Acta Psychiatr Scand 2007: 116: 165–173
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DOI: 10.1111/j.1600-0447.2007.01049.x

ACTA PSYCHIATRICA SCANDINAVICA

Review

Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies

Gross M, Nakamura L, Pascual-Leone A, Fregni F. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies.

Objective: To investigate whether the recent repetitive transcranial magnetic stimulation (rTMS) studies on depression using new parameters of stimulation have shown improved clinical results.
Method: We performed a systematic review and a meta-analysis of the rTMS studies on depression published in the past 12 months comparing these results with an earlier meta-analysis that analyzed the results of the initial rTMS studies on depression.
Results: Using our inclusion criteria, we selected the meta-analysis of Martin [Br J Psychiatry (2003) Vol. 182, 480–491] that included 13 studies (324 patients) and five studies for the recent meta-analysis (274 patients). The pooled effect size (standardized mean difference between pretreatment vs. post-treatment) from the random effects model was −0.76 (95% confidence interval, CI, −1.01 to −0.51). This result was significantly larger than that of the earlier meta-analysis (−0.35, 95% CI −0.66 to −0.04).
Conclusion: Our findings suggest that recent rTMS clinical trials have shown larger antidepressant effects when compared with the earlier studies.

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Key words: depression; antidepressive agents; meta-analysis; transcranial magnetic stimulation; electric stimulation therapy

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Accepted for publication May 2, 2007

Summations

- The 10-year experience with rTMS for the treatment of major depression has optimized the parameters of stimulation, resulting in improved clinical effects of this technique.
- Recent rTMS trials used novel parameters of stimulation, such as more sessions of rTMS, and had better study designs with larger sample sizes.
- Our findings showing that the recent TMS trials had larger effect sizes when compared with the earlier rTMS studies give additional support for the antidepressant effects of rTMS.

Considerations

- Although the number of patients included in both meta-analyses (recent and earlier) is similar (324 vs. 274), we only found five studies for the recent meta-analysis; and thus, the power of our recent meta-analysis was reduced.
- The placebo effect for rTMS might have been larger in the recent trials as patients might have had a greater expectation about the technique of rTMS; however, all the trials included in our meta-analysis were sham controlled.
- The quality of the studies was variable and therefore this must also be considered as a reason to explain the different results between the two sets of rTMS studies.

Introduction

Transcranial magnetic stimulation (TMS) was introduced in 1985 when Barker et al. developed a compact machine that allowed non-invasive stimulation of the cerebral cortex (1). Because TMS, if applied repetitively (rTMS), can modulate cortical excitability; soon after its introduction, rTMS began to be investigated for the treatment of several neuropsychiatric diseases. To date, the best clinical gains have been observed on the use of rTMS for the treatment of major depression. Indeed, the largest number of clinical studies have been performed to evaluate the effects of rTMS for the treatment of depression and, in fact, a few meta-analyses have been published. Although most of them showed results favoring active rTMS when compared with sham rTMS, they also concluded that 'effect sizes are heterogeneous' (2) and that 'current trials are of low quality and provide insufficient evidence to support the use of rTMS in the treatment of depression' (3). Some of the reasons to explain the initial poor results are that these trials included small sample sizes (in some cases, less than 10 patients) and might have used ineffective parameters of stimulation.

Ten years have passed since the publication of the first randomized clinical trial evaluating the effects of rTMS on major depression has been published (4) and an important question is whether the more recent studies using the information learned from past studies and thus adopting novel parameters of stimulation and better study designs have shown different results when compared with the earlier clinical trials of rTMS on depression.

Aims of the study

The aim of this study was to investigate whether there has been a change in the clinical effects induced by rTMS in depression, performing a systematic review and meta-analysis of the rTMS studies in depression published in the past 12 months and comparing these results with an earlier meta-analysis that analyzed the results of the first rTMS clinical trials on depression.

Material and methods

Systematic review and meta-analysis of the recent rTMS clinical trials on depression

Literature review The first step of our review of the recent rTMS clinical trials on depression was a selective literature search for articles published from December 2005 to November 2006 (period of 12 months). Our key search terms were *major depression*, *depression*, *transcranial magnetic stimulation*, *rTMS* and *TMS*. This strategy yielded 70 studies.

