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Short communication

Acute reduction in anxiety after deep transcranial magnetic stimulation (DTMS) in unipolar major depression- a systematic review and meta-analysis

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ABSTRACT

The current study investigated the anxiolytic properties of the deep transcranial magnetic stimulation (DTMS) in unipolar major depression using a systematic literature review and meta-analysis. Compared to baseline, large anxiolytic and antidepressant outcomes were obtained after 20 daily sessions of high-frequency DTMS according to data from six open-label studies with 95 patients. Unlike the antidepressant effect, the anxiolytic effect was more heterogeneous among studies and did not depend on concurrent treatment with antidepressants.

1. Introduction

Deep transcranial magnetic stimulation (DTMS) is a non-invasive brain stimulation method utilising the so-called H-coil system (Zangen et al., 2005). Compared to the conventional repetitive transcranial magnetic stimulation (rTMS) typically administered with the figure-of-eight coil, H-coil stimulates wider and, most likely, deeper neural structures (Roth et al., 2014). A recent sham-controlled, randomized-controlled trial (RCT) with 181 patients has shown that high-frequency DTMS has acute antidepressant effects when administered as a monotherapy in patients with treatment-resistant, unipolar major depression (Levkovitz et al., 2015). Acute antidepressant effects of high-frequency DTMS were also shown in one meta-analysis of nine open-label studies with 150, mostly unipolar and treatment-resistant, patients with major depression (Kedzior et al., 2015).

While DTMS appears to be a promising antidepressant treatment, particularly in unipolar depression, it is not clear if it could also reduce anxiety symptoms in major depression. In general, patients with anxious depression show worse acute clinical responses to pharmacotherapy (Fava et al., 2008). Similarly, presence of concurrent anxiety disorder was associated with a worse clinical response to the conventional high-frequency rTMS (HF-rTMS) in unipolar major depression (Lisanby et al., 2009). However, evidence from open-label trials suggests that conventional HF-rTMS of the left dorsolateral prefrontal cortex might acutely lower anxiety symptoms in those with major depression (Berlim et al., 2011; Diefenbach et al., 2013). The aim of the current study was to investigate if DTMS has acute anxiolytic properties in the treatment of unipolar major depression using a systematic literature review and meta-analysis.

2. Methods

2.1. Systematic search strategy

A systematic literature search of Medline and PsycInfo databases (any time-January 2015) identified $k=17$ studies containing terms 'deep transcranial magnetic stimulation' and 'depression' (see Table S1 for the full search strategy). Following exclusion of studies without anxiety scores ($k=3$), with data already reported in other studies included in the current analysis ($k=3$), case reports with one patient each ($k=2$), a review ($k=1$), a study with primary diagnosis of alcohol use disorder ($k=1$), and a study with bipolar depression ($k=1$), six open-label studies were included in the quantitative analysis (Fig. S1). All studies reported anxiety and depression severity scores according to Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959) and Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) respectively.

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2.2. Meta-analysis

Random-effects meta-analysis with inverse-variance weights (the inverse of the sum of within- and between-study variance) (Borenstein et al., 2009) was performed using Comprehensive Meta-Analysis (CMA 2.0) software. The effect size (Cohen's *d*) was the standardised paired mean difference in anxiety or depression scores between baseline and last acute DTMS session. The magnitude of Cohen's *d* is interpreted as small (< .50), moderate (.50–.80), or large (> .80) (Borenstein et al., 2009). Since Cohen's *d* can be inflated in small sample studies, the sample-size adjusted effect size, Hedges' *g*, was also computed (Borenstein et al., 2009). The heterogeneity among effect sizes was quantified using the I^2 index and interpreted as small (< 25%), moderate (50%), or large (> 75%) (Borenstein et al., 2009). Publication bias was assessed using Rosenthal's Fail-Safe *N* and funnel plots (Borenstein et al., 2009).

3. Results

3.1. Study details

Study details are shown in Table 1. Five studies were conducted in Israel (at three research centres) and one in Canada.

