Transcranial magnetic stimulation in depression – Lessons from the multicentre trials


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Abstract. Looking at novelties and advances in medicine in particular in the treatment of major depressive disorder no principally new antidepressant treatment strategy has been implanted in clinical routine in the last fifty years. However, regarding the considerable issue of treatment resistance in depression, new therapeutic strategies are urgently required. In this context, repetitive transcranial magnetic stimulation above the dorsolateral prefrontal cortex has been proposed as a potential new treatment option for depression; furthermore, in October 2008 a first rTMS-device (NeuroStar TMS Therapy SystemTM) has been recently approved by the FDA for the treatment of treatment resistant major refractory depression in adults. Yet, despite now nearly two decades of research in this field, no final answer concerning its validity for antidepressant treatment in the clinical practice is given. Numerous studies with small sample sizes and heterogeneous designs have been performed in this field yielding to different results. These were subjected to meta-analyses, assessing the antidepressant effect of rTMS, which are briefly summarized in this article. Further, multicentre-trials with larger amounts of patients were performed, which are presented and critically discussed here in more detail. This short review shall thus provide an overview of the current status of knowledge concerning rTMS in depression and it also provides some recommendations for future research in this field.

Keywords: Depression, Repetitive transcranial magnetic stimulation, meta-analysis, antidepressant treatment trial

1. Introduction

Antidepressant rTMS

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that was developed by Anthony Barker and colleagues in Sheffield, UK about 25 years ago (Barker et al., 1985). It was then rapidly introduced as diagnostic tool in clinical neurology (Barker et al., 1986; Eisen and Shtybel, 1990; Hess et al., 1986). Technical advances in the field of electronics in subsequent years made repetitive transcranial magnetic stimulation (rTMS) up to 100 Hz frequency possible. Basic research on motor cortex showed that extended rTMS protocols were able to induce changes in cortical excitability that lasted from minutes to hours. The modulatory properties of rTMS (excitatory or inhibitory effects), so called after-effects, depend principally on the frequency and intensity used and probably corresponded to long-term potentiation (LTP)- and long-term depression (LTD)-like mechanisms, and were thought to be able to change cortical activation of stimulated networks. These neuro-modulatory effects are nowadays still not completely understood and appear to depend also on factors that deal with the type of magnetic coil used, pulse waveform, current direction, orientation and position of the coil over the scalp, train length, intertrain interval, total number of magnetic pulses delivered in the stimulation session, and the basal cortical activation state of the stimulated area (Siebner et al., 2004). In the last
eighteen years, rTMS has been used in psychiatry and neurology to explore pathophysiological aspects and neurobiological dynamics of mental processes and to modulate neuronal activity in intracortical circuitry in order to treat brain disorders.

Since the introduction of rTMS in 1993 in the experimental treatment of major depression (Höflich et al., 1993) more than 100 studies have been published, using various stimulation parameters and designs, and yielding heterogeneous results with regard to the therapeutic outcome of the method. Several neuroimaging studies using positron emission tomography (PET), single photon emission tomography (SPECT) and functional magnetic resonance imaging (fMRI) reported activation changes in medial and dorsolateral regions of the prefrontal cortex (M-, DLPFC) in depressed patients as pathophysiological correlate to the depressive state (Drevets, 2001; Leppanen, 2006), that normalized after symptom recovery, independently of the therapeutic strategy used (Drevets, 2001; Fales et al., 2008; Grimm et al., 2008; Leppanen, 2006; Vasic et al., 2008). Thus, the therapeutic efficacy of rTMS might result from two mechanisms, either restoring a normal processing or interfering with an aberrant processing in functionally altered brain regions. In the last fifteen years the DLPFC has been defined as the candidate target region for rTMS in the treatment of depression and is still the focus of the antidepressant rTMS trials, however, without systematically testing other relevant candidate cortex regions such as the medial prefrontal cortex (MPFC).