Selection criteria We included prospective studies that evaluated the effects of rTMS on mood in patients with major depression. We adopted the following inclusion criteria [similar to the previous meta-analysis of Martin et al. (3)]: 1) written in English (although we only selected manuscripts in English there were no manuscripts written in another language); 2) use of rTMS given at any frequency (low and high frequencies) and any localization (left or right dorsolateral prefrontal cortex, DLPFC); 3) mood effects assessed by a continuous mood scale such as Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI) or Montgomery–Åsberg Depression Rating Scale (MADRS); 4) randomized, double-blind studies with a sham rTMS group; 5) the studies had to report the mean and standard deviation of the mood scores before and after the treatment or provide other statistical parameters that could be used to deduce these values; 6) studies published in the past 12 months (from December 2005 to November 2006). We used the period of only 12 months as we wanted to compare the results of these studies with the meta-analysis published in 2003 that analyzed studies published up to January 2002. As a study may take an average of 3–4 years to be performed and published, the studies from the past 12 months (from December 2005 to November 2006) are likely to have benefited from the insights gained in the trials performed before January 2002.

Extraction of the outcome measures The data were collected using a semi-structured form for each study by one of the authors and checked by another investigator. The discrepancies were resolved by consensus and a third author consulted if needed. All the following variables were extracted: 1) mean and standard deviation of the mood assessment (as indexed by HDRS or MADRS) for baseline and after the treatment for the active and placebo group; 2) demographic and clinical characteristics (e.g. number of patients, age, medication refractoriness and use of medications); 3) TMS parameters (frequency, intensity, number of pulses and number of sessions).

Qualitative analysis For the quality assessment, we used the same criteria used by Martin et al. (3) [and also suggested by Egger et al. (5)]. The following criteria were used: 1) adequate concealment of

treatment allocation (as defined by evidence of a centralized system of randomization, e.g. randomization was prenumbered, coded and sealed, opaque envelopes were used and kept in a locked cabinet); 2) patient attrition – we looked for evidence of an intention-to-treat analysis; and 3) blinding – as defined in Martin et al.'s study, rTMS treatment might be viewed as a single-blind procedure with blind raters as the technician applying the treatment is not blind; we also checked whether blinding of patients and physicians were tested.

Quantitative analysis – meta-analysis approach All of our analyses were performed using Stata statistical software, version 9.0 (Statacorp, College Station, TX, USA). We initially calculated the standardized mean difference and the pooled standard deviation between pretreatment and post-treatment HDRS (or MADRS) of the two independent subject groups (sham and active rTMS). In the next step, we measured the pooled weighted effect size (comparing the active with the sham rTMS group) using the random and fixed effects models. An important point, especially considering that we added five studies only to our meta-analysis, is the determination of the optimum pooled effect size. For instance, a simple average of the effect sizes from these five studies would have produced a suboptimum result. We therefore used the method of inverse-variance weighting to calculate the random effects summary estimates (the weight reflects, therefore, the amount of information that each trial contains). This method is considered adequate to determine the optimum effect size (5). Finally, the random effects model gives relatively more weight to smaller studies and wider confidence intervals than the fixed effects models and its use has been advocated if there is heterogeneity between studies (6).

Heterogeneity was evaluated with Q-statistic. Although we found a non-significant heterogeneity, this test may have been underpowered due to the small number of studies; therefore, we synthesized the results from individual studies by using the DerSimonian and Laird random effects model to incorporate both within- and between-study variability.

We assessed publication bias using Begg-modified funnel plot (7), in which the standardized mean difference from each plot was plotted against the standard error.

Meta-analysis of the earlier rTMS clinical trials on depression

To compare the results of the recent rTMS clinical trials on depression with the earlier studies; we used the results of the meta-analysis of rTMS treatment for depression by Martin et al. (3). There have been five meta-analyses on rTMS treatment for depression published to date (2, 3, 8–10) and our main decision criterion was the publication date (we chose the most recent meta-analysis). However, we did not use the meta-analysis of Couturier (10) published in 2005; as this meta-analysis had some methodological limitations that were discussed in a previous communication (11). As mentioned above, the meta-analysis of Martin et al. (3) was adequate for such comparison as this meta-analysis evaluated the studies published up to January 2002 thus the more recent studies probably considered the information from the studies included in that meta-analysis.

