Should We Expand the Toolbox of Psychiatric Treatment Methods to Include Repetitive Transcranial Magnetic Stimulation (rTMS)? A Meta-Analysis of the Efficacy of rTMS in Psychiatric Disorders

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Objective: Repetitive transcranial magnetic stimulation (rTMS) is a safe treatment method with few side effects. However, efficacy for various psychiatric disorders is currently not clear.

Data sources: A literature search was performed from 1966 through October 2008 using PubMed, Ovid Medline, Embase Psychiatry, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and PsycINFO. The following search terms were used: *transcranial magnetic stimulation*, *TMS*, *repetitive TMS*, *psychiatry*, *mental disorder*, *psychiatric disorder*, *anxiety disorder*, *attention-deficit hyperactivity disorder*, *bipolar disorder*, *catatonia*, *mania*, *depression*, *obsessive-compulsive disorder*, *psychosis*, *posttraumatic stress disorder*, *schizophrenia*, *Tourette's syndrome*, *bulimia nervosa*, and *addiction*.

Study selection: Data were obtained from randomized, sham-controlled studies of rTMS treatment for depression (34 studies), auditory verbal hallucinations (AVH, 7 studies), negative symptoms in schizophrenia (7 studies), and obsessive-compulsive disorder (OCD, 3 studies). Studies of rTMS versus electroconvulsive treatment (ECT, 6 studies) for depression were meta-analyzed.

Data extraction: Standardized mean effect sizes of rTMS versus sham were computed based on pretreatment-posttreatment comparisons.

Data synthesis: The mean weighted effect size of rTMS versus sham for depression was 0.55 ($P < .001$). Monotherapy with rTMS was more effective than rTMS as adjunctive to antidepressant medication. ECT was superior to rTMS in the treatment of depression (mean weighted effect size −0.47, $P = .004$). In the treatment of AVH, rTMS was superior to sham treatment, with a mean weighted effect size of 0.54 ($P < .001$). The mean weighted effect size for rTMS versus sham in the treatment of negative symptoms in schizophrenia was 0.39 ($P = .11$) and for OCD, 0.15 ($P = .52$). Side effects were mild, yet more prevalent with high-frequency rTMS at frontal locations.

Conclusions: It is time to provide rTMS as a clinical treatment method for depression, for auditory verbal hallucinations, and possibly for negative symptoms. We do not recommend rTMS for the treatment of OCD.

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The first modern transcranial magnetic stimulation (TMS) device was developed during the early 1980s by Barker et al.[1,2] The device creates a strong pulse of electrical current which is sent through a coil and which induces a magnetic field pulse in a small area underlying the coil. When applied over the skull, this pulse has the capacity to depolarize local neurons up to a depth of 2 cm. TMS can be used as a brain-mapping tool, as a tool to measure cortical excitability, as a probe of neuronal networks, and as a modulator of brain function. When repetitive TMS (rTMS) pulses are applied, a longer lasting effect can be induced which is thought to result from a long-term potentiation or depression at the neuronal level.[3] High frequent rTMS can induce an epileptic seizure, which is a dangerous side effect. However, since the introduction of specific safety guidelines, rTMS is considered a safe treatment method.[4] Its side effects are generally mild. They include headache, local discomfort as a consequence of direct stimulation of the facial musculature, and transient changes in the auditory threshold. To prevent this latter side effect, the use of earplugs is recommended.[5] Initially, rTMS was investigated chiefly as a tool for the treatment of depression.[6] A few years later, it was explored by Hoffman and colleagues[7] for the treatment of auditory verbal hallucinations (AVH). Further research with rTMS has involved the experimental treatment of mood disorders, negative symptoms of schizophrenia, obsessive-compulsive disorder (OCD), Tourette's syndrome, posttraumatic stress disorder, panic disorder, Alzheimer's disease, bulimia nervosa, conversion, catatonia, and various forms of substance addiction.

Twenty-three years after its introduction, the number of publications reporting on the effects of rTMS treatment in psychiatric disorders has increased dramatically (263 published studies between 2000 and June 2008, as compared to 26 between 1990 and 2000). This 10-fold increase in the number of publications was accompanied by an even larger increase in sample size, which developed from single cases to samples of over 100 patients in recent publications.[8,9] Furthermore, the US Food and Drug Administration approved rTMS for the treatment of depression in October 2008.

Due to its mild side effects and its relatively low costs, rTMS tends to be considered an attractive therapeutic tool. The TMS equipment can be obtained at the price of approximately €25,000, and the stimulation technique is relatively easy to acquire. However, mental health professionals may hesitate to embrace rTMS as a routine treatment method because its efficacy is as yet uncertain. A number of

meta-analyses quantified the effects of rTMS for depressive disorder, but even these results are ambiguous.[10–15] As the effect sizes of these studies differed substantially, no general conclusions can be drawn. More details are presented in the Discussion. The effects of rTMS treatment in AVH has been meta-analyzed once before, indicating a moderate mean effect size.[16] No meta-analyses have been published on the effects of rTMS for other psychiatric disorders or symptom clusters. According to Loughlin et al[17] and Kozel et al,[18] the mean costs of an rTMS treatment for depression, consisting of 15 treatment sessions, are £1,444 and $1,422, respectively. The duration of the effect of rTMS is as yet unknown, but for an effect of 4 months,[19] the mean costs of antidepressant agents for the same period lie around $110. The question remains whether patients benefiting from medication are comparable with patients having rTMS treatment. In our opinion, the data currently available do not allow for any firm conclusions about the costs of rTMS versus medication.

This review aims to assess the value of rTMS as a therapeutic tool for psychiatric disorders and for individual psychiatric symptoms.

