raclopride and positron emission tomography study is important as dopamine has been implicated in depression, as well as schizophrenia and addiction.

Evidence of an antidepressant action for FF-rTMS comes from a number of open studies [24,25]. There have been case reports of good recoveries by individuals [26]. There is evidence that FF-rTMS can induce mania [27]. The ability of FF-rTMS to normalize abnormal dexamethasone suppression test results in depression, an objective measure of clinical remission, has been demonstrated [28]. Also, FF-rTMS treatments have been substituted for ECT treatments, in courses of ECT, without loss of antidepressant effect [29].

In a survey of the experience and attitudes of 48 patients who had received FF-rTMS for major depressive disorder, either as a treatment option or as a study subject, 63% believed TMS had been helpful, 87% would recommend it to a family member, and 90% stated TMS was preferable to having, or the prospect of having, ECT [30].

Important Open Study

Some open studies have been mentioned. One other is of particular importance. In 1995, George et al. [31] reported the first use of FF-rTMS in the treatment of depression in humans. It was a landmark paper as it established some methodological features. A figure of eight shaped coil was used, which focused the electric field beneath the mid-point. All subsequent FF-rTMS studies have used this coil arrangement. They applied stimulation to the left prefrontal cortex. This was based on three observations, 1) that FF-rTMS increases the excitability of neurons, 2) that major depression is frequently associated with under activity of the left prefrontal cortex, and 3) unpublished pilot studies indicated this arrangement gave the best results. It is probable that in the future, the frequency and site of stimulation used in the treatment of depression will be tailored for the individual, based on imaging studies. To the present, all FF-rTMS studies have used left prefrontal stimulation. They treated medication-resistant patients; this too has become a feature of all subsequent FF-rTMS studies. They stimulated the prefrontal cortex with a stimulus intensity of 80% of the motor threshold on five days. (The motor threshold is the smallest intensity which, when applied to one side of the motor cortex, causes motor activity in the hand of the other side.) Subsequent studies have varied the intensity and the number of days of treatment. They treated six patients and the depression scores for the group improved significantly. Two patients showed robust improvement, two showed slight improvement and two showed no improvement. These results were encouraging. It is argued that this was an open study and these may have been placebo responses, however, it must also be registered that these patients suffered medication-resistant

depression, which is relatively unlikely to exhibit strong placebo responses.

Blind Sham Controlled Studies

In 1996 Pascual-Leone et al. [32] published the first blind placebo controlled study of FF-rTMS depression. This was a cross over study. Stimulation was at 90% of motor threshold. Seventeen patients received sham or active stimulation over the left and right prefrontal cortex and active stimulation was also applied at the cortex. All patients received each experimental condition for one week, followed by three weeks of observation, such that each patient remained in the study for five months. Active FF-rTMS over the left prefrontal cortex (but no other treatment condition) resulted in a significant reduction in the group depression score. Eleven patients experienced pronounced improvement, but this faded over the following two weeks. This remains the most successful study to date.

In 1997, George et al. [33] conducted a double blind cross over study. Twelve depressed patients received sham and active FF-rTMS at 80% of motor threshold for two weeks. Compared to sham, active treatment significantly improved the group depression score. However, on an individual basis, the active treatment led to a 25% or greater reduction in depression scores in only five patients. These results indicated that FF-rTMS could reduce the symptoms of depression, but left doubt about clinical utility.

In 1999, Padberg et al. [34] conducted a blind comparison of SF-rTMS, FF-rTMS and sham, in 18 depressed patients who were divided into three groups. They used 90% of motor threshold and 250 stimuli per day, for five days. There was no significant difference in the effects of FF-rTMS and sham. However, this study has a methodological limitation. The number of stimuli provided at each session (250) was only 25% and 32% of the daily stimuli provided by the previous studies [32,33] and as little as 12.5% of the daily stimulation of some subsequent studies [35]. Accordingly, adequate active stimulation was not provided.

