Equivalent beneficial effects of unilateral and bilateral prefrontal cortex transcranial magnetic stimulation in a large randomized trial in treatment-resistant major depression

Paul B. Fitzgerald1,2, Kate E. Hoy3, Ajeet Singh3, Ranil Gunewardene4, Christopher Slack5, Samir Ibrahim6, Phillip J. Hall1 and Z. Jeff Daskalakis7

1 Monash Alfred Psychiatry Research Centre, The Alfred and Monash University Central Clinical School, Melbourne, Victoria, Australia
2 The Victoria Clinic, Prahran, Victoria, Australia
3 The Geelong Clinic and Deakin University School of Medicine, Geelong, Victoria, Australia
4 Mosman Private Hospital, Mosman, New South Wales, Australia
5 Pine Rivers Private Hospital, Strathpine, Queensland, Australia
6 Northpark Private Hospital, Bundoora, Victoria, Australia
7 Centre for Addiction and Mental Health, Clarke Division, Toronto, Ontario, Canada

Abstract

Repetitive transcranial magnetic stimulation treatment (rTMS) is an effective treatment for depression but the optimal methods of administration have yet to be determined. Recent studies have produced conflicting results as to whether unilateral rTMS is more or less effective than sequentially applied bilateral rTMS. To address this we conducted a trial comparing sequential bilateral rTMS to right-sided unilateral rTMS using a priming protocol. Patients with treatment-resistant depression (n=179) were enrolled in a two-arm randomized controlled trial across a 4-wk time period. The primary outcome assessment was the Hamilton Depression Rating Scale. Overall, there was a substantial response rate of >50% (and a 40% remission rate); however, there were no significant differences in clinical response between the two treatment groups. rTMS was well tolerated with a very low discontinuation rate. There was no relationship between response in the current trial and previous response, or non-response, to electroconvulsive therapy. We found no significant differences in clinical response between sequential bilateral rTMS and right-sided unilateral rTMS applied with a priming protocol. The results of this study do not support superior efficacy of bilateral rTMS and instead suggest that other approaches should be explored to increase treatment efficacy.

Received 4 December 2012; Reviewed 21 January 2013; Revised 3 February 2013; Accepted 15 March 2013; First published online 13 May 2013

Key words: Antidepressant, depression, prefrontal cortex, remission, repetitive transcranial magnetic stimulation, response.

Introduction

Major depressive disorder (MDD) is a substantial psychiatric disorder that results in significant individual suffering, disability and socio-economic impact (Greenberg et al., 1993; Kessler et al., 2003; Simon, 2003). It is common, affecting approximately 15% of people across the lifespan and has a reported 1-yr prevalence of approximately 6.7% (Murray and Lopez, 1996). There are a range of established treatments for MDD including antidepressant medications and psychotherapy. However, a substantial percentage of patients, usually estimated as between 20 and 30%, fail to respond to initial treatments (Fava, 2003). These patients are generally referred to as having treatment-resistant depression. There are few established treatments for treatment-resistant depression, with the main approach being electroconvulsive therapy (ECT).
Over recent years, repetitive transcranial magnetic stimulation (rTMS) has been developed as an alternative approach for these patients, as well as for less refractory cases of MDD. The main rTMS approach developed involves the application of high-frequency rTMS pulses to the left dorsolateral prefrontal cortex (PFC). The antidepressant efficacy of this type of rTMS is clearly supported by many clinical trials (e.g. O’Reardon et al., 2007; Lisanby et al., 2009; George et al., 2010) and a number of substantive positive meta-analyses (e.g. McNamara et al., 2001; Burt et al., 2002; Lam et al., 2008; Slotema et al., 2010). This evidence has led to clinical approval and use of the technique in a number of countries although the overall response rates to rTMS in most trials have been relatively low (e.g. remission rates between 15 and 20%; O’Reardon et al., 2007; George et al., 2010).