Importantly, the inclusion criteria of Matin et al.'s meta-analysis were very similar to our inclusion criteria. In summary, in Martin et al.'s meta-analysis (3), studies were included if there were randomized controlled trials comparing active rTMS given at any frequency and any localization with sham rTMS.

Results

Using the words 'Transcranial magnetic stimulation' and 'depression' and limiting our search to the past 12 months, we could find 70 citations. Only five references met our inclusion criteria. References were excluded mainly because of: 1) reviews; 2) use of rTMS in other neuropsychiatric diseases; 3) case reports; 4) lack of sham rTMS group; and 5) other topics (Fig. 1).

As observed in the previous meta-analysis (3), there was a significant heterogeneity among these five trials regarding the parameters of stimulation. For instance, the site and frequency of stimulation varied from a single-site stimulation on either right DLPFC with low frequency (12) or left DLPFC with high frequency (13, 14) or bilateral stimulation (15, 16). Furthermore, the number of sessions also varied from 10 to 16. An important observation here is that we only considered the first 10 sessions of rTMS in the Fitzgerald study (15) and the reason for that is because, after 2 weeks, patients in the sham and active groups only received extra sessions if the depression scores had reduced more than 10%; thus in the weeks 5 and 6 of this study, only active treatment was administered and thus the calculation of the effect size would not have been accurate after 2 weeks of treatment.

Regarding the method of evaluation, quantitative information on depression was provided with HDRS for all the studies, except for the study of

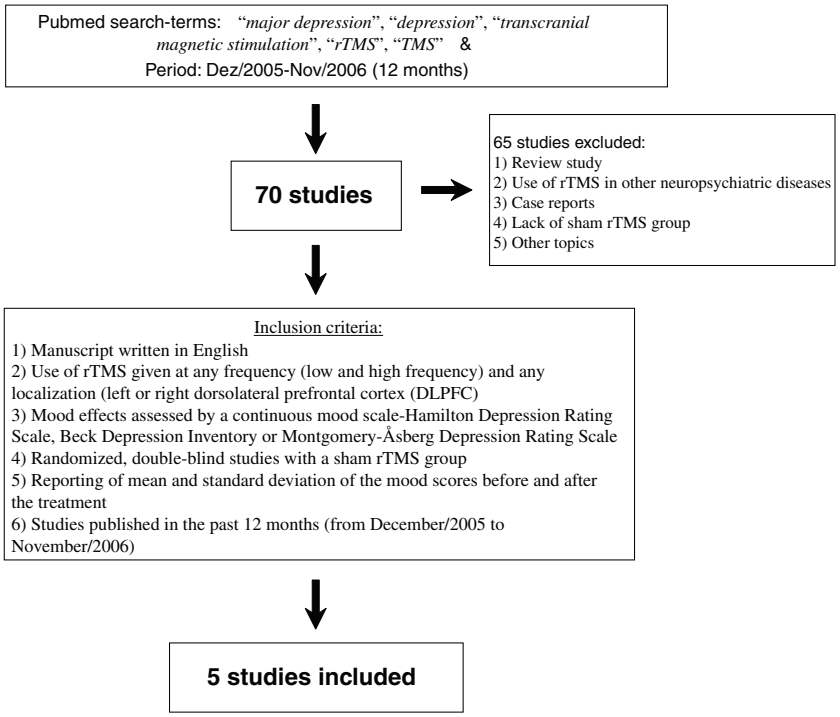

Fig. 1. Trial flow used to identify studies for detailed analysis.

Fitzgerald et al. (15), in which this information was provided with MADRS (also MADRS was the primary outcome measure in this study). Finally, most of the studies included patients who were refractory to antidepressants (at least to two antidepressant drugs), except for the study of Januel (12) and Rossini (14) that included patients who were not refractory to antidepressants.

