Systematic Review

Repetitive Transcranial Magnetic Stimulation Over the Dorsolateral Prefrontal Cortex for Treating Posttraumatic Stress Disorder: An Exploratory Meta-Analysis of Randomized, Double-Blind and Sham-Controlled Trials

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Objective: Repetitive transcranial magnetic stimulation (rTMS) applied to the dorsolateral prefrontal cortex (DLPFC) has yielded promising results as a treatment for posttraumatic stress disorder (PTSD). However, to date, no quantitative review of its clinical utility has been published.

Method: We searched for randomized and sham-controlled trials from 1995 to March 2013 using MEDLINE, Embase, PsycINFO, CENTRAL, and SCOPUS. We then performed an exploratory random effects meta-analysis.

Results: Studies on rTMS applied to the right DLPFC included 64 adults with PTSD. The pooled Hedges g effect size for pre and post changes in clinician-rated and self-reported PTSD symptoms were, respectively, 1.65 ($P < 0.001$) and 1.91 ($P < 0.001$), indicating significant and large-sized differences in outcome favouring active rTMS. Also, there were significant pre and post decreases with active rTMS in overall anxiety (Hedges $g = 1.24$; $P = 0.02$) and depressive (Hedges $g = 0.85$; $P < 0.001$) symptoms. Dropout rates at study end did not differ between active and sham rTMS groups. Regarding rTMS applied to the left DLPFC, there is only one study published to date (using a high frequency protocol), and its results showed that active rTMS seems to be superior overall to sham rTMS.

Conclusions: Our exploratory meta-analysis shows that active rTMS applied to the DLPFC seems to be effective and acceptable for treating PTSD. However, the small number of subjects included in the analyses limits the generalizability of these findings. Future studies should include larger samples and deliver optimized stimulation parameters.

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Stimulation magnétique transcrânienne répétitive sur le cortex dorsolatéral préfrontal pour traiter le trouble de stress post-traumatique : une méta-analyse exploratoire d'essais randomisés à double insu et contrôlés par simulation

Objectif : La stimulation magnétique transcrânienne répétitive (SMTr) appliquée au cortex dorsolatéral préfrontal (CDLPF) a produit des résultats prometteurs comme traitement du trouble de stress post-traumatique (TSPT). Cependant, jusqu'ici, aucune revue quantitative de son utilité clinique n'a été publiée.

Méthode : Nous avons cherché des essais randomisés et contrôlés par simulation de 1995 à mars 2013 à l'aide de MEDLINE, Embase, PsycINFO, CENTRAL, et SCOPUS. Nous avons ensuite procédé à une méta-analyse exploratoire des effets aléatoires.

Résultats : Les études sur la SMTr appliquée au CDLPF droit comportaient 64 adultes souffrant du TSPT. La taille d'effet calculée selon le g de Hedges pour les changements avant et après des symptômes de TSPT cotés par les cliniciens et auto-déclarés était, respectivement, 1,65 (P < 0,001) et 1,91 (P < 0,001), indiquant des différences significatives et de forte taille des résultats favorisant la SMTr active. De même, il y avait des diminutions significatives avant et après la SMTr active dans les symptômes d'anxiété généralisée

(g de Hedges = 1,24; P = 0,02) et dépressifs (g de Hedges = 0,85; P < 0,001). Les taux d'abandon au terme de l'étude ne différaient pas entre les groupes de SMTr active et de SMTr simulée. En ce qui concerne la SMTr appliquée au CDLPF gauche, il n'y a qu'une étude publiée à ce jour (utilisant un protocole de haute fréquence), et les résultats indiquent que la SMTr active semble être généralement supérieure à la SMTr simulée.

Conclusions : Notre méta-analyse exploratoire indique que la SMTr active appliquée au CDLPF semble être efficace et acceptable pour traiter le TSPT. Toutefois, le nombre réduit de sujets inclus dans les analyses limite d'une certaine manière la généralisabilité de ces résultats. En résumé, les futures études devraient inclure des échantillons plus grands et produire des paramètres de stimulation optimisés.

Asevere and often chronic psychiatric illness with a lifetime prevalence in community samples of up to 8%,[1,2] PTSD occurs in susceptible people who have been exposed to extremely traumatic events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others.[3] PTSD is characterized by pervasive hyperarousal, intrusive thoughts, exaggerated startle response, flashbacks, nightmares, sleep disturbances, emotional numbness, and persistent avoidance of trauma-associated stimuli,[4] and is associated with significant personal distress and disability, as well as with high social and economic costs.[5,6]

Current first-line treatment strategies for PTSD include ADs (for example, selective serotonin reuptake inhibitors, and serotonin–norepinephrine reuptake inhibitors) and psychotherapy (for example, prolonged exposure or trauma-focused cognitive-behavioral therapy).[7,8] However, a considerable proportion of patients with PTSD remain significantly ill despite undergoing such relatively diverse therapeutic options, and are thereby left with lasting negative repercussions on their global functioning and well-being.[9] Therefore, novel treatments for PTSD are of considerable interest, one of which is rTMS.[10]

rTMS is a noninvasive neuromodulation technique that is able to modulate cortical and subcortical function with the use of rapidly changing electromagnetic fields generated by a coil of wire placed over the scalp.[11] Depending on the parameters of stimulation, rTMS can either decrease or increase cortical excitability in relatively focal areas, with frequencies of 1 Hz or less (LF-rTMS) usually being inhibitory and higher frequencies (≥5 Hz; HF-rTMS)