Considering these issues, the aim of the antidepressant rTMS was suggested to “normalize” the activity of the DLPFC by means of high-frequency (excitatory) rTMS of the left hemisphere, or to reduce the activity of the right DLPFC by means of low-frequency (inhibitory) rTMS in order to restore, for instance, the interhemispheric balance of DLPFC activity or to override (or compensate) dysfunctional local activation. The site of stimulation for antidepressant rTMS when trying to reach the DLPFC was earlier defined on the assumption that this brain region is situated 5cm anterior to M1_Hand and (Pascual-Leone et al., 1996), according to Talairach atlas coordinates (Talairach and Tournoux, 1988). In daily practice, the location of M1_Hand is determined electromyographically (or visually) by stimulating the cortical area representing the abductor pollicis brevis muscle. This coil positioning strategy (so called “5cm-rule”) became the standard procedure for reaching the DLPFC. However, this method does not take into account inter-individual anatomical variability, and was demonstrated to lack anatomical precision (Herwig et al., 2001). For this reason a key issue for rTMS in a clinical purpose is the placement of the coil above the desired cortical site of stimulation. Therefore other positioning strategies like orientation to the international 10-20 system of EEG positioning or neuronavigation devises should be used (Schönfeldt-Lecuona et al., 2010).

Since studies with small collectives were inconclusive, the antidepressant efficacy of real rTMS to the left DLPFC in relation to a placebo rTMS has been addressed in the last decade in various meta-analyses. Most meta-analyses attributed a significant antidepressant efficacy to real rTMS of the DLPFC at a statistical level, but rather moderate and equivocal effects from a clinical point of view, when compared to placebo (Gross et al., 2007; Martin et al., 2003; Rachid and Bertsch, 2006; Schutter, 2009). The scientific and clinical discussion about whether rTMS has clinically meaningful antidepressant properties is still ongoing, considering recent multicentre trials (Herwig et al., 2007; O’Reardon et al., 2007). The aim of our article is to summarize what recent meta-analyses report and to highlight the main findings of existing rTMS-multicentre trials on depression.

2. What do Meta-analyses report?

Whereas earlier meta-analyses on rTMS in depression provided an inconsistent view concerning the therapeutic efficacy, recent published analyses are more encouraging. By 2002 a small amount of trials with tiny sample sizes were available. Nevertheless, Kozel and George (2002) performed the first relevant meta-analysis including all studies until April 2002. For the meta-analysis only randomized, placebo controlled studies stimulating the left DLPFC in depression (12 studies, 230 patients) were included. Mean changes in the Hamilton Depression Rating Scale (HAMD) for real and sham rTMS between pre and post rTMS rating scores were 7.2 and 3.6 respectively. They reported a statistically significant superiority of real rTMS compared to sham, while the clinical meaningfulness was stated to be very modest (Kozel and George, 2002). Martin et al. (2003) provided a meta-analysis that also showed moderate effects of rTMS in depression, but highlighted the most important methodological issues of the available studies as for instance unclear randomization and small sample sizes (Martin et al., 2003). Couturier and co-workers came to a different conclusion in their meta-analysis: applying strict method
C. Schönfeldt-Lecuona et al. / Antidepressant rTMS multicentre trials

Table 1 Comparison of parameters and design of both multicentre studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Herwig et al. (2007)</th>
<th>O’Reardon et al. (2007)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulation intensity</td>
<td>110 % of rMT</td>
<td>120 % of rMT</td>
</tr>
<tr>
<td>Stimulation Frequency</td>
<td>10 Hz</td>
<td>10 Hz</td>
</tr>
<tr>
<td>Number of pulses per session</td>
<td>2000</td>
<td>3000</td>
</tr>
<tr>
<td>Coil positioning strategy</td>
<td>10–20 EEG-system (F3)</td>
<td>5 cm rule</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>3 weeks (15 sessions)</td>
<td>4–6 weeks (20–30 sessions)</td>
</tr>
<tr>
<td>Sham condition</td>
<td>normal coil, angled at 45° over left temporal muscle (90% rMT)</td>
<td>sham coil with an embedded magnetic field</td>
</tr>
<tr>
<td>Medication</td>
<td>venlafaxine/mirtazapine</td>
<td>free of medication</td>
</tr>
<tr>
<td>N Age</td>
<td>127 (62 real/65 sham) 18–75</td>
<td>301 (155 real/146 sham) 18–70</td>
</tr>
</tbody>
</table>

rMT = resting motor threshold; 10–20 EEG-system (F3) = the magnetic coil was positioned over F3 after the international 10–20 EEG positioning system for the active condition; N = number of participants.

ological inclusion criteria for rTMS studies, the authors analysed 5 clinical trails and reported that real rTMS was not superior to sham (Couturier, 2005). An influential review (Ridding and Rothwell, 2007) particularly raised the question about the functional principles of rTMS in depression and recommended more basic research concerning the mechanisms of efficacy in order to develop more targeted rTMS treatment strategies (Ridding et al., 2007). A more recent review by Padberg and George in 2009 states that rTMS has “clearly” antidepressant effects but also stresses that more research needs to be done to establish effect sizes and to improve the method (Padberg and George, 2009). Further, current meta-analyses (Schutter, 2009; Schutter, 2010) come to the conclusion that high- and also low-frequency rTMS “might be beneficial” for depressed patients. For the high frequency conditions, this most recent analysis included data from 1164 patients from thirty studies and reported a moderate mean effect size ($d = 0.63$, 95% confidence interval $= 0.03–1.24$) for active treatment. In this context, reviews and meta-analyses strongly recommended multi-centre trials to further assess the antidepressant efficacy of rTMS protocols.