METHOD

Study Selection

A literature search was performed using PubMed 1990 through October 2008, Ovid Medline 1990 through October 2008, Embase Psychiatry 1997 through October 2008, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and PsycINFO 1990 through October 2008.

The following search terms were used: *transcranial magnetic stimulation*, *TMS*, *repetitive TMS*, *psychiatry*, *mental disorder*, *psychiatric disorder*, *anxiety disorder*, *attention-deficit hyperactivity disorder*, *bipolar disorder*, *catatonia*, *mania*, *depression*, *obsessive-compulsive disorder*, *psychosis*, *posttraumatic stress disorder*, *schizophrenia*, *Tourette's syndrome*, *bulimia nervosa*, and *addiction*.

The following criteria for inclusion were used:

1. Treatment with repetitive TMS.
2. Symptom severity of a psychiatric disorder is used as an outcome measure, and the psychiatric disorder being diagnosed in accordance with *DSM* and/or *ICD* criteria.
3. No specific "narrow" diagnosis or subgroup, such as depression after stroke or vascular depression
4. The study was performed in a parallel, double-blind, randomized controlled parallel design using a sham condition; an exception was made to the criterion "double-blind" for studies comparing rTMS with ECT, which cannot be blinded. We chose for parallel designs only, because patients cannot remain blinded in crossover studies, which may influence the results.
5. The data were sufficient to compute Hedges' g (sample size, means, and standard deviations or exact *t* or *P* values for rTMS main effect for change scores).
6. At least 3 studies per psychiatric disorder/symptom cluster.
7. More than 3 patients per study.
8. Articles written in English. When various articles described overlapping samples, the article with the largest sample size was included.

Data Extraction

The following data were acquired: number of treated patients, mean and standard deviation of the outcome measure at baseline and at the end of treatment (or exact *F* or *P* value), study design, and treatment parameters (type of coil used, localization of treatment, frequency, intensity, number of stimuli per session, and number of treatment sessions). Whenever publications contained insufficient or incomplete data, the authors in question were contacted and invited to send additional data so that their study could be included in the meta-analysis. All meta-analyses were checked for cross-references.

Effect Size Calculation

Effect sizes were calculated for the mean differences (sham treatment versus rTMS) of the pretreatment-posttreatment change in rating scales. The mean gain for each study was computed using Comprehensive Meta Analysis Version 2.0 (Biostat, Englewood, New Jersey) in a random effects model. After the computation of individual effect sizes for each study, meta-analytic methods were applied to obtain a combined, weighted effect size, Hedges' g, for each psychiatric disorder or symptom. The means of separate studies were weighted according to sample size. A homogeneity statistic, I^2,[20] was calculated to test whether the studies could be taken to share a common population effect size. High I^2 statistic (ie, 30% or higher) indicates heterogeneity of the individual study effect sizes, which poses a limitation to a reliable interpretation of the results. Whenever significant heterogeneity was found, a moderator analysis was performed to investigate the potential moderating factors. We expected the effects of rTMS to vary substantially according to localization, frequency, number of stimuli, and treatment sessions; as a consequence, subanalyses were performed to investigate different treatment conditions. The parameters were correlated with Hedges' g using Pearson's correlations in SPSS version 12 (SPSS Inc, Chicago, Illinois).

In studies comparing 3 treatment conditions, the 2 actual treatments were compared separately with the sham condition. In a number of studies on depression, rTMS was started simultaneously with antidepressant drug therapy or compared with electroconvulsive therapy (ECT). The results of these studies are presented separately.

Because the effect size can be overestimated due to the omission of studies in which rTMS was not effective, the fail-safe number of studies was computed.[21] This fail-safe number is an estimation of the number of missing studies that is needed to change the results of the meta-analysis to nonsignificant.

Side effects and dropouts are presented according to rTMS frequency and localization.

Table 1. Number of Included Studies and Reasons for Exclusion

Psychiatric Disorder	No. of RCTs Included in Meta-Analysis	Reasons for Exclusion of Other Studies	No. of Excluded Studies
Depression	40	No (randomized) sham condition	58
		Overlap	15
		Insufficient data	14
		Outcome no severity of psychiatric symptoms	9
		Not in English	8
		Crossover design	6
		Patient no. lower than 3	3
		Maintenance or second rTMS treatment	3
		Single-pulse TMS	2
		rTMS as add-on with ECT	1
		Vascular depression	1
Auditory verbal hallucinations	7	Overlap	4
		Crossover design	4
		Insufficient data	3
		rTMS maintenance therapy	4
		No sham condition	2
		Outcome not severity of psychiatric symptoms	2
Negative symptoms of schizophrenia	7	Insufficient data	4
		No sham condition	3
		Crossover design	1
		Outcome not severity of psychiatric symptoms	1
		Not in English	1
		Overlap	1
Obsessive-compulsive disorder	3	No sham condition	2
		Insufficient data	1
		Outcome not severity of psychiatric symptoms	1
		Not in English	1
Tourette's syndrome	2	Insufficient data	1
Panic disorder	1	Not in English	1
Bulimia nervosa	1	Less than 3 studies for this disorder	
Mania	1	No sham condition	2
Posttraumatic stress disorder	1	No sham condition	2
Cigarette addiction		Insufficient data	1
		Not in English	1
Alzheimer's disease		Insufficient data	1
		Crossover design	1
Cocaine addiction		No sham condition	1
Motor conversion		Patient no. < 3	1
Catatonia		Case reports	2

Abbreviations: ECT = electroconvulsive therapy, RCT = randomized controlled trial, rTMS = repetitive transcranial magnetic stimulation, TMS = transcranial magnetic stimulation.

