

Review

A review of the efficacy of transcranial magnetic stimulation (TMS) treatment for depression, and current and future strategies to optimize efficacy

Colleen K. Loo ^{a,*}, Philip B. Mitchell ^b

^a School of Psychiatry, University of NSW, Psychiatrist, Black Dog Institute and South Eastern Sydney Illawarra Area Health Service, Australia

^b School of Psychiatry, University of NSW, Psychiatrist, Black Dog Institute, Australia

Received 28 June 2005; received in revised form 2 August 2005; accepted 2 August 2005

Available online 2 September 2005

Abstract

Background: There is a growing interest in extending the use of repetitive transcranial magnetic stimulation (rTMS) beyond research centres to the widespread clinical treatment of depression. Thus it is timely to critically review the evidence for the efficacy of rTMS as an antidepressant treatment. Factors relevant to the efficacy of rTMS are discussed along with the implications of these for the further optimization of rTMS.

Method: Clinical trials of the efficacy of rTMS in depressed subjects are summarized and reviewed, focusing mainly on sham-controlled studies and meta-analyses published to date.

Results: There is a fairly consistent statistical evidence for the superiority of rTMS over a sham control, though the degree of clinical improvement is not large. However, this data is derived mainly from two-week comparisons of rTMS versus sham, and evidence suggests greater efficacy with longer treatment courses. Studies so far have also varied greatly in approaches to rTMS stimulation (with respect to stimulation site, stimulus parameters etc) with little empirical evidence to inform on the relative merits of these approaches.

Limitations: Only studies published in English were reviewed. Many of the studies in the literature had small sample sizes and different methodologies, making comparisons between studies difficult.

Conclusions: Current published studies and meta-analyses have evaluated the efficacy of rTMS as given in treatment paradigms that are almost certainly suboptimal (e.g. of two weeks' duration). While the data nevertheless supports positive outcomes for rTMS, there is much scope for the further refinement and development of rTMS as an antidepressant treatment. Ongoing research is critical for optimizing the efficacy of rTMS.

© 2005 Elsevier B.V. All rights reserved.

Keywords: Transcranial magnetic stimulation; Depression; Efficacy

* Corresponding author. Black Dog Institute, Prince of Wales Hospital, Barker St, Randwick. NSW 2031, Australia. Tel.: +61 02 93823721; fax: +61 02 93828208.

E-mail address: colleen.loo@unsw.edu.au (C.K. Loo).

Contents

1. Introduction	256
2. Studies of the efficacy of rTMS in depression	256
3. Strategies to optimize the efficacy of rTMS.	261
3.1. Stimulation site.	261
3.2. rTMS parameters — stimulus frequency.	262
3.3. rTMS parameters — stimulus frequency and site of stimulation.	262
3.4. rTMS parameters — stimulus intensity	263
3.5. Number of stimuli, length of treatment course	263
3.6. Further considerations	263
4. Conclusion	264
Acknowledgements	264
References	264

1. Introduction

There is a considerable interest worldwide in the use of subconvulsive repetitive transcranial magnetic stimulation (rTMS) for the treatment of depression. rTMS has excited the interest of clinicians and been highly acceptable to patients (Walter et al., 2001), because of its ability to stimulate focal areas of brain cortex non-invasively using magnetic fields. Unlike ECT, it does not involve a general anaesthetic or seizure. In some countries, e.g. Canada and Israel, rTMS is approved for the clinical treatment of depression. In Australia, the [Royal Australian and New Zealand College of Psychiatrists Position Statement on TMS \(2003\)](#) recognizes the need for further research into TMS but cautiously allows for its clinical use to treat depression in limited circumstances, with recommended caveats, including that the patient sign a consent form acknowledging that “the most efficacious manner of administering rTMS has not yet been established”.

The International Society for Transcranial Stimulation Consensus Statement on the use of rTMS is mainly concerned with advising on safety and procedural issues in whatever context rTMS is used (Belmaker et al., 2003). There has been a debate on the advisability of broadening the use of rTMS to clinics beyond research centres, with discussion of associated regulatory issues (e.g. Fitzgerald, 2003a; Sachdev, 2003). Apart from considerations of safety, adequate regulatory safeguards and the limitations of current therapeutic options in treatment resistant depression, a critical

appraisal of the efficacy of rTMS as a treatment for depression is central to this debate. This article evaluates the efficacy outcomes reported so far in clinical trials of rTMS, and discusses the potential of future strategies to optimize the efficacy of rTMS.

2. Studies of the efficacy of rTMS in depression

Given the relatively large number of published rTMS treatment trials but relatively small sample sizes in each (see [Table 1](#) for summary of sham-controlled trials), it is perhaps most constructive to begin by reviewing the seven published meta-analyses (including a Cochrane Review) (McNamara et al., 2001; Holtzheimer et al., 2001; Burt et al., 2002; Kozel and George, 2002; Martin et al., 2003; Aarre et al., 2003; Couturier, 2005).

The earliest meta-analysis (McNamara et al., 2001) only included five controlled studies and excluded the only negative depression trial for rTMS published at the time (Loo et al., 1999), yielding unsurprisingly, a positive result for rTMS compared to a sham control.

Holtzheimer et al. (2001) identified 12 controlled rTMS depression trials, 11 of which involved rTMS to the left dorsolateral prefrontal cortex and seven of which involved a parallel design. The latter distinction is important as the blinding of subjects in crossover studies is questionable, given the difference in scalp sensation with active and sham rTMS (Loo et al., 2000). They calculated the weighted mean effect sizes (based on the difference in outcome between

Table 1
Summary of sham-controlled studies of rTMS for the treatment of depression