Regarding the quality of the studies according to the criteria used by Martin et al. (3); it appears that recent studies had a quality improvement. On the criterion 'concealment of treatment allocation', three studies (60%) report methods of randomization concealment such as computer-generated list (13); closed envelopes (16) and number sequence in sealed envelopes (15); in contrast to Martin et al.'s meta-analysis in which only two of 13 studies (15%) showed some evidence of randomization concealment. On the criterion 'patient attrition', similar results were found: whereas three of five studies (60%) performed an intention-to-treat analysis (15); this analysis was only performed by two studies (15%) included in the meta-analysis of Martin et al. (3). Finally, regarding the criterion of blinding; no different method was used in the recent studies; thus they should all be considered as single-blind studies with external blind raters. However, two studies in our recent meta-analysis (40%) report a method of checking integrity of blinding, whereas this was not reported in the studies of Martin et al.'s meta-analysis (3).

The characteristics of the five selected trials are summarized in Table 1. In summary, these five studies included 274 patients. Table 2 shows the individual characteristics of each trial. Pooling the data of these five trials, we found a pooled effect size (standardized mean difference between the active and sham rTMS groups) from the random effects model of −0.76 (95% CI −1.01 to −0.51). The test for heterogeneity failed to show a significant heterogeneity (Q3, $\chi^2 = 3.52$, $P = 0.45$) – indeed the results using the fixed effects model showed similar results. Figure 2 shows the forest plot for this analysis. Interestingly, the results for the individual trials showed that all of them had a significant effect size favoring the active rTMS treatment.

As expected, based on Fig. 2, the results of the sensitivity analysis (Fig. 3) in which one study was omitted at the time showed that the results would

Table 1. Summary of the recent rTMS trials meta-analysis

	Mean/*n*
Number of studies	5
Number of patients	274
Age (years, mean ± SD)	44.7 (4.2)
Gender (F/M) (% female)	183/91 (66.8)
Refractory to antidepressants (Y/N)	3/2
Duration of current episode (months, mean ± SD)	17.3 (14.8)
Baseline HDRS (mean ± SD)	23.5 (4.2)

Refractory to antidepressants indicates the number of studies.

Table 2. Individual characteristics of the recent repetitive transcranial magnetic stimulation (rTMS) trials

Trial name	Rossini et al. (14)	Fitzgerald et al. (15)	Garcia-toro et al. (16)	Januel et al. (12)	Avery et al. (13)
Year	2005	2006	2006	2006	2006
n	99	50	30	27	68
Refractoriness (Y/N)	N	Y	Y	N	Y
Age (mean)	47.4	45.2	48.9	37.8	44.25
Gender (F/M) (% female)	79/20 (79.8)	31/19 (61)	15/15 (50)	21/6 (77.8)	37/31 (55)
Number of episodes of depression (mean ± SD)	3.1	4.1	4.9	2.6	N/A
Mean duration of the episode (months)	10.5	6.6	32.6	N/A	27.2
Baseline HDRS (or MADRS) – active group (mean ± SD)	25.1 (3.5)	34.0 (5.9)	26.1 (4.5)	21.7 (3.5)	23.5 (3.9)
Baseline HDRS (or MADRS) – sham group (mean ± SD)	25.1 (3.1)	34. 2 (5.2)	25.1 (7.3)	22.5 (2.7)	23.5 (2.9)
Site of stimulation	Left DLPFC	Bilateral	Bilateral	Right DLPFC	Left DLPFC
Frequency of stimulation (Hz)	15	1 and 10	1 and 20	1	10
Number of rTMS sessions	10	10*	10	16	15
Pulses per session	900	1170	3000	120	1600
Intensity of stimulation (% MT)	100	105	110	90	110
Type of TMS coil	Figure-of-eight	Figure-of-eight	Figure-of-eight	Figure-of-eight	Figure-of-eight
Antidepressants (Y/N)	Y	Y	Y	N	Y

*Note that we computed values of only the first 10 sessions of rTMS as explained in detail in the Material and methods.
DLPFC, dorsolateral prefrontal cortex; N/A, data not available; Y = yes; N = no.