Abbreviations

AD	antidepressant
AP	antipsychotic
DLPFC	dorsolateral prefrontal cortex
ES	effect size
HF	high frequency
LF	low frequency
LOCF	last observation carried forward
MDD	major depressive disorder
PTSD	posttraumatic stress disorder
RCT	randomized controlled trial
rTMS	repetitive transcranial magnetic stimulation

Clinical Implications

- A considerable proportion of patients with PTSD remain significantly ill despite receiving several therapeutic interventions.

- rTMS applied to the DLPFC is a promising therapeutic approach for patients with resistant PTSD.

- Our exploratory meta-analysis has shown that active rTMS applied to the DLPFC seems to be effective and acceptable for treating PTSD.

Limitations

- The generalizability of our findings is somewhat limited by the small number of subjects included in the analyses, the heterogeneity of the stimulation protocols, and the lack of medium- to long-term effectiveness data on rTMS for PTSD.

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usually being excitatory.[12] To date, rTMS has been shown, for example, to be an effective treatment for MDD and schizophrenia.[13,14]

Although the pathophysiology of PTSD remains unclear, growing evidence from functional neuroimaging studies suggest that it is consistently associated with hypoactivation of the prefrontal cortex (including medial and dorsolateral regions) and hyperactivation of deeper brain structures, such as the amygdala.[15–17] The DLPFC, in particular, is involved in many complex cognitive and behavioural functions that are relevant to PTSD[18,19] and that have been shown to be reliably modulated by rTMS (for example, executive functioning,[20,21] working memory,[22,23] verbal memory,[24] supervisory attentional control,[25,26] and reasoning and decision making[27,28]). As a result, numerous recent open-label trials and RCTs have been carried out and have shown that rTMS targeting the DLPFC is potentially useful for treating PTSD.[29–34] However, to date, no attempt has been made to integrate the findings from these studies to produce a more accurate estimation of the efficacy and acceptability of rTMS applied to the right and the left DLPFC for PTSD. Therefore, we conducted the present systematic review and exploratory meta-analysis to examine this issue.

Methodology of the Literature Review

Search Strategy

We identified articles for inclusion in this meta-analysis by searching MEDLINE, Embase, PsycINFO, CENTRAL, and SCOPUS from January 1, 1995, to March 12, 2013, and

by screening the bibliography of all included studies. The search syntaxes included a combination of the following key words: "transcranial magnetic," "rTMS," "magnetic stimulation," "stress*," "PTSD," and "trauma*." Detailed information regarding the search procedures (including syntaxes, parameters, and results) are shown in the online eAppendix.

Study Selection

Candidate studies (judged by their title and abstract) had to satisfy the following criteria[35]: study validity—random allocation, double-blinded, sham-controlled (that is, coil angled on the scalp or use of a sham coil), parallel design, of 5 subjects or more with PTSD randomized per study arm; sample characteristics—subjects aged 18 to 75 years with a diagnosis of primary PTSD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,[36] or the International Classification of Diseases, Tenth Revision[37] criteria; treatment characteristics—LF- (≤ 1 Hz) or HF- (≥ 5 Hz) rTMS applied over the left or the right DLPFC for 5 or more sessions; and, publication-related—articles written in English. Studies were excluded if their protocol involved rTMS started concomitantly with new psychotropics (for example, ADs or APs).

Data Extraction

Data were recorded in a structured fashion as follows: sample characteristics—mean age, sex, and illness severity; rTMS-related—stimulation frequency and intensity (including the total number of stimuli delivered), number of treatment sessions, and type of sham; primary outcome measure—score changes (pre- and post-rTMS) on validated clinician-reported measures (for example, the Treatment-Outcome PTSD Scale[38]); secondary outcome measure—score changes (pre- and post-rTMS) on validated self-reported measures (for example, the PTSD Checklist[39]); tertiary outcome measures—score changes (pre- and post-rTMS) on validated anxiety (for example, the Hamilton Anxiety Rating Scale[40] and the State-Trait Anxiety Inventory[41]), and depression (for example, the Hamilton Depression Rating Scale[42] and the Beck Depression Inventory[43]) measures; and, acceptability of treatment—overall dropout rates for active and sham rTMS groups at study end.

Study Quality

We used the well-known Jadad Scale to assess the quality of the included RCTs.[44] Criteria evaluated by this scale include randomization, blinding, and report of participant withdrawal, and possible scores range from 0 to 5. A priori, studies with a Jadad score of 3 or more were deemed higher quality and those with a score of 0 to 2 were classified as lower quality.[45]

Data Synthesis and Analyses

Analyses were performed using Comprehensive Meta-Analyses version 2.0 (Biostat, Englewood, NJ) and IBM SPSS version 20 (IBM Corporation, Chicago, IL).

