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Review article

An updated meta-analysis: Short-term therapeutic effects of repeated transcranial magnetic stimulation in treating obsessive-compulsive disorder

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ABSTRACT

Background: This study was conducted to evaluate the short-term therapeutic effects of using repeated transcranial magnetic stimulation (rTMS) to treat obsessive-compulsive disorder (OCD) and to examine potential influencing factors.

Method: We searched the PubMed, EMBASE, CENTRAL, Wanfang, CNKI, and Sinomed databases on September 18, 2016 and reviewed the references of previous meta-analyses. Sham-controlled, randomized clinical trials using rTMS to treat OCD were included. Hedge's g was calculated for the effect size. Subgroup analyses and univariate meta-regressions were conducted.

Results: Twenty studies with 791 patients were included. A large effect size (g=0.71; 95%CI, 0.55–0.87; P < 0.001) was found for the therapeutic effect. Targeting the supplementary motor area (SMA) (g=0.56; 95%CI, 0.12–1.01; P < 0.001), left dorsolateral prefrontal cortex (DLPFC) (g=0.47; 95%CI, 0.02–0.93; P=0.02), bilateral DLPFC (g=0.65; 95%CI, 0.38–0.92; P < 0.001) and right DLPFC (g=0.93; 95%CI, 0.70–1.15; P < 0.001), excluding the orbitofrontal cortex (OFC) (g=0.56; 95%CI, −0.05–1.18; P=0.07), showed significant improvements over sham treatments. Both low-frequency (g=0.73; 95%CI, 0.50–0.96; P < 0.001) and high-frequency (g=0.70; 95%CI, 0.51–0.89; P < 0.001) treatments were significantly better than sham treatments, with no significant differences between the effects of the two frequencies. The subgroup analyses indicated that patients who were non-treatment resistant, lacked concurrent major depressive disorder (MDD) and received threshold-intensity rTMS showed larger therapeutic effects than the corresponding subgroups. The subgroup analysis according to sham strategy showed that tilted coils yielded larger effects than sham coils. Meta-regression analyses revealed that none of the continuous variables were significantly associated with the therapeutic effects.

Limitations: Only short-term therapeutic effects were assessed in this study.

Conclusions: Based on this study, the short-term therapeutic effects of rTMS are superior to those of sham treatments. The site of stimulation, stimulation frequency and intensity and sham condition were identified as potential factors modulating short-term therapeutic effects. The findings of this study may inspire future research.

1. Introduction

Approximately 1–3% of the global population suffers from obsessive-compulsive disorder (OCD) (Horwath and Weissman, 2000). Pathological obsessions and compulsions can lead to significant distress and functional impairment. In addition, approximately 40–60% of OCD patients remain resistant to current first-line therapies (Pallanti and Quercioli, 2006).

Several randomized control trials using repeated transcranial magnetic stimulation (rTMS) to treat OCD have been published since 1997, but their results are inconclusive. The differences in results may be due to their use of different rTMS protocols or the inclusion of patients with different characteristics. Three meta-analyses evaluating the efficacy of rTMS for treating OCD have been conducted (Berlim et al., 2013; Ma and Shi, 2014; Trevizol et al., 2016). Berlim et al. (2013) included 10 RCTs with 282 subjects and identified a significant and medium effect size in favor of active rTMS (g=0.59), and the subgroup analyses in their study (which were only performed according to stimulation frequency and target) indicated that there was no significant difference in the high-frequency (HF) and dorsolateral

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prefrontal cortex (DLPFC) subgroups. A second meta-analysis (Ma and Shi, 2014) was limited to SSRI-resistant OCD patients and included 9 RCTs with 290 subjects. It found that rTMS can be an effective addition to SSRI therapy and subgroup analyses were conducted only for the weeks of rTMS treatment. In the third meta-analysis (Trevizol et al., 2016), 15 studies (n=483) were included, and a medium effect size (g=0.45) was found. The meta-regression identified no significant variables. Recently, several RCTs using rTMS to treat OCD have been published (Elbeh et al., 2016; Hawken et al., 2016; Pelissolo et al., 2016; Seo et al., 2016). Thus, it is necessary to perform an updated meta-analysis to explore other important factors which may be associated with the efficacy of rTMS for treating OCD.

Before conducting this meta-analysis, we made several assumptions. OCD symptoms are correlated with hyperactivity in the cortico-striato-thalamo-cortical circuits (Anticevic et al., 2014; Milad and Rauch, 2012), and we assumed that the inhibitory effect of LF stimulation would be more effective than the excitatory effect of HF stimulation (Speer et al., 2009). The DLPFC, which is connected to the striatum, the anterior cingulate cortex, and the thalamus (Barbas, 2000; Paus et al., 2001; Petrides and Pandya, 1999), is the most common target for rTMS. Stimulating the DLPFC can also affect connected areas, some of which are associated with OCD symptoms. Therefore, we assumed that stimulating the DLPFC could result in effective treatment.

2. Methods

This meta-analysis adhered to the Cochrane Handbook 5.1.0 (Higgins and Green, 2013). It followed a predetermined but unpublished protocol and was not registered.