3.2. Patient characteristics

The patients in all studies were middle-aged and approximately half or more were female. All studies included patients with treatment-resistant, unipolar major depression. Treatment-resistance was defined as a failure to respond to at least one pharmacological trial or lack of response to two antidepressants. DTMS was administered as a monotherapy in two studies.

3.3. DTMS parameters

Open-label designs without sham control groups were used in all six studies. All studies utilised the H1-coil and the following stimulation parameters: high frequency (20 Hz), high intensity (120% of the resting motor threshold), 20 s inter-train interval, and 20 daily sessions during the acute stimulation phase. A total of 33,600 stimuli/study (1680 stimuli/session) were applied in 42 trains/session in all studies except for one study utilising 60,000 stimuli/study (3000 stimuli/session) applied in 75 trains (Berlim et al., 2014).

3.4. Anxiolytic effect of DTMS

There was a large acute anxiolytic effect after DTMS compared to baseline (pooled weighted $d=1.45$; 95% confidence interval, 95%CI: 1.10–1.80; $p < .001$; $k=6$ studies; $N=95$ patients; Fig. 1A and S2). The individual study effect sizes varied between .98 to 2.40 (Fig. 1A) suggesting that there was some heterogeneity in anxiolytic responses to DTMS ($I^2=26\%$). The anxiolytic effect did not depend on the concurrent treatment with antidepressants (Fig. S3). There was little evidence for publication bias in this analysis (Fig. S4).

3.5. Antidepressant effect of DTMS

The anxiolytic effect was accompanied by a large acute reduction in depression severity after DTMS compared to baseline in the same studies (pooled weighted $d=1.69$; 95%CI: 1.38–2.01; $p < .001$; $k=6$ studies; $N=95$ patients; Fig. 1B and S5). The individual study effect sizes varied between 1.39 and 1.98 (Fig. 1B) suggesting that there was little heterogeneity in antidepressant responses to DTMS ($I^2=0\%$). The antidepressant effect tended to be higher in two studies with 37 patients on concurrent antidepressants (pooled weighted $d=1.87$, 95%CI: 1.33–2.40) compared to two other studies with 26 patients who received DTMS as a monotherapy (pooled weighted $d=1.45$, 95%CI: .90–2.00; Fig. S6). There was little evidence for publication bias in this analysis (Fig. S7).

4. Discussion

Current preliminary results suggest that, similarly to conventional HF-rTMS (Berlim et al., 2011; Diefenbach et al., 2013), high-frequency DTMS might be effective at acutely reducing severity of anxiety and depression in patients with unipolar major depression who fail to respond to pharmacotherapy. These effects in open-label studies might be similar to those observed in 'real world' patients who also receive non-blinded stimulation as part of their clinical treatment. Future RCTs with inactive sham groups are necessary to compare the magnitudes of anxiolytic effects of DTMS and conventional rTMS.

Similarly to current results, evidence from the only double-blind RCT to date suggests that the antidepressant effects of DTMS (HDRS change scores, response and remission rates) are superior compared to sham in 181 medication-free, treatment-resistant patients with unipolar depression (Levkovitz et al., 2015). However, the acute anxiolytic effect of DTMS was similar in the active stimulation and sham groups in the same RCT (personal communication with study authors). Therefore, it cannot be ruled out that the anxiolytic effect observed in the current study was at least partially due to placebo although placebo alone cannot explain this effect for a number of reasons. First, the anxiolytic effect tended to be heterogeneous (smaller in some and larger in other studies) while the antidepressant effect was relatively consistent in all studies. Therefore, antidepressant and anxiolytic effects of DTMS might be mediated by different neural regions. Second, current results show that the highest anxiolytic effect was observed in the study with the highest proportion of male patients (Rosenberg et al., 2010a) suggesting that demographic and/or clinical characteristics of patients might predict the response to DTMS. Third, the anxiolytic effect did not depend on antidepressants, while the antidepressant effect might be enhanced by concurrent treatment with antidepressants. Fourth, the anxiolytic effect cannot be entirely explained by selection of studies with unusually high effect sizes because there was little evidence for publication bias in the current analysis. Fifth, similarly to HF-rTMS (Berlim et al., 2011), the anxiolytic effect could be associated with improvements in psychosocial domains (quality of life, cognitive functioning) observed after high-frequency DTMS (Levkovitz et al., 2009).

