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Left versus right repetitive transcranial magnetic stimulation in treating major depression: A meta-analysis of randomised controlled trials

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ABSTRACT

Although the majority of randomised controlled trials suggest that major depressive disorder (MDD, major depression) and treatment-resistant depression can be effectively treated by applying either high- (HF) or low-frequency (LF) repetitive transcranial magnetic stimulation (rTMS) to the left and right dorsolateral prefrontal cortex (DLPFC), respectively, it is not clear which rTMS approach is more effective or safer. This systematic review and meta-analysis was conducted on randomised controlled trials on HF and LF rTMS applied to the left and right DLPFC, respectively, for the treatment of MDD. Eight randomised controlled trials composed of 249 patients were selected to compare the effects of LF (≤ 1 Hz) rTMS over the right DLPFC to HF (10–20 Hz) rTMS over the left DLPFC. The therapeutic effects of both approaches were similar (odds ratio (OR) = 1.15; 95% confidence interval = 0.65–2.03). Dropout analysis based on only two studies was insufficient to draw a conclusion on the tolerability of LF rTMS. The pooled examination demonstrated that both rTMS methods were equally effective therapies for MDD. However, considering that LF right-sided rTMS produces fewer side effects and is more protective against seizures, its clinical applicability shows greater promise and should be explored further.

Contents

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1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that induces currents in focal brain areas by electromagnetic stimulation (Fitzgerald and Daskalakis, 2011). By switching 'on–off' currents, TMS induces a magnetic field that depolarises neurons and affects brain activity (Barker, 1991). Repetitive TMS (rTMS), a technique that repeatedly applies either low-frequency (LF) or high-frequency (HF) TMS pulses to a focal cortical area, is capable of modulating cortical excitability in the treated area beyond the duration of the TMS train (Fitzgerald et al., 2006). LF rTMS (≤ 1 Hz) is inhibitory, while HF rTMS (10–20 Hz) increases cortical excitability (Leyman et al., 2011; Theodore et al., 2002).

A range of randomised controlled trials (RCTs) have focussed on whether HF left or LF right rTMS delivered to the dorsolateral prefrontal cortex (DLPFC) has a therapeutic effect in major depression (MDD, major depressive disorder) and treatment-resistant depression (TRD). As HF rTMS is thought to increase cortical excitability, initial RCTs demonstrated the antidepressant effect of HF rTMS applied to the left DLPFC (HFL-DLPFC); theoretically, this treatment ameliorates depressive symptoms by modulating abnormally low levels of left DLPFC activity (Avery et al., 2006; George et al., 2010). Besides, in recent years, LF rTMS applied to the right DLPFC (LFR-DLPFC) has also shown a similar anti-depressive effect through decreasing right-sided cortical activity. Mounting evidence indicates that HFL-DLPFC is as effective as LFR-DLPFC in the treatment of MDD (Isenberg et al., 2005; Pallanti et al., 2010; Rossini et al., 2010).

However, some confusion exists as to the optimal stimulation area to target as well as the best rTMS parameters to apply. In addition, factors other than therapeutic efficacy must be taken into account when selecting an rTMS method. For example, the most serious side effect of rTMS is seizure, and evidence suggests that LFR-DLPFC is less prone to seizure activity than HFL-DLPFC (Fitzgerald et al., 2003). To date, only a small number of RCTs have compared HFL-DLPFC to LFR-DLPFC and they have shown no significant differences between these two approaches. Consequently, this meta-analysis was conducted to investigate which modality produces greater antidepressant effects and fewer adverse side effects in the treatment of MDD.

2. Methods

2.1. Study selection

The first step of this meta-analysis was a selective article search. Scientific and medical databases, including international databases (PubMed, Cochrane Controlled Trials Register (CCTR), Web of Science and Embase), two Chinese databases (CBMdisc
and CNKI) and relevant websites dated up to March 2013, were searched for RCTs on rTMS in the treatment of MDD. The search terms used were 'depression', 'TMS' and 'transcranial magnetic stimulation'. In order to mitigate language bias, no language restriction was imposed. In order to avoid omitting relevant RCTs, conference summaries and reference documents listed in the articles were also researched.

Among the studies identified in the initial search, the following inclusion criteria were applied for subsequent analysis: (i) RCTs comparing HFL-DLPFC and LFR-DLPFC; (ii) MDD patients over 18 years of age; (iii) informed consent provided; and (iv) mood assessed by the Hamilton Depression Rating Scale (HDRS), the Montgomery–Åsberg Depression Rating Scale (MADRS) or the Clinical Global Impression (CGI) scale.