3. What can we learn from the multicentre trials?

To our knowledge, only two multicentre trials aimed to test the antidepressant properties of high-frequency rTMS over the left DLPFC have been published (Herwig et al., 2007; O’Reardon et al., 2007). A third one supported by the U.S. National Institute of Mental Health has not yet been published. A forth one is initiated by the Veterans Administration of which data are expected in some years. While O’Reardon and colleagues (North-American-Australian multicentre trial) tested the impact of rTMS in the acute treatment of non-medicated, therapy resistant patients with major depression, Herwig and co-workers (German-Austrian multicentre trial) used an add-on approach to standard antidepressants (venlafaxine or mirtazapine). The comparison of both studies is somehow difficult, since both designs differ considerably, even when chosen stimulation parameters were in a comparable range (Table 1).

3.1. North-American-Australian multicentre trial:

The O’Reardon et al. study, initiated by a TMS device manufacturer, was conducted at 23 study sites in USA (20), Australia (2), and Canada (1). Patients were therapy-resistant (failed at least one attempt but no more than 4 adequate treatment trials), and medication-free, and had a score of at least 20 on the 17-itemed Hamilton Depression Rating Scale (HAMD17). A 6-weeks acute treatment period (random 1:1 to active or sham rTMS) was initiated. After 4 weeks, if patients failed to show benefit (reduction of HAMD $<25\%$ from baseline), a crossover to an open-label (acute treatment extension study) was possible. The stimulation parameters were a frequency of 10 Hz with an intensity of 120% resting motor threshold (rMT) for both conditions; the sham stimulation was performed using a coil with an embedded magnetic field (Table 1 for parameters and design). Active rTMS was shown to be significantly superior on the MADRS at week 4 and on the HAMD17 on weeks 4 and 6. The $a$ priori defined primary outcome variable was the MADRS, which did not show significant effects at week 6. At week 4, active rTMS resulted in a mean reduction in HAMD17 score of approximately 23% compared with 15% in the sham group; this represents an overall relative advantage of 8% for the active rTMS. Looking at the scores
after 4 weeks of treatment, MADRS scores decreased on average 5.8 points after active rTMS and 4.1 points after sham rTMS; HAMD17 scores decreased on average 5.2 after active and 3.5 after placebo rTMS. After 6 weeks, MADRS scores decreased on average 3.2 points more in the active condition as in the placebo condition; the difference for HAMD17 scores was 2.5 points. Responder rates in the active and sham condition were 18.1% res. 11.0% (week 4) and 23.9% res. 12.3% (week 6) for the MADRS scores and 20.6% res. 11.5% (week 4) and 24.5% res. 13.7% (week 6) for the HAMD17 scores. Remission rates were comparable at week 2 and 4 (≈ 6.5%) in both conditions; a significant difference was observed at week 6 (active = 14.6%, sham = 5.5%) only in the MADRS (Table 2 for results). Summarizing study outcomes, the findings indicate that 10 Hz (3000 stimuli per day) and suprathreshold rTMS applied for a period of 4–6 weeks is safe and effective for the treatment of major depression in non-medicated patients. Active rTMS was well tolerated with a low drop-out rate for adverse events (4.5% mostly scalp discomfort or pain). No adverse effects on mood (suicidality or treatment-emergent mania) were observed.