Publication	Study design	N	Medication resistance	rTMS treatment	Mean % change HRSD ^a	Number of responders ^b
Pascual-Leone et al., 1996	Multiple crossover: L ^d active R active L sham (active coil at 45°) R sham Vertex active	17	Yes	10 Hz, 90%, 20 × 10 s, 5 days × 2000 stim ^c	L active: 48%; Other: 4%–12%	L DLPFC active: 4/17 Other: 0/17
George et al., 1997	Crossover: L active L sham (active coil at 45°)	12	No	20 Hz, 80%, 20 × 2 s, 10 days × 800 stim	Active: 16% Sham: 13% ↑	Active: 1/12 Sham: 0/12
Loo et al., 1999	Parallel: L active L sham (active coil at 45°)	18	Yes	10 Hz, 110%, 30 × 5 s, 10 days × 1500 stim	Active: 23% Sham: 25%	Active: 0/9 Sham: 1/9
Padberg et al., 1999	Parallel: L active 10 Hz L active 0.3 Hz L sham 10 Hz (active coil, 1 wing at 90°)	18	Yes	90%, 5 days × 250 stim 10 Hz: 5 × 5 s 0.3 Hz: 75 s	Active 10 Hz: 6% Active 0.3 Hz: 19% Sham: 6% ↑	All: 0/6
Klein et al., 1999	Parallel: L active L sham (active coil off scalp, at 90°)	70	No	1 Hz, 110%, 2 × 60 s, 10 days × 120 stim	Active: 47% Sham: 22%	Active: 17/36 Sham: 8/34
Berman et al., 2000	Parallel: R active R sham (active coil at 45°)	20	Yes	20 Hz, 80%, 20 × 2 s, 10 days × 800 stim	Active: 39% Sham: 0.5%	Active: 1/10 Sham: 0/10
Eschweiler et al., 2000	Parallel: L active L sham (active coil at 90°)	12	? ^f	10 Hz, 90%, 20 × 10 s, 5 days × 2000 stim	Active: 22% Sham: 7% ↑	?
George et al., 2000	Parallel: L active 20 Hz L active 5 Hz L sham (20/5 Hz) (active coil, 1 wing at 45°)	30	Yes	100%, 10 days × 1600 stim 20 Hz: 40 × 2 s 5 Hz: 40 × 8 s	Active 20 Hz: 26% Active 5 Hz: 48% Sham: 21%	20 Hz: 3/10 5 Hz: 6/10 Sham: 0/10
Garcia-Toro et al., 2001	Add-on ^g to sertraline Parallel: L active L sham (active coil at 90°)	28	No	20 Hz, 30 × 2 s, 90%, 10 days × 1200 stim 10 days × 1200 stim	Active: 38% Sham: 34% Sham: 34%	Active: 4/11 Sham: 3/11 Sham: 3/11
Lisanby et al., 2001a	Add-on to sertraline Parallel: L active 10 Hz R active 1 Hz Sham (active coil, 1 wing at 90°)	36	Most	L 10 Hz: 20 × 8 s R 1 Hz: 2 × 800 s 110%, 1600 stim	L 10 Hz: 21% R 1 Hz: 20% Sham: 13%	?

(continued on next page)

Table 1 (continued)

Publication	Study design	N	Medication resistance	RTMS treatment	Mean % change HRSD ^a	Number of responders ^b
Manes et al., 2001	Parallel: L active L sham (active coil— handle on head)	20	Yes	20 Hz, 20 × 2 s, 80% 5 days × 800 stim	Active: 37% Sham: 32%	Active: 3/10 Sham: 3/10
Dolberg et al., 2002	Parallel: Active Sham(?)	20	?	10days	Active: 29% Sham: 17%	?
Padberg et al., 2002	Parallel: L active 100% L active 90% L sham (active coil, 1 wing at 90°)	30	Yes	10 Hz, 15 × 10s, 10 days × 1500 stim 100%/90%/sham	100%: 30% 90%: 15% Sham: 7%	100%: 3/10 90%: 2/10 Sham: 0/10
Loo et al., 2003	Parallel: Bilateral active Bilateral sham (inactive coil)	19	Yes	15 Hz, 24 × 5 s, 90%, 15 days × 1800	Active: 24% Sham: 21%	Active: 2/9 Sham: 1/10
Nahas et al., 2003	Parallel: L active L sham (active coil, 1 wing at 45°)	23	No	5 Hz, 40 × 8s, 110%, 10 days × 800 stim	Active: 25% Sham: 25%	Active: 4/11 Sham: 4/12
Hoppner et al., 2003	Parallel: L active 20 Hz L sham 20 Hz (active coil, at 90°) R Active 1 Hz	30	No	L 20 Hz: 20 × 2s, 90%, 800 stim R 1 Hz: 2 × 60 s, 110%, 120 stim 10 days	L 20 Hz: 17% R 1 Hz: 10.5% Sham: 23%	L 20 Hz: 2/9 R 1 Hz: 1/10 Sham: 2/10
Fitzgerald et al., 2003b	Parallel: L active 10 Hz R active 1 Hz Sham — L 10 Hz or R 1 Hz (active coil, at 45°)	60	Yes	L 10 Hz: 20 × 5s, 1000 stim R 1 Hz: 5 × 60 s, 300 stim 100%, 10 days	USED MADRS not HRSD Active: 13.5% Low freq: 15% Sham: 0.76%	Active: 8/20 Low freq: 7/20 Sham: 2/20
Jorge et al., 2004	Parallel: L active L sham (active coil, 1 wing at 90°)	20	Yes	10 Hz, 110% 20 × 5 s, 10 days × 1000 stim	Active: 38% Sham: 13%	Active: 3/10 Sham: 0/10
Kauffmann et al., 2004	Parallel: R active R sham (active coil at 45°)	12	Yes	1 Hz, 2 × 60 s, 10 days × 120 stim	Active: 48% Sham: 30%	Active: 4/7 Sham: 2/5
Holtzheimer et al., 2004	Parallel: L active L sham (active coil at 45°)	15	Yes	10 Hz × 5 s, 110%, 10 days × 1600 stim	Active: 32% Sham: 28%	Active: 2/7 Sham: 1/8
Mosimann et al., 2004	Parallel: L active L sham (active coil at 90°)	24	No	20 Hz, 40 × 2 s, 100%, 10 days × 1600 stim	Active: 20% Sham: 17%	Active: 4/5 Sham: 0/9
Koerselman et al., 2004	Parallel: L active	55	No	20 Hz, 20 × 2 s, 80% MT, 10 days × 800 stim	Active: 18.5% Sham: 15.4%	?

Table 1 (continued)

Publication	Study design	N	Medication resistance	RTMS treatment	Mean % change HRSD ^a	Number of responders ^b
Rumi et al., 2005	L sham (active coil at 45°) Add-on to amitriptyline Parallel: L active L sham (placebo coil)	46	No	5 Hz, 25 × 10 s, 120%, 20 days × 1250 stim	Active: 57% Sham: 35%	Active:21/22 Sham:11/24
Miniussi et al., 2005	Crossover (8 week washout between): L active 17 Hz L sham 17 Hz (active coil, 60% MT, 25 cm wood between coil and scalp)	29	Yes	17 Hz, 40 × 3 s, 110% 5 days × 1250 stim	Active 17 Hz: 32% Active 1 Hz: 23% Sham (both groups): 17%	?
Christyakov et al., 2005	Crossover (8 week washout): L active 1 Hz L sham 1 Hz Parallel: L active 3 Hz+placebo L active 10 Hz+placebo R active 3 Hz+placebo R active 10 Hz+placebo Sham rTMS (active coil at 90°)+clomipramine	22	Yes	1 Hz, 40 × 10 s, 110% 5 days × 2000 stim		
		59	No	3 Hz: 5 × 30 s, 110%, ? 10 days × 450 stim 10 Hz: 10 × 5 s, 100%, 10 days × 500		L 3 Hz: 6/12 L 10 Hz: 1/10 R 3 Hz: 2/12 R 10 Hz: 2/9 Clomipramine: 2/16

^a i.e. Mean percentage reduction in Hamilton Rating Scale for Depression scores; increases indicated by ↑.