RESULTS

The following disorders and individual symptoms were included in the meta-analysis: depression (40 studies), AVH (7 studies), negative symptoms of schizophrenia (7 studies), and OCD (3 studies) (Table 1). One hundred sixty-nine studies were excluded from the meta-analysis (for reasons for exclusion, see Table 1). No meta-analysis could be performed on rTMS for the treatment of Tourette's syndrome, panic disorder, posttraumatic stress disorder, mania, and bulimia nervosa, due to the small number of studies, ie, < 3. None of the studies concerning attention-deficit hyperactivity disorder, somatoform disorder, Alzheimer's disease, addiction, and catatonia fulfilled the stated criteria for inclusion.

Repetitive TMS in the Treatment of Depression

Forty studies were included in the meta-analysis. The studies were divided into 2 groups: rTMS versus sham (34 studies) and rTMS versus ECT (6 studies).

rTMS versus sham in the treatment of depression. Thirty-four studies fulfilled the criteria for inclusion in the meta-analysis.[8,9,22–53] The studies and treatment parameters are listed in Table 2. Seven hundred fifty-one patients were randomly assigned to rTMS treatment and 632 patients for the sham condition. Patients were free of antidepressant agents in 7 studies, antidepressant agents were continued during rTMS in 17 studies, and rTMS was started simultaneously with an antidepressant agent in 5 studies. Results of the meta-analysis are shown in Figure 1.

Effect sizes were computed for each study and weighted according to sample size. The mean weighted effect size for all studies comparing rTMS with sham treatment was 0.55 ($P < .001$). I^2 was 54% ($P < .001$). The fail-safe number was 18,462 studies. Since heterogeneity was high, moderator analyses were performed for the different stimulation parameters. When correlating the individual effect sizes of the studies to stimulation parameters, such as localization, frequency, intensity (percentage of motor threshold), number of stimuli per session, total number of stimuli, and number

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Table 2. rTMS Parameters in the Treatment of Depression[a]

Study	Location	Frequency, Hz	Motor Threshold, %	No. of Stimuli	No. of Sessions
O'Reardon et al,[8] 2007	L DLPF	10	120	3,000	25
Herwig et al,[9] 2007	L DLPF	10	110	2,000	15
Mogg et al,[22] 2008	L DLPF	10	110	1,000	10
Anderson et al,[23] 2007	L DLPF	10	110	1,000	12
Bortolomasi et al,[24] 2007	L DLPF	20	90	800	5
Koerselman et al,[25] 2004	L DLPF	20	80	800	10
Fitzgerald et al,[26] 2008	R DLPF	6 and 1	110	1,500	10
Loo et al,[27] 2007	L DLPF	10	110	1,500	10
Stern et al,[28] 2007	L DLPF	10	110	1,600	10
	L DLPF	1	110	1,600	10
	R DLPF	1	110	1,600	10
Fitzgerald et al,[29] 2006	L and R DLPF	10 and 1	100 and 110	750 and 420	10
Garcia-Toro et al,[30] 2006	LR DLPF	20 and 1	110	1,800 and 1,200	10
	L and R DLPF, PET	20 and 1	110	1,800 and 1,200	10
Janual et al,[31] 2006	R DLPF	1	90	120	16
Su et al,[32] 2005	L DLPF	20	100	1,600	10
	L DLPF	5	100	1,600	10
Buchholtz Hansen et al,[33] 2004	L DLPF	10	90	2,000	15
Holtzheimer et al,[34] 2004	L DLPF	10	110	1,600	10
Kauffmann et al,[35] 2004	R DLPF	1	110	120	10
Mosimann et al,[36] 2004	L DLPF	20	100	1,600	10
Fitzgerald et al,[37] 2003	L DLPF	10	100	100	10
	R DLPF	1	100	300	10
Herwig et al,[38] 2003	L or R DLPF, PET	15	110	3,000	10
Hoppner et al,[39] 2003	L DLPF	20	90	400	10
	R DLPF	1	110	120	10
Loo et al,[40] 2003	LR DLPF	15	90	1,800	15
Boutros et al,[41] 2002	L DLPF	20	80	800	10
Garcia-Toro et al,[42] 2001	L DLPF	20	90	1,200	10
Manes et al,[43] 2001	L DLPF	20	80	800	5
Berman et al,[44] 2000	L DLPF	20	80	800	10
George et al,[45] 2000	L DLPF	20	100	1,600	10
	L DLPF	5	100	1,600	10
Avery et al,[46] 1999	L DLPF	10	80	1,000	10
Klein et al,[47] 1999	R DLPF	1	110	120	10
Loo et al,[48] 1999	L DLPF	10	110	1,500	10
Padberg et al,[49] 1999	L DLPF	0.3	90	250	5
	L DLPF	10	90	250	5
Rossini et al,[50] 2005	L DLPF	15	100	900	10
Haussmann et al,[51] 2004	L DLPF and half R	20	100	2,000	10
Poulet et al,[52] 2004	L DLPF	10	80	400	10
Garcia-Toro et al,[53] 2001	L DLPF	20	90	1,200	10

[a]Parameters are localization, frequency, motor threshold, stimuli per session, and number of sessions.
Abbreviations: DLPF = dorso-lateral prefrontal cortex, L = left, LR = bilateral, PET = positron emission tomography, R = right.