Also in 1999, Loo et al. [36] compared FF-rTMS and sham in two groups of nine patients suffering depression. Both groups improved significantly, but there was no significant difference between them. Thus, FF-rTMS was found to be no more effective in the treatment of depression than sham. The improvement in the sham treated patients was surprising, given that they suffered medication-resistant depression and such conditions are not expected to medication-resistant depression and such conditions are not expected to demonstrate strong placebo responses. Recently, Lisanby et al. [37], using single pulses and electrodes placed on the prefrontal cortex of

rhesus monkeys, showed that sham of the type used by Loo et al. creates a voltage across contact sites of 76% of active stimulation. This may have been greater in the Loo et al. study as stimulation was provided at 10 Hz, and summation of neuronal response to FF-rTMS has been demonstrated [38]. Loo et al. used 110% of motor threshold and George et al. [33] have demonstrated that an antidepressant effect with 80% of motor threshold. Thus, the sham used by Loo et al. may have been active, which could explain why their "sham" treated medication-resistant patients improved. This view may be contested, however, as Loo et al (2000) [39] studied the motor cortex and various positions of the active coil and concluded that their sham of the previous year reduced the stimulation level to less than 50% for most subjects, albeit with several caveats.

In 2000, Berman et al. [40] reported a comparison of sham and active FF-rTMS in two groups of 10 patients. These patients had failed to respond to a median of four medication trials and were drug free during the study. Stimulation was at 80% of motor threshold and 10 treatment sessions were provided. The decrease in group depression scores was significantly greater for active treatment compared to sham. Four patients receiving FF-rTMS and none of the sham group obtained clinically useful reductions. The authors described these results as "clinically modest", however, it should be remembered that these patients had failed to respond to various antidepressants and a response in four of 10 is not inconsequential.

Also in 2000, Eschweiler et al. [41] reported a comprehensive blind study of the effect of FF-rTMS and sham on mood and prefrontal haemodynamic function in twelve patients with major depression who were taking antidepressant medication. They found that FF-rTMS resulted in significant reduction in depression scores. Moreover, they defined response as a 30% reduction in depression scores, and using this criterion, five out of 12 receiving FF-rTMS but only one out of 10 receiving sham, achieved this status.

Again in 2000, George et al. [35] reported a double blind placebo controlled study of FF-rTMS at 100% of motor threshold. The active treatment was at 5 Hz for one half and 20 Hz for the other half of the group, but these will be considered together. Response was defined as 50% reduction in depression scores. FF-rTMS resulted in significantly more responders (9/20) than did sham (0/10). Considering the change in group means, compared to sham, active treatment resulted in significantly greater reduction on the Beck Depression Inventory and the Hamilton Anxiety Rating Scale, but not the Hamilton Depression Rating Scale.

In 2001, Garcia-Toro et al. [42] reported a blind trial of FF-rTMS and sham in 40 patients suffering from medication-resistant depression. Stimulation was at 90% of motor threshold and stimulation was provided on 10 days. FF-rTMS induced a significantly greater decrease in group depression scores than did sham. Five of those receiving FF-rTMS but only one of those receiving sham, experienced a decrease of 50% of depression score. In an open continuation, nine

patients who had received but failed to respond to FF-rTMS accepted a further 10 sessions at 110% of motor threshold and three of them achieved a 50% decrease in depression score.

These studies are summarized in Table 1. There have been eight blind sham controlled studies. Six studies, involving 131 patients have shown FF-rTMS has an antidepressant action. One study showed no antidepressant action for either FF-rTMS or sham, but used a very small number of stimuli and should therefore be discounted. The final study showed an antidepressant action for both FF-rTMS and sham. The sham used in this study may have been active. Thus, all unproblematic, controlled sham controlled studies to the present, indicate an antidepressant action for FF-rTMS.

Comparisons With ECT

There have been three comparisons of FF-rTMS and electroconvulsive therapy (ECT). In 2000 the first was an open study by Grunhaus et al. [43]. They randomly assigned 40 patients into two groups and treated one with unilateral ECT and the other with FF-rTMS at 90% motor threshold for up to 20 treatment sessions. Overall, patients responded significantly better to ECT. However, when patients were divided in groups according to the presence or absence of psychosis, those with psychosis (19 patients) responded significantly better to ECT, but those without psychosis (21 patients) responded equally to FF-rTMS.