We used a random-effects model as we assumed that the true ESs had likely varied between the included RCTs.[46] If provided, intention-to-treat data, using a method, such as LOCF, were preferred over data from completers.[47] Score changes (pre- and post-rTMS) were investigated with pooled Hedges g ESs. As we could not retrieve the correlations between pre- and post-rTMS measures from the individual RCTs, we followed the recommendation by Rosenthal[48] and assumed a conservative estimation ($r = 0.7$). Also, as recommended by the Cochrane Collaboration,[35] in studies comparing 3 treatment conditions (that is, 2 active, compared with 1 sham), we split the control group into 2 equal parts (so that the total number of control subjects added up to its original size) and compared each half with the 2 active conditions. For the study by Boggio et al,[31] we had to estimate the means and standard deviations by, respectively, reviewing the published graphs and imputting average values from other RCTs included in this meta-analysis.[49] Acceptability of treatment was assessed with odds ratios for differential dropout rates between active and sham rTMS groups.[50,51] Also, to rule out the presence of baseline between-group differences in illness severity, we computed pooled Hedges g ESs for subjects' PTSD, depression, and anxiety scores. Finally, we carried out an exploratory analysis by subgrouping the included studies into LF- and HF-rTMS protocols.

Heterogeneity was assessed using the Q statistic and I^2 index.[52] Values of $P < 0.1$ for the former and (or) more than 35% for the latter were deemed as indicative of significant between-study heterogeneity.[50] We further used funnel plots, the fail-safe number (that is, the number of missing studies that would make a specific result statistically nonsignificant at $P > 0.05$),[53] and Egger's Regression Intercept[54] to test for the presence of publication bias.[50,52]

Pooled statistical analyses were not conducted when 2 studies or less were available for a particular brain target (that is, left or right DLPFC) owing to the impossibility of producing funnel plots and estimating publication bias.[55] Instead, in this context we reported individual study results in a descriptive manner only.

Results

Literature Search

We retrieved 98 references (after discarding duplicates) from MEDLINE, PsycINFO, Embase, CENTRAL, and SCOPUS. Among these, 3 met the eligibility criteria,[31–33] comprising 4 comparisons between active and sham rTMS applied to the right DLPFC and a single comparison between active and sham rTMS applied to the left DLPFC.

Table 1 Included RCTs on rTMS over the DLPFC for PTSD: main characteristics

Study	Active rTMS			Sham rTMS			
	n	Age, years (SD)	Female/male, *n*	*n*	Age, years (SD)	Female/male, *n*	Strategy
Cohen et al[32]	8	40.8 (9.9)	1/7	6	42.8 (14.8)	2/4	90° angulation
	10	41.8 (11.4)	4/6	6	42.8 (14.8)	2/4	90° angulation
Boggio et al[31]	10	40.7 (13.6)	6/4	10	45.9 (11.4)	7/3	Sham coil
	10	47.1 (12.1)	7/3	10	45.9 (11.4)	7/3	Sham coil
Watts et al[33]	10	54.0 (12.3)	1/9	10	57.8 (11.8)	1/9	Sham coil

DLPFC = dorsolateral prefrontal cortex; LOCF = last observation carried forward; PTSD = posttraumatic stress disorder;

Study Quality and Strategy for Missing Data

The 3 included RCTs had a score of 3 or more in the Jadad Scale and were thus considered to have a high overall methodological quality. Regarding the strategies used by the RCTs to deal with missing data, 1 employed the LOCF approach,[31] 1 performed completers-only analyses,[32] and 1 reported no patient dropout at study end.[33]

Repetitive Transcranial Magnetic Stimulation Over the Right Dorsolateral Prefrontal Cortex

Included Randomized Controlled Trials:

Main Characteristics

Three RCTs on rTMS applied to the right DLPFC were included in this meta-analysis, comprising 64 subjects with PTSD, of whom 38 were randomized to active rTMS (mean age 44.3 years [SD 6.5]; 68.4% males), and 26 were randomized to sham rTMS (mean age 48.8 years [SD 7.9]; 61.5% males). All RCTs administered 10 rTMS sessions in total, and the mean number of magnetic pulses delivered was 6250 (SD 6652).[1] The main characteristics of the included RCTs are described in Table 1. The funnel plots and the additional forest plots are shown in the online eAppendix.

Clinician-Reported Posttraumatic Stress Disorder Symptoms

The pooled Hedges *g* ES for changes from baseline to end point on clinician-reported PTSD symptoms was 1.65 (95% CI 1.08 to 2.23; $z = 5.66$, $P < 0.001$), indicating a significant and large-sized difference in outcome favouring active rTMS (Figure 1).

Heterogeneity between RCTs did not exceed that expected by chance (Q = 2.63, $df = 3$, $P = 0.45$; $I^2 = 0$), implying that the variance among the ESs was not greater than expected by sampling error. Finally, the associated funnel plot was reasonably symmetrical, the fail-safe *N* was 28 and Egger's regression intercept was –1.77 ($t = 0.43$, $df = 2$, 2-tailed $P = 0.71$), all suggesting a low risk of publication bias.