4. German-Austrian multicentre trial

The Herwig et al. study was conducted at 7 sites in Germany (6) and Austria (1) with study management in Switzerland. Altogether, 127 patients were included (Herwig et al., 2007). Participants had a baseline score of at least 18 on two of three scales: Becks Depression Inventory (BDI), Montgomery-Asberg Depression Rating Scale (MADRS), and the HAMD 21-item version. rTMS was applied in parallel to simultaneously initiated standardized antidepressant medication (venlafaxine 75 mg or mirtazapine 15 mg, initial dosage, both could have been increased up to 225 or 45 mg respectively according to clinical needs). The rationale was that if rTMS would ever be implemented in clinical routine, it should demonstrate the benefit of its application in a clinical routine setting which would be in parallel to other treatment strategies. The stimulation parameters were a frequency of 10 Hz with an intensity of 110% rMT, 2000 stimuli per session, and 15-sessions on consecutive working days (3 weeks), with a follow up rating after 6 weeks. Participants were randomized to an active or sham rTMS. Sham was applied using a real coil positioning it above the left temporal muscle, angled at 45° (one wing), and a reduced intensity at 90% of the resting motor threshold (Table 1 for parameters and design). The primary outcome variable was the responder rate; the secondary variable the change in the rating scores. Notably, both groups, real and sham, showed the same responder rate after three weeks: 31% (Table 2 for results). This non-superiority of the real rTMS was also reflected by changes in the rating scores. Neither after the three weeks stimulation period nor in the follow-up, the rating scores differed significantly between both conditions, real and sham. The drop-out rate for adverse events in the active and the sham condition was comparable (< 1%). Following side effects were the most complained: headache (real, n = 3; sham, n = 1), dizziness (real, n = 0; sham, n = 1), painful local sensation (real, n = 1; sham, n = 2). No epileptic seizure or other severe side effects were observed.

5. Discussion

To assess whether rTMS is effective in the treatment of depression, two international multicentre trials have been performed in the last years. Although both studies used the same stimulation frequency (10 Hz) and a suprathreshold intensity (110 and 120% rMT), they showed marked differences in design, since they were conceived to test two different purposes. While O’Reardon and colleagues (North-American-Australian trial) tested the impact of rTMS in the acute treatment of non-medicated, therapy-resistant pa-
patients with major depression, Herwig and co-workers (German-Austrian trial) used an add-on approach to standard antidepressants (venlafaxine or mirtazapine) in patients with uni- or bipolar depressive phase. The North-American-Australian study found an advantage in favour of the active condition. The German-Austrian study failed to demonstrate an advantage of the active rTMS condition, showing that rTMS had no augmentative antidepressant effect with the mentioned design.

Obviously, differences in study design are very likely to account for the difference in results.

Firstly, an explanation for the comparably better outcome in the North-American-Australian trial for the active rTMS condition may be the number of pulses delivered in each session and the total number of sessions were considerably higher in the North-American-Australian trial (see Table 1). It might be that longer periods of daily treatment lead to bigger improvement (Padberg and George, 2009). Observing the results between the forth and sixth week the North-American-Australian trial showed duplication in the remission rates during that period of time, indicating a better outcome in longer trials. Further, the O’Reardon et al. study reported that the remission rate increased from week 6 (15.5%) to week 9 (22.6%) during the taper phase of the study.

Looking at the response rates in the German-Austrian study, the percentage of responders (HAM-D scale) was considerably higher (31%) in the real add-on condition at the final assessment (after 3 weeks of treatment) than in the real condition in the O’Reardon trial both after 4 (19%) and 6 weeks (24%) of rTMS (Table 2 for results). Thus, in absolute terms, independently of the response to sham, active rTMS showed in both studies a reduction of depressive symptoms, which in comparison was larger in the German-Austrian group. Nonetheless, because of the clear superiority of the active as compared to the control condition in the O’Reardon trial, this study has been interpreted as evidence for the antidepressant effectiveness of the method. An essential discrepancy in both studies, as mentioned, was the improvement under the sham condition. While in the multicentre trial by Herwig et al. the response to the placebo add-on condition was 31% (within the range of placebo effects in medication trials, s. below), the response to sham rTMS in the North-American-Australian trial was 15.2% (after three and six weeks of rTMS); a fact, which makes the interpretation of the antidepressant properties of rTMS very difficult.

Secondly, the add-on administration of antidepressant medication in the German-Austrian trial might also have influenced the results. The comparable responder rates observed by Herwig et al. in both groups may be explained as an effect of co-medication, since both groups showed a similar improvement of their depression scores. Therefore, any antidepressant effect of rTMS might have been masked by the strong effect of antidepressants. An alternative argument might be that the study by Herwig and co-workers pictures the natural evolution of depression: Placebo groups (measured against active antidepressant medication) reached a similar mean reduction in the HAMD (largest analysis of FDA database of approved antidepressants) of 30.9% compared to baseline (Kahn et al., 2000); thus, rTMS and medicaments could have been ineffective or might not have reached more than a placebo level of efficacy. However, this argument is strongly contradicted by the small placebo effect in the O’Reardon study and also in earlier studies, e.g. by Herwig et al. (2003a).