of sessions, no significant correlations emerged (P value between .38 and .95). The mean effect size for rTMS applied at the left dorso-lateral prefrontal cortex (DLPF) was 0.53 ($P < .001$); for rTMS directed to the right DLPF, it was 0.82 ($P < .001$); and for rTMS applied to both left and right DLPF (not simultaneously), it was 0.47 ($P = .03$). Mean Hedges' g for rTMS focused on the left or right DLPF was not statistically different from rTMS to the right DLPF ($t = -9.66$, $P = .34$). Another reason for heterogeneity was the variation in inclusion criteria. We calculated whether rTMS as a monotherapy was more effective than rTMS started simultaneously with antidepressant medication or during continuation of preexisting antidepressant treatment. The mean weighted effect sizes for rTMS as a monotherapy was 0.96 ($P < .001$) ($I^2 = 81\%$, $P < .001$); for rTMS with continuation of an antidepressant agent, it was 0.51 ($P < .001$) ($I^2 = 32\%$, $P = .08$); and for rTMS started simultaneously with an antidepressant agent, it was 0.37 ($P = .03$) ($I^2 = 44\%$, $P = .13$). The difference in efficacy between rTMS as a monotherapy and rTMS with continuation of an antidepressant agent was marginally significant in favor of rTMS as a monotherapy ($t = 2.12$, $P = .06$). There was a trend for rTMS being more effective as a monotherapy than as an adjunctive to priorly started antidepressant agents ($t = 1.747$, $P = .09$). There was homogeneity if studies with rTMS as a monotherapy were excluded ($I^2 = 23.9$, $P = .11$); Hedges' g became 0.46 ($P < .001$). No difference between baseline mean severity scores for these 3 groups could be found ($t = 9.34$, $P = .36$), thus ruling out severity as a confounding factor. In a minority of studies (6 studies), patients with psychotic features were explicitly excluded. These studies yielded a better effect of rTMS than studies that did not use this exclusion criterion ($t = .128$, $P = .04$).

Reported side effects and dropouts for rTMS delivered at high frequency, at low frequency, and for sham treatment are presented in Tables 3 and 4. Reports of frequent headache, scalp discomfort, facial twitching, tearfulness, local erythema, and drowsiness were mentioned. Side effects occurred more often in high-frequency than in low-frequency rTMS.

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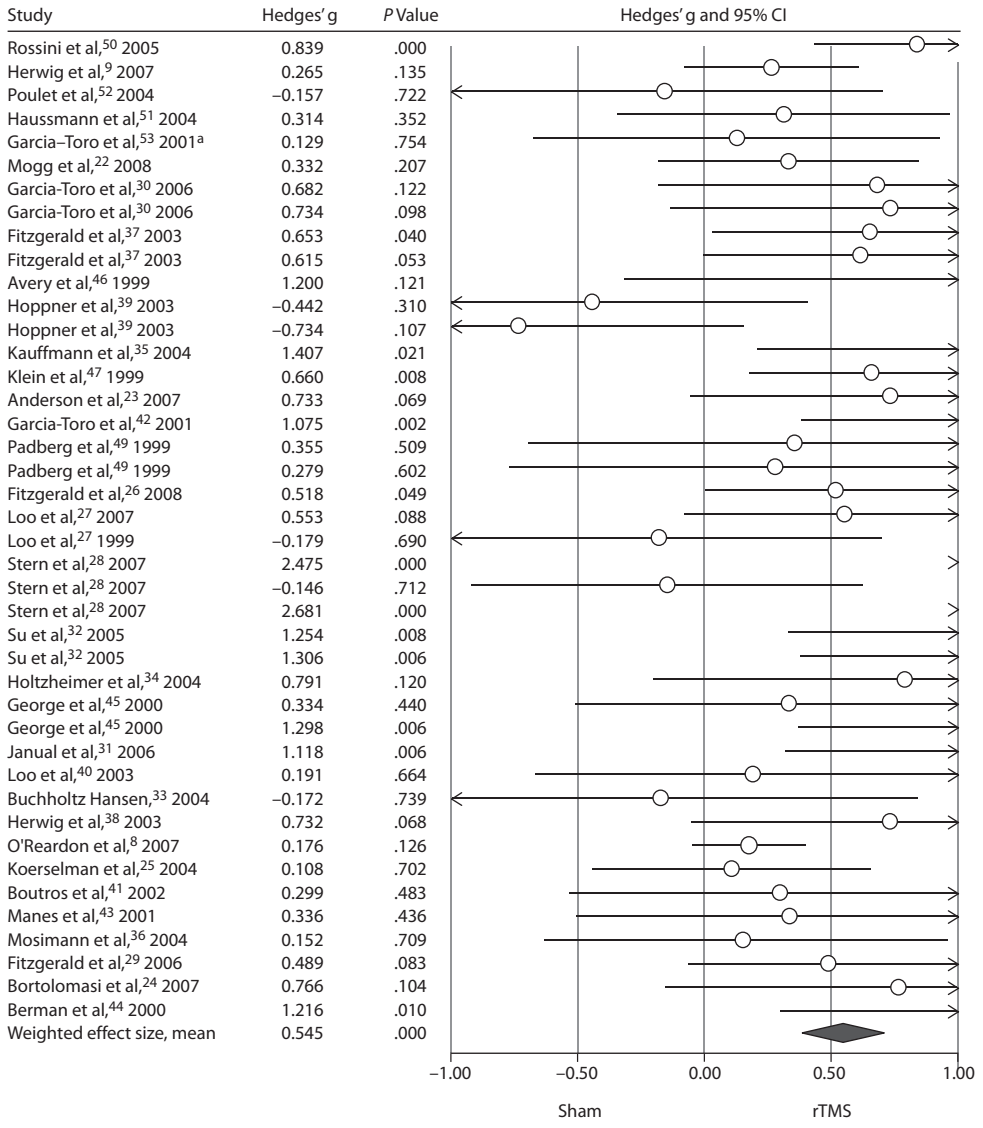
Figure 1. rTMS for Depression, Results of the Meta-Analysis



[a]Add-on therapy.
Abbreviation: rTMS = repetitive transcranial magnetic stimulation.

rTMS versus ECT in the treatment of depression. ECT is a potent intervention in the treatment of depression, but complications associated with anesthesia,[54] cardiac risks, and memory disturbances are disadvantages[55] that are absent in rTMS treatment. For this reason, 6 additional studies were analyzed in which rTMS was compared with ECT in a randomized fashion.[56–61] A total of 215 patients were included in the meta-analysis, among which 113 were treated with rTMS, and 102 with ECT. The parameters of the rTMS treatment conditions are presented in Table 5. ECT consisted of unilateral and/or bilateral treatment at a frequency of 2 or 3 times a week.