Self-Reported Posttraumatic Stress Disorder Symptoms

The pooled Hedges *g* ES for changes from baseline to end point on self-reported PTSD symptoms was 1.91 (95% CI 1.07 to 2.74; $z = 4.48$, $P < 0.001$), indicating a significant and large-sized difference in outcome favouring active rTMS (Figure 2).

Heterogeneity between RCTs was significant (Q = 5.58, $df = 3$, $P = 0.13$, $I^2 = 46.21\%$). Visual inspection of the forest plot suggested that this was caused by the Cohen et al[32] LF-rTMS protocol, and its removal from the analysis resulted in nonsignificant heterogeneity (Q = 0.49, $df = 2$, $P = 0.78$, $I^2 = 0\%$), although the clinical results remained unaltered in terms of a statistically significant between-group difference (Hedges *g* = 2.33, 95% CI 1.63 to 3.02; $z = 6.54$, $P < 0.001$). Finally, the associated funnel plot was reasonably symmetrical, the fail-safe *N* was 36, and Egger's regression intercept was –5.46 ($t = 0.63$, $df = 2$, 2-tailed $P = 0.59$), all suggesting a low risk of publication bias.

Overall Anxiety Symptoms

The pooled Hedges *g* ES for changes from baseline to end point on anxiety symptoms was 1.24 (95% CI 0.21 to 2.27; $z = 2.37$, $P = 0.02$), indicating a significant and large-sized difference in outcome favouring active rTMS (Figure 3).

| | rTMS parameters | | | | |
Brain target	Frequency, Hz / Sessions	rMT, % / total pulses	Type of trauma	Missing data approach	Study quality[44]
Right DLPFC	1/10 10/10	80/1000 80/4000	Combat (*n* = 4), motor vehicle accident (*n* = 11), sexual abuse (*n* = 2), assault (*n* = 2), work accident (*n* = 4), or death of a relative (*n* = 1). Time since the trauma = 5.4 years (SD 7.0).	Completers-only analyses	4
Right DLPFC	20/10	80/16 000	Sexual abuse (*n* = 3), assault (*n* = 4), death or severe disease of a relative (*n* = 11), or kidnapping or death threats (*n* = 2). Time since the trauma = 3.9 years (SD 4.3).	LOCF	4
Left DLPFC	20/10	80/16 000	Sexual abuse (*n* = 3), assault (*n* = 4), death or severe disease of a relative (*n* = 10), or kidnapping or death threats (*n* = 3). Time since the trauma = 3.8 years (SD 4.3).	LOCF	4
Right DLPFC	1/10	90/4000	Combat (*n* = 8), sexual abuse (*n* = 1), assault (*n* = 1), or multiple (*n* = 10). Time since the trauma = 39.7 years (13.9).	No patient drop out	3
RCT = randomized controlled trial; rMT = resting motor threshold; rTMS = repetitive transcranial magnetic stimulation					

Heterogeneity between RCTs was significant (Q = 9.83, *df* = 3, *P* = 0.02, I^2 = 69.49%). Visual inspection of the forest plot suggested that this heterogeneity resulted from RCTs clearly subdivided into 2 groups: 1 reporting relatively high pre and post changes in anxiety symptoms (that is, the HF-rTMS protocols of Cohen et al[32] and Boggio et al[31]), and the other reporting relatively low pre and post changes in anxiety symptoms (that is, the LF-rTMS protocols of Cohen et al[32] and Watts et al[33]). Finally, the associated funnel plot was reasonably symmetrical, the fail-safe *N* was 16, and Egger's regression intercept was 1.24 (*t* = 0.19, *df* = 2, 2-tailed *P* = 0.87), all suggesting a low risk of publication bias.

Depressive Symptoms
The pooled Hedges *g* ES for changes from baseline to end point on depressive symptoms was 0.85 (95% CI 0.34 to 1.36; *z* = 3.28, *P* = 0.001), indicating a significant and large-sized difference in outcome favouring active rTMS (Figure 4).

Heterogeneity between RCTs was not statistically significant (Q = 0.85, *df* = 3, *P* = 0.84, I^2 = 0%). Finally, the associated funnel plot was reasonably symmetrical, the fail-safe *N* was 8, and Egger's regression intercept was 1.84 (*t* = 1.6, *df* = 2, 2-tailed *P* = 0.25), all suggesting a low risk of publication bias.

Acceptability of Repetitive Transcranial Magnetic Stimulation Treatment
Overall, no differences on dropout rates at study end were observed between active and sham rTMS groups (10.52% [4/38], compared with 21.87% [7/32], respectively; OR 0.42; *z* = −1.21, *P* = 0.23).