Pridmore et al. [44] reported a blind study of 32 patients randomly assigned to either FF-rTMS or unilateral ECT. FF-rTMS was at 100% and was continued as long as improvement continued. Those who achieved remission received 13.1 (SD=3.1) treatments. Three measures of depression were used, and overall, ECT demonstrated a significant treatment

Table 1. Blind controlled studies of FF-rTMS in major depression

Study	Type	No. Patients	Results	Comments
1. Pascual-Leone et al, 1996. [32]	Double blind, sham controlled, multiple crossover	17	FF-rTMS to DLPFC associated with significantly reduced depression scores	Antidepressant action demonstrated
2. George et al, 1997. [33]	Double blind, sham controlled, crossover	12	FF-rTMS significantly superior to sham.	Antidepressant action demonstrated
3. Padberg et al, 1999. [34]	Double blind 3 parallel streams, sham SF-rTMS, FF-rTMS	18	No significant change with any condition: sham, SF-rTMS or FF-rTMS.	Only 250 stimuli per day. All others have used 800-2000 stimuli per day
4. Loo et al, 1999. [36]	Double blind sham controlled crossover	18	Both sham and FF-rTMS showed significant improvement. No sig. difference	Sham may have been active (Lisanby et al, 2001. [37]; Loo et al, 2000. [39])
5. Berman et al, 2000. [40]	Double blind sham controlled parallel	20	FF-rTMS signif. greater reduction of mean scores. 40-45% reduction FF-rTMS, 4/10. Sham, 0/10.	Antidepressant action demonstrated
6. Eschweiler et al, 2000. [41])	Double blind sham controlled cross-over	12	FF-rTMS, signif. reduction in mean depression scores. Sham, worsening of mean scores. 30% reduction FF-rTMS, 4/10. Sham, 1/10.	Antidepressant action demonstrated
7. George et al, 2000. [35]	Double blind sham controlled parallel	30 (20, FF-rTMS 10, sham)	FF-rTMS, signif. more responders. Response = 50% decrease in score. FF-rTMS, 9/20. Sham, 0/10.	Antidepressant action demonstrated
8. Garcia-Toro et al, 2001. [42]	Double blind Sham controlled	40	FF-rTMS, signif. reduction in mean depression scores. Sham, no change. 50% reduction FF-rTMS, 5/17. Sham, 1/18.	Antidepressant action demonstrated

advantage. However, the number achieving remission (Hamilton Depression Rating Scale score of ≤ 8) was the same (11 of 16 patients). The mean improvement on the Hamilton Depression Rating Scale favored ECT, but was not significantly different from that of FF-rTMS.

Grunhaus et al. [45] are reporting a blind, comparison of FF-rTMS and ECT in the treatment of non-delusional major depression. FF-rTMS was provided at 90% of motor threshold and continued for 20 sessions. Response was defined as decrease in depression scores of 50 %, and remission was defined as a final Hamilton Depression Rating Scale score of ≤ 10 . Response rate was not significantly different (12 for ECT; 11 for FF-rTMS) and the remission rate was the same (6 for both groups).

These blind studies are summarized in Table 2. In one blind trial FF-rTMS was shown to have an antidepressant effect approaching that of ECT. In the other, in non-delusional major depression, FF-rTMS had an antidepressant effect the same as that of ECT. Seventy two patients were involved in these studies. However, blinding is difficult to achieve in these studies, and these results must be viewed cautiously. Further comprehensive studies will be necessary before a final position can be confidently stated.

Future Directions

There would appear to be strong evidence from blind, sham controlled studies that FF-rTMS has antidepressant effects. However, these results have been disappointingly small in some studies. It may be that the intensity of stimulation, the number of stimuli per session and the number of treatment sessions, are important. In the above cases the intensity and number of treatment session were as follows: George et al. [33], 80% and 10 days, and Berman et al [40] 80% and 10 days. In a later study, George et al. [41] obtained much better results when they increased the intensity to 100% and doubled the number of stimuli per day (from 800 to 1600). Another important factor is the level of treatment resistance of the subjects.

Even the most effective antidepressant, ECT, has limited effectiveness in severely treatment resistant patients.

Pridmore et al. [44] and Grunhaus et al. [45] obtained better results than expected. They used 100% and 90% respectively, and extended treatment beyond 10 sessions (Pridmore et al., 12.2 (SD \pm 3.4); Grunhaus et al., 20).