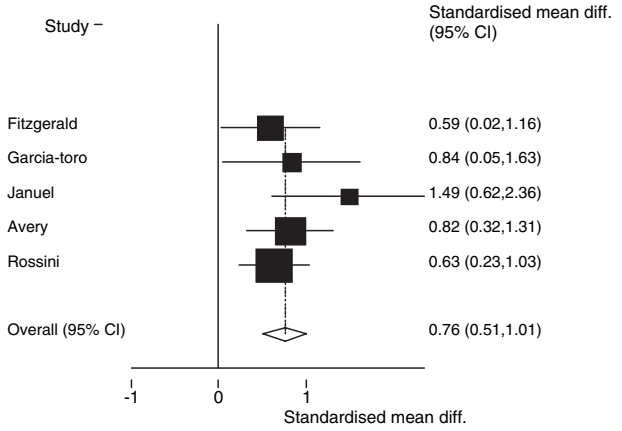

Fig. 2. Forest plot showing effect sizes (standardized mean difference of mood scores from baseline to after treatment between the active and placebo group) from the random effects model. A negative effect indicates a superior mood improvement in the active group compared to placebo group. Effect sizes are Cohen d (standardized mean difference), error bars represent the 95% confidence interval.

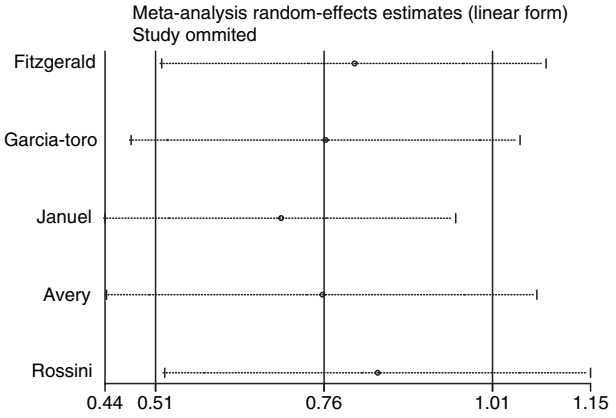

Fig. 3. Assessment of the individual influence of each study. The change in the overall effect size and 95% confidence intervals for the meta-analysis after eliminating the indicated study is shown. Effect sizes are Cohen d (standardized mean difference), error bars represent the 95% confidence interval.

not change significantly after the exclusion of any of these studies. Indeed the main change would be caused by the omission of the study of Avery et al. (13) that would result in a wider confidence interval as this study had a large sample size of 68 patients. The exclusion of the study of Rossini et al. (14) would increase the pooled effect size to −0.84 and the exclusion of Januel's study (12) would decrease this estimate to−0.69.

To test for publication bias, we performed the funnel plot for the visual assessment. The funnel plot is helpful to identify if smaller studies with no statistically significant effect remain unpublished as this would lead to an asymmetrical appearance of the funnel plot. This plot shows a relatively symmetric appearance as there were two studies below and three studies above the horizontal line (representing the pooled effect size). Finally, all of the studies are included into the 95% CI range (Fig. 4). This result speaks against a publication bias. Finally, the *P*-value for the Egger test was not significant ($P = 0.15$), therefore supporting that the results of this meta-analysis are not the result of publication bias.

The results of Martin et al.'s meta-analysis (3) including 175 patients showed a significant effect in decreasing depression scores also favoring active rTMS when compared with sham rTMS (difference of −0.35; 95% CI −0.66 to −0.04) after 2 weeks of stimulation of the left dorsolateral prefrontal cortex. In the meta-analysis of our recent study, there was only one study that performed high-

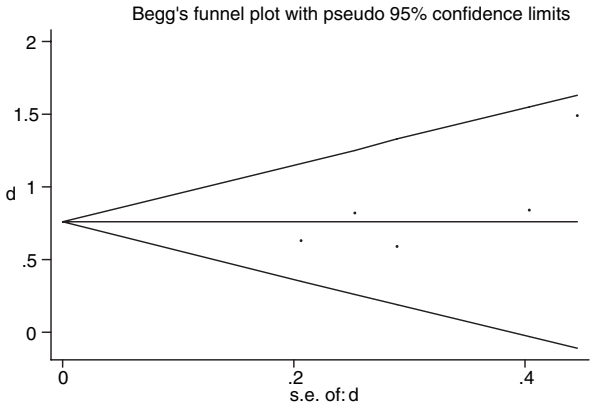

Fig. 4. Funnel plot (publication bias assessment) of the effect sizes (Cohen d) according to their standard errors. The horizontal solid line is drawn at the pooled effect size, and angled lines represent the expected 95% confidence interval for a given standard error, assuming no between-study heterogeneity.