Heterogeneity between RCTs was not statistically significant (Q = 1.26, *df* = 3, *P* = 0.74, I^2 = 0%). Finally, the associated funnel plot was reasonably symmetrical, and Egger's regression intercept was −0.52 (*t* = 0.26, *df* = 2, 2-tailed *P* = 0.82), all suggesting a low risk of publication bias.
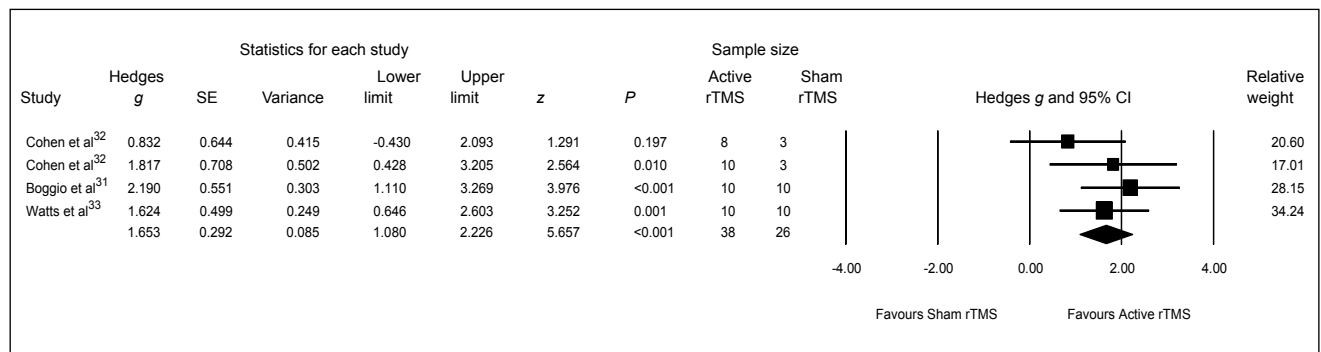
Baseline Illness Severity
Subjects receiving active rTMS (compared with those receiving sham rTMS) had significantly higher baseline scores on clinician-reported PTSD symptoms (Hedges *g* = 0.74, *z* = 2.86, *P* = 0.004), self-reported PTSD symptoms (Hedges *g* = 0.75, *z* = 2.87, *P* = 0.004), and depressive symptoms (Hedges *g* = 0.59, *z* = 2.33, *P* = 0.02). However, they did not differ in their baseline overall anxiety symptoms (Hedges *g* = 0.34, *z* = 1.34, *P* = 0.18).

Subgroup Analyses: High Frequency, Compared With Low Frequency, Repetitive Transcranial Magnetic Stimulation Protocols
Because of the small number of included RCTs we did not perform between-group statistical analyses. HF-rTMS protocols resulted in significant and large-sized improvements in clinician-reported PTSD symptoms (Hedges *g* = 2.05, *z* = 4.71, *P* < 0.001), self-reported PTSD symptoms (Hedges *g* = 2.32, *z* = 5.07, *P* < 0.001), overall anxiety symptoms (Hedges *g* = 2.15, *z* = 4.6, *P* < 0.001), and depressive symptoms (Hedges *g* = 0.79, *z* = 2.17, *P* = 0.03). In contrast, LF-rTMS protocols yielded statistically significant improvements in clinician-reported PTSD symptoms (Hedges *g* = 1.33, *z* = 3.36, *P* = 0.001), self-reported PTSD symptoms (Hedges *g* = 2.34, *z* = 4.13,

Figure 1 Meta-analysis of active, compared with sham, rTMS for PTSD: clinician-reported PTSD symptoms

Study	Hedges g	SE	Variance	Lower limit	Upper limit	z	P	Active rTMS	Sham rTMS	Hedges g and 95% CI	Relative weight
Cohen et al[32]	0.832	0.644	0.415	-0.430	2.093	1.291	0.197	8	3		20.60
Cohen et al[32]	1.817	0.708	0.502	0.428	3.205	2.564	0.010	10	3		17.01
Boggio et al[31]	2.190	0.551	0.303	1.110	3.269	3.976	<0.001	10	10		28.15
Watts et al[33]	1.624	0.499	0.249	0.646	2.603	3.252	0.001	10	10		34.24
	1.653	0.292	0.085	1.080	2.226	5.657	<0.001	38	26		

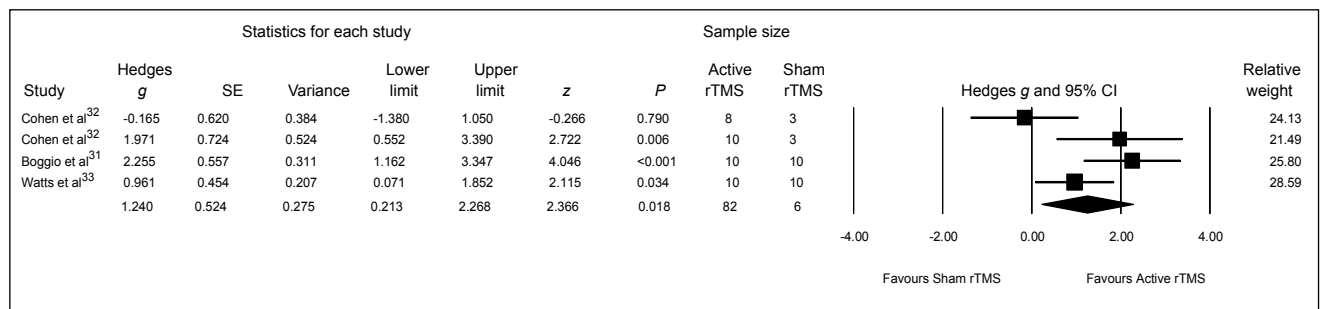Favours Sham rTMS   Favours Active rTMS

PTSD = posttraumatic stress disorder; rTMS = repetitive transcranial magnetic stimulation; SE = standard error