^b Defined as ≥50% reduction in HRSD score from baseline. Denominator is number of subjects in that treatment group.

^c Treatment parameters are 10 Hz, 90% resting motor threshold, 20 trains of 10 s duration, daily sessions for 5 days, total 2000 stimuli per stimulation session.

^d L = left, R = right. Refers to dorsolateral prefrontal cortex except where stated otherwise.

^e Arrangement used for sham TMS. 45° means coil was tilted to contact the scalp at 45°. For “1 wing” only 1 side of the figure of eight coil was in contact with the scalp.

^f ? = data not available.

^g i.e. rTMS was commenced simultaneously with new course of antidepressant medication

active and sham treatment and with studies weighted for sample size and variability) to be 0.81, 0.89 and 0.88, respectively, for the groups of 12, 11 and 7 trials mentioned above. All of these outcomes represent large effect sizes unquestionably favouring active rTMS over sham. However, though statistically shown to be efficacious, the authors noted that the studies analysed did not demonstrate a high degree of clinical efficacy, with none of the studies showing a mean reduction in Hamilton Rating Scale for Depression (HRSD) scores of ≥50% and only 22% of subjects showing this degree of improvement with active rTMS, compared with 7.9% of subjects after sham

rTMS. (See also Table 1 for summary of mean improvement in HRSD scores and number of responders for individual studies.)

A comprehensive review by Burt et al. (2002) reported on two separate meta-analyses, for nine open depression trials of rTMS and 16 controlled trials. Calculations yielded weighted mean effect sizes of 1.37 for the open studies and 0.67 for the controlled studies. These are moderate to large effect sizes, though the difference between the two figures is interesting, suggesting that placebo effects contributed substantially to positive outcomes in the open studies. Again, though the results show strong statistical sup-

port for the efficacy of rTMS, the clinical results are not impressive, with subjects improving by 37% on average (as measured by Hamilton and Montgomery–Asberg Depression Rating Scales) in the open studies, and 23.8% (active) and 7.3% (sham) in the controlled studies.

The authors also noted that the effect sizes for rTMS treatment were far smaller than those calculated for electroconvulsive therapy (ECT), e.g. 2.26 for bilateral ECT and 2.12 for high dose right unilateral ECT from recent research (Sackeim et al., 2000). The results overall of studies which randomized depressed subjects to receive rTMS or ECT support a superior efficacy for ECT (Grunhaus et al., 2000, 2003; Janicak et al., 2002; Pridmore et al., 2000a). In some of these studies the emerging trend in favour of ECT did not reach statistical significance (Janicak et al., 2002), or was only significant on some measures (Pridmore et al., 2000a), probably because of the small sample sizes involved. Of interest, Grunhaus et al. (2000) found a clear difference between psychotic and non-psychotic depression, with rTMS equivalent to ECT in efficacy only for the latter group. It should be noted that the mean improvement with rTMS in these studies (40%–56% decrease in HRSD scores) is higher than in most depression treatment trials of rTMS. There was no sham comparison in these studies, making interpretation of this result difficult. Another important factor is that the outcomes of a four-week course of rTMS were evaluated in these studies, in contrast to the two-week treatment course in most sham-controlled studies. These studies have also been criticized for their modest ECT response (mean decrease in HRSD scores 48%–66%), though these may reflect treatment outcomes in community ECT services, which have been found to be poorer than those in research settings (Prudic et al., 2004).

Similarly, Kozel and George (2002) calculated a mean effect size of 0.53 for 10 controlled depression trials of left prefrontal rTMS, supporting the positive statistical evidence for rTMS as an antidepressant treatment.

A Cochrane Review by Martin et al. (2003) compared the results of 14 randomized controlled studies suitable for quantitative analysis. They found that high frequency (>1 Hz) left prefrontal rTMS and low frequency (≤ 1 Hz) right prefrontal rTMS were statistically superior to a sham comparison, but only at one time point (immediately after the two weeks of

treatment, with the difference not sustained two weeks later) and only for the HRSD. As the overall difference between active and sham treatment was not large, though significant (standardised mean difference of -0.35 for high frequency left prefrontal rTMS), they concluded that there was not strong evidence at this stage to support the benefit of rTMS as an antidepressant treatment.

Aarre et al. (2003) found the 12 published studies which met inclusion criteria too diverse in patient sample characteristics and rTMS parameters for formal meta-analysis. On qualitative review they concluded that efficacy was inconsistently shown between studies, and that where demonstrated, improvements were clinically modest and not sustained. Thus they also concluded that there was insufficient evidence as yet to support the use of rTMS as an antidepressant treatment and that further research was warranted.

The only meta-analysis to find a negative result for high frequency left dorsolateral prefrontal rTMS compared to a sham control applied a number of selection criteria that excluded 13 of 19 eligible trials (Couturier, 2005). The remaining six trials analysed included a total of 91 subjects and had low power to detect a difference.

Overall the meta-analyses indicate that rTMS treatment has been shown to have superior outcomes compared with a sham control, though inspection of the mean change in rating scale scores suggests that a two-week treatment course provides modest clinical outcomes.

The choice of an appropriate sham form of TMS has been a difficult methodological issue in these controlled studies. Tilting the active treatment coil to reduce cortical stimulation but preserve the sensation of scalp stimulation (which is important for the simulation of real TMS) may involve low levels of cortical stimulation (Loo et al., 2000; Lisanby et al., 2001b), while forms of sham TMS with negligible stimulation are less convincing and subject blinding may be ineffective, particularly where subjects are not TMS naïve, e.g. in studies with a crossover design. The sham approaches used in studies to date are summarized in Table 1.

There are inherent limitations in the meta-analysis method, arising from the need to conform studies of different designs, patient samples, and rTMS technique to a single method of analysis. In particular,

unique or notable features of individual studies may be overlooked. These variations between studies may be important in identifying strategies which may optimize the efficacy of rTMS.

