A Systematic Review of the Efficacy of Repetitive Transcranial Magnetic Stimulation as Treatment for Posttraumatic Stress Disorder

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Repetitive transcranial magnetic stimulation (rTMS) is an alternative treatment option for drug-resistant mental illnesses, such as Major Depressive Disorder (MDD). More recent clinical trials have investigated whether rTMS can also be used in the treatment of Posttraumatic Stress Disorder (PTSD). To synthesize current evidence on the use of rTMS to treat PTSD, a qualitative systematic review was carried out. This review focused on clinical trials that featured both a comparison group and distinct scales to separate PTSD symptoms from any comorbid illnesses. Presently, rTMS seems to be a relatively safe treatment for PTSD, however, it is likely no more effective than current treatments. Additionally, missing clinical trial data casts doubt on whether the present literature is representative of the true effect of rTMS on PTSD. Based on these conclusions, rTMS does not seem a suitable replacement for more popular treatments. However, rTMS is a relatively affordable and noninvasive treatment option, and may be worth continued investigation as an option for those with drug-resistant PTSD, in particular.

Abbreviations: rTMS – repetitive transcranial magnetic stimulation; PTSD – posttraumatic stress disorder; TMS – transcranial magnetic stimulation; DTMS – deep transcranial magnetic stimulation; MDD – major depressive disorder; DLPFC – dorsolateral prefrontal cortex

Keywords: rTMS; PTSD; trauma; treatment efficacy; mental illness; novel treatments

Introduction

Posttraumatic stress disorder (PTSD) is a debilitating mental illness caused by a range of traumatic experiences, such as military combat, sexual assault, and personal injury. Symptoms include, but are not limited to, flashbacks, intrusive thoughts, sleep problems, and hyperarousal, all of which can have a negative impact on an individual’s day-to-day quality of life (Boggio et al., 2010). For many people, PTSD can drastically impede their social lives and careers.

Due to the number of similar symptoms exhibited across both depression and PTSD, antidepressant drugs are the most common medication used to treat PTSD (Hamner et al., 2004). Other drugs have been tested, including anxiolytics, mood stabilizers, and even some atypical antipsychotics. Aside from drug treatment, patients may undergo different therapies, such as exposure therapy, stress inoculation, or cognitive-behavioral therapy. Most often, the treatment regimen for PTSD features multiple approaches simultaneously, which may entail patients taking medication in conjunction with therapy, or taking multiple medications at once. Despite this, some patients fail to respond well to the present treatment options (Hamner et al., 2004).

Because current treatments are not always effective, alternative treatments are being sought out. One newer approach that has been examined for individuals who have not responded to traditional treatments for PTSD is the use of repetitive transcranial magnetic stimulation (rTMS), a treatment that uses strong
magnets to alter brain activity in a noninvasive manner.

In the application of rTMS, an electromagnetic coil is placed against the head of the patient. Specific regions of the brain can be targeted based on the location of the coil, which is set to either excite or inhibit neurons in the target area (Watts et al., 2012). Past research has found rTMS to be a promising treatment for disorders such as Major Depressive Disorder (MDD), especially in patients who fail to respond to traditional treatment (Simpson et al., 2009). As rTMS provides benefits for those suffering from depression, more recent studies have extended its use to examine the utility of rTMS as a treatment for PTSD.

In previous studies, over-activation of the right hemisphere has been cited as a possible factor in PTSD. The right hemisphere is associated with anxiety and negative emotions, which are common in patients with PTSD (Cohen et al., 2004; Osuch et al., 2009; Rosenberg et al., 2002). If a brain region associated with negative emotions is overactive, rTMS may be used to lessen the activity, and thus lessen negative emotions. Most studies testing rTMS on patients with PTSD focus on inhibiting right hemisphere activity, but this is not exclusively the case.