frequency rTMS only in the right DLPFC (the other study that applied rTMS of left DLPFC only associated this treatment with antidepressants) – the study of Avery et al. (13). In this study, the effect size was −0.82 (95% CI −1.31 to −0.32). Indeed this effect was significantly larger than that of Martin et al.'s meta-analysis ($P < 0.001$). When comparing with the pooled effect size of the five studies together, this difference was also significant ($P < 0.001$).

In Martin et al.'s meta-analysis (3), there was only one study that used the strategy of low-frequency rTMS (1 Hz) of the right DLPFC and the authors did not include this study into the main analysis. This study by Klein et al. showed an effect size of −0.80 (95% CI −1.29 to −0.30). In our meta-analysis, there was only one study that applied low-frequency rTMS to right DLPFC only – this study by Januel et al. showed an effect size of −1.49 (95% CI −2.36 to −0.62) that was significantly larger when compared with the earlier study of Klein et al. ($P < 0.001$).

Finally, there were no studies included in Martin et al.'s meta-analysis that performed bilateral stimulation. Therefore, the two bilateral stimulation studies included in our meta-analysis of recent studies cannot be compared with specific initial studies. Interestingly, the effect sizes of these two studies (−0.59 and −0.84) do not differ from the overall result of our recent meta-analysis effect size (effect size of −0.76, $P > 0.05$ for both comparisons).

Discussion

The results of our study show that the recent clinical trials of rTMS on depression induced a larger effect size when compared with the initial studies as summarized in Martin et al.'s meta-analysis. This superior difference of the recent studies when compared with earlier studies was observed when analyzing the left DLPFC high-frequency rTMS studies only and also the right DLPFC low-frequency rTMS studies only. Possible reasons for the enhanced effects of rTMS on depression in recent studies are discussed below.

Comparison of the studies performing high-frequency rTMS over the left prefrontal dorsolateral cortex

The rationale of targeting the left dorsolateral prefrontal cortex is that lesion and imaging studies show that left prefrontal cortex dysfunction is pathophysiologically linked to primary and secondary depression (17, 18). Because this dysfunction is associated with a decrease in the left dorsolateral prefrontal cortex activity, high-frequency rTMS is used as it induces larger cerebral blood flow in the stimulated area in the majority of subjects (19). Indeed, the vast majority of the initial rTMS studies applied high-frequency rTMS on the left DLPFC. As mentioned above, the analysis in the study of Martin et al. (3) pooling the results of these studies showed an effect size of −0.35 (95% CI −0.66 to −0.04).

When we compared with the results of our meta-analysis of the recent rTMS studies (excluding the study of Januel et al. that applied rTMS to the right DLPFC only) the results showed a larger effect size. In addition, the results do not change if we also exclude the studies using bilateral stimulation and also the study in which rTMS was combined with antidepressants – only one study performed stimulation of the left DLPFC only – the study of Avery et al. (13). In fact, this study alone showed a larger effect size when compared with the earlier studies. An evident difference is that the studies included in Martin et al.'s meta-analysis analyzed studies that applied only 10 sessions of rTMS and in the study of Avery et al. 15 sessions of rTMS were applied. It has been shown by other studies – such as the study of Rumi et al. (20) – that the number of sessions is an important parameter to predict the clinical effects of rTMS and indeed in our recent meta-analysis two of the three studies that employed 10 sessions only [Rossini's and Fitzgerald's studies (14, 15)] had the smallest effect sizes. Furthermore, Avery et al. showed that the clinical effects of rTMS increase with the duration of the treatment providing almost a linear effect between the number of sessions and depression scores reduction (13).

