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Different frequency repetitive transcranial magnetic stimulation (rTMS) for posttraumatic stress disorder (PTSD): A systematic review and meta-analysis

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ABSTRACT

Posttraumatic stress disorder (PTSD) is a psychiatric disorder. Repetitive transcranial magnetic stimulation (rTMS) has been found to be effective for treating PTSD, but whether different frequencies have different effects remains controversial. We conducted this systematic review and meta-analysis to address this question. We searched the literature for studies written in English or Chinese in 9 electronic databases from the databases' inception to August 1, 2016. Additional articles were identified from the reference lists of identified studies and from personal reference collections. Eighteen articles were included, and 11 were suitable for the meta-analysis (Combined sample size was 377 (217 in active rTMS groups, 160 in sham-controlled groups)). Low-frequency (LF) rTMS resulted in a significant reduction in the PTSD total score and the depression score (1. PTSD total score: pooled SMD, 0.92; CI, 0.11−1.72; 2. Depression: pooled SMD, 0.54; CI, 0.08−1.00). High-frequency (HF) rTMS showed the following results: 1. PTSD total score: pooled SMD, 3.24; CI, 2.24−4.25; 2. re-experiencing: pooled SMD, −1.77; CI, −2.49-(-1.04); 3. Avoidance: pooled SMD, −1.57; CI, −2.50-(-0.84); 4. hyperarousal: pooled SMD, −1.32; CI, −2.17-(-0.47); 5. depression: pooled SMD, 1.92; CI, 0.80−3.03; and 6. Anxiety: pooled SMD, 2.67; CI, 1.82−3.52. Therefore, both HF and LF rTMS can alleviate PTSD symptoms. Although the evidence is extremely limited, LF rTMS can reduce overall PTSD and depression symptoms. HF rTMS can improve the main and related symptoms of PTSD. However, additional research is needed to substantiate these findings.

1. Introduction

Posttraumatic stress disorder (PTSD) is a chronic psychiatric disorder that commonly occurs among trauma survivors. In recent years, researchers have started to recognize the characteristics of this complicated mental disorder. According to Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), PTSD is characterized by three main symptom clusters: re-experiencing, avoidance and hyperarousal (APA, 1994). In the United States, PTSD has a 12-month prevalence of 3.5% and a lifetime prevalence of 7% (Kessler et al., 2005a, 2005b, 1995). For the affected person's family, PTSD is a huge economic burden (Thomas et al., 2010).

In two-thirds of patients, PTSD symptoms can be alleviated with commonly used treatment methods (APA, 2004; D. G. Baker et al., 2009; Cloitre M., 2009; Kessler et al., 1995; Institute of Medicine Committee on the Treatment of Posttraumatic Stress Institute of Medicine Committee on Treatment of Posttraumatic Stress Disorder, 2007). However, the symptoms of the remaining one-third of patients are very difficult to treat (Bisson and Andrew, 2007; Kessler et al., 1995; Stein et al., 2006).

Repetitive transcranial magnetic stimulation (rTMS) is a new, noninvasive technique that alters brain activity through repeated changes of the coil's magnetic field. This modulation effect can

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reach both the cortex and subcortical areas, and depending on the frequency, rTMS can either decrease (low-frequency [LF], ≤ 1 Hz) or increase (high-frequency [HF], >1 Hz) cortical excitability (George and Post, 2011; Rosa and Lisanby, 2012).

As early as 1998, Grisaru et al. and McCann et al. investigated the use of rTMS or TMS in PTSD patients (Grisaru et al., 1998; McCann et al., 1998). In 2014, Karsen et al. conducted the first systematic review and meta-analysis on this topic. In addition, as of 2016, three more systematic reviews had been published. All of them suggested that rTMS might be an effective treatment for PTSD. However, whether different frequencies might have different effects is still under debate (Berlim and Van den Eynde, 2014; Clark et al., 2015; Karsen et al., 2014; Trevizol et al., 2016).

We explored this question by examining the previously published articles. In the two preliminary studies published in 1998, TMS with LF stimulation (0.3 Hz−1 Hz) was shown to be effective for treating PTSD patients (Grisaru et al., 1998; McCann et al., 1998), and according to functional neuroimaging research, PTSD patients show increased oxygen perfusion in the right prefrontal cortex (Rauch et al., 1996). This abnormal increase in the activation of the right prefrontal cortex may be the cause of PTSD symptoms related to hyperarousal and anxiety (Simmons et al., 2004). LF rTMS has been shown to decrease cortical excitability; by applying 1-Hz rTMS to the right dorsolateral prefrontal cortex (DLPFC) or the right frontal cortex, Osuch et al. and Tillman et al. found that hyperarousal symptoms could be improved (Osuch et al., 2009; Tillman et al., 2011). However, in other studies, the use of HF rTMS (5 Hz, 10 Hz or 20 Hz) also significantly alleviated core PTSD symptoms, such as re-experiencing and avoidance (Bie and Wang, 2011; Cohen et al., 2004; Isserles et al., 2013). One possible explanation of the effects of HF rTMS is that it might activate the hypoactivated medial prefrontal cortex (mPFC), which is one part of PTSD patients' impaired stress-induced fear circuitry (Shin and Handwerger, 2009).