Another possibility that has been explored is rTMS activation of the left hemisphere. This has generally been used in the treatment of Major Depressive Disorder (MDD) due to the mood-elevating effects of increased left hemisphere activation (Watts et al., 2012). Although changes in left hemisphere functioning have not been cited in PTSD literature, activation of brain regions associated with positive emotions may serve as a treatment for PTSD. Based on this line of reasoning, a few clinical trials have examined rTMS of both sides of the brain in treatment of PTSD.

Since the use of rTMS is relatively new as a possible treatment of PTSD, investigation into the effectiveness of treatment is necessary. An exploratory meta-analysis undertaken in 2014 examined the use of rTMS on the right hemisphere, specifically in the dorsolateral prefrontal cortex (DLPFC), a brain region that has been associated with processes believed to be involved in PTSD (Berlim and Van den Eynde, 2014). The analysis found that rTMS applied to the right DLPFC improved PTSD symptoms across three studies examined (Boggio et al., 2010; Cohen et al., 2004; Watts et al., 2012; as cited in Berlim and Van den Eynde, 2014).

Although exacting in its quantitative approach, the prior meta-analysis was somewhat limited in its examination of the literature. In order to generate a group of studies sufficiently homogeneous as to be appropriate for meta-analysis, Berlim and Van den Eynde (2014) applied stringent selection criteria, excluding studies that could offer insight into the use of this new treatment option. In particular, the effectiveness of rTMS was not examined for any brain region other than the right DLPFC.

As this is a relatively new treatment, it seems unlikely that sufficient research has been done to prove that the right DLPFC is the only brain region worth targeting. In the more common use of rTMS for treatment of MDD, left hemisphere rTMS has proven effective for reasons of antidepressant effects (Watts et al., 2012). As antidepressants are one of the most common forms of PTSD treatment, it is too soon to discount the possibility that a treatment for MDD could work for PTSD. Therefore, it seems important to include studies in which left hemisphere rTMS was administered, in the hopes of forming a meaningful comparison.

Additionally, the prior meta-analysis did not include clinical trials that lacked a sham group, which excluded case studies and studies with a comparison group that did not receive sham stimulation. Although case studies were excluded from the present review, differences in treatment effect for low- and higher-frequency rTMS have been suggested in the literature (Watts et al., 2012). This justified the inclusion of a study that compared the two and did not include a sham group (Rosenberg et al., 2002).

Although the present collection of studies is not suitable for meta-analysis, due to differences in design, qualitative examination remains a useful possibility. The goal of this review was to conduct a broader and qualitative review of clinical trials and determine whether the current literature suggests that rTMS should continue to be pursued as a beneficial treatment.
for PTSD symptoms. In total, six studies were examined, including a total of 121 participants.

Materials and Methods

Search Methods

Studies were gathered from PubMed, PsycINFO, EBSCOhost, and Google Scholar. Keywords for searching included rTMS and TMS, as well as both “posttraumatic stress disorder” and PTSD. The vast number of studies found were screened to exclude any studies not related specifically to rTMS treatment for PTSD. Ten papers were identified which included both placebo-controlled clinical trials and case studies.

Selection Criteria

In order to examine the effect of rTMS on PTSD clearly, any trial without a comparison group was excluded from further review, as it was felt that no effect could be accurately detected without an alternate treatment group. This excluded one case study and two clinical trials in which all participants received the same treatment. In the previous meta-analysis of the literature, only sham-controlled groups were included in analysis (Berlim and Van den Eynde, 2014). The present review also included one study comparing low frequency with high frequency rTMS (Rosenberg et al., 2002). Studies examining PTSD with comorbid disorders were included, provided that separate measures made it possible to distinguish PTSD from comorbid disorders; one study examined PTSD and MDD (Rosenberg et al., 2002). Finally, one study was excluded due to using a different form of TMS referred to as Deep Transcranial Magnetic Stimulation (DTMS); this was considered distinct enough from rTMS to be excluded due to the differences in brain regions reachable by DTMS vs rTMS. The present review focuses on the six studies that met all criteria, selected from ten clinical trials identified during the initial screen (see Table 1).