Another important consideration is that the sample size of Avery's study was considerably larger when compared with the studies included in the Martin et al.'s meta-analysis. In this meta-analysis, the studies had sample sizes varying from six to 35 patients; therefore, larger or smaller effects due to chance are more likely in these small studies (wider confidence intervals were shown in this study). By contrast, the study of Avery et al. (13) enrolled 68 patients. Although small compared with the large drug studies, this is a relatively large trial compared with past TMS studies and therefore provides a more accurate effect estimate.

Another potential difference is patient selection – in other words, patients selected in the recent studies might be less refractory to antidepressants and therefore might respond more – we showed in a recent study that less refractory patients had a larger response to rTMS (21). However, in Avery et al.'s and most of the other studies included in the present meta-analysis, patients were refractory to at least two adequate trials of antidepressants – similar to the inclusion criteria of the initial rTMS studies. Finally, the sham rTMS method is also a potential source of heterogeneity. In Avery et al.'s study, the authors used the coil rotated at 90° from the scalp as sham condition. As this sham method might induce a small current in the cortex, patients in the sham group might have had a greater placebo effect what speaks against a larger effect size as a result of the sham method.

Comparison of the studies using low-frequency rTMS over the right dorsolateral prefrontal cortex

Although the most used rTMS strategy for the treatment of depression is high-frequency rTMS of the left DLPFC, this strategy has an important cost: it may increase the risk of seizure. Therefore, lower frequency rTMS strategies are potentially advantageous if clinical efficacy can be demonstrated (22). Although, the mechanisms of action of low-frequency rTMS over the right DLPFC in depression remain unclear, it has been speculated that an inhibition of the right prefrontal cortex (based on the inhibitory effects of 1 Hz rTMS and the notion of a laterality in prefrontal activity in depression) might correct the interhemispheric imbalance of dorsolateral prefrontal cortex activity in depression (23).

The meta-analysis of early studies included one study by Klein et al. (23) that used low-frequency rTMS over the right DLPFC. This study showed an effect size favoring the active treatment when compared with sham rTMS of −0.8 (95% CI −1.29 to −0.3). This is, however, significantly smaller than the results of the more recent study using the right DLPFC strategy by Januel et al. (12) included in the present meta-analysis (effect size of −1.49, 95% CI −2.36 to −0.62). The main factor to explain the difference between the two studies might also be related to the number of rTMS sessions. Whereas in Klein et al.'s study, 10 consecutive sessions of rTMS were applied, in Januel et al.'s study 16 sessions of rTMS were applied over the period of 1 month. As mentioned above, the number of sessions of rTMS seems to be an important factor to determine the clinical gains associated with this therapy.

Another potential reason to explain this difference is that patients in the Januel et al.'s study were not refractory to antidepressants and therefore might have responded more to the rTMS treatment. Although this is also a likely explanation, such patients might also have had a higher placebo response and thus the effect size in this situation would change less.

Other differences in the parameters of stimulation are likely to have played a minor role as the number of pulses per session was the same for both studies and the intensity of stimulation was higher for Klein's study (110% vs. 90% respectively).

A new strategy of stimulation–bilateral stimulation of the right and left DLPFC

Because high-frequency rTMS of the left DLPFC and low-frequency rTMS of the right prefrontal cortex have been shown to induce antidepressant effects, it has been suggested that a combined therapy with high-frequency left-side stimulation and low-frequency right frequency stimulation might in fact be most effective in improving depression. In our meta-analysis, we found two studies using bilateral stimulation that met our inclusion criteria and could be included – the studies by Fitzgerald et al. (15) and Garcia-Toro et al. (16).

An important question is whether this alternative approach (bilateral stimulation) offers an additional benefit over the approach of unilateral stimulation of either the left or the right DLPFC. Although the comparison of the effect size of these two studies with studies of unilateral stimulation suggests that bilateral stimulation does not induce a larger effect size (−0.59 and −0.84 vs.−0.82 and −1.49 for the two bilateral stimulation, unilateral left and unilateral right stimulation studies respectively), the ability to make any conclusions is limited by the small number of studies. Further studies should perform this comparison directly.