The results of the meta-analysis are presented in Figure 2. Analysis showed that ECT yields more favorable results than rTMS, with a weighted effect size of −0.47 ($P = .004$). Heterogeneity was moderately low: $I^2 = 28\%$, $P = .23$. The fail-safe number for these studies was 106 studies. See Tables 3 and 4 for side effects and dropouts.

rTMS in the Treatment of AVH

Seven randomized controlled trials were included in the meta-analysis, with a total number of 189 patients, of which 105 received rTMS treatment and 84, sham treatment.[19,62–67] The parameters of the rTMS treatments are presented in Table 6.

In 7 studies, rTMS treatment was applied to the left temporoparietal cortex (ie, T3P3, according to Electroencephalogram Electrodes, Wernicke's area), and in 1 study to its right-sided homolog. The results of the meta-analysis are presented in Figure 3.

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Table 3. Side Effects of rTMS Treatment Occurring in at Least 1% of the Participants per Indication

Side Effect	High-Frequency DLPF, n (%)	Low-Frequency DLPF, n (%)	Low-Frequency Temporoparietal, n (%)	Sham, n (%)
Depression				
Headache	46 (9.7)	4 (3.7)	…	12 (2.5)
Scalp discomfort	45 (9.3)	2 (1.8)	…	9 (1.9)
Facial twitching	9 (1.9)	5 (4.6)	…	0
Tearfulness	7 (1.5)	0	…	0
Local erythema	6 (1.3)	0	…	0
Drowsiness	12 (2.5)	0	…	0
Other	22 (4.7)	1 (0.9)	…	11 (2.4)
Total	145/472 (30.7)	12/109 (11)	…	32/461 (6.9)
Auditory verbal hallucinations				
Headache	…	…	6 (5.7)	2 (1.9)
Dizziness	…	…	2 (1.9)	1 (0.9)
Amnesia	…	…	1 (1.9)	0
Other	…	…	0	1 (0.9)
Total	…	…	9/105 (8.6)	4/108 (3.7)
Negative symptoms of schizophrenia				
Headache	6 (10.3)	2 (12.5)	…	1 (1.4)
Scalp discomfort	5 (8.6)	0	…	1 (1.4)
Facial twitching	0	3 (25)	…	0
Increase of akathisia	0	1 (6.3)	…	0
Increase of OCD symptoms	0	1 (6.3)	…	0
Total	11/58 (19)	7/16 (43.8)	…	2/74 (2.7)
OCD				
Headache	7 (70)	1 (3.6)	…	1 (3.6)
Scalp discomfort	12	0	…	0
Dizziness/fainting	3 (30)	0	…	1 (3.6)
Tearfulness	2 (20)	0	…	0
Total	24/10	1/28 (3.6)	…	2/28 (71)
Total for all groups	180/540 (33.3)	20/153 (13.1)	9/105 (8.6)	40/696 (5.7)

Abbreviations: DLPF = dorso-lateral prefrontal cortex, OCD = obsessive-compulsive disorder, rTMS = repetitive transcranial magnetic stimulation.
Symbol: … = not applicable.

The effect size of rTMS was 0.54 ($P < .001$), indicating a moderate effect. The percentage for heterogeneity was 0 ($P = .61$). Therefore, no additional moderator analysis was performed. The fail-safe number was 269 studies.

Side effects are described in Table 3. They occurred in 8.6% of the participants during rTMS treatment and in 3.9% during sham treatment. Reasons for dropout are listed in Table 4.

rTMS in the Treatment of Negative Symptoms of Schizophrenia

A meta-analysis of 7 studies was performed, with a total number of 148 participating patients, of which 74 received rTMS treatment, and an equal number sham treatment.[68–74] Table 7 lists the parameters of rTMS in the treatment of negative symptoms of schizophrenia. Except for 1 study, the left DLPF served as the focus of treatment. Figure 4 shows details of the results of the meta-analysis. Hedges' g was 0.39 ($P = .11$). I^2 was 56% ($P = .03$). The fail-safe number was 13 studies. Because of the high heterogeneity a moderator analysis was performed; no significant correlation was found between individual effect sizes and rTMS parameters such as frequency, number of sessions, duration, percentage of the motor threshold, and total number of stimulations.

In Tables 3 and 4, side effects and dropouts are presented. Side effects occurred in 24% of the patients during rTMS treatment, compared to none during placebo treatment. They consisted of headache, scalp discomfort, facial twitching, increase in akathisia, and increase in comorbid OCD symptoms.

Obsessive-Compulsive Disorder

Three articles were included in the meta-analysis of rTMS for the treatment of OCD, yielding a total number of 38 patients receiving rTMS and 28 receiving sham treatment.[75–77] Details of the rTMS parameters are listed in Table 8.

Figure 5 displays the results of the meta-analysis. Hedges' g was 0.15 ($P = .52$), which is not significantly more favorable than sham treatment. The score for heterogeneity was 0 ($P = .89$), indicating no bias as a consequence of moderators. See Table 4 for an overview of the side effects, which consisted of headache, scalp discomfort, dizziness, and tearfulness. Dropouts did not occur.

DISCUSSION

This study provides a critical and quantitative summary of clinical studies using rTMS as a treatment method for psychiatric indications. It aims to formulate a carefully considered recommendation for psychiatric professionals whether or not to adopt this treatment method as a standard therapy. The literature includes ample high-quality studies to allow for meta-analyses of the efficacy of rTMS for depression, AVH, negative symptoms in schizophrenia, and OCD. We also meta-analyzed the efficacy of rTMS versus ECT in the treatment of depression.