Based on the findings above, we observed that HF and LF rTMS have both achieved some success in treating PTSD. The effects of HF and LF rTMS may be moderated by other characteristics of the stimuli, such as the site, total number of stimulation pulses, and research design. Accordingly, we conducted this systematic review and meta-analysis to explore the effects of different frequencies in a more quantified manner.

2. Materials and methods

2.1. Search strategy

The review was conducted according to the Cochrane handbook, version 5.3. We searched the English and Chinese literature for articles published in 9 electronic databases (English databases: Pubmed, The Cochrane Library, EMBASE, Psychinfo, ISI Web of Knowledge; Chinese databases: the Chinese Biomedical Literature Database (CBM), the Chinese National Knowledge Infrastructure (CNKI), Weipu, WanFang) from their inception dates to August 1, 2016. The search terms included medical subject headings (MeSH), text keywords and their combinations (such as "transcranial magnetic stimulation," "TMS," "posttraumatic stress disorder," "posttraumatic," "post traumatic" or "stress"). Additional articles were identified from the reference lists of identified studies and from personal reference collections. For the entire search strategy, please refer to Supplementary Fig. 1. A total of 541 articles were found; after we examined the titles, abstracts and full-texts, 18 studies remained.

2.2. Selection criteria

The inclusion criteria were as follows: (a) subjects must be aged between 18 and 75 years and have a diagnosis of PTSD according to the DSM-IV (APA, 1994) or other qualified mental disorder classification criteria; (b) any research design could be used if the study's aim was to investigate TMS (or rTMS) treatment for PTSD symptoms. The exclusion criterion was that TMS (or rTMS) was not used as a treatment method for PTSD patients.

2.3. Data extraction

YTT and XQL independently extracted the data from the included studies. ZZ checked the extraction results. The extracted data included the following items: sample characteristics, psychiatric comorbidity, drug treatment, psychological treatments, stimulators, rTMS protocol and treatment outcomes. Based on the criteria from the Cochrane handbook (version 5.3), ZK and WLJ independently appraised the quality of the included studies. The quality appraisal was performed according to the criteria listed in the Review Manager Handbook, and the results are listed in Supplementary Fig. 2. When the evaluations of the first two reviewers differed, YTT was included in the discussions until a final consensus had been achieved (Supplementary Tables 1–3).

2.4. Data analysis

We used RevMan software (version 5.3) to calculate the standard mean difference and confidence intervals [CI]. We tested the effects of rTMS treatment on changes in total PTSD symptoms, the three core symptom clusters and symptoms related to PTSD (depression and anxiety). We also separately calculated the treatment effects of HF and LF rTMS.

To estimate heterogeneity, we performed the I^2 test (25%, 50% and 75% represented low, medium and high heterogeneity, respectively) (Higgins et al., 2003). Based on the heterogeneity test, we used a fixed-effects model for the groups that had no significant heterogeneity and a random-effects model for the significantly heterogeneous groups. Funnel plots generated using the trim-and-fill method were used to test for publication bias (W. L. Baker et al., 2009; Duval, S. and Tweedie, R., 2000).

3. Results

3.1. Main characteristics of the included studies

Overall, 18 studies were included in this systematic review and meta-analysis: After excluding dropouts, the combined sample consisted of 377 subjects (217 in active rTMS groups, 160 in sham-controlled groups). The total number of female participants was 195. Three of the eighteen studies included only male subjects (Oznur et al., 2014; Rosenberg et al., 2002; Tillman et al., 2011). In three of the studies, more than half of the participants had been exposed to combat (Isserles et al. 15/26, Rosenberg et al. 12/12, and Oznur et al. 20/0) (Supplementary Tables 1–4).

Regarding psychiatric comorbidity, four studies reported the exact percentage of comorbidity within their samples. The most prevalent comorbidity was major depressive disorder (MDD) and PTSD, which occurred in approximately 70% (Watts et al., 2012) to 100% (McCann et al., 1998; Osuch et al., 2009; Rosenberg et al., 2002) of the included subjects. In most of the studies, rTMS was an augmentative treatment; that is, the previously used drug and/or psychological intervention was not stopped or changed during the 3 weeks before the study or during the study (Boggio et al., 2010; Cohen et al., 2004; Grisaru et al., 1998; Huang and Wang,