The following exclusion criteria were applied for subsequent analysis: (i) non-random allocation; (ii) subjects with 'narrow' or secondary depression diagnoses (e.g., post-partum depression, vascular depression); (iii) case reports and reviews; (iv) rTMS compared with sham or other treatment modalities; and (v) combined HF and LF rTMS in one side.

2.2. Outcome measures

The response rate was chosen as the primary outcome. Response was defined as at least a 50% reduction in the absolute HDRS or MADRS score from baseline or significant improvement in the CGI, at the conclusion of therapy (Hamilton, 1960; Montgomery, Asberg, 1979). If all three rating scales were used to evaluate the outcome, HDRS was preferentially selected. The dropout rate was chosen as the secondary outcome. These two outcome measures were the most consistently reported estimates of acute-phase treatment's efficacy and acceptability. The treatment 'end' point was preferentially viewed as the study 'end' point.

2.3. Data extraction

Two reviewers independently verified all potentially suitable RCTs by the aforementioned inclusion and exclusion criteria and assessed the quality of the identified RCTs and the completeness of data abstraction. Any disagreement as to study quality or data extraction was resolved by consensus and, if needed, a third reviewer was consulted. Data retrieved from the RCTs included the first author, year of publication, country of origin, study design, participant characteristics, therapy period and outcomes (response and dropout rates). For data that could not be directly retrieved, good faith efforts were applied to obtain the data by dispatching
e-mails to the author, researching other studies citing the RCT in question and researching associated conference summaries.

2.4. Statistical analysis

Dichotomous data were chosen for clinical reasons. In order to make the interpretation of results easier for clinicians (Guyatt et al., 1998), the response rate was used as an efficacy measure in lieu of the continuous symptom score. If baseline scores, standard deviations (SDs) and 'end' point means were provided instead of dichotomous efficacy outcomes, the number of responsive patients was estimated through a validated imputation method (Furukawa et al., 2005).

This meta-analysis was conducted according to the recommendations of Sacks et al. (Sacks et al., 1987). RevMan5.0 software (Cochrane Information Management System (IMS)) and STATA software 8.0 (Stata Corporation, College Station, TX, USA) were used to perform statistical analyses. The summary odds ratios (ORs) and 95% confidence intervals (CIs) were used as the effect parameters. The Mantel–Haenszel fixed-effects model was used to calculate the combined ORs for each outcome. For each analysis, heterogeneity was assessed using the chi-squared-based Q test and *I*-squared index (I^2) (Higgins et al., 2003). To perform a clinically sound analysis, a worst-case scenario analysis of dropouts was used, under the assumption that all such patients did not respond to treatment (Cipriani et al., 2009). Both inverted funnel plots and Egger's test were used to assess the potential presence of publication bias. All tests were two-sided with statistical significance set to a P value of <0.05 unless otherwise stated.

3. Results

3.1. Literature search

The initial Internet search yielded 657 potentially relevant RCTs. Among these, 321 RCTs were removed because the titles did not meet the inclusion and exclusion criteria; 287 additional RCTs were excluded by abstract review. A total of 40 additional RCTs were excluded after two reviewers independently read the full texts. Therefore, only eight RCTs met all inclusion and exclusion criteria. These eight RCTs contained 249 patients in the aggregate, composed of 123 HFL-DLPFC and 126 LFR-DLPFC patients. Only seven of the eight RCTs were used for pooled analysis, as there was one article unavailable in full text; despite good faith efforts, the full text of the RCT conducted by Isenberg (2005) (Fig. 1) was not recoverable. References from these RCTs were researched for possibly omitted RCTs. All screening steps were independently completed by two reviewers, and any disagreements were resolved by discussion.

3.2. Included RCTs: Main characteristics

Seven RCTs composed of 221 adult subjects (83% MDD and 17% bipolar depression (BD)) were included in the study (Eche et al., 2012; Fitzgerald et al., 2003; Fitzgerald et al., 2009; Fitzgerald et al., 2007; Higgins et al., 2003; Rossini et al., 2010; Stern et al., 2007). The mean time of rTMS treatment was 2.57 weeks (S.D. = 0.78). RTMS was used as an augmentation strategy for MDD in six of the seven RCTs, and all included subjects had some degree of