Two studies [36,12] gave patients, on the completion of blind studies, further open treatments. In both instances, improvement continued. An open study by Lyndon [25] has shown that non-responders plateau after a few days, while responders continue to improve for up to 20 treatment sessions.

In the future, it may be possible to tailor TMS treatment according to imaging results [46]. It is possible that areas of the cortex found to be under and over active areas could be treated differently. Further clinical studies simply using higher intensities, greater numbers of stimuli per session and greater numbers of treatment sessions, may demonstrate improved treatment outcomes.

Investigations are required to determine whether there is a particular profile of patients which responds well to FF-rTMS. Other remaining questions include the period for which the antidepressant effect of FF-rTMS is sustained, and whether medication has a place in combination with FF-rTMS in the acute treatment and alone, following the acute treatment, as a prophylactic. The issue of maintenance FF-rTMS is still to be addressed.

Summary

A large number of animal studies and introductory clinical studies suggest that FF-rTMS has an antidepressant action. There have been eight blind sham controlled studies. In one too few pulses may have been provided, such that the active stimulus may have been inadequate. In another, the sham may have been active. All of the remaining six studies showed a significant antidepressant action for the active treatment.

There have been two blind comparisons of FF-rTMS and ECT. In one, FF-rTMS was shown to have an antidepressant

Table 2. Blind comparison studies of FF-rTMS and ECT

Study	Design	No. Patients	Results
Pridmore et al, 2000. [44]	Blind, parallel comparison with ECT	32	Overall, ECT signif. advantage. Mean reduction on HDRS not signif. different Remission: both groups 11/16
Grunhaus et al, submitted for publication. [45]	Blind, parallel Comparison with ECT	40	Response: 50% depression scores reduction ECT, 12 FF-rTMS, 11 Remission: final HDRS ≤ 10 - 6 for both groups

effect approaching that of ECT. In the other, in non-delusional major depression, FF-rTMS had an antidepressant effect the same as that of ECT.

The evidence strongly supports an antidepressant effect for FF-rTMS. Maximizing this effect is a task for the future. The evidence suggests that higher doses (stimulation intensity and number of stimuli per day) and greater numbers of treatment sessions should be investigated.