Study Characteristics

Each trial consisted of at least two groups, typically a control group and an experimental group. In all but one study, a sham condition was used for the comparison group, during which participants would receive sham rTMS. Sham conditions varied across studies, with some using an imitation coil (Boggio et al., 2010; Watts et al, 2012), and others using the real rTMS coil, but held at an angle away from the head so it would have no effect (Cohen et al., 2004; Nam et al., 2013; Osuch et al., 2009). One study lacked a sham group, and instead compared low-frequency and higher frequency rTMS (Rosenberg et al., 2002).

Participants covered a large range of ages. Across all studies, the youngest was 22 years old and the eldest was 75 (Nam et al., 2013; Rosenberg et al., 2002). Additionally, causes of PTSD were diverse, encompassing military combat, traffic accidents, sexual assault, and other forms of trauma (Watts et al., 2012; Nam et al., 2013; Boggio et al., 2010). Two studies focused on participants with treatment-resistant PTSD (Osuch et al., 2009; Rosenberg et al., 2002). Most studies lasted ten days, with one session of rTMS or sham treatment administered each day (Boggio et al., 2010; Cohen et al., 2004; Rosenberg et al., 2002; Watts et al., 2012).

Prior to the beginning of treatment, all participants were tested to determine the lowest magnetic power at which stimulation was still able to affect their brain. This was performed by testing the rTMS coil on a known location in the brain that contracted a muscle unrelated to the treatment for PTSD; the lowest magnetic power at which the muscle was affected set the level at which later stimulation would occur (Nam et al., 2013). Once the necessary strength of the coil was determined, the actual study would begin. Participants were blinded to whether they received real or sham rTMS.

In most sessions across studies, participants received rTMS treatment to the specific brain region of interest for a total of 20 minutes, though the region of focus varied across studies. Depending on the study, participants received different frequencies of rTMS. Cohen et al. (2004) and Rosenberg et al. (2002) both compared low frequency 1Hz rTMS
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with higher frequency rTMS (10Hz and 5Hz, respectively). Low-frequency rTMS in this review consists of trials using 1Hz rTMS, while high-frequency ranges from 5Hz to 20Hz. This distinction was included in the present review due to previous researchers suggesting a possible discrepancy between the effectiveness of low- and higher-frequency rTMS (Watts et al., 2012).

To determine the effectiveness of the treatment, tests measuring PTSD symptoms, as well as depression, anxiety, and other commonly overlapping mental illnesses, were completed by participants (Osuch et al., 2009). The measures were completed at the beginning and end of each study, and most studies also had a post-treatment follow-up of the same measures, to determine whether the effects of rTMS on PTSD had any longevity (Boggio et al., 2010; Cohen et al., 2004; Nam et al., 2013; Rosenberg et al., 2002; Watts et al., 2012).

### Results

#### Effects of Left Hemisphere rTMS

Only two studies within the present review used left side rTMS in the treatment of PTSD. Boggio et al. (2010) compared rTMS in both hemispheres and found symptom improvements for both right ($p = .0039$) and left rTMS ($p = .0042$) over sham treatment. They reported that improvements for left side rTMS were smaller than right rTMS, which was statistically significant on one outcome scale ($p = .03$, PTSD Checklist), but marginally significant for another ($p = .051$, Treatment Outcome PTSD Scale).

Rosenberg et al. (2002) found a small improvement in PTSD with left rTMS over baseline PTSD scores ($p \leq .02$ on all scales). They reported that left rTMS was most effective against depressive symptoms of PTSD, and not trauma-related symptoms. No comparison was made between left and right rTMS.

#### Effects of Right Hemisphere rTMS

As right rTMS has been more explicitly linked to PTSD treatment, greater improvements were anticipated. Three studies reported moderate, statistically significant improvements in PTSD symptoms (Boggio et al., 2010; Nam et al., 2013; Watts et al., 2012). The remaining two studies on right rTMS found different results, detailed below.