This efficacy limitation has motivated the search for alternative methods of rTMS application that might improve response rates and/or limit side-effects such as headache and site discomfort. A number of studies have found that low-frequency stimulation applied to the right dorsolateral PFC has antidepressant activity superior to sham stimulation (Klein et al., 1999) and similar efficacy to high-frequency left-sided stimulation (Fitzgerald et al., 2003, 2009; Isenberg et al., 2005). Low-frequency stimulation applied to the right dorsolateral PFC has some advantages over high-frequency treatment in that it is better tolerated and has a lesser risk of seizure induction (Fitzgerald et al., 2003). The efficacy of this form of rTMS compared to sham has been supported in two recent meta-analyses (Schutter, 2010; Berlim et al., 2012b). Low- and high-frequency stimulation appears to have opposite effects on cortical excitability (Fitzgerald et al., 2003): in motor cortex and PFC, low-frequency stimulation reduces and high-frequency stimulation increases cortical excitability (Fitzgerald et al., 2006b, 2007). These disparate effects are proposed to relate to antidepressant efficacy based on models that propose hypoactivity of the left PFC and/or hyperactivity of the right PFC in depression.

Another novel approach has been the sequential combination of low-frequency stimulation applied to the right PFC followed by high-frequency stimulation applied to the left PFC. Similar effects to unilateral treatment have been reported in several small studies (e.g. Conca et al., 2002) and one larger study demonstrated that sequential bilateral rTMS produces considerable antidepressant effects with response rates considerably higher than in most of the studies of unilateral treatment (Fitzgerald et al., 2006a). Studies exploring the relative efficacy of unilateral and sequential bilateral rTMS have yielded contradictory results: some studies have suggested greater antidepressant effects of bilateral treatment (Blumberger et al., 2011) but no difference in efficacy or an advantage of unilateral treatment has been found in other studies (Fitzgerald et al., 2011; Pallanti et al., 2010). A recent meta-analysis concluded that sequential bilateral rTMS was superior to sham stimulation but no differences with unilateral rTMS were found (Berlim et al., 2012a). One complication with the interpretation of these studies is that bilateral stimulation usually involves the application of a substantially greater number of stimuli than unilateral treatment; therefore, greater effects may relate to the increased stimulation pulse number rather than a specific feature of bilateral treatment.

Another approach that has been trialled to a limited degree is the use of ‘priming stimulation’. When low-frequency stimulation is usually applied to the right dorsolateral PFC, it is done in a single long (~15 min) train applied at 1 Hz. It has been demonstrated in the motor cortex that greater suppression of excitability is produced if the 1 Hz train is preceded, or ‘primed’, by a short period of low-intensity higher-frequency stimulation (~6 Hz; Iyer et al., 2003). We previously conducted a randomized controlled trial comparing low-frequency right-sided rTMS to priming stimulation and found patients in the priming group achieved a greater reduction in depressive symptoms than with standard right-sided stimulation alone (Fitzgerald et al., 2008).

The aim of this study was to explore in a randomized trial whether there were efficacy differences between sequential bilateral rTMS and priming stimulation applied to the right dorsolateral PFC. The study was motivated by several considerations. At the time of the study our previous study data had suggested that both sequential bilateral rTMS (Fitzgerald et al., 2006a; Blumberger et al., 2011) and priming stimulation (Fitzgerald et al., 2008) may have greater effects than standard unilateral treatment approaches. Therefore, we were interested in whether one of these approaches would prove superior and thus warrant further investigation. In addition, as a comparison of unilateral and bilateral rTMS, the use of priming as the unilateral approach was attractive as we could more closely control both the pulse number and experience for the subjects (i.e. patients would receive largely equivalent pulse numbers of both high- and low-frequency stimulation). We hypothesized that bilateral rTMS would result in a greater improvement in depressive symptoms than the priming unilateral stimulation condition.
Method

Study design
The study involved a two-arm double-blind randomized controlled trial (n=179; Fig. 1) conducted across four sites. Patients were randomized using a separate computer-generated random number sequence at each site. The patients and raters were blind to treatment but the clinician administering rTMS was aware of the treatment group. The patients and raters were advised that there was a difference in the stimulation parameters in the two comparison groups but specifics of the differences between unilateral and bilateral approaches and the rationale for these were not described in any detail. The duration of the trial was 20 sessions of treatment provided on 5 d/wk.