Figure 2 Meta-analysis of active, compared with sham, rTMS for PTSD: patient-reported PTSD symptoms
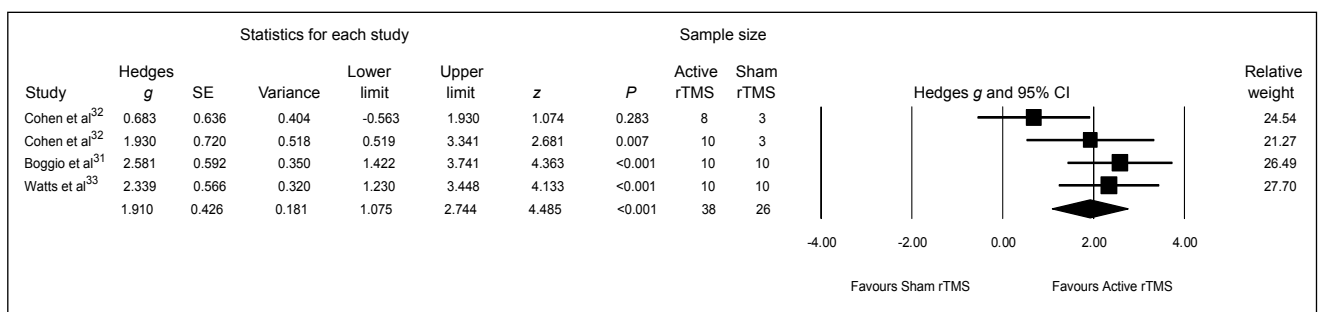
Study	Hedges g	SE	Variance	Lower limit	Upper limit	z	P	Active rTMS	Sham rTMS	Hedges g and 95% CI	Relative weight
Cohen et al[32]	0.683	0.636	0.404	-0.563	1.930	1.074	0.283	8	3		24.54
Cohen et al[32]	1.930	0.720	0.518	0.519	3.341	2.681	0.007	10	3		21.27
Boggio et al[31]	2.581	0.592	0.350	1.422	3.741	4.363	<0.001	10	10		26.49
Watts et al[33]	2.339	0.566	0.320	1.230	3.448	4.133	<0.001	10	10		27.70
	1.910	0.426	0.181	1.075	2.744	4.485	<0.001	38	26		

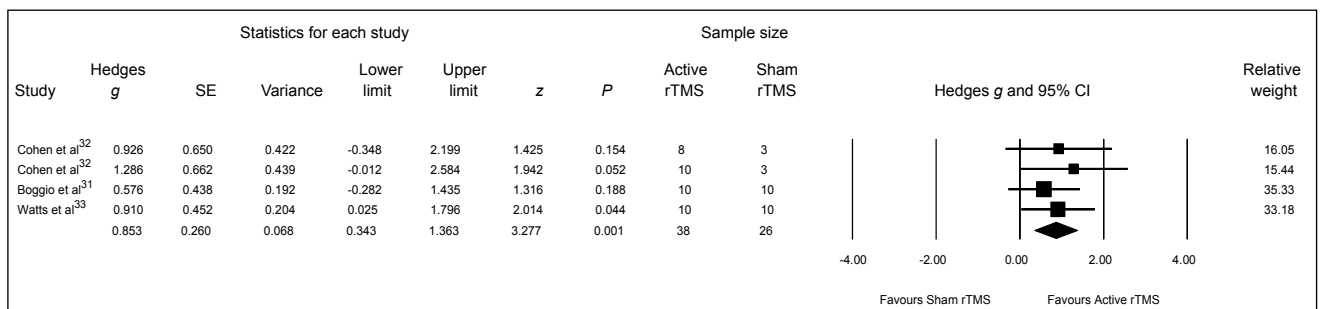Favours Sham rTMS   Favours Active rTMS

PTSD = posttraumatic stress disorder; rTMS = repetitive transcranial magnetic stimulation; SE = standard error

Figure 3 Meta-analysis of active, compared with sham, rTMS for PTSD: overall anxiety symptoms