It is also worthy of note that a previous small study not included in the Martin et al.'s meta-analysis and neither in the meta-analysis of the recent studies (as it was published in 2003) examined the efficacy and safety of bilateral prefrontal rTMS for treating resistant major depression in a double-blind, placebo-controlled study with 19 medication-resistant depressed subjects and showed that bilateral rTMS was not superior to sham in treating resistant major depression (24).

Limitations

An important limitation of this meta-analysis needs to be discussed: the small number of included studies (five studies only). This might be viewed as a limitation especially if considered that these studies used different parameters of stimulation such as the site of stimulation (bilateral DLPFC, left DLPFC or right DLPFC). However, we were interested in the general antidepressant effect of rTMS using novel parameters of stimulation such as the number of pulses and sessions of rTMS. In addition, we showed that all the individual studies had an effect size larger than the one from the meta-analysis of Martin et al. (3). Furthermore, a study from Fitzgerald et al. (25) comparing antidepressant effects of left high-frequency rTMS vs. right low-frequency rTMS showed no significant differences between these two strategies of stimulation (25). Although we included only five studies, these studies were larger studies and indeed the total number of subjects was comparable with Martin et al.'s meta-analysis (274 vs. 324 subjects respectively). Finally, the sensitivity analysis revealed that the results from this meta-analysis are robust and do not seem to be dependent on a particular study design.

Clinical implications

Because our results suggest that rTMS treatment for depression might have improved due to the development of new paradigms of stimulation; a critical matter is the clinical implications of these results. Importantly, although our results are suggestive that rTMS has significant antidepressant effects, larger multicenter studies are still necessary and are indeed underway to confirm these trends. We discuss then important factors when considering this treatment in the clinical practice such as: 1) short- vs. long-term effects – maintenance treatment; 2) use of rTMS in patients who do not have medically refractory depression; and 3) new uses of rTMS such as for the treatment of depression in children.

An important consideration is that all of these studies only evaluated the short-term effects of rTMS – for a few months only; therefore, the question of whether the beneficial effects of rTMS can be extended for a long period of time remains unknown. There are only few published open-label studies regarding the maintenance rTMS treatment for patients with major depressive disorder who have responded acutely to rTMS. One study examined the long-term maintenance therapy with high-frequency (10 Hz) rTMS of the left prefrontal cortex in 10 adult patients with major depression, for periods ranging from 6 months to 6 years. rTMS sessions frequency averaged one to two per week. Seven of the 10 subjects experienced either marked or moderate benefit, which was sustained without the need of addition of concomitant antidepressant medication in three cases (26). These data, while open label, suggest that maintenance rTMS might have a positive effect in some patients with unipolar depression. However, there is certainly a need for further studies.

Finally, another area of research is the use of rTMS in patients not refractory to medication as most of the studies included patients who were refractory to antidepressants. In the meta-analysis of our recent studies, two of the studies included patients not refractory to antidepressants. In one of these studies (12), the effect size was almost twice as large as the second largest effect size. The other study (14) showed a moderate effect size; however, this study tested rTMS in combination with drugs. Therefore, further studies should explore the comparison of drugs alone vs. rTMS alone in patients who are not refractory to medications.

Our study suggests that recent rTMS trials on depression show larger clinical antidepressant effects. There are many potential reasons to explain this difference such as better study designs and more effective parameters of stimulation (such as number of rTMS sessions). Other questions still remain to be answered such as the use of this therapy in children and adolescents [especially because the relatively lack of efficacy of antidepressants in this population of patients (27) and concerns with increased suicidal risk (28)]; long-term effects of this therapy; its use in minor depression [as this condition is associated with an increased risk of major depression (29)] and the effects of rTMS treatment in patients who are not refractory to medications.

Acknowledgements

F.F. is supported by grants from NIH (DK071851-01) and the Harvard University David Rockefeller Center – Jorge Paulo

Lemann Fellowship. A.P.-L. is supported by a NIH K24 RR018875 grant and Harvard-Thorndike General Clinical Research Center at Beth Israel Deaconess Medical Center (NCRR MO1 RR01032). We would like to thank Prof. Tianxi Cai, from the Department of Biostatistics of Harvard School of Public Health, for her comments during the revision of this manuscript.

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