Thirdly, a central issue in rTMS trials is selecting a suitable sham condition. Although both studies had a sham condition, one study used a coil with an embedded magnetic field (O’Reardon et al., 2007), whereas the German-Austrian study used a real coil and positioned the coil above the left temporal muscle, angled at 45°, one wing, reduced intensity at 90% of the motor threshold. Thus, with regard to the lack of a local sensation in the O’Reardon trial one might argue that their sham condition was not suitable for a real blinding of the patients. On the other hand, Herwig et al. reported that within the German-Austrian multicentre trial in one centre, 29 patients were asked about their impression whether they received the sham or the real treatment, and if they would recommend the treatment to others (Herwig et al., 2010). 73% of the subjects with real stimulation suggested to have obtained real stimulation and 65% of the patients with sham stimulation suggested to have obtained the real condition. The results imply the feasibility of a valid sham condition with a “real” coil. In the North-American-Australian study a formal query of patients to assess the adequacy of blinding was not conducted and therefore it was not possible to determine if patients realized what kind of stimulation they received.

Finally, the concept of therapy resistance differed considerably between both studies, and this topic seems to be a core issue in terms of therapy response. It is of particular importance to note that prior resistance to antidepressant treatment diminishes the likelihood of responding to subsequent interventions with electroconvulsive therapy (Sackeim et al., 1996), pharmacotherapy (Trivedi et al., 2006) and vagus nerve stimulation.
(Sackeim et al., 2001). A similar effect might be true for rTMS. However, when following this argument one would have expected an effect of rTMS in the multicentre trial by Herwig et al., which was not primarily designed to be restricted to treatment resistant patients, while those were also included. On the other hand, the O’Reardon study aimed at including only treatment resistant patients. Their average treatment resistance score was 1.6, meaning that the included patients had on average 1.6 failed prior conventional treatment trials. This is a rather low grade of treatment resistance when considering that at least two or three different antidepressant pharmacologic strategies could be tried in clinical routine (e.g.: other neurotransmitter profile, combined medication, augmentation strategies) apart the rTMS strategy. Regarding the low response rate, patients might benefit more from another conventional treatment.

A further issue to discuss is the coil positioning method use to stimulate the left DLPFC. O’Reardon and colleagues used the so called “5cm-rule”, a relatively imprecise method that often (in about two-thirds of the cases) fails to reach Brodmann areas (BA) 46 and 9, the core of the DLPFC as demonstrated with a navigational device (Herwig et al., 2001). Herwig et al. used a novel strategy oriented to the international 10–20 system of EEG positioning, placing the coil over F3. This method enables a higher anatomical precision as verified by Herwig and co-workers (Herwig et al., 2003b). The currently most accurate and elegant positioning strategy for coil placement is the use of a frameless, optical-tracked stereotactical devise that enables a precision in the range of a few millimeters (Schönfeldt-Lecuona et al., 2005). However, this technique is still too expensive for a wider use in clinical settings.

Considering the safety of the method, both studies suggested the rTMS with reported parameters to be safe and well tolerated. No study observed epileptic seizure or other severe side effects related to the stimulation. This factor raises the question whether antidepressant rTMS therapy would achieve a better outcome if it used higher intensities and frequencies, possibly without generating more severe side effects. Besides severe complications, an important limitation would be the painful sensation caused by higher intensities that could be solved by using the rTMS associated to narcosis like in ECT (e.g. so called magnetic seizure stimulation (MST), (Lisanby et al., 2003). However, this would pose major restrictions to the use of rTMS in clinical practice.

Considering the overall low response rate in rTMS in the O’Reardon study of about 25%, particularly when compared with the response rates of medicinal treatment (40–70%), the clinical impact of rTMS remains considerably low. Just giving alternative antidepressant medication may be more beneficial for the patients than applying rTMS. Since the superiority of rTMS in a direct comparison is not yet demonstrated, it remains difficult to definitely recommend rTMS as a valid alternative to medication. Even though the data concerning the efficacy of antidepressant rTMS is not unequivocal, a first rTMS-device (NeuroStar TMS Therapy System TM) has recently been approved by the FDA for the treatment of treatment resistant major refractory depression in adults (October, 2008). We encourage the rTMS community to continue to perform multicentre trials to further clarify the therapeutic antidepressant potential of this method, and to evaluate cost-effectiveness and quality of life aspects.

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Conflict of interest

None.

References