Table 4. Reasons for Dropout

Reason	High-Frequency DLPF, n (%)	Low-Frequency DLPF, n (%)	Low-Frequency Temporoparietal, n (%)	Sham, n (%)
Depression				
Side effects	22 (4.7)	0	…	11 (2.3)
Worsening of symptoms	17 (3.6)	1 (0.9)	…	12 (2.5)
Other/unknown	11 (2.3)	8 (7.3)	…	26 (5.3)
Total	50/472 (10.6)	9/109 (8.3)	…	49/486 (10.1)
Auditory verbal hallucinations				
Side effects	…	…	2 (1.9)	1 (0.9)
Worsening of symptoms	…	…	0	3 (2.8)
Other/unknown	…	…	0	0
Total	…	…	2/105 (1.9)	4/108 (3.7)
Negative symptoms of schizophrenia				
Side effects	3 (5.2)	0	…	1 (1.4)
Worsening of symptoms	1 (1.7)	2 (7.1)	…	0
Other/unknown	1 (1.7)	0	…	3 (4.1)
Total	5/58 (8.6)	2 (7.1)	…	4/74 (5.4)
Obsessive-compulsive disorder				
Side effects	0	0	…	0
Worsening of symptoms	0	0	…	0
Other/unknown	0	0	…	0
Total	0	0	…	0
Total for all groups	55/540 (10.2)	11/165 (6.7)	2/105 (1.9)	57/696 (8.2)

Abbreviation: DLPF = dorso-lateral prefrontal cortex.

Table 5. rTMS Parameters for Depression Versus Electroconvulsive Therapy

Study	Location	Frequency, Hz	Motor Threshold, %	No. of Stimuli	No. of Sessions
Eranti et al,[56] 2007	L DLPF	10	110	1,000	15
Rosa et al,[57] 2006	L DLPF	10	110	2,500	20
Grunhaus et al,[58] 2003	L DLPF	10	90	1,200	20
Janicak et al,[59] 2002	L DLPF	10	110	1,500	15
Grunhaus et al,[60] 2000	L DLPF	10	90	800	20
Pridmore[61] 2000	L DLPF	20	100	1,300	12

Abbreviations: DLPF = dorso-lateral prefrontal cortex, L = left, rTMS = repetitive transcranial magnetic stimulation.

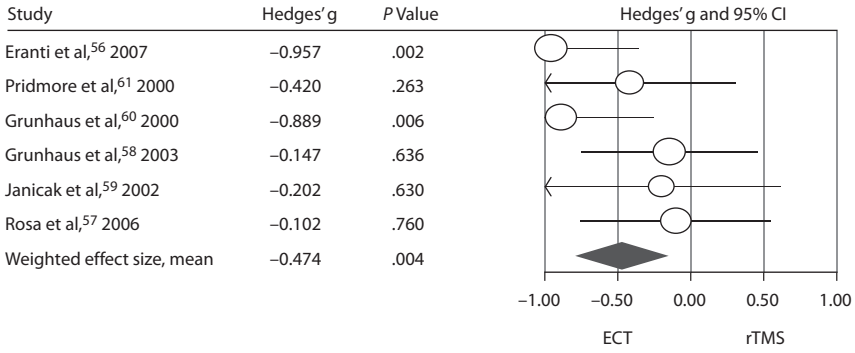
The new information presented in this article is based primarily on the inclusion of the highest number of studies to date considering rTMS for depression, and the performance of subanalyses of rTMS as monotherapy, of rTMS as an adjunctive to antidepressant medication, and of rTMS started simultaneously with an antidepressant agent. This study provides more evidence that ECT is superior to rTMS in contrast to the previous meta-analysis by Burtin et al,[11] who found no significant difference between ECT and rTMS. Moreover, this is the first meta-analysis of rTMS as a treatment method for negative symptoms of schizophrenia and OCD.

Our results indicate that repetitive TMS is more effective than sham treatment in the treatment of depression, but less effective than ECT. rTMS is also effective for AVH in schizophrenia, even for AVH resistant to antipsychotic medication. We found a trend toward an effect of rTMS for negative symptoms in schizophrenia, but more studies are needed to confirm this finding. rTMS is not superior to sham treatment for the treatment of OCD. Thus it appears to be a useful method in the treatment of common conditions such as depression and AVH. In addition, it is one of the very few treatment methods that may have some effect on negative symptoms of schizophrenia, although the evidence for this indication is currently insufficient. Findings for the different disorders are discussed in detail below.

rTMS for Depression

Repetitive TMS directed to the DLPF (either left or right) has a moderate mean effect size in the treatment of depression according to the results of 34 studies. In comparison with sham treatment, the highest effect size was found for studies using rTMS as monotherapy, followed by studies with rTMS as an adjunctive to continuation of pharmacotherapy. The analysis of 5 randomized controlled studies shows evidence for a small, but significant additional effect of rTMS when it is started simultaneously with pharmacotherapy. This lower effect of cotherapy as compared to monotherapy was not explained by a difference in baseline

Figure 2. Meta-Analysis of rTMS Versus ECT in the Treatment of Depression



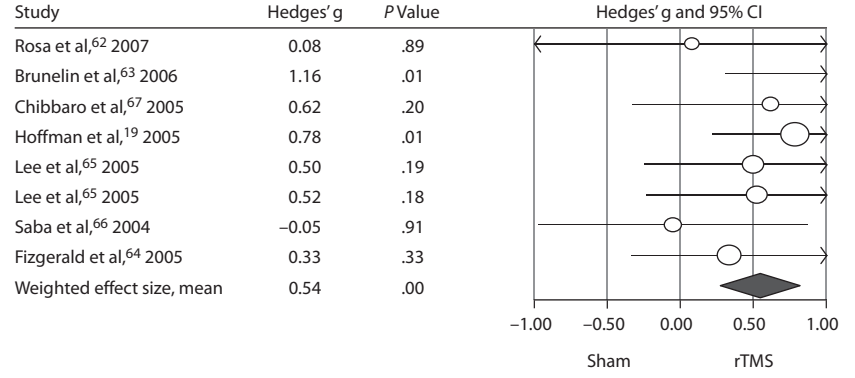
Abbreviations: ECT = electroconvulsive therapy, rTMS = repetitive transcranial magnetic stimulation.

Table 6. rTMS Parameters for Auditory Verbal Hallucinations

Study	Location	Frequency, Hz	Motor Threshold, %	No. of Stimuli	No. of Sessions
Hoffman et al,[19] 2005	T3P3	1	90	900	10
Rosa et al,[62] 2007	T3P3	1	90	960	10
Brunelin et al,[63] 2006	T3P3	1	90	1,000	10
Chibbaro et al,[67] 2005	T3P3	1	90	900	4
Fitzgerald et al,[64] 2005	T3P3	1	90	900	10
Lee et al,[65] 2005	T3P3	1	100	1,600	10
	T4P4	1	100	1,600	10
Saba et al,[66] 2004	T3P3	1	80	300	10

Abbreviation: rTMS = repetitive transcranial magnetic stimulation.

Figure 3. Results of the Meta-Analysis of rTMS in the Treatment of Auditory Verbal Hallucinations



Abbreviation: rTMS = repetitive transcranial magnetic stimulation.

depression severity or by differences in stimulation parameters. Rather, the different effect sizes may be due to variability in treatment resistance among the 3 treatment groups or to an additional effect following the withdrawal of medication. Furthermore, lower expectations and hope to benefit from this treatment could form an alternative explanation. Low-frequency right-sided rTMS showed a trend toward better response than high-frequency left-sided rTMS, but full statistical significance was not achieved. rTMS had a better effect in studies that explicitly excluded patients with psychotic depression, as compared to samples that did not exclude this patient group.

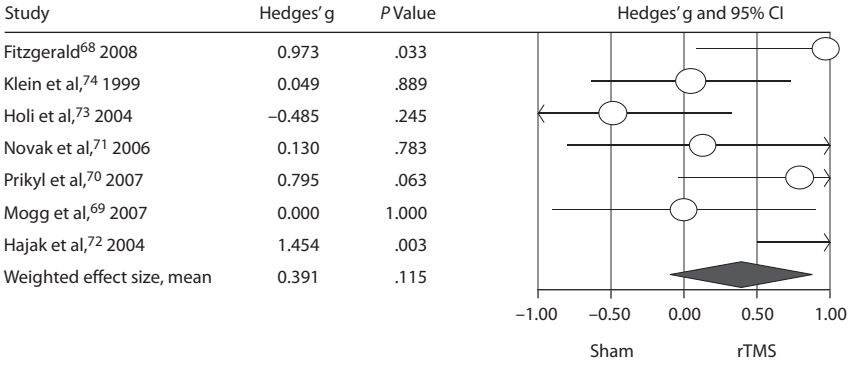
The mean effect size found for rTMS treatment in depression (ie, 0.55) is high when compared to effect sizes commonly reported for pharmacotherapy in depression (ie, between 0.17 and 0.46).[78–81] Our results are in concordance with the meta-analysis of Schutter et al,[15] who found an effect size of 0.39 in 30 studies. The established difference may be explained by the inclusion of only high-frequent rTMS treatments directed to the left DLPF in their meta-analysis. The effect sizes of 2 meta-analyses of 33 studies by Hermann et al[14,82] were 0.65 and 0.59 respectively, which were comparable to our results, although those meta-analyses also included crossover studies. In a crossover design, patients cannot remain completely blind in the treatment condition, as actual rTMS produces loud clicks and twitching sensations in the skin that are difficult to mimic in a sham condition and may influence the results in favor of rTMS.

Table 7. rTMS Parameters in the Treatment of Negative Symptoms of Schizophrenia

Study	Location	Frequency, Hz	Motor Threshold, %	No. of Stimuli	No. of Sessions
Fitzgerald[68] 2008	L and R DLPF	10	110	1,000	15
Mogg et al,[69] 2007	L DLPF	10	110	2,000	10
Prikyl et al,[70] 2007	L DLPF	10	110	1,500	15
Novak et al,[71] 2006	L DLPF	20	90	2,000	10
Hajak et al,[72] 2004	L DLPF	10	110	1,000	10
Holi et al,[73] 2004	L DLPF	10	100	1,000	10
Klein et al,[74] 1999	R DLPF	1	110	120	10

Abbreviations: DLPF = dorso-lateral prefrontal cortex, L = left, R = right, rTMS = repetitive transcranial magnetic stimulation.

Figure 4. Meta-Analysis of rTMS for Negative Symptoms of Schizophrenia



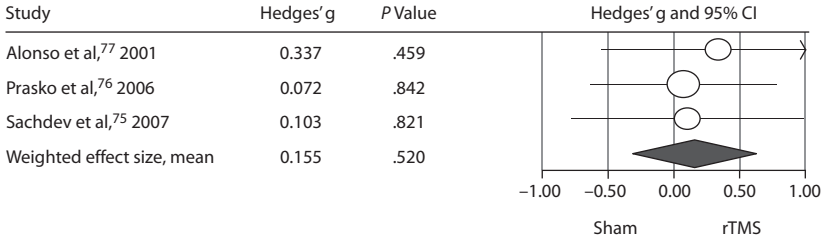
Abbreviation: rTMS = repetitive transcranial magnetic stimulation.