In conclusion, current results suggest that high-frequency DTMS might have both anxiolytic and antidepressant properties in treatment-resistant, unipolar major depression. Future controlled studies are necessary to investigate the neural correlates, predictors, and durability of anxiolytic effects of DTMS in unipolar major depression.

Conflict of interest

Dr. Kedzior and Ms. Gellersen report no conflicts of interest. Dr. Roth and Prof. Zangen are co-inventors of the deep TMS H-coil technology, serve as consultants, and have financial interests in Brainsway which produces the H-coil system. Current results were presented at the Magstim 2015 Neuroscience Conference (May 9–10, 2015), Oxford, UK.

Table 1
Study details.

Study (by year and first author); country (research centre)	Sample size at baseline	Age (mean ± *SD*) of all patients at baseline	Female patients at baseline	Concurrent antidepressants (% of patients at baseline)	Dropouts (number of patients and reasons)	Scale	Baseline score Mean ± *SD* (*N*)	Final score (after 20 DTMS sessions) Mean ± *SD* (*N*)
Levkovitz et al. (2009); Israel (Shalvata Mental Health Centre)[a]	23	46 ± 13	48%	0%	1 sensory disturbance unrelated to treatment, 2 uncooperative with treating staff, 1 responded well and withdrew early	HDRS24 HARS	31 ± 4 (19) 18 ± 4 (19)	15 ± 13 (19)[b] 9 ± 6 (19)[b]
Rosenberg et al. (2010a); Israel (Beer Ya'akov Mental Health Centre)	7	47 ± 12	14%	0%	1 insomnia, 1 lack of response	HDRS24 HARS	27 ± 4 (7) 22 ± 4 (7)	17 ± 7 (7) LOCF 11 ± 5 (7) LOCF
Rosenberg et al. (2010b); Israel (Beer Ya'akov Mental Health Centre)	6	41 ± 13	67%	50%	3 lack of response, 1 suicidal ideation	HDRS24 HARS	31 ± 4 (6) 25 ± 9 (6)	16 ± 10 (6) LOCF 13 ± 9 (6) LOCF
Isserles et al. (2011); Israel (Beer Ya'akov Mental Health Centre & Hadassah-Hebrew University Medical Centre)[c]	25	45 ± 13	45%	100%	1 seizure, 1 suicidal ideation, 1 intolerance, 1 high motor threshold, 4 lack of response, 2 personal reasons	HDRS24 HARS		16 ± 2 (20) LOCF[d] 8 ± 1 (20) LOCF[d]
Berlim et al. (2014); Canada (Douglas Mental Health University Institute)	17	47 ± 13	76%	100%	2 scalp discomfort	HDRS21 HARS	22 ± 6 (17) 19 ± 8 (17)	11 ± 5 (17) LOCF 9 ± 5 (17) LOCF
Harel et al. (2014); Israel (Shalvata Mental Health Centre)	29	41 ± 11	48%	38%	1 safety reasons before 1st treatment, 2 non-compliance with study protocol	HDRS21 HARS		9 ± 1 (26)[d] 5 ± 1 (26)[d]

Notes. All values ending with exactly 0.5 were rounded as follows to reduce the rounding error in the current analysis: zero and uneven numbers were rounded upwards (1.5=2), even numbers were rounded downwards (2.5=2).
Abbreviations: DTMS, deep transcranial magnetic stimulation; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; LOCF, last observation carried forward; *N*, number of patients; *SD*, standard deviation; *SEM*, standard error of the mean.

[a] Data from H1-coil group only (the other three groups were stimulated with different intensity-laterality using different H-coil types in this study).
[b] Scores one week after DTMS.
[c] Data from the control group only ('No cognitive-emotional reactivation group'; the other two groups received either positive or negative cognitive-emotional priming prior to DTMS).
[d] Mean difference (baseline – final) ± *SEM*.

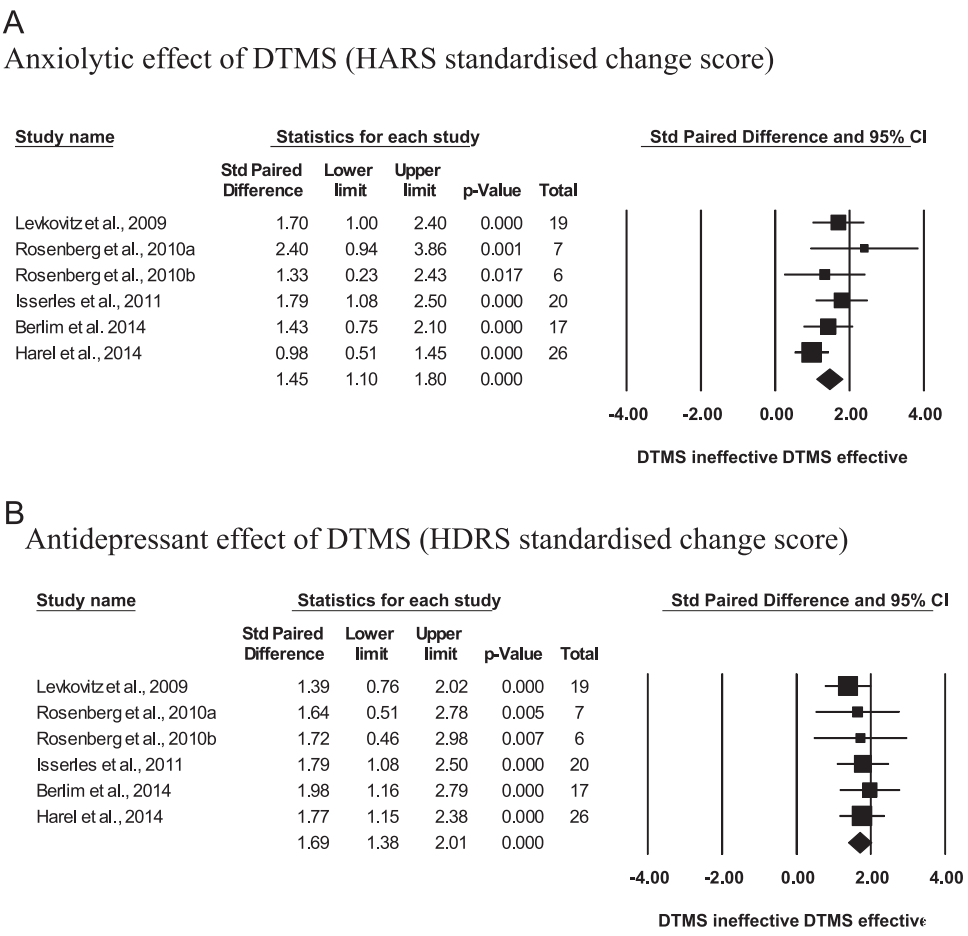

Fig. 1. Forest plots of random-effects meta-analyses of six open-label studies. Note. The effect sizes are standardised paired mean differences (Cohen's d) between baseline and after last acute DTMS. Both figures show the effect sizes in individual studies and the pooled weighted effect sizes of all studies (last row of each figure). Abbreviations: *CI*, confidence interval; DTMS, deep transcranial magnetic stimulation; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; Std Paired Difference, standardised paired difference in means (Cohen's *d*; effect size).

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.psychres.2015.11.032.

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