3. Strategies to optimize the efficacy of rTMS

As can be seen from Table 1, studies have varied greatly in the choice of rTMS parameters used (stimulus frequency (i.e. number of pulses per second), intensity, number of stimuli), with an even larger range of possible combinations of these. Almost no two studies have used identical rTMS parameters, except in deliberate attempts at replication, making comparisons of efficacy difficult. As yet, there is little empirical evidence to guide the choice of these parameters.

3.1. Stimulation site

Most rTMS depression trials have given high frequency rTMS to the left prefrontal cortex, encouraged by positive early results for this approach (Pascual-Leone et al., 1996). Studies using this form of rTMS contributed the vast majority of data pooled for the meta-analyses. As noted above, though yielding statistically robust findings, the clinical outcomes from a two-week course of left prefrontal high frequency rTMS were not impressive. The results of sham-controlled studies published since the meta-analyses were conducted have not challenged this conclusion (see Table 1).

A few investigators have chosen to trial low frequency (≤ 1 Hz) rTMS to the right prefrontal cortex. These are several theoretical reasons for this approach. 1 Hz rTMS is relatively safe, with a much lower risk of inducing an accidental seizure (Wassermann, 1998). It is more tolerable at a given stimulus intensity (personal observations) and does not require expensive TMS machines capable of high frequency stimulation. Motor cortex studies suggest that high and low frequency rTMS have opposite effects on the excitability of neurons in brain cortex (Chen et al., 1997; Pascual-Leone et al., 1994). Stimulation of the motor cortex and electromyographic (EMG) measurement of outcomes in contralateral muscles has been a convenient experimental paradigm for investigating the effects of TMS, though caution is required in applying these findings to

the prefrontal cortex, which has a different cytoarchitecture and connections (Van Economo, 1929). There is a considerable evidence from neuropsychological, lesion and imaging studies that the left and right hemispheres have contrasting roles in mood regulation (Davidson and Hugdahl, 1995; Silberman and Weingartner, 1987). Thus it might be expected that low frequency rTMS to the right prefrontal cortex may be as likely to have antidepressant effects as high frequency rTMS to the left prefrontal cortex.

Five open studies reported the treatment of depressed subjects with rTMS at ≤ 1 Hz to the right prefrontal cortex, or to a combination of right and left prefrontal cortices (Dragasevic et al., 2002; Feinsod et al., 1998; Geller et al., 1997; Kapiletti et al., 2001; Menkes et al., 1999). Overall results were positive, with mean changes in HRSD scores ranging from 26% to 42% over a two-week period, though it is uncertain how much of this should be attributed to a placebo effect.

Several sham-controlled have examined the antidepressant effects of low frequency right prefrontal rTMS in depressed subjects (Klein et al., 1999; Lisanby et al., 2001a,b,c; Hoppner et al., 2003; Fitzgerald et al., 2003b; Kauffmann et al., 2004). In the first study Klein et al. (1999) reported promising results with 17 of 35 subjects improving by more than 50% in HRSD scores in the active group, compared with eight responders from the sham group of 32. However, subjects in this study were not medication-resistant. Replication studies using the same rTMS treatment parameters have reported both negative (Hoppner et al., 2003) and positive findings (Kauffmann et al., 2004). Other studies using a much higher number of TMS pulses either failed to find a significant difference between sham and active treatment (Lisanby et al., 2001a) or found significant differences though the overall degree of improvement was small (Fitzgerald, 2003a,b). Some of the above studies directly compared low frequency right prefrontal rTMS and high frequency left prefrontal rTMS but failed to find significant differences between the two approaches (Lisanby et al., 2001a; Hoppner et al., 2003; Fitzgerald et al., 2003b). Taken together, the results of the above studies do not allow conclusions that low frequency right prefrontal rTMS is more or less efficacious than high frequency left prefrontal rTMS. However, it is important to note that the sham-controlled studies used a two-week treatment

period and that a longer treatment period may yield more definitive results.

Another strategy has been the development of “bilateral” rTMS, i.e. rTMS to both left and right prefrontal cortices. In the first study of simultaneous bilateral prefrontal rTMS, Loo et al. (2003) tested the hypothesis that the superior efficacy of bilateral ECT over unilateral ECT arose from the stimulation of both frontal cortices. Subjects received simultaneous high frequency rTMS to both prefrontal cortices or a sham control. Results were negative, with suggestions that high frequency right prefrontal rTMS may have induced tearfulness in some subjects (Loo et al., 2003). Other investigators have trialled different combinations of low and high frequency rTMS to the left and right prefrontal cortices — these are considered in the section below on variations in site and frequency of stimulation.

Novel approaches involving rTMS to other cortical areas have also been proposed. Arguing from evidence for parietal cortex involvement in depression and empirical observations of mood elevation after cerebellar rTMS, Schutter and van Honk (2005) suggested that low frequency rTMS to the right parietal cortex and high frequency rTMS to the cerebellar cortex may be beneficial, particularly for certain subtypes of depression. This proposal is highly speculative and their group is at present studying empirically the effectiveness of this approach in depressed subjects.

3.2. rTMS parameters — stimulus frequency

Apart from the low frequency studies, most studies have given rTMS within the range of 5–20 Hz, as changes in cortical excitability have been demonstrated after rTMS in this range of frequency (Pascual-Leone et al., 1994). Preliminary results from rat studies suggest that higher stimulus frequencies may have greater antidepressant potency (Sachdev et al., 2002). Three sham-controlled studies have directly compared rTMS at different stimulus frequencies to the left prefrontal cortex (Padberg et al., 1999; George et al., 2000; Miniussi et al., 2005). Padberg et al. (1999) stimulated at 10 and 0.3 Hz, George et al. (2000) used 20 and 5 Hz rTMS and Miniussi et al. (2005) compared 17 and 1 Hz rTMS. The total number of stimuli was kept constant as far as possible for the different groups within each study (see Table 1). The two earlier studies found that

the lower frequency stimulation yielded superior outcomes though a statistical difference between the two groups was not demonstrated and the sample sizes ($N=18, 30$, respectively) were too small for firm conclusions. Miniussi et al. (2005) found better results with 17 than 1 Hz rTMS, though the comparison was only over a one-week treatment period and larger differences may have emerged over a longer treatment course.

Shajahan et al. (2002) attempted to investigate the differential effects of 5, 10 and 20 Hz rTMS to the left prefrontal cortex. Unfortunately the sample only included 5 subjects per group and no sham control group. Though on average subjects improved in depression scores by 40% and 5 subjects showed $\geq 60\%$ improvement, no difference was evident between treatment groups. Thus the optimum stimulus frequency for antidepressant efficacy remains unclear and the field awaits large, adequately powered trials directly comparing the effects of a range of treatment frequencies in depressed subjects.