Study	Hedges g	SE	Variance	Lower limit	Upper limit	z	P	Active rTMS	Sham rTMS	Hedges g and 95% CI	Relative weight
Cohen et al[32]	-0.165	0.620	0.384	-1.380	1.050	-0.266	0.790	8	3		24.13
Cohen et al[32]	1.971	0.724	0.524	0.552	3.390	2.722	0.006	10	3		21.49
Boggio et al[31]	2.255	0.557	0.311	1.162	3.347	4.046	<0.001	10	10		25.80
Watts et al[33]	0.961	0.454	0.207	0.071	1.852	2.115	0.034	10	10		28.59
	1.240	0.524	0.275	0.213	2.268	2.366	0.018	82	6		

Favours Sham rTMS   Favours Active rTMS

PTSD = posttraumatic stress disorder; rTMS = repetitive transcranial magnetic stimulation; SE = standard error

Figure 4 Meta-analysis of active, compared with sham, rTMS for PTSD: depressive symptoms

Study	Hedges g	SE	Variance	Lower limit	Upper limit	z	P	Active rTMS	Sham rTMS	Hedges g and 95% CI	Relative weight
Cohen et al[32]	0.926	0.650	0.422	-0.348	2.199	1.425	0.154	8	3		16.05
Cohen et al[32]	1.286	0.662	0.439	-0.012	2.584	1.942	0.052	10	3		15.44
Boggio et al[31]	0.576	0.438	0.192	-0.282	1.435	1.316	0.188	10	10		35.33
Watts et al[33]	0.910	0.452	0.204	0.025	1.796	2.014	0.044	10	10		33.18
	0.853	0.260	0.068	0.343	1.363	3.277	0.001	38	26		

Favours Sham rTMS   Favours Active rTMS

PTSD = posttraumatic stress disorder; rTMS = repetitive transcranial magnetic stimulation; SE = standard error

$P < 0.001$), and depressive symptoms (Hedges $g = 0.91$, $z = 2.47$, $P = 0.001$), although there was no significant change in overall anxiety symptoms (Hedges $g = 0.55$, $z = 1.38$, $P = 0.17$).

Repetitive Transcranial Magnetic Stimulation Over the Left Dorsolateral Prefrontal Cortex

Only the RCT by Boggio et al[31] has reported efficacy data on rTMS applied to the left DLPFC. Briefly, they have shown that an HF protocol administered over 10 sessions was associated with a Hedges g ES for pre and post changes in clinician-rated and self-reported PTSD symptoms of 0.97 (95% CI 0.08 to 1.86; $P = 0.03$) and 1.29 (95% CI 0.36 to 2.22; $P = 0.007$), respectively. Further, they have reported a significant decrease in clinician-rated overall anxiety symptoms (Hedges $g = 1.01$; 95% CI 0.12 to 1.91, $P = 0.03$), but only a statistical trend toward a decrease in clinician-rated depressive symptoms (Hedges $g = 0.86$; 95% CI –0.02 to 1.75, $P = 0.05$).

Discussion

The main objective of our meta-analysis was to assess the efficacy and the acceptability of rTMS applied to the right and to the left DLPFC for treating PTSD. Briefly, we have shown that active rTMS applied to the right DLPFC significantly reduced clinician-rated and patient-reported core PTSD symptoms, as well as overall anxiety and depressive symptoms following 10 daily sessions. Importantly, we found that patients who received active rTMS over the right DLPFC were significantly more ill at baseline, and it is possible that active treatment might have been even more effective than sham rTMS if both groups were comparable in terms of baseline psychopathology. Regarding rTMS applied over the left DLPFC, the only RCT published to date has shown promising results for an HF protocol although additional studies are needed to allow for pooled analyses. Finally, rTMS over the DLPFC seemed to be an acceptable treatment for PTSD as indexed by differential dropout rates at study end.

It is of interest that both LF- and HF-rTMS applied to the right DLPFC exerted a positive clinical effect on PTSD and its associated symptoms; this is counterintuitive, at least neurophysiologically, as LF- and HF-rTMS are believed to have opposite effects on cortical excitability (that is, usually inhibitory and excitatory effects, respectively).[56,57] At present, there is no clear explanation for this paradoxical observation, although recent studies have shown, for example, that LF-rTMS at relatively low intensities (for example, ≤90% of the resting motor threshold) sometimes fails to induce a measurable change on motor excitability, and that its effects are associated with a large inter-individual variability (perhaps related to the baseline excitability level of the targeted cortical area[58–60]), with some subjects even showing facilitatory effects.[61] Nevertheless, our exploratory subgroup analyses further indicated that HF-rTMS protocols (compared with LF-rTMS protocols) may be associated with slightly greater clinical improvements

in core PTSD symptoms (as assessed by clinician-rated measures), as well as in overall anxiety symptoms. This finding, although clearly preliminary, could be explained, at least in part, by the excitatory effects of HF-rTMS on the underlying cortical tissue that may have counteracted the hypofrontality usually observed in patients with PTSD and thus enhanced the modulation of fear-related emotional responses and encoding or consolidation of traumatic memories by indirectly inhibiting the amygdala.[15,16,62–64] Additionally, HF-rTMS might have inhibited contralateral brain structures involved in memory retrieval networks.[31] In summary, the results of our meta-analysis only partially support the conventional model of the neurocircuitry underlying PTSD (involving relative hypoactivity of frontal regions and hyperactivity of subcortical regions, such as the amygdala[65]), as we have shown that LF-rTMS (an inhibitory intervention) is also potentially effective for PTSD and might produce its therapeutic effects by inhibiting a possibly lateralized right-sided hyperactivity of the DLPFC.[31] However, one has to be extremely careful when attempting to explain the underlying neurobiology of PTSD and (or) the putative mechanisms of action of rTMS based on the results from these small RCTs.