Subjects
A total of 179 patients participated (54 male, 125 female, mean age=47.6±15.0 yr). Diagnosis was determined using the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) by a study psychiatrist for each patient. Patients were categorized as having either: MDD, single episode (n=39); MDD, relapse (n=97); bipolar I disorder, depressive episode (n=27); bipolar II disorder, depressive episode (n=13). Co-morbid diagnoses were also recorded using the MINI and are listed in Table 1. The presence of co-morbid borderline personality disorder was based on the clinical diagnosis of the referring psychiatrist confirmed by a study psychiatrist. Patients were not excluded with a co-morbid Axis I...
or II disorder except for current alcohol or substance dependence. This exclusion was based on seizure risk. The broad exclusion criteria were established to allow generalizability/translation of the findings to clinical practice.

Patients were recruited by referral from a number of private psychiatrists between February 2009 and October 2010. All patients were in-patients during the trial which was conducted across four private psychiatric hospitals in the Australian states of Victoria, New South Wales and Queensland. As for several previous studies (e.g. Fitzgerald et al., 2006c; Fitzgerald et al., 2011), training in the TMS methods, trial management and ratings were conducted by the lead study site. This assured the uniformity of delivery across sites.

The inclusion criteria included a diagnosis of moderate-to-severe depression (scoring >13; Bech et al., 1986) on the 17-item version of the Hamilton Depression Rating Scale (HAMD; Hamilton, 1967). Patients were required to have failed to respond to a minimum of two courses of antidepressant medications for at least 6 wk in the current episode (Stage II, Thase and Rush Definition; Thase and Rush, 1997; mean number of courses across episodes=5.10±3.1). A total of 79 of the patients had received previous treatment with ECT: 44 of these reported having responded to ECT; 34 having not responded (most of these received ECT during the current episode); one was unsure. Medications were not allowed to have changed in the 4 wk prior to commencement of the trial or during the trial itself. A total of 149 patients were taking antidepressant medication during the study and 72 were receiving concurrent treatment with a mood stabilizer. Psychotherapy was not permitted to commence during the trial period.

Exclusion criteria were the presence of a current and significant active medical illness, current neurological disease or a contraindication to rTMS (e.g. history of

<table>
<thead>
<tr>
<th>Table 1. Demographic and baseline clinical variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
</tr>
<tr>
<td>Diagnosis (number of subjects)</td>
</tr>
<tr>
<td>MDD; single episode</td>
</tr>
<tr>
<td>MDD; relapse</td>
</tr>
<tr>
<td>BPAD I</td>
</tr>
<tr>
<td>BPAD II</td>
</tr>
<tr>
<td>Melancholia (yes/no)</td>
</tr>
<tr>
<td>Psychotic symptoms (yes/no)</td>
</tr>
<tr>
<td>Age of illness onset</td>
</tr>
<tr>
<td>Number of failed antidepressant trials</td>
</tr>
<tr>
<td>HAMD</td>
</tr>
<tr>
<td>BDI</td>
</tr>
<tr>
<td>BAI</td>
</tr>
<tr>
<td>Concurrently taking antidepressant medication (yes/no)</td>
</tr>
<tr>
<td>Concurrently taking mood stabilizer medication (yes/no)</td>
</tr>
<tr>
<td>Previous course of ECT (lifetime; yes/no)</td>
</tr>
<tr>
<td>Self-report ECT responder (yes/no)</td>
</tr>
<tr>
<td>Co-morbid diagnoses (number of subjects)</td>
</tr>
<tr>
<td>Panic disorder</td>
</tr>
<tr>
<td>GAD</td>
</tr>
<tr>
<td>OCD</td>
</tr>
<tr>
<td>PTSD</td>
</tr>
<tr>
<td>BPD</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
</tbody>
</table>

M, Male; F, female; MDD, major depressive disorder; BPAD, bipolar affective disorder; OCD, obsessive compulsive disorder; GAD, generalized anxiety disorder; PTSD, post-traumatic stress disorder; BPD, borderline personality disorder; HAMD, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; ECT, electroconvulsive therapy.

There were no significant differences across the groups on any variables.
a seizure disorder; the presence of a pacemaker or metal somewhere in the head other than the teeth).

After complete description of the study to the subjects, written informed consent was obtained from all patients and the study received Human Research Ethics Committee approval (at the Melbourne Clinic).

The study was powered (0.88) to show a 5-point difference in the study end-point variable (mean total HAMD scores at treatment end) between the two groups (two-sided, α<0.05, S.D.=10) with a planned sample size of 80 per group. This difference is small but we believed it was unlikely that a trial of active treatments in a treatment-resistant population would be likely to show greater differences. Given an average baseline HAMD level of about 25 this would mean a 20% difference between the groups in final scores, which is likely to be of clinical significance. The variance data (10) were based as a relatively conservative estimate from our previous comparative trials.

**TMS treatment**

Across all study sites rTMS was administered using Medtronic Magpro30 magnetic stimulators (Medtronic Inc, USA) using fluid filled 70 mm figure-of-eight coils held in custom-made stands. The coils were held tangential abutting the scalp with the handle pointing back and away from the midline at 45°. The site of stimulation during the TMS treatment sessions was defined by a point 6 cm anterior to that required for maximum stimulation of the abductor pollicis brevis muscle. The resting motor threshold (RMT) was measured bilaterally using standard visual methods (Pridmore et al., 1998). The mean RMT was 49.5±22.7 on the left and 55.3±13.7 on the right (p=0.001; percentage of total machine output). Patients sat in a comfortable reclining chair during treatment.

rTMS in the two groups was provided as follows: (1) sequential bilateral dorsolateral PFC rTMS: right-sided TMS at low frequency (1 Hz, 110% of motor threshold, one continuous train of 900 pulses) followed by left-sided TMS at high frequency (10 Hz, 110% of motor threshold, 15 trains of 50 pulses each with 25 s interval between trains); (2) priming stimulation: 20 trains of 5 s duration at 6 Hz and 90% of the RMT followed by 1 Hz stimulation (110% of motor threshold, one continuous train of 900 pulses).

Each treatment was administered for up to 4 wk, 5 d/wk (total of 20 treatment sessions).

**Clinical assessment**

Patients were assessed at baseline, 2 and 4 wk. The primary outcome for the study was scores on the 17-item version of HAMD (Hamilton, 1967). In addition, all patients completed the Beck Depression Inventory (BDI; Beck et al., 1961) and the Beck Anxiety Inventory (BAI; Beck et al., 1988).

**Data analysis**

For the primary analysis we compared the percentage of patients meeting response and remission criteria with χ² tests. Response criteria was a >50% reduction in HAMD score and remission defined as HAMD score <8. We also conducted a mixed-model analysis using the PROC Mixed procedure in SAS (SAS Version 9.1; SAS Institute Inc., USA) with the covariance structure treated as unstructured. The PROC Mixed procedure does not delete missing values listwise, but rather handles missing values by treating them as missing at random. The PROC Mixed procedure uses a restricted maximum likelihood algorithm that enables specific modelling of the within-patient covariance structure. Using the lowest Akaike’s Information Criteria as a guide to goodness of fit enables the most appropriate covariance structure to then be evaluated for each situation. Empirical studies have confirmed the advantages of mixed models over last observation carried forward analysis, with mixed-effects (Mallinckrodt et al., 2001a, b).

Correlations and a linear regression analysis were then calculated to investigate potential predictors of response to treatment. Percentage change in HAMD score was the dependent variable. Potential predictors included: age; sex; illness and current episode duration; number of previous medications; baseline depression severity; diagnostic group; co-morbid diagnosis.

All procedures were two-tailed and significance was set at a level of 0.05, with Bonferroni’s correction used for post hoc comparisons. All statistical analysis was conducted with SPSS 16.0 (SPSS for Windows, 16.0; SPSS, USA) unless otherwise stated.

**Results**

**Patients**

Baseline clinical characteristics are summarized in Table 1. A total of 179 were initially enrolled and randomized. Eight patients (three bilateral, five priming) failed to complete 2 wk treatment and have a single post-baseline assessment. Of these, four withdrew consent, three ceased due to adverse events (one severe headache, one site pain and one developed hypomania) and in one case treatment ceased due to...
equipment malfunction requiring repair and treatment delay.

An additional 10 patients were withdrawn between the 2-wk assessment and treatment end (nine bilateral, one priming). Of these, five withdrew consent, three were withdrawn to have treatment with ECT due to perceived urgency and lack of efficacy, one withdrew due to perceived worsening of depression and one patient committed suicide despite in-patient care.

Categorical analysis

Overall 100 patients (56%) met response criteria at trial end. Of these, there were 50 responders (50/88) to bilateral treatment (57%) and 50 responders (50/91) to priming treatment (55%; \( \chi^2 = 0.06, p = 0.80 \)).

With regard to remission, at study end a total of 72 patients (40.2%) met remission criteria. There were 35 (40%) remitters in the bilateral group and 37 (40.1%) remitters in the priming group (\( \chi^2 = 0.15, p = 0.90 \)).

Primary outcome analysis: continuous data

For the mixed-model analysis of the HAMD data, there was a significant overall improvement (effect of time: \( p < 0.001 \)) but no difference in response over time between the groups (group × time interaction: \( p = 0.38 \); Table 2; Fig. 2).

Secondary variables

For BDI scores, there was a significant overall improvement (effect of time: \( p < 0.001 \)) and no significant difference in response over time between the groups (group × time interaction: \( p = 0.58 \)). For BAI scores, there was also a significant overall improvement (effect of time: \( p < 0.001 \)) and no difference in response over time for the two groups (\( p = 0.36 \)). There was a significant relationship between improvement in HAMD and BAI scores (\( \chi^2 = 0.44, p < 0.001 \)).

Predictors of response

Predictors were explored with correlations and regression analysis; there was no clear relationship between any demographic or clinical variables and response to treatment. A greater proportion of male patients (65%) than female patients (52%) met response criteria, but this did not reach significance (\( p > 0.05 \)). Notably, there was no difference in response rates for patients who had previous treatment with ECT (53%) or not (58%) (\( p = 0.50 \)) or between patients who described themselves as having previously responded to ECT (50%) or not (56%; \( p = 0.63 \)).

Discussion

The results of this study clearly failed to support our hypothesis: there was no difference in efficacy between
bilateral and priming forms of rTMS. There was clearly a substantial overall response rate to rTMS, >50%, but no between group differences of any substance. Notably, given the treatment-resistant nature of the sample, we achieved an impressive 40% remission rate which clearly indicates the clinical utility of these approaches. Overall treatment was well tolerated with only eight patients (<5%) failing to complete at least 2 wk treatment, of which only three were withdrawals directly related to treatment related side-effects.

This study adds to a growing literature that has failed to support a systematically greater response to bilateral compared to unilateral rTMS. Based on an earlier study, in which we achieved substantial response and remission rates with bilateral rTMS in a sham controlled protocol (Fitzgerald et al., 2006a), it was reasonable to assume that bilateral rTMS may result in greater effects than unilateral. This hypothesis was supported in a recent sham controlled study of unilateral and bilateral rTMS where superior response rate was seen in the bilateral condition (Blumberger et al., 2011). However, we did not see differences between unilateral and bilateral rTMS in the current study, or in a similar recent study in which we compared unilateral right-sided rTMS to two forms of bilateral stimulation (Fitzgerald et al., 2011). We also failed to see an advantage of bilateral stimulation compared to left-sided stimulation in a recent smaller sham controlled study (Fitzgerald et al., 2012) and in a separate trial greater effects of right-sided rTMS compared to bilateral stimulation were found (Pallanti et al., 2010).

Given that we have now shown equivalence between right-sided stimulation and bilateral rTMS in two studies which combined included almost 400 patients (Fitzgerald et al., 2011 and the current study), it seems unlikely that unilateral stimulation is truly superior but it is just as clear that bilateral also holds no efficacy advantage. However, as unilateral treatment is generally likely to be faster to administer (as even if pulse numbers are the same there is additional time required setting up treatment bilaterally) it is likely to be less costly to provide and thus would seem to be the superior option.

The current study also adds to the substantial literature indicating that rTMS is generally a very well tolerated treatment with low drop-out rates in clinical trials. However, one patient in this trial did commit suicide. The particular patient had received approximately 3 wk rTMS and at the time of suicide had not experienced any substantial clinical response. The patient had not expressed suicidal ideation on regular reviews prior to this event and did not have a history of recurrent suicide attempts. It is not possible to conclude this event was directly rTMS related and given the absence of reports of suicide related to rTMS previously it seems unlikely.

It is notable that we saw no relationship between demographic or clinical variables and the likelihood of response to rTMS. Previous studies, e.g. Fregni et al. (2006), have reported relationships between response and a number of factors such as age, illness duration and number of failed medication trials. We found no relationship with these or other factors including baseline illness severity. The last factor is notable in that we included quite a broad range of illness severity from a baseline HAMD >13: this was a deliberate decision to allow us to make judgments about the effectiveness of rTMS in a broad clinical population. In several previous studies in large samples (Fitzgerald et al., 2006c, 2011) we have not established a clear predictive relationship with any of the clinical or demographic factors questioning whether they are of any clinical relevance. A more successful way to explore for potential predictors of response might be to evaluate the potential of biomarkers or aspects of the assessment of brain function with imaging of electroencephalography.

One substantially novel and significant finding was the lack of a relationship between ECT treatment history, in particular ECT non-response, and response to rTMS. Although we did not collect ECT treatment history comprehensively, it is still notable that there was absolutely no relationship between patients’ reports of ECT non-response and current rTMS response. We have assumed previously that previous ECT non-response would likely be related to poor rTMS outcomes and thus patients who have failed to respond to ECT are often excluded from rTMS trials. However, results of this study suggest that a trial of rTMS may still be warranted in this patient group.

The most obvious limitation in the study is the lack of a sham control and the failure to fully blind patients by providing inactive stimulation to the left side in the unilateral rTMS group. However, we do not believe a sham was necessary as the efficacy of rTMS is well established (Schutter, 2009; Slotema et al., 2010) and our direct concern was to explore relative efficacy between treatment conditions. In this regard, it is notable that the response rates seen here, and in previous large open label studies (Fitzgerald et al., 2006c, 2011), are significantly greater than those seen in the main large blinded studies (e.g. O’Reardon et al., 2007; George et al., 2010). In addition, the broad exclusion criteria in this study and the heterogeneity of the sample (e.g. including both unipolar...
and bipolar patients and the commitment to use of medications), does significantly increase the risk of confounding factors influencing the study results. However, significant differences of these variables were not seen between the groups and the large sample size significantly mitigates this risk. Also, the clinical severity of the sample was defined as a HAMD score >13: although there is variability in the use of HAMD cut-off scores, this will include some patients at a milder end of the depression spectrum that would have been excluded from other rTMS studies. With regard to the blinding, patients were told that they would receive two types of rTMS (low and high frequency) but not provided a rationale for the different types or information that would systematically bias them towards the likelihood to respond to one or other of the groups. The study also did not compare ‘standard’ low-frequency right-sided rTMS, instead using the priming protocol. This allowed us to more evenly match the treatment conditions (i.e. provide both low- and high-frequency stimulation to all subjects). In addition, as we had previously shown superior responses to priming over standard right-sided rTMS (Fitzgerald et al., 2008) we felt that this would make for a more interesting and useful comparison. Finally, it is likely that the high overall response rate was somewhat influenced by the range of severity of depression seen in this sample given that high placebo response rates are likely in samples with milder forms of depression.

In summary, this study adds to a growing literature clearly indicating the lack of advantage of bilateral over unilateral rTMS. Given that there is a finite amount of time that a patient can receive stimulation in any session, a better approach to exploring enhanced efficacy may well be to adjust other variables such as coil placement/localization or the dose of stimulation administered. In the context of an open label trial, rTMS is well tolerated and with current parameters results in a response rate of at least 50%.

Acknowledgements

P.B.F. was supported by a Practitioner Fellowship grant from National Health and Medical Research Council (NHMRC). K.E.H. was supported by a post-doctoral Fellowship from the NHMRC. Resources for the study were supplied by Healthscope Ltd. We thank the patients whose participation was essential in the successful completion of the study. We also thank the nursing staff at the hospitals that assisted with study coordination and the provision of rTMS during the trial.

The trial was registered on the Australian and New Zealand Clinical Trials Register; http://www.anzctr.org.au/ (ACTRN12610000998044).

Statement of Interest

P.B.F. has received equipment for research from Medtronic, MagVenture A/S andBrainsway Ltd and research funding from Cervel Neurotech.

References


Fitzgerald PB, Brown T, Marston NAU, Daskalakis ZJ, Kulkarni J (2003) a double-blind placebo controlled trial of...
transcranial magnetic stimulation in the treatment of depression. Arch Gen Psychiatry 60:1002–1008.


Mallinckrodt C, Clark W, David S (2001b) Type I error rates from mixed effects model repeated measures compared with fixed effects ANOVA with missing values imputed via LOCF. Drug Information J 35:1215–1225.