3.3. rTMS parameters — stimulus frequency and site of stimulation

Several studies have compared forms of rTMS involving a variety of combinations of stimulus frequencies and stimulation to the left and right prefrontal cortices. In a novel study, Conca et al. (2002) assigned 36 subjects to receive either 10 Hz rTMS to the left prefrontal cortex and 1 Hz rTMS to the right prefrontal cortex consecutively in each session (i.e. non-simultaneous bilateral rTMS), 10 and 1 Hz rTMS (alternating trains) to the left prefrontal cortex, or 10 Hz to the left prefrontal cortex (i.e. a control group receiving more typical rTMS treatment). The total number of stimuli was the same for each group. All groups improved (23%–31% reduction in HRSD scores) but no significant difference was found between them. It is possible that differences may have emerged with a much larger sample. Hausmann et al (2004) compared 20 Hz left prefrontal rTMS alone, 20 Hz left prefrontal rTMS followed by 1 Hz right prefrontal rTMS, and a sham control. Disappointingly, no differences were found between the groups despite the use of relatively intense rTMS parameters (i.e. long stimulus trains, large number of stimuli). In the most comprehensive study of this type to date, Christyakov et al. (2005) randomized

depressed subjects to receive placebo medication and rTMS to the left or right prefrontal cortices, at 10 or 3 Hz, or to sham rTMS and clomipramine, over a two-week period. Results clearly favoured left prefrontal rTMS at 3 Hz, though the advantage over 10 Hz left prefrontal rTMS could have also resulted from the higher stimulation intensity used for the 3 Hz group (110% versus 100%).

3.4. rTMS parameters — stimulus intensity

Most rTMS trials have reported stimulus intensity relative to the subject's resting motor threshold, i.e. the lowest stimulus intensity necessary to produce a motor response in a relaxed contralateral muscle when TMS is given over the primary motor cortex. Researchers have reported that stimulus intensity is an important factor in determining the induction of long-term potentiation after seven days of rTMS in rats, with subthreshold rTMS giving the best results (Kozel et al., 2000). Thus stimulus intensity may be an important factor in inducing lasting changes in cortical excitability that may be responsible for antidepressant effects. In depressed subjects, only one controlled study ($N=30$) compared different intensities of stimulation — 100% and 90% of motor threshold, and a sham condition mathematically modelled as corresponding to 40% (Padberg et al., 2002) (see Table 1). Mathematical modelling also demonstrated that higher intensities of stimulation were associated with higher peak current intensities in underlying brain cortex. Higher stimulation intensity was significantly associated with greater improvement, supporting intuitive expectations that a higher intensity of stimulation would lead to a greater clinical effect.

The same phenomenon was described from a different perspective by Kozel et al. (2000) and Mosimann et al. (2002). Mosimann et al. (2002) found that in older depressed subjects, a greater distance between the stimulating coil and brain cortex, i.e. greater prefrontal atrophy, was associated with a poorer antidepressant response to rTMS. Kozel et al. (2000) did not find this association in a younger sample. In these studies greater coil-cortex distance is a proxy for stimulation at reduced intensities as the intensity of the magnetic field in TMS diminishes rapidly with distance from the stimulating coil (Barker, 1991).

Previous reviews of the rTMS literature have suggested that studies using higher stimulus intensities

were more likely to have positive results (Gershon et al., 2003). However, an overview of sham-controlled studies published to date does not support this observation, with a large proportion of negative studies using stimulus intensities at the higher end of the range (110%–120% motor threshold) (see Table 1).

3.5. Number of stimuli, length of treatment course

Likewise, an inspection of the published sham-controlled studies does not support the conclusion that treatment protocols using a higher total number of TMS stimuli per session had better therapeutic outcomes (see Table 1), though this may be possible. As mentioned above, it is difficult to compare studies directly due to the number of differences in treatment parameters and patient subtypes between studies. The few studies that reported a longer (4-week) course of rTMS, have generally demonstrated continued improvement over the third and fourth weeks, though apart from Rumi et al. (2005), these studies were either not sham-controlled (Grunhaus et al., 2000, 2003; Janicak et al., 2002) or provided continued rTMS in an open extension after an initial sham-controlled phase (Loo et al., 1999; Fitzgerald et al., 2003b). Given that optimal efficacy is not achieved with other antidepressant treatments (e.g. medications) in a two-week period (Stassen et al., 1993), it is to be expected that a treatment period of greater than two weeks would be necessary for optimal outcomes with rTMS.

3.6. Further considerations

Apart from the above, there are a number of other factors in the way TMS is administered which have been minimally investigated.

Extrapolating from animal studies on the electrophysiological phenomena of long-term depression and long-term potentiation (Christie and Abraham, 1994), it is likely that apart from stimulus parameters such as frequency and intensity, the frequency of TMS sessions and prior stimulation conditioning may be important factors in the attempt to produce lasting effects on neuronal excitability. rTMS has been given each weekday in most studies so far but there is little information on the optimal frequency of treatment sessions — in practice this could range from multiple sessions per day to two to three sessions per week.

Recent TMS motor cortex studies support earlier observations from investigations in animals that prior conditioning of the cortex, perhaps by stimulation at different parameters, can enhance the effects of stimulation. For example, [Iyer et al. \(2003\)](#) demonstrated that the physiological depressant effect of 1 Hz rTMS on motor cortical excitability was considerably enhanced by prior conditioning with 6 Hz rTMS given at subthreshold stimulus intensity. Thus, optimal therapeutic effects with rTMS may require treatment with a particular sequence of stimulus parameters (varying in frequency, intensity, number of stimuli, length of stimulus trains and/or intervals between trains), with the sequence extending either across individual treatment sessions, over the treatment course, or possibly, both. Furthermore, drawing parallels from the ECT literature, it may also be that adjustment of stimulus parameters over a treatment course, e.g. a gradual increase in stimulus intensity, is necessary for maximal therapeutic effects. Though researchers may be guided by findings from motor cortex and animal studies in understanding the likely implications of the above factors for the efficacy of rTMS, clinical trials involving large numbers of subjects will be necessary to test the relative outcomes of different stimulation paradigms.

The waveform of the electrical pulse used in TMS (and hence induced magnetic and electrical fields) varies between machines from different manufacturers. There is evidence from motor cortex studies to suggest that TMS with stimuli of different waveforms (e.g. biphasic versus monophasic) leads to discernibly different outcomes in terms of lasting changes in cortical excitability. Thus, as in the development of ECT ([Abrams, 2002](#)), refinement of the stimulus waveform may emerge as an important factor in optimizing therapeutic outcomes with TMS.