References

1. Menkes D, Bodnar P, Ballesteros R, Swenson M. Right frontal slow frequency repetitive transcranial magnetic stimulation (SF-rTMS) is an effective treatment for depression: a case-control pilot study of safety and efficacy. *Journal of Neurology, Neurosurgery and Psychiatry* 1999; 67:113-115.
2. Klein E, Kreinin I, Chistyakov A, Koren D, Mecz L, Marmur S, Ben-Shachar D, Feinsod M. Therapeutic efficiency of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double blind controlled trial. *Archives of General Psychiatry* 1999; 56:315-320.
3. Fleischmann A, Prolov K, Abarbanel J, Belmaker R. The effect of transcranial magnetic stimulation of rat brain on behavioral models of depression. *Brain Research* 1995; 699:130-132.
4. Zyss T, Gorka Z, Kowalska M, Vetulani J. Preliminary comparison of behavioral and biochemical effects of chronic transcranial magnetic stimulation and electroconvulsive shock in the rat. *Biological Psychiatry* 1997; 42:920-924.
5. Ebert U and Ziemann U. Altered seizure susceptibility after high-frequency transcranial magnetic stimulation in rats. *Neuroscience Letters* 1999;273:155-158.
6. Ben-Shachar D, Belmaker R, Grisaru N, Klein E. Transcranial magnetic stimulation induces alterations in brain monoamines. *Journal Neural Transmission* 1997;104:191-197.
7. Ben-Shachar D, Gazawi H, Riboyand-Levin J, Klein E. Chronic repetitive transcranial magnetic stimulation alters beta-adrenergic and 5-HT₂ receptor characteristics in rat brain. *Brain Research* 1999; 816:78-83.
8. Fujiki M, Steward O. High frequency TMS mimics the effects of ECS upregulating astroglial gene expression in the murine CNS. *Molecular Brain Research* 1997; 44:301-308.
9. Ji R, Schlaepfer T, Aizenman C, Qiu D, Huang J, Rupp F. Repetitive transcranial magnetic stimulation activates specific regions in rat brain. *Proceedings National Academy Science USA* 1998; 95:15635-15640.
10. Kole M, Fuchs E, Ziemann U, Paulus W, Ebert U. Changes in 5HT_{1A} and NMDA binding sites by a single rapid transcranial magnetic stimulation procedure in rats. *Brain Research* 1999; 826:309-312.
11. Post A, Muller M, Engelmann M, Keck M. Repetitive transcranial magnetic stimulation in rats: evidence for a neuroprotective effect in vitro and in vivo. *European Journal of Neuroscience* 1999; 11:3247-3254.
12. Muller M, Toschi N, Kresse A, Post A, Keck M. Long-term repetitive transcranial magnetic stimulation increases the expression of brain-derived neurotrophic factor and cholecystokinin mRNA, but not neuropeptide tyrosine mRNA in specific areas of rat brain. *Neuropsychopharmacology* 2000; 23:205-215.
13. Keck M, Welt T, Post A, Muller M, Toschi N, Wigger A, Landgraf R, Holsboer F, Engelmann M. Neuroendocrine and behavioral effects of repetitive transcranial magnetic stimulation in a psychopathological animal model are suggestive of antidepressant-like effects. *Neuropsychopharmacology* 2001; 24:337-349.
14. Levkovitz Y, Ng M. Transcranial magnetic stimulation and antidepressive drugs share similar cellular effects in rat hippocampus. *Neuropsychopharmacology* 2001; 24:608-616.
15. Belmaker R, Grisaru N. Magnetic stimulation of the brain in animal depression models responsive to ECS. *Journal of ECT* 1998; 14:194-205.
16. Lisanby S, Belmaker R. Animal models of the mechanisms of action of repetitive transcranial magnetic stimulation (RTMS): comparisons with electroconvulsive shock (ECS). *Depression and Anxiety* 2000; 12:178-187.
17. Cohrs S, Tergau F, Riech S, Kastner S, Paulus W, Ziemann U, Ruther E, Hajak G. High-frequency repetitive transcranial magnetic stimulation delays rapid eye movement sleep. *NeuroReport* 1998; 9:3439-3443.
18. Benca R, Obermeyer W, Thisted R, Gillin J. Sleep and psychiatric disorders. A meta-analysis. *Archives of General Psychiatry* 1992; 49:651-668.
19. Speer A, Kimbrell T, Wassermann E, Repella J, Willis M, Herscovitch P, Post R. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. *Biological Psychiatry* 2000; 48:1133-1141.
20. Ebmeier K, Cavanagh J, Moffoot A, Glabus M, O'Carroll R, Goodwin G. Cerebral perfusion correlates of depressed mood. *British Journal of Psychiatry* 1997; 170:77-81.
21. Cohrs S, Tergau F, Becker W, Hajak G. Suprathreshold repetitive transcranial magnetic stimulation elevates thyroid-stimulating hormone in health male subjects. *Journal of Nervous and Mental Disorders* 2001; 189:393-397.
22. Szuba M, O'Reardon J, Rai A, Snyder-Kastenber J, Amsterdam J, Gettes D, Wassermann E, Evans D.