2.1. Search strategy

We searched the CENTRAL, EMBASE, PubMed, Wanfang, China National Knowledge Internet (CNKI) and Sinomed databases on September 18, 2016, and we also reviewed the references in previous meta-analyses (Berlim et al., 2013; Ma and Shi, 2014; Trevizol et al., 2016). The keywords used in the literature search were as follows: “magnetic stimulation” or “rTMS” or “transcranial magnetic” and “obsessive” or “compulsive” or “OCD”. Our inclusion criteria were as follows: a) Participants: subjects who were diagnosed with OCD; b) Intervention: rTMS was performed as the intervention, and studies using single TMS were excluded; c) Comparison: active rTMS was compared with sham rTMS; d) Outcome: the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was used to evaluate the severity of symptoms; e) studies with a randomized, single-blind or double-blind design; f) articles that provided the statistical parameters necessary to calculate Hedge's g or articles written by authors who were willing to provide these parameters upon request; and g) published articles that were written in English or Chinese. Studies examining deep rTMS, priming rTMS, or theta-burst rTMS were not included in this study.

2.2. Data extraction

Three investigators extracted the following variables from the studies: a) participant characteristics (i.e., percentage of female subjects, mean age, presence of concurrent major depressive disorder (MDD), presence of treatment resistance, baseline score on the Y-BOCS, duration of illness, and onset of illness); b) rTMS parameters (i.e., stimulation frequency, targets, number of sessions, total pulses, total pulses per session (TPPS), weeks of treatment, stimulation intensity, trains per session, inter-train interval, duration of single trains, and sham strategy); and c) sample size, all-cause dropouts, and mean and standard deviations (SDs) of the post-intervention Y-BOCS scores (the first assessment after treatment) in both groups.

2.3. Data processing

This meta-analysis was conducted in Comprehensive Meta-Analysis (CMA version 2), and a random-effects model was used. To explore potential influencing factors (e.g., the clinical characteristics of subjects and rTMS parameters), subgroup analyses were conducted for categorical variables and a meta-regression was conducted for continuous variables. Hedge's g was computed for the post-intervention Y-BOCS scores to determine the effect size of the study. According to the Cochrane Handbook 5.1.0, effect sizes that are < 0.4, 0.4–0.7 and > 0.7 indicate small, moderate and large effects, respectively. The risk difference (RD) was computed for all-cause dropouts to evaluate the acceptability of treatment. Heterogeneity was evaluated using I^2 statistics (Cooper et al., 2009). Egger's tests (Egger et al., 1997) were performed to evaluate publication bias.

2.4. Risk of bias assessment

According to the Cochrane Handbook 5.1.0 (Higgins and Green, 2013), the risk of bias was assessed for six domains. Because it is impossible to blind the rTMS operator, a low risk of performance bias implied blinding the participants. We excluded studies in which the selection bias was evaluated as high risk.

3. Results

The literature search is described in Fig. 1 and resulted in 24 eligible studies (Alonso et al., 2001; Badawy et al., 2010; Cheng et al., 2013; Elbeh et al., 2016; Gomes et al., 2012; Haghighi et al., 2015; Han and Jiang, 2015; Hawken et al., 2016; Jahangard et al., 2016; Kang et al., 2009; Luo et al., 2015; Ma et al., 2014; Mansur et al., 2011; Mantovani et al., 2010; Nauczyciel et al., 2014; Pelissolo et al., 2016; Prasko et al., 2006; Ruffini et al., 2009; Sachdev et al., 2007; Sarkhel et al., 2010; Seo et al., 2016; Tang et al., 2010; Zhang et al., 2010; Zhang, 2016). Elbeh et al. (2016) included two intervention arms, and both were included, along with a shared sham group. We followed the suggestion of the Cochrane Handbook 5.1.0 (Higgins and Green, 2013) and divided the sample size of the sham group into approximately equal groups. Haghighi et al. (2015), Jahangard et al. (2016) and Nauczyciel et al. (2014) used a cross-over design, and thus, data from only the first phase were included to prevent carry-over effects. The main characteristics (e.g., participant characteristics, rTMS parameters) of those eligible studies are described in Table 1, and additional characteristics are available in Supplementary Table 1.

The bias risk assessment is described in Supplementary Table 2. A high risk of bias in randomization was found in Badawy et al. (2010) and Sarkhel et al. (2010). The baseline Y-BOCS scores differed significantly between the intervention and control groups in Gomes et al. (2012) and Prasko et al. (2006), and this difference may have led to systematic differences between groups. These studies were therefore excluded from the quantitative synthesis. Only 6 studies (Gomes et al., 2012; Hawken et al., 2016; Mantovani et al., 2010; Pelissolo et al., 2016; Sachdev et al., 2007; Tang et al., 2010) excluded subjects who had received rTMS in the past, and only 3 studies (Kang et al., 2009; Mansur et al., 2011; Sachdev et al., 2007) assessed the effectiveness of the blinding procedures they used.

3.1. Meta-analysis of OCD symptoms

In this study, Hedge's g was 0.71 (95%CI, 0.55–0.87; $P < 0.001$), with low heterogeneity (I^2=10%) (Fig. 2), and Egger's regression was non-significant (P=0.58). In addition, the funnel plot was approximately symmetrical (Supplementary Fig 1).