The most appropriate role for rTMS as a treatment in depression, whether it be a stand-alone treatment, add-on to other treatments (antidepressants, ECT, etc) for synergistic effects ([Garcia-Toro et al., 2001](#); [Hausmann et al., 2004](#); [Rumi et al., 2005](#); [Pridmore, 2000b](#)), or an alternative means of inducing seizures ([Lisanby et al., 2001c](#)) is yet to be determined.

An appraisal of the efficacy of rTMS by necessity includes the identification of patient subgroups most likely to respond. So far, there are suggestions that rTMS may be less effective in psychotic depression

([Grunhaus et al., 2000, 2003](#)), elderly subjects ([Figiel et al., 1998](#); [Padberg et al., 1999](#)) and those with depressive episodes of longer duration ([Holtzheimer et al., 2004](#)). It is also likely that subjects who are more treatment resistant would be less likely to respond to rTMS, as is the case with other antidepressant treatments ([Mitchell et al., 2000](#)). Taking the sample characteristics into account is important when comparing or pooling the results from different studies as they may obscure the apparent relative benefits of different forms of rTMS. For example, it is now widely accepted that the large number of responders to low frequency right prefrontal rTMS in the [Klein et al. \(1999\)](#) study is due at least in part to the non-resistant nature of their sample.

4. Conclusion

Most of the sham-controlled data for the efficacy of rTMS in treating depression comes from studies with a two-week sham-controlled period. The outcomes suggest clear statistical proof of superiority over placebo effects but not large clinical effects. However, the few studies which have reported results of longer periods of stimulation suggest that a longer course of rTMS is necessary for optimal therapeutic outcomes. Thus evidence for the efficacy of rTMS should be derived from sham-controlled studies of four to six weeks duration.

Acknowledgements

Dr. Loo is a part-time Senior Research Fellow supported by a National Health and Medical Council Program Grant no. 2223208. The authors thank Kate Manollaras for assistance in manuscript preparation.

References

- Aare, T., Dahl, A.A., Johansen, J.B., Kjonniksen, I., Neckelman, D., 2003. Efficacy of repetitive transcranial magnetic stimulation in depression: a review of the evidence. *Nordic Journal of Psychiatry* 57 (3), 227–232.
- Abrams, R., 2002. *Electroconvulsive Therapy* (4th edn). Oxford University Press, Oxford.
- Barker, A.T., 1991. An introduction to the basic principles of magnetic nerve stimulation. *Journal of Clinical Neurophysiology* 8, 26–37.

- Belmaker, B., Fitzgerald, P., George, M., Lisanby, S., Pascual-Leone, A., Schlaepfer, T., Wassermann, E., 2003. Managing the risks of repetitive transcranial stimulation. *CNS Spectrums* 8, 489.
- Berman, R.M., Narasimhan, M., Sanacora, G., Miano, A.P., Hoffman, R.E., Hu, X.S., Charney, D.S., Boutros, N.N., 2000. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. *Biological Psychiatry* 47, 332–337.
- Burt, T., Lisanby, H., Sackeim, H., 2002. Neuropsychiatric applications of transcranial magnetic stimulation: a meta-analysis. *International Journal of Neuropsychopharmacology* 5, 73–103.
- Chen, R., Classen, J., Gerloff, C., Celnik, P., Wassermann, E., Hallett, M., Cohen, L., 1997. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* 48, 1398–1403.
- Christie, B., Abraham, W., 1994. Flip side of synaptic plasticity: long term depression mechanisms in the hippocampus. *Hippocampus* 4, 127–135.
- Christyakov, A., Kaplan, B., Rubichek, O., Kreinin, I., Koren, D., Feinsod, M., Klein, E., 2005. Antidepressant effects of different schedules of repetitive transcranial magnetic stimulation vs. clomipramine in patients with major depression: relationship to changes in cortical excitability. *International Journal of Neuropsychopharmacology* 8, 223–233.
- Conca, A., Di Pauli, J., Beraus, W., Hausmann, A., Peschina, W., Schneider, H., König, P., Hinterhuber, H., 2002. Combining high and low frequencies in rTMS antidepressive treatment: preliminary results. *Human Psychopharmacology* 17, 353–356.
- Couturier, J.L., 2005. Efficacy of rapid-rate repetitive transcranial magnetic stimulation in the treatment of depression: a systematic review and meta-analysis. *Journal of Psychiatry and Neuroscience* 30 (2), 83–90.
- Davidson, R., Hugdahl, K. (Eds.), 1995. *Brain Asymmetry*. MIT Press, Cambridge, pp. 361–387.
- Dolberg, O.T., Dannon, P.N., Schreiber, S., Grunhaus, L., 2002. Transcranial magnetic stimulation in patients with bipolar depression: a double blind, controlled study. *Bipolar Disorders* 4, 94–95.
- Dragasevic, N., Potrebic, A., Damjanovic, A., Stefanova, E., Kostic, V., 2002. Therapeutic efficacy of bilateral prefrontal slow repetitive transcranial magnetic stimulation in depressed patients with Parkinson's disease: an open study. *Movement Disorders* 17, 528–532.
- Eschweiler, G., Plewnia, C., Batra, A., Bartels, M., 2000. Does clinical response to repetitive prefrontal transcranial magnetic stimulation (rTMS) predict response to electroconvulsive therapy (ECT) in cases of major depression? *Canadian Journal of Psychiatry* 46, 845–846.
- Feinsod, M., Kreinin, B., Chistyakov, A., Klein, E., 1998. Preliminary evidence for a beneficial effect of low-frequency, repetitive transcranial magnetic stimulation in patients with major depression and schizophrenia. *Depression and Anxiety* 7, 65–68.
- Figiel, G.S., Epstein, C., McDonald, W.M., Amazon-Leece, J., Figiel, L., Saldivia, A., Glover, S., 1998. The use of rapid-rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. *Journal of Neuropsychiatry and Clinical Neurosciences* 10, 20–25.
- Fitzgerald, P., 2003. Is it time to introduce repetitive transcranial magnetic stimulation into standard clinical practice for the treatment of depressive disorders? *Australian and New Zealand Journal of Psychiatry* 37, 5–11.
- Fitzgerald, P.B., Brown, T.L., Marston, N.A., 2003. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Archives of General Psychiatry* 60 (10), 1002–1008.
- Garcia-Toro, M., Pascual-Leone, A., Romera, M., Gonzalez, A., Mico, J., Ibarra, O., Arnillas, H., Capllonch, I., Mayol, A., Tormos, J.M., 2001. Prefrontal repetitive transcranial magnetic stimulation as add on treatment in depression. *Journal of Neurology, Neurosurgery and Psychiatry* 71, 546–548.
- Geller, V., Grisaru, N., Abarbanel, J.M., Lemberg, T., Belmaker, R.H., 1997. Slow magnetic stimulation of prefrontal cortex in depression and schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 21, 105–110.
- George, M.S., Wassermann, E.M., Kimbrell, T.A., Little, J.T., Williams, W.E., Danielson, A.L., Greenberg, B.D., Hallett, M., Post, R.M., 1997. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. *American Journal of Psychiatry* 154, 1752–1756.
- George, M.S., Nahas, Z., Molloy, M., Speer, A.M., Oliver, N.C., Li, X.B., Arana, G.W., Risch, S.C., Ballenger, J.C., 2000. A controlled trial of daily left prefrontal cortex TMS for treating depression. *Biological Psychiatry* 48, 962–970.
- Gershon, A., Dannon, P., Grunhaus, L., 2003. Transcranial magnetic stimulation in the treatment of depression. *American Journal of Psychiatry* 160, 835–845.
- Grunhaus, L., Dannon, P., Schreiber, S., Dolberg, O., Amiaz, R., Ziv, R., Lefkewer, E., 2000. Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. *Biological Psychiatry* 47, 314–324.
- Grunhaus, L., Schreiber, S., Dolberg, O., Polak, Dannon, P., 2003. A randomised controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. *Biological Psychiatry* 53, 324–331.
- Hausmann, A., Kemmler, G., Walpoth, M., Mechtcheriakov, S., Kramer-Reinstadler, K., Lechner, T., Walch, T., Deisenhammer, E., Kofler, M., Rupp, C., Hinterhuber, H., Conca, A., 2004. No benefit derived from repetitive transcranial magnetic stimulation in depression: a prospective, single centre, randomised, double blind, sham controlled “add on” trial. *Journal of Neurology, Neurosurgery and Psychiatry* 75 (2), 320–322.
- Holtzheimer, P.E., Russo, J., Avery, D.H., 2001. A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. *Psychopharmacology Bulletin* 35, 149–169.
- Holtzheimer, P.E., Avery, D., Schlaepfer, T.E., 2004. Antidepressant effects of repetitive transcranial magnetic stimulation. *British Journal of Psychiatry* 184, 541–542 (Jun).
- Hoppner, J., Schulz, M., Irmisch, G., Mau, R., Schlafke, D., Richter, J., 2003. Antidepressant efficacy of two different rTMS procedures. High frequency over left versus low frequency over right prefrontal cortex compared with sham stimulation. *European*

- Archives of Psychiatry and Clinical Neuroscience 253 (2), 103–109.
- Iyer, M., Schleper, N., Wassermann, E., 2003. Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. *The Journal of Neuroscience* 23 (34), 10867–10872.
- Janicak, P.G., Dowd, S.M., Martis, B., Alam, D., Beedle, D., Krasuski, J., Strong, M.J., Sharma, R., Rosen, C., Viana, M., 2002. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: preliminary results of a randomized trial. *Biological Psychiatry* 51, 659–667.
- Jorge, R.E., Robinson, R.G., Tateno, A., Narushima, K., Acion, A., Moser, D., Arndt, S., Chernerinski, E., 2004. Repetitive transcranial magnetic stimulation as treatment of poststroke depression: a preliminary study. *Biological Psychiatry* 1555 (4), 398–405.
- Kapillett, S., Tsoukarzi, E., Copolov, D., 2001. Efficacy pilot study of right prefrontal TMS in depression. *World Journal of Biological Psychiatry* 2 (suppl 1), p1.
- Kauffmann, C.D., Cheema, M.A., Miller, B.E., 2004. Slow right prefrontal transcranial magnetic stimulation as a treatment for medication-resistant depression: a double-blind, placebo-controlled study. *Depression and Anxiety* 19 (1), 59–62.
- Koerselman, F., Laman, D.M., van Duijn, H., van Duijn, M., Willems, M., 2004. A 3-month, follow-up, randomized, placebo-controlled study of repetitive transcranial magnetic stimulation in depression. *Journal of Clinical Psychiatry* 65 (10), 1323–1328.
- Klein, E., Kreinin, I., Chistyakov, A., Koren, D., Mecz, L., Marmur, S., Ben-Shachar, D., Feinsod, M., 1999. Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. *Archives of General Psychiatry* 56, 315–320.
- Kozel, F., George, M., 2002. Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression. *Journal of Psychiatric Practice* 8, 270–275.
- Kozel, A., Nahas, Z., deBrux, C., Molloy, M., Lorberbaum, J., Bohning, D., Risch, C., George, M., 2000. How coil-cortex distance relates to age, motor threshold, and antidepressant response to transcranial magnetic stimulation. *Journal of Neuropsychiatry and Clinical Neuroscience* 12, 376–384.
- Lisanby, H., Pascual-Leone, A., Sampson, S., Boylan, L., Burt, T., Sackeim, H., 2001a. Augmentation of sertraline antidepressant treatment with transcranial magnetic stimulation. *Biological Psychiatry* 49, 81.
- Lisanby, S., Gutman, D., Luber, B., Schroeder, C., Sackeim, H., 2001b. Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. *Biological Psychiatry* 49, 460–463.
- Lisanby, S.H., Schlaepfer, T.E., Fisch, H.U., Sackeim, H.A., 2001c. Magnetic seizure therapy of major depression. *Archives of General Psychiatry* 58, 303–305.
- Loo, C., Mitchell, P., Sachdev, P., McDarmont, B., Parker, G., Gandevia, S., 1999. Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. *American Journal of Psychiatry* 156, 946–948.
- Loo, C., Taylor, J., Gandevia, S., McDarmont, B., Mitchell, P., Sachdev, P., 2000. Transcranial magnetic stimulation (TMS) in controlled treatment studies: are some “sham” forms active? *Biological Psychiatry* 47, 325–331.
- Loo, C., Mitchell, P., Croker, V., Malhi, G., Wen, W., Gandevia, S., Sachdev, P., 2003. Double-blind controlled investigation of bilateral prefrontal transcranial magnetic stimulation for the treatment of resistant major depression. *Psychological Medicine* 33, 33–40.
- Manes, F., Jorge, R., Morcuende, M., Yamada, T., Paradiso, S., Robinson, R.G., 2001. A controlled study of repetitive transcranial magnetic stimulation as a treatment of depression in the elderly. *International Psychogeriatrics* 13, 225–231.
- Martin, J.L.R., Barbanjo-Rodriguez, M., Schlaepfer, T., Clos, S., Perez, V., Kulisevsky, J., Gironell, A., 2003. Transcranial magnetic stimulation for treating depression (Cochrane Review). The Cochrane Library, Issue 1. Update Software, Oxford.
- McNamara, B., Ray, J.L., Arthurs, O.J., Boniface, S., 2001. Transcranial magnetic stimulation for depression and other psychiatric disorders. *Psychological Medicine* 31, 1141–1146.
- Menkes, D.L., Bodnar, P., Ballesteros, R.A., Swenson, M.R., 1999. Right frontal lobe slow frequency repetitive transcranial magnetic stimulation (SF r-TMS) is an effective treatment for depression: a case-control pilot study of safety and efficacy. *Journal of Neurology, Neurosurgery and Psychiatry* 67, 113–115.
- Miniussi, C., Bonato, C., Bignotti, S., Gazzoli, A., Gennarelli, M., Pasqualetti, P., Tura, G., Ventriglia, M., Rossini, P., 2005. Repetitive transcranial magnetic stimulation (rTMS) at high and low frequency: an efficacious therapy for major drug-resistant depression? *Clinical Neurophysiology* 116, 1062–1071.
- Mitchell, P.B., Schweitzer, I., Burrows, G., Johnson, G., Polonowita, A., 2000. Efficacy of venlafaxine and predictors of response in a prospective open-label study of patients with treatment-resistant major depression. *Journal of Clinical Psychopharmacology* 20, 483–487.
- Mosimann, U., Marre, S., Werlen, S., Schmitt, W., Hess, C., Fisch, H., Schlaepfer, T., 2002. Antidepressant effects of repetitive transcranial magnetic stimulation in the elderly: correlation between effect size and coil-cortex distance. *Archives of General Psychiatry* 59, 560–561.
- Mosimann, U.P., Schmitt, W., Greenberg, B.D., Kosel, M., Muri, R., Berkhoff, M., Hess, C., Fisch, H., Schlaepfer, T., 2004. Repetitive transcranial magnetic stimulation: a putative add-on treatment for major depression in elderly patients. *Psychiatry Research* 30;126 (2), 123–133.
- Nahas, Z., Kozel, A., Li, X., Anderson, B., George, M., 2003. Left prefrontal transcranial stimulation (TMS) treatment of depression in bipolar affective disorder: a pilot study of acute safety and efficacy. *Bipolar Disorders* 5, 40–47.
- Padberg, F., Zwanzger, P., Thoma, H., Kathmann, N., Haag, C., Greenberg, B.D., Hampel, H., Moller, H.J., 1999. Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. *Psychiatry Research* 88, 163–171.
- Padberg, F., Zwanzger, P., Keck, M.E., Kathmann, N., Mikhael, P., Ella, R., Rupprecht, P., Thoma, H., Hampel, H., Toschi, N., Moller, H.J., 2002. Repetitive transcranial magnetic stimulation