Cohen et al. (2004) tested both high- and low-frequency rTMS on the right hemisphere to determine if different stimulation patterns led to different outcomes. Across multiple scales, they reported no difference in PTSD improvement between the sham group and the low-frequency rTMS group, but found multiple statistically significant improvements for high-frequency over both sham and low-frequency rTMS. This seems counterintuitive, as two other studies using the same frequency that Cohen et al. (2004) used as their low-frequency condition reported moderate improvement in PTSD symptoms (Nam et al., 2013; Watts et al., 2012). There is no reasoning indicated by Cohen et al. (2004) to explain the lack of change in PTSD symptoms in the low-frequency group.

### Table 1. Summary of studies.

<table>
<thead>
<tr>
<th>Citation</th>
<th>Conditions</th>
<th>N&lt;sub&gt;total&lt;/sub&gt;</th>
<th>Hemisphere</th>
<th>Duration</th>
<th>Treatment Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boggio et al., 2010</td>
<td>20Hz right, left, sham</td>
<td>30</td>
<td>right vs left</td>
<td>10 days</td>
<td>medium*</td>
</tr>
<tr>
<td>Cohen et al., 2004</td>
<td>1Hz, 10Hz, sham</td>
<td>29</td>
<td>right</td>
<td>10 days</td>
<td>medium (10Hz)*, none (1Hz)</td>
</tr>
<tr>
<td>Nam et al., 2013</td>
<td>1Hz right, sham</td>
<td>18</td>
<td>right</td>
<td>15 days</td>
<td>medium*</td>
</tr>
<tr>
<td>Osuch et al., 2009</td>
<td>1Hz right, sham</td>
<td>9</td>
<td>right</td>
<td>40 sessions&lt;sup&gt;a&lt;/sup&gt;</td>
<td>small</td>
</tr>
<tr>
<td>Rosenberg et al., 2002</td>
<td>1Hz, 5Hz</td>
<td>15</td>
<td>left</td>
<td>10 days</td>
<td>small*</td>
</tr>
<tr>
<td>Watts et al, 2012</td>
<td>1Hz, sham</td>
<td>20</td>
<td>right</td>
<td>10 days</td>
<td>medium*</td>
</tr>
</tbody>
</table>

*Treatment effect was statistically significant in one subscale or more.

<sup>a</sup>Treatments in this study were administered over two, three-week courses, based on patient needs rather than a set schedule. As a result, the duration was variable, although all patients experienced the same number of sessions.
Osuch et al. (2009) found only a marginally significant improvement of PTSD symptoms, specifically in the hyperarousal subscale ($p = .08$). Notably, this finding occurred in the only within-subjects design so far reported. Participants received either sham or real rTMS treatment for three weeks, before a break of at least two weeks in between. This was followed by three weeks of the opposite condition. The modest effects could be due to two sources. First, it is possible that the better control afforded by within-subjects designs found a more accurate representation of effectiveness. Alternatively, initial treatment may have produced lasting benefits, serving to mask a larger effect of treatment.

Additionally, right rTMS seems to have a stronger effect on particular types of PTSD symptoms than left rTMS. PTSD is divided into subsets of symptoms, such as hyperarousal symptoms (e.g., difficulty sleeping), avoidance symptoms (e.g., avoiding crowds), and re-experiencing symptoms (e.g., flashbacks; Symptoms of PTSD, 2015). These symptom subsets appear differentially affected by rTMS treatment in different trials. Boggio et al. (2010) found greater improvements in specifically hyperarousal and avoidance symptoms of PTSD. Such et al. (2009) found a marginally significant effect of rTMS treatment only on hyperarousal symptoms ($p = .08$). In contrast, Nam et al. (2013) reported statistically significant improvements in re-experiencing symptoms, but not in hyperarousal symptoms ($p = .273$), while avoidance symptoms were only marginally significant ($p = .055$). The variation in symptom improvement suggests a possible inconsistency of effect, an inconsistency of rTMS application, or sampling error.

**Longevity of rTMS Treatment**

Because rTMS as a clinical treatment would need to have a lasting effect on patients with PTSD, most studies completed a follow-up to determine if symptoms continued to be reduced after rTMS treatment was over. Follow-ups ranged between 14 and 94 days after the end of treatment, with most studies reporting that improvements were long-lasting (Boggio et al., 2010; Cohen et al., 2004; Nam et al., 2013; Rosenberg et al., 2002). Watts et al. (2012) reported that PTSD symptoms had gotten slightly worse again two months post-treatment, although the symptoms were still reduced compared to baseline measurements ($p = .001$). Maintenance of rTMS may be necessary to maintain maximum effectiveness, but some effectiveness seems to remain even without follow-up treatment.

**Side Effects**

The most common side-effects were headaches and dizziness. More unusual side-effects ranged from one participant experiencing a sudden bout of rage, to extreme cluster headaches following treatment (Cohen et al., 2004; Rosenberg et al., 2002). No side-effects reported were worse than the above, and side-effects were relatively rare in general. In one example study, side-effects occurred less than 10% of the time, with participants reporting side-effects after just 21 out of 250 treatment sessions (across all participants; Cohen et al., 2004).

Side-effects were reported in real rTMS groups, and frequently also in sham groups as well. Sham rTMS was carried out in one of two ways, either with an imitation coil or by positioning a real coil so it would not have an effect. Holding a real coil, even incorrectly, still produced some stimulation in locations other than the target of real rTMS, and may have resulted in side-effects as a result (Osuch et al., 2009).

Exclusions were generally made on the basis of brain trauma, seizure conditions, or other illnesses that may have made rTMS unsafe for participants (Boggio et al., 2010; Cohen et al., 2004; Nam et al., 2013; Rosenberg et al., 2002; Watts et al., 2012). Therefore, any side-effects were not likely due to exacerbation of preexisting problems. The safety of rTMS for any individuals with conditions that fit the exclusion criteria is unknown, and may be unsafe.

**Overall Results**

The treatment appears to have a moderate effect. Compared to sham groups, patients receiving rTMS experienced a 20-40% decrease in number and severity of symptoms.
Patients reported reduction of sleep disturbance, re-experiencing symptoms, and hyperarousal (Rosenberg et al., 2002; Nam et al., 2013). In all trials, participants maintained any medication or therapy they were presently receiving, which may have artificially enhanced rTMS effectiveness. However, use of rTMS activation of the right hemisphere does seem to help patients with PTSD, and has been reported as a fairly long-lived effect, sometimes lasting at least three months after treatment has ended (Boggio et al., 2010).

**Discussion**

In light of what information is available, rTMS does seem like a possible treatment option. Because side-effects are minor, the use of rTMS in the treatment of a drug-resistant patient represents a safe alternative, even if success is not guaranteed. When weighing the effectiveness of rTMS on PTSD, it is important to note that the present data available is incomplete, and of a fairly small sample size. For example, only 22 people received left hemisphere stimulation across two studies, and this number may be too small to detect differences in PTSD improvement due to the side of stimulation. A larger data set exists for evaluating right side rTMS, but still only 54 total participants received right hemisphere stimulation, across five studies.

As the overall sample size remains small, it may be possible that the effectiveness of rTMS is not accurately reflected in the small sample reported across the literature. Given the inconsistent pattern of symptom improvements reported, it may even be possible that the benefits of rTMS on PTSD are a result of sampling error, magnified by publication bias. During the process of searching for studies, a possible case of publication bias was identified, which may impact decision-making with regards to the usefulness of rTMS for PTSD treatment.

In an effort to assess the presence of publication bias in the literature, trials were searched on ClinicalTrials.gov. Some trials reported on ClinicalTrials.gov could be traced to their finished manuscripts, but three studies registered as complete on ClinicalTrials.gov remain unreported in any journals. One of these has remained unreported since 2000, and the other two since 2012 and 2013 (Beersheva Mental Health Center (NCT01196624), National Institute of Mental Health (NCT00001657), Queen’s University (NCT00685152)). Search techniques to uncover data from the trials included seeking out contact information for corresponding authors and scouring search engines using key terms such as author names and clinical trial titles. For the oldest of the three trials, no contact information was supplied, and a thorough search did not turn up any data (National Institute of Mental Health).

Corresponding author information was available for the second clinical trial, which took place at Queen’s University, and the author was contacted for information. This trial, although listed as complete on ClinicalTrials.gov, was abandoned due to issues with comorbidities, and poor recruitment of participants (M. Roumen, personal communication, April 16, 2016).

The final study was started in Israel, and no author information could be located on any websites in the English language (Beersheva Mental Health Center). However, a careful search located a summary of the clinical trial as it had been presented at a conference. In this summary, the clinical trial was not yet completed, and had only recruited seven participants of a desired 40 (Levine et al., 2010). Although there is no further information on this trial, given the reason that the other trial was discontinued, it may be possible that Levine and colleagues were unable to locate enough participants to complete the trial with their desired number.

Since two of the missing trials remain unexplained, their lack of reporting may be indicative of either an inability to recruit participants, or a contrary result that they did not wish to publish. Unfortunately, it may also be possible that more trials remain unreported. Registration of clinical trials is not yet universal, and clinical trials have a higher chance of remaining unreported if they are not pre-registered and subjected to mandated reporting periods (Prayle et al., 2012). While we are certain that three clinical trials were never reported, the actual number may be higher.
Also important to note is that no clinical trials listed any conflicts of interest or the absence of such. It seems unlikely that the researchers were biased, given that the field has little research, and financial incentive would be comparatively rare relative to drug testing. Still, caution is necessary when considering the data. If any of the researchers are involved in an industry that would benefit from increased popularity of rTMS, bias may be present.

If an effect does exist, treatment with rTMS seems to produce mostly moderate improvements. It is not a cure for PTSD, although it may produce a beneficial reduction in symptoms. As rTMS was found to have few side-effects across studies, it may prove a beneficial avenue for those with treatment-resistant PTSD who are seeking alternative options. However, given that there is no proof of the effectiveness of the treatment, it should not be undertaken in the absence of other treatment attempts. Note that patients even within prior studies continued any drug treatments or therapy throughout the course of rTMS treatment. The treatment should be considered only as an additional option for those who are unable to receive relief from common treatment methods.

Presently, there is no way to be confident that rTMS is an effective treatment. Since rTMS does not represent a cure for PTSD, and treatment effects may be limited, the cost-effectiveness of rTMS treatment must be taken into account when considering its applications. As rTMS for PTSD is new, cost-effectiveness has not been examined yet, but research has found that rTMS is an affordable option for treating depression, as compared to electroconvulsive therapy (McLoughlin et al., 2007). Furthermore, compared to drug treatment, rTMS is particularly useful in cases of treatment-resistant depression (Simpson et al., 2009). Given that rTMS is an affordable treatment for difficult cases of depression, it may be a viable option for symptom management in treatment-resistant PTSD, even in light of the present uncertainty.

To determine the effectiveness of rTMS on PTSD more thoroughly, more clinical trials would be needed to assess if any pattern of stronger improvement exists. Results from clinical trials have been inconsistent, which may suggest discontinuing trials, however the treatment of PTSD is full of inconsistencies, even in the most commonly used approaches. Currently, there is no treatment for PTSD that is universally effective (Hamner et al., 2004). For patients with treatment-resistant PTSD, the use of rTMS may represent symptom relief that is not possible with present methods of treatment. Additionally, present treatments for PTSD often overlap with MDD treatments, and rTMS has already been established as an option for treatment-resistant MDD (Simpson et al., 2009). Finally, rTMS is relatively safe, with few side-effects reported across the trials, and nothing serious or life-threatening. The risk of harm from continued investigation is low, and outweighed by the possible benefits for those who have been suffering from PTSD and have been thus far unable to find relief.

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