Although clearly preliminary, our findings are encouraging when viewed in the context of more established treatments for PTSD. For example, a recent large meta-analysis has shown that ADs given for 4 to 12 weeks (compared with placebo) were associated with a Hedges g ES of 0.23 (95% CI 0.15 to 0.31; $n = 4112$) for reducing clinician-reported PTSD symptoms.[7] Further, prolonged exposure, a specific therapy that includes multiple sessions of imaginal and in vivo exposure, has been associated with a Hedges g ES of 1.08 (95% CI 0.69 to 1.46; $n = 675$) for improving core PTSD symptoms.[66] Also, a meta-analysis reported that the atypical APs risperidone and olanzapine, when used as add-ons or monotherapy (compared with placebo), were associated with a small-to-medium ES for reducing clinician-reported PTSD symptoms (that is, standardized mean difference = 0.45, 95% CI 0.14 to 0.75; $n = 192$).[67]

Nevertheless, as the optimum rTMS protocol for PTSD has yet to be determined, future studies should investigate the use of more intense treatment protocols (for example, higher numbers of total magnetic pulses and [or] percentage of the resting motor threshold), identify more clinically relevant neuromodulation protocols (for example, preconditioning paradigms or priming and different waveforms),[68,69] as well as apply baseline electrophysiological and neuroimaging evaluations to better predict which patients will benefit from treatment.[70,71] Also, further research should assess whether rTMS can potentiate the efficacy of a concomitantly administered psychotherapy.[10] Finally, novel developments in the field of neuromodulation, such as the H coil,[72] might also enhance the clinical utility of rTMS for PTSD by allowing the direct stimulation of relatively deeper brain structures, while theta burst stimulation might produce more consistent and enduring positive after-effects.[73]

Limitations

First, we only retrieved 3 RCTs with relatively small samples. Nevertheless, pooled analyses for rTMS applied to the right DLPFC already indicated significantly better clinical results for active, compared with sham, rTMS. Second, the quality of the available sham rTMS conditions is still unresolved,[12] and the use of coil tilting and (or) first-generation sham coils may not have been optimal.[74] In addition, we could not assess the integrity of blinding in the included RCTs owing to the absence of information in this regard. However, we have recently shown that a similar percentage of subjects with MDD receiving active, compared with sham, rTMS were able to correctly guess their treatment allocation at study end (that is, 52%, compared with 59%, respectively; risk difference = –0.04, z = –0.51, P = 0.61).[75] Third, the strategy most commonly used for locating the right DLPFC (that is, the 5 cm method) has been recently criticized for its inaccuracy[12] and future studies may benefit from the use of neuronavigation.[76] Fourth, we could not estimate the stability of the medium- to long-term effects of rTMS for PTSD or its cost-effectiveness, and this is especially relevant considering the labour-intensive and time-consuming nature of this treatment.[77] Nevertheless, preliminary evidence suggests that the positive clinical effects of rTMS for PTSD are sustained for up to 3 months following the study end.[31,33] Fifth, the subgroup analyses should be seen as exploratory in nature and thus far from conclusive. Sixth, the reliability of the analyses of heterogeneity and publication bias might have been relatively low owing to the small number of included studies.[78] Seventh, the extensive use of imputation and the lack of an analysis of rTMS-related side effects are additional limitations of our study. Eight, our decision to pool the results of LF- and HF-rTMS protocols applied to the right DLPFC is also a potential limitation of our study, particularly considering their likely distinct neurophysiological basis. Finally, meta-analyses have often been criticized for the potential of publication bias and for the inclusion of poor-quality trials.[50] However, in our study these concerns were addressed by the comprehensive and systematic review of the literature and by the use of stringent inclusion criteria.

Conclusion

Our exploratory meta-analysis suggests that rTMS applied to the DLPFC is a promising new treatment for PTSD, even though its evidence base is still limited to a few clinical studies. Clearly, future larger-scale RCTs should first and foremost investigate the putative differential efficacy of HF-, compared with LF-, rTMS protocols, as well as of left, compared with right DLPFC coil placements. Additionally, they should explore whether patients with distinct subtypes of PTSD preferentially respond to rTMS, whether its beneficial effects are maintained over time, and whether the improvement in PTSD symptoms observed after rTMS treatment is mediated, for example, by changes in related psychopathological dimensions, such as depressive symptoms. Finally, considering its overall safety record[74,79] and potential efficacy, we believe that rTMS could be currently offered, on a strictly humanitarian and compassionate basis, to patients with PTSD who remain significantly ill despite having received several conventional treatments for this condition (for example, pharmacotherapy and psychotherapy).

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