- (rTMS) in major depression: relation between efficacy and stimulation intensity. *Neuropsychopharmacology* 27, 638–645.
- Pascual-Leone, A., Valls-Sole, J., Wassermann, E.M., Hallett, M., 1994. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain* 117, 847–858.
- Pascual-Leone, A., Rubio, B., Pallardo, F., Catala, M., 1996. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *The Lancet* 348, 233–237.
- Pridmore, S., Bruno, R., Turnier-Shea, Y., Reid, P., Rybak, M., 2000. Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. *International Journal of Neuropsychopharmacology* 3, 129–134.
- Pridmore, S., 2000. Substitution of rapid transcranial magnetic stimulation for electroconvulsive therapy treatments in a course of electroconvulsive therapy. *Depression and Anxiety* 12, 118–123.
- Prudic, J., Olfson, M., Marcus, S.C., Fuller, R.B., Sackeim, H.A., 2004. Effectiveness of electroconvulsive therapy in community settings. *Biological Psychiatry* 55, 301–312.
- Royal Australian and New Zealand College of Psychiatrists. Position Statement #40 on Transcranial Magnetic Stimulation (TMS). June 2003.
- Rumi, D.O., Gattaz, W.F., Rigonatti, S.P., Rosa, M., Fregni, F., Rosa, M., Mansur, C., Myczkowski, M., Moreno, R., Marcolin, M., 2005. Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: a double-blind placebo-controlled study. *Biological Psychiatry* 15;57 (2), 162–166.
- Sachdev, P., 2003. Comment on “Is it time to introduce repetitive transcranial magnetic stimulation into standard clinical practice for the treatment of depressive disorders?” *Australian and New Zealand Journal of Psychiatry* 37, 12–14.
- Sachdev, P., McBride, R., Loo, C., Mitchell, P., Malhi, G., Croker, V., 2002. Effects of different frequencies of transcranial magnetic stimulation (TMS) on the forced swim test model of depression in rats. *Biological Psychiatry* 51, 474–479.
- Sackeim, H., Prudic, J., Devanand, D., Nobler, M., Lisanby, S., Peyser, S., Fitzsimons, L., Moody, B., Clark, J., 2000. A prospective, randomised, double-blind comparison of bilateral and right unilateral ECT at different stimulus intensities. *Archives of General Psychiatry* 57, 425–434.
- Schutter, D., van Honk, J., 2005. A framework for targeting alternative brain regions with repetitive transcranial magnetic stimulation in the treatment of depression. *Journal of Psychiatry and Neuroscience* 30, 91–97.
- Shajahan, P.M., Glabus, M.F., Steele, J.D., Doris, A.B., Anderson, K., Jenkins, J.A., Gooding, P.A., Ebmeier, K.P., 2002. Left dorso-lateral repetitive transcranial magnetic stimulation affects cortical excitability and functional connectivity, but does not impair cognition in major depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 26, 945–954.
- Silberman, E., Weingartner, H., 1987. Hemispheric lateralisation of functions related to emotion. *Brain and Cognition* 5, 322–353.
- Stassen, H., Delini-Stula, A., Angst, J., 1993. Time course of improvement under antidepressant treatment: a survival-analytical approach. *European Journal of Neuropsychopharmacology*, 127–135.
- Van Economo, C., 1929. *The Cytoarchitectonics of the Human Cerebral Cortex*. Oxford University Press, Oxford.
- Walter, G., Martin, J., Kirkby, K., Pridmore, S., 2001. Transcranial magnetic stimulation: experience, knowledge and attitudes of recipients. *Australian and New Zealand Journal of Psychiatry* 35, 58–61.
- Wassermann, E., 1998. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalography and Clinical Neurophysiology* 108, 1–16.