- Acute mood and thyroid stimulating hormone effects of transcranial magnetic stimulation in major depression. *Biological Psychiatry* 2001; 50:22-27.
23. Strafella A, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *The Journal of Neuroscience* 2001, 21:RC157(14).
 24. Figiel G, Epstein C, McDonald W, Amazon Leece J, Figiel L, Saldivia A, Glover S. The use of rapid-rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. *Journal of Neuropsychiatry and Clinical Neurosciences* 1998; 10:20-25.
 25. Lyndon R W. The time course of antidepressant response to transcranial magnetic stimulation. Royal Australian and New Zealand College of Psychiatrists 36th Congress, Book of Abstracts 2001; pp 32-33.
 26. Avery D, Claypoole K, Robinson L, Neumaier J, Dunner D, Scheele L, Wilson L, Roy-Byrne P. Repetitive transcranial magnetic stimulation in the treatment of medication-resistant depression: preliminary data. *Journal Nervous and Mental Disease* 1999; 187:114-117.
 27. Dolberg O, Schreiber S, Grunhaus L. Transcranial magnetic stimulation-induced switch into mania: a report of two cases. *Biological Psychiatry* 1001, 49, 468-70.
 28. Pridmore S. Rapid Transcranial magnetic stimulation (rTMS) and normalization of the dexamethasone suppression test (DST). *Psychiatry and Clinical Neurosciences* 1999; 53:33-37.
 29. Pridmore S. Substitution of rapid transcranial magnetic stimulation treatments for electroconvulsive therapy treatments in a course of electroconvulsive therapy. *Depression and Anxiety* 2000; 12:118-123.
 30. Walter G, Martin J, Kirkby K, Pridmore S. Transcranial magnetic stimulation: experience, knowledge and attitudes of recipients. *Australian and New Zealand Journal of Psychiatry* 2001, 35, 58-61.
 31. George M, Wassermann E, Williams W, Callahan A, Ketter T, Basser P, Hallett M, Post R. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *NeuroReport* 1995, 6, 1853-1856.
 32. Pascual-Leone A, Rubio B, Pallardo, Catala D. Beneficial effect of rapid-rate transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet* 1996, 348, 233-238.
 33. George M, Wassermann E, Kimbrell T, Little J, Williams W, Danielson A, Greenberg B, Hallett M, Post R. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo controlled crossover trial. *American Journal of Psychiatry* 1997, 154, 1752-1756.
 34. Padberg F, Zwanzger P, Thoma H, Kathmann N, Haag C, Greenberg B, Hampel H, Moller HJ. Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. *Psychiatry Research* 1999; 88:163-171.
 35. George M, Nahas Z, Molloy M, Speer A, Oliver N, Li X-B, Arana G, Risch S, Ballenger J. A Controlled trial of daily left prefrontal cortex TMS for treating depression. *Biological Psychiatry* 2000, 48, 962-970.
 36. Loo C, Mitchell P, Sachdev P, McDarmont B, Parker G, Gandevia S. Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. *American Journal of Psychiatry* 1999, 156, 946-948.
 37. Lisanby S, Gutman D, Luber B, Schroeder C, Sackeim H. Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. *Biological Psychiatry* 2001, 49, 460-463.
 38. Pascual-Leone A, Valls-Sole J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain* 1994, 117, 847-858.
 39. Loo C, Taylor J, Gandevia S, McDarmont B, Mitchell P, Sachdev P. Transcranial magnetic stimulation (TMS) in controlled treatment studies: are some "sham" forms active? *Biological Psychiatry* 2000, 47:325-331.
 40. Berman R, Narasimhan M, Sanacora G, Miano A, Hoffman R, Hu X, Charney D, Boutros N. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. *Biological Psychiatry* 2000, 47, 332-337.
 41. Eschweiler G, Wegerer C, Schlotter W, Spandl C, Stevens A, Bartels M, Buchkremer G. Left prefrontal activation predicts therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) in major depression. *Psychiatry Research: Neuroimaging Section* 2000, 99, 161-172.
 42. Garcia-Toro M, Mayol A, Arnillas H, Capllonch I, Ibarra O, Crespi M, Mico J, Lafau O, Lafuente L. Modest adjunctive benefit with transcranial magnetic stimulation in medication-resistant depression. *Journal of Affective Disorders* 2001, 64, 271-275.
 43. Grunhaus L, Dannon P, Schreiber S, Dolberg O, Amiaz R, Lefkifker E. Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. *Biological Psychiatry* 2000, 47, 314-324.
 44. Pridmore S, Bruno R, Turnier-Shea Y, Reid P, Rybak M. Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. In-

ternational Journal of Neuropsychopharmacology 2000, 3, 129-134.

45. Grunhaus L, Schreiber S, Dolberg O, Polak D, Dannon P. A randomized controlled comparison of ECT and repetitive transcranial magnetic stimulation in the treatment of severe and resis-

tant non-delusional major depression. Submitted for publication.

46. Post R, Speer A. Speculations on the future of rTMS and related therapeutic modalities. In: George M S, Belmaker R, eds. *Transcranial magnetic stimulation in neuropsychiatry*. Washington: American Psychiatric Press, Inc., 2000:269-287.