Table 8. Parameters of rTMS for Obsessive-Compulsive Disorder

Study	Location	Frequency, Hz	Motor Threshold, %	No. of Stimuli	No. of Sessions
Sachdev et al,[75] 2007	L DLPF	10	110	1,500	10
Prasko et al,[76] 2006	L DLPF	1	110	1,800	10
Alonso et al,[77] 2001	R DLPF	1	110	1,200	18

Abbreviations: DLPF = dorso-lateral prefrontal cortex, L = left, R = right, rTMS = repetitive transcranial magnetic stimulation.

Figure 5. rTMS for Obsessive-Compulsive Disorder, Results of the Meta-Analysis



Abbreviation: rTMS = repetitive transcranial magnetic stimulation.

Burt et al[11] included studies with other conditions (such as high- versus low-frequency rTMS, and rTMS with antidepressant agents, versus antidepressant agents alone) and found equal results for 16 studies with an effect size of 0.67. Holtzheimer et al[10] meta-analyzed 12 studies, some of which used a crossover design, and found a large mean effect size of 0.81. Conversely, no effect was found in comparison with sham treatment in the meta-analysis by Couturier et al,[13] in which only 6 trials were included due to stringent criteria for sham treatment, side of treatment, and statistical methods. Thirteen studies were analyzed by Martin et al,[12] showing a significantly more favorable effect of rTMS focused on the left DLPF (standardized posttreatment difference of −0.35) as compared to sham treatment.

Our meta-analysis including 6 studies comparing rTMS for depression to ECT showed that rTMS cannot replace ECT, as patients improved significantly better with ECT. As only patients indicated for ECT participated in these studies, the majority had severe depression. Burt et al[11] also performed a meta-analysis of 3 studies comparing rTMS to ECT and found a nonsignificant difference in favor of ECT. The difference with our mean effect size (−0.47) is explained

by the inclusion of 3 more studies with negative effects in our analysis. Thus, when considering rTMS for depression, it appears to be more effective when given as a monotherapy. Depressive patients with psychotic symptoms may profit less from rTMS treatment, as the results of rTMS are less favorable than those of ECT.

Repetitive TMS for AVH

Meta-analysis shows a moderate effect of rTMS on the severity of AVH in 7 studies. Most studies include patients with medication-resistant AVH, indicating a group with intractable symptomatology. A mean effect size of 0.76 was found in a previous meta-analysis investigating rTMS for AVH by Aleman et al.[16] This mean effect was higher than that of the current study (0.54), which may be due to the exclusion of crossover studies in our analysis. As patients with medication-resistant AVH have few other possibilities for treatment, we definitely recommend offering rTMS treatment for this group.

rTMS for Negative Symptoms of Schizophrenia

Following the results of 7 studies, rTMS directed at the DLPF may improve negative symptoms of schizophrenia compared to sham, but the number of included studies was too low to reach statistical significance. Given the mild side effect profile of rTMS and the current poverty of therapeutic options for negative symptoms, we recommend that rTMS may be attempted as a possibility to improve negative symptoms.

Repetitive TMS for OCD

For the treatment of OCD no significant effect of rTMS was found in the 3 included studies. In spite of the small number of studies, the results were homogeneous. This indicates that OCD is not a psychiatric indication for rTMS.

Tolerability

Side effects reported for different indications were headache, scalp discomfort, drowsiness, facial muscle twitching, tearfulness, dizziness, and nausea. All of these side effects were transient and mild and occurred more often with high-frequency than with low-frequency rTMS, and more often in rTMS directed to the DLPF than in rTMS to the temporoparietal areas. The percentage of dropouts was equal for rTMS and sham treatment, and lower for AVH and OCD than for depression and negative symptoms.

Limitations

Study numbers and patient samples were rather small in the meta-analyses for AVH, negative symptoms of schizophrenia and OCD. Another matter of concern is that half of the studies including patients with major depression and AVH selected patients who were "therapy resistant," using varying definitions. This may have led to the selection of patients with refractory symptoms, which may in turn have lowered the success rate of rTMS. Secondly, several studies mentioned the number of dropouts but not the reasons for it. It is important to know the reasons for dropout and the way the data on dropout were analyzed, since this may have affected the final results.

Although the efficacy of rTMS in the treatment of depression and AVH may be considered proven, the duration of the effect is as yet unknown. Effect sizes were measured immediately after the cessation of rTMS treatment. There are indications that the effect of rTMS may last for several weeks to months.[19,22–25,67] Future studies should assess symptom relief with longer follow-up periods to assess the cost-effectiveness of rTMS treatment, and to indicate its economic advantages and disadvantages. A few case reports have described rTMS as maintenance therapy for AVH; long-term treatment with rTMS resulted in a marked improvement of AVH,[83–87] but more studies are needed to decide which maintenance treatment strategy may yield the best results.

CONCLUSION

rTMS deserves a place in the standard toolbox of psychiatric treatment methods, as it is effective for depression and AVH and has a mild side effect profile. Although the working mechanism of rTMS has not been fully elucidated, it would seem to affect the central nervous system in a way that is fundamentally different from pharmacotherapy. This may well be the reason why it may be effective in patients who are resistant to medication, both in depression and in individuals suffering from AVH. A trend was observed toward efficacy of rTMS treatment of negative symptoms of schizophrenia. On the other hand, OCD patients appeared not to benefit from it. It is noteworthy that rTMS was more effective for depression when applied in the form of a monotherapy, which indicates that rTMS should not be regarded as an adjuvant treatment for this disorder. Although rTMS cannot replace ECT in depressive patients, there may be subgroups in which rTMS can replace antidepressant medication.

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