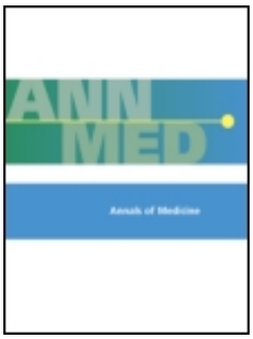

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ORIGINAL ARTICLE

Repetitive transcranial magnetic stimulation (rTMS) for treating major depression and schizophrenia: a systematic review of recent meta-analyses

Cindy L. Hovington[1,2], Alexander McGirr[3], Martin Lepage[1,2] & Marcelo T. Berlim[1,4]

[1]*Neuromodulation Program, Douglas Mental Health University Institute and McGill University, Montréal, Québec, Canada,* [2]*Brain Imaging Group, Douglas Mental Health University Institute and McGill University, Montréal, Québec, Canada,* [3]*Department of Psychiatry, University of British Columbia, British Columbia, Canada, and* [4]*Depressive Disorders Program, Douglas Mental Health University Institute and McGill University, Montréal, Québec, Canada*

Background. **In recent years, repetitive transcranial magnetic stimulation (rTMS) has been developed for the treatment of major depression (MD) and schizophrenia. Although rTMS has shown some promising findings, the lack of standardization in the methodology employed has resulted in discordant findings.**
Objectives. **The objective of this systematic review was to summarize several meta-analytical studies exploring the efficacy of rTMS in either MD or schizophrenia in order to examine the methodologies that increase the efficacy of rTMS and to provide some recommendations for future studies.**
Methods. **We searched the MEDLINE database for potentially relevant meta-analytic studies on the use of rTMS for treating major depression and schizophrenia published from January 2000 to October 2011.**
Results. **Fifteen rTMS meta-analytical studies were reviewed (11 on MD and 5 on schizophrenia). Several variables were reviewed including outcome measures, side-effects of rTMS, site of stimulation, frequency and intensity of stimulation, and number of treatment sessions.**
Conclusions. **Overall, rTMS appears to be an effective and promising therapeutic for both MD and schizophrenia.**

Key words: Major depression, meta-analysis, neuromodulation, repetitive transcranial magnetic stimulation, schizophrenia, systematic review

Key messages

- rTMS seems to be effective and safe for treating acute major depression.
- rTMS is a promising therapeutic intervention for both positive and negative symptoms of schizophrenia, although further studies are needed to clarify its role better in the management of this pervasive illness.

Major depression (MD) is characterized by the presence of depressed mood and/or loss of interest, as well as a number of somatic, vegetative, and psychological symptoms (1). Schizophrenia, on the other hand, is mostly characterized by the presence of positive (e.g. delusions and hallucinations) and negative (e.g. lack of motivation, social withdrawal) symptoms (2). Both are debilitating conditions that exact enormous personal, social, and economic costs (3,4). In particular, they are associated with grave consequences in terms of excessive mortality, disability, and secondary morbidity (5,6). The World Health Organization recently reported that both MD and schizophrenia rank among the leading causes of disability worldwide (7).

While pharmacological therapies remain the cornerstone of the management of both MD and schizophrenia, they are often unable to yield adequate clinical improvements in a relatively large portion of subjects (6,8). In fact, up to 20%–30% of subjects suffering from MD and schizophrenia remain significantly ill despite the use of multiple therapeutic approaches (9,10). Furthermore, several medications, including some newer antipsychotics and antidepressants, present with significant side-effects such as metabolic abnormalities and sexual dysfunction (3,11).

Fortunately, a variety of novel neuromodulation techniques targeting MD and schizophrenia are gradually becoming available (12). Among these, repetitive transcranial magnetic stimulation (rTMS) seems to be the most promising, as it allows for discrete and safe non-invasive modulation of cortical excitability and function (13). Based on the principle of electromagnetic induction, rTMS involves the induction of electrical currents within the brain produced by pulsating magnetic fields generated through a coil-of-wire near the scalp (14,15). These currents, in turn, are able to depolarize neurons by passing through the membrane of the nerve fibre, and when applied repetitively can modulate cortical excitability in relatively small brain regions, decreasing or increasing it, depending on the parameters of stimulation (16,17). When applied as a train of TMS pulses, or repetitive TMS (rTMS), it also induces a modulation of cortical

Correspondence: Marcelo T. Berlim, MD, MSc, Douglas Mental Health University Institute, 6875 LaSalle Blvd., FBC-3 Pavilion, Rm. F-3131-2, Montréal, Québec, Canada, H4H 1R3. E-mail: nrc.douglas@me.com

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excitability. Repetitive TMS can be applied as high (5–20 Hz) or low (≤ 1 Hz) frequency, with the former being usually excitatory and the latter being inhibitory (18,19). More recently, rTMS has been combined with fMRI in multimodal studies to block brain activity during cognitive tasks to determine whether those specific brain areas are involved in the task (20,21). Furthermore, advances in TMS such as deep TMS have shown promise as a novel and effective TMS technique (22,23).

Repetitive TMS has been shown, in a number of randomized controlled trials (RCT), to be effective for treating mood- and psychosis-related symptomatology (24). However, most trials to date have been limited to a relatively small number of patients, and overall results have been often mixed (25). This, in turn, has led some authors to question the therapeutic relevance of rTMS in psychiatry (26).

Results from past meta-analytical (M-A) studies have yielded divergent findings and make it difficult to render any firm conclusions regarding the efficacy of rTMS in MD and schizophrenia. In order to understand this issue better, we have carried out a systematic review of M-As published between 2000 and 2011 on the use of rTMS in MD and schizophrenia. Our main goal was to summarize qualitatively these M-As with an attempt to decipher which TMS parameters may be more efficient for rTMS in both these populations. Furthermore, we aim to critically examine relevant methodological, efficacy, and tolerability data in order to provide some recommendations on the utility of rTMS for treating these disorders.

Methodology of the literature review

Search strategy

We searched the PubMed® database from January 2000 to October 2011 for potentially relevant M-As on rTMS for MD and/or schizophrenia. We used the following search syntax: (neuromodulat*[TIAB] OR "brain stimulation"[TIAB] OR "transcranial magnetic stimulation"[TIAB] OR rTMS[TIAB] OR TMS[TIAB]) AND (depress*[TIAB] OR schizophr*[TIAB]) AND (Meta-Analysis[ptyp] AND English[lang] AND ("2000/01/01"[PDAT] : "2011/11/30"[PDAT]).

Inclusion/exclusion criteria

Relevant M-As (judged on the basis of the title and abstract) were retrieved for more detailed evaluation. They were included if they: 1) enrolled patients at least 18 years old with a primary diagnosis of either MD and/or schizophrenia, 2) were published in peer-reviewed journals, and 3) were written in English. Finally, the bibliographies of relevant articles were hand-searched for additional references.

Results

Twenty-five publications were retrieved from PubMed®, as well as from visual inspection of reference lists. Of the 25 articles, 11 papers did not meet our inclusion criteria: four were excluded because patients had a diagnosis other than MD or schizophrenia (27–30), three were not a M-A (25,31,32), and four did not have a primary focus on the therapeutic aspects of rTMS (33–36). Two additional M-As was identified through hand-searching (37,38). In the end, a total of 15 M-As (published from 2001 to 2010) were included in this systematic review: 11 on MD (24,37–46) (1 of which included both schizophrenia and MD (24)), and 5 on schizophrenia (24,47–50) (including 2 on positive symptoms (47,50), 1 on negative symptoms (48), and 2 on both positive and negative symptoms (24,49)). See Figure 1 for a description of our search criteria and inclusion/exclusion of M-As. Publication dates of primary studies included in M-As ranged from 1993 to 2008 for MD and from 1999 to 2008 for schizophrenia. Please see Tables I and II for a summary of the main methodological aspects of each M-A, and for rTMS treatment-related information, respectively.

Major depression disorder

Meta-analytical methods and characteristics

Search criteria

Regarding inclusion and exclusion criteria, most M-As provided concise criteria in terms of their requirements including the following: 1) presence of sham stimulation (24,37,38,40–42,44–46); 2) diagnosis of MD (17,24,40–42,44,46); 3) specific rTMS parameters (7,37,40,42–44); 4) and/or documentation of pre- and post-rTMS scores of the outcome measures (24,40–42,46). Couturier (40) had more stringent criteria and required specific characteristics regarding study validity (e.g. clinical trials had to have randomized parallel or cross-over designs with sham controls), outcome measures (i.e. clinical trials had to employ the 21-item Hamilton Depressed Rating Scale (HAM-D)), and rTMS parameters (e.g. frequency had to be greater than 10 Hz, and duration of treatment had to be between 5 and 10 days). Finally, some M-As narrowed their searches by excluding any RCT that did not have the left dorsolateral prefrontal cortex (DLPFC) as the main site of neuromodulation (37,40,44).

Outcome measures

The HAM-D was the primary outcome measure in 9 of 11 M-As (37–44,46). One study did not provide this information (24). Martin et al. (45) defined their primary outcome measure as 'remission of symptoms', which was determined by several measures including, but not limited to, the following: readmission to the hospital, time to adjunctive treatment, and suitable psychometric scales. Lam et al. (43) included the HAM-D to help define clinical response by a distinct percentage improvement on this or the Montgomery–Asberg Depression Rating Scale (MADRS). Only 36% of the M-As (4 out of 11) provided information on which of the various versions of the HAM-D had been used (including the 17-, 21-, and 25-item versions) (38,40,42,44), while the remainder provided scant details (24,37,39,41,43,45,46).

Reasons for excluding RCTs

The majority of M-As excluded numerous RCTs for reasons such as not having a control/sham group (45,46), lack of treatment-resistant depression (TRD) definition (43), no report of the randomization process (45), or insufficient data to calculate the effect size (ES) (24).

Total number of RCTs and subjects included

Some M-As reviewed as few as 5 RCTs (46), while others reviewed up to 34 (24). The total number of subjects included per M-A ranged from 91 (40) to 1,383 (24).

Pharmacological treatment pre-rTMS

Information regarding TRD definitions was limited. Only 4 of 11 (36%) M-As provided various definitions used by the reviewed RCTs (38,43–45). Not all RCTs had patients who were stabilized on antidepressants prior to beginning rTMS. A total of 4 of the 11 M-As (36%) stated they had patients who had been taking their medication(s) for several weeks prior to rTMS (37,41–43), while 3 of the 11 M-As did not provide any information regarding prior use of antidepressants (24,38,44). On the contrary, some patients

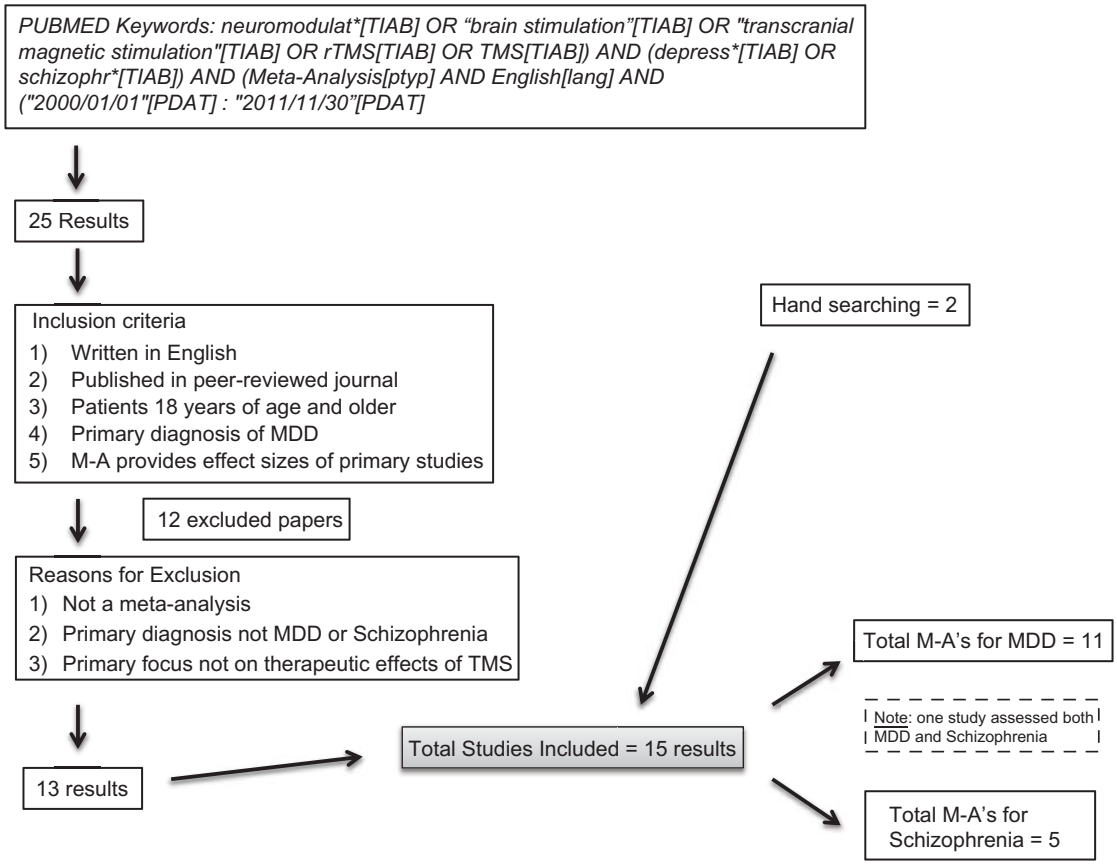

Figure 1. Flow diagram describing search techniques and inclusion/exclusion of meta-analyses.

included in the M-As were medication-free during rTMS treatment (37,43,46).

Efficacy

Significant heterogeneity was found among the reviewed RCTs, which resulted in subsequent variability in ES across M-As. Effect sizes ranged from –1.1 to 13.3 and remained inconsistent throughout the years. A summary of ES's for both MD and schizophrenia are presented in Table III.

Overall, most M-As concluded that active rTMS appeared to be more effective than sham rTMS for treating MD (24,37,39,41–44,46,51). Yet, of the 11 M-As on MD, 2 did not support this conclusion. Specifically, Couturier (40) concluded that rTMS was not effective for treating MD, and Martin et al. (45) refrained from making conclusions regarding the efficacy of rTMS in depression due to the poor quality of the RCTs reviewed.

Given the variability in the methods employed across RCTs over the years, it is difficult to ascertain whether there has been any significant improvement in the efficacy of rTMS across the past decade. Although there were no obvious increases in its efficacy over time, this may be a consequence of more recent M-As also including older RCTs. For instance, both Kozel et al. (37) and Slotema et al. (24) found similar ES (0.53 and 0.55, respectively) despite being published 8 years apart. Gross et al. (46), on the other hand, limited their literature search to articles published between 2005 and 2006 and obtained a higher ES (0.75) in favour of rTMS as a treatment for MD.

Tolerability and side-effects

Few details were provided in most RCTs regarding the tolerability of TMS. However, few withdrawals were reported, and only one case of a rTMS-induced seizure was documented (44); therefore, it can be assumed that TMS was well tolerated by most participants. The most common side-effects were transient headaches, dizziness, and scalp discomfort at the site of stimulation.

Repetitive TMS parameters

No clear standardization of rTMS parameters was observed in MD RCTs.

Sites of stimulation

The left DLPFC was included as a site of stimulation in all 11 M-As. Right DLPFC was also a common site (63%, or 7 out of 11 studies), whereas bilateral was less common (27%, or 3 out of 11 studies) yet spanned M-As across the evolution of rTMS in MD (24,38,42). In a M-A that also included open-labelled trials (39), more uncommon sites were targeted such as the motor cortex.

Frequency and intensity of stimulation

Frequency of rTMS ranged from as little as 0.17 Hz (39) up to 40 Hz (39). This wide range was consistent from 2001 to 2010. The intensity of rTMS stimulation ranged from 80% to 120% of the resting motor threshold.

Number of treatment sessions and magnetic pulses per session

On average, the number of treatment sessions ranged between 5 and 10 days (37,40,42,45). In M-As published in 2008 and later, the range increased to 5–20 days (43,44). Regarding magnetic pulses given per treatment session, there was a wide range varying from as few as 30 pulses (45) up to 4,800 (45).

Table I. Summary of meta-analyses methods for study selection and patient medication characteristics.

	Meta-analytical methods				Patient medication characteristics	
Major Depression						
Authors	Database / Period How about period searched / include	Primary outcome/ secondary outcome	Inclusion criteria	Exclusion criteria	Medication-resistant (#yes / #no / #N/A)	Medications at the start of rTMS (#stable/#unstable/ #off meds/#N/A)
McNamara et al. 2001	MEDLINE (1966-Jan 2000) EMBASE (1980-Jan 2000) Biological Abstracts and Index of Scientific and Technical Proceedings, Meta register of Controlled Trials, national register, Cochrane Library	HAM-D 17-21-25	• Must be a randomized controlled trial • Must be a placebo-controlled trial	N/A	N/A	0/0/1/4
Holtzheimer et al. 2001	MEDLINE Avery–George–Holtzheimer Database of rTMS Depression Trials	HAM-D 17-21-25	• Sham controlled design with cross-over or parallel groups • Diagnosis of depression (MDD, bipolar disorder, depressed) • Must have reported means and standard deviations for HAM-D (pre/post) • Prefrontal cortical stimulation (left or right) • Cannot have any overlap with another included study	• Studies that used alternative depression treatments as their 'control' condition	8/2/2	4/5/0/0
Kozel et al. 2002	PsycINFO (1887-Apr 2002), MEDLINE (1966-Apr 2002), CURRENT CONTENTS (Apr 2001-Apr 2002)	HAM-D	• English language only • Randomized sham-controlled trials • Double-blinded; naïve to TMS • rTMS of left prefrontal cortex treatment	N/A	N/A	7/2/3/0
Burt et al. 2002	N/A	HAM-D MADRS	N/A	N/A	7/1/1	N/A
Martin et al. 2003	MEDLINE (1966- Mar 2002), EMBASE (1974-Mar 2002, PsycLit (1980-2001), Register of Clinical Trials of the Cochrane Collaboration Depression, Neurosis and Anxiety Review Group (Jan 2002), Cochrane Controlled Trials Register (Jan 2002)	Symptom remission	• Randomized, sham-controlled trials • Any localization of coil, any rTMS frequency • Diagnosis of depression without psychotic symptoms	N/A	7/7/0	3/0/0/11
Couturier 2005	MEDLINE/2000-2003	HAM-D 21 BDI MADRS CGI	• Randomized parallel or cross-over design with sham control • Allocation concealment; double-blind; use of an intent-to-treat analysis • MDD diagnosis (DSM-IV)	• Open trials • Investigations including MDD with psychotic features • Populations including children and elderly	2/0/4	6/0/0/0

(Continued)

Table I. *(Continued).*

Meta-analytical methods					Patient medication characteristics	
Major Depression						
Authors	Database / Period How about period searched / include	Primary outcome/ secondary outcome	Inclusion criteria	Exclusion criteria	Medication-resistant (#yes / #no / #N/A)	Medications at the start of rTMS (#stable/#unstable/ #off meds/#N/A)
			• If cross-over design, then must have attest for interaction or carry-over effect that is non-significant • TMS parameters: rTMS frequency ≥ 10 Hz, applied over L-DLPFC; intensity greater than 80%; duration of 5-10 days; coil angled between 45° to 90° from scalp for sham condition • Outcome: Data reported must be adequate to be used for meta-analysis (i.e. post-treatment SD) • 21-item HAM-D must be primary outcome measure	• rTMS protocols combined with initiation of medications		
Herrmann et al. 2006	MEDLINE, EMBASE, Cochrane/N/A	HAM-D MADRS	• Double-blind randomized parallel or cross-over design with sham control • Diagnosis of depression • Must use HAM-D or MADRS as outcome measure • Must have required info needed for meta-analysis (baseline and follow-up depression scores, SD, etc.)	N/A	18/12/0	25/5/0/0
Gross et al. 2007	PubMed Dec 2005-Nov 2006	HAM-D, MADRS	• Must be written in the English language • Randomized double-blind studies with sham • rTMS at any frequency and any localization • DSM diagnosis of MDD • Mood assessment using the following scales: HAM-D, BDI, or MADRS • Pre/post-treatment mean and SD of scores (from above-mentioned scales)	• Reviews • Neuropsychiatric diseases other than MDD • Case reports • No sham	3/2/0	4/5 studies were taking meds (no info as to whether they were stable)
Lam et al. 2008	MEDLINE (1966-2008), EMBASE (1980-2008), PsycINFO (1974-2008), Cochrane (up to May 2008)	Clinical response / clinical remission	• RCTs with sham condition • Well-defined TRD (must include at least 1 failed AD trial) • Details rTMS parameters	• Inclusion of depression co-morbid to other conditions	24/0/0	18/2/4/0
Schutter 2009	PubMed, Web of Science/ January 1980- November 2007	HAM-D 6,17,21,28 MADRS	• English language • MDD without psychotic features • High frequency rTMS over L-DLPFC, 80% MT, min 5 treatments, sham coil or 45° and 90° from scalp • HAM-D or MADRS as primary outcome measure	N/A	17/8/5	N/A
Slotema et al. 2010	PubMed (1990-Oct 2008), Ovid MEDLINE (1990-Oct 2008), EMBASE Psychiatry (1997-Oct 2008),	N/A	• English language • Parallel, double-blind, randomized controlled parallel design using a sham condition	N/A	N/A	N/A

	Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, PsycINFO (1990-Oct 2008)		• Diagnosis of psychiatric disorder in accordance with the DSM and or ICD criteria; not a 'narrow' diagnosis such as vascular depression • Sufficient data to calculate Hedges's g • Minimum of 3 studies for the psychiatric disorder • Minimum of 3 patients per study • If articles describe overlapping samples, the study with the largest sample size was included			
Schizophrenia						
Aleman et al. 2007	PubMed, Web of Science /1966-February 2006	PANSS, BPRS	• Parallel or cross-over design with sham or active control • Diagnosis of schizophrenia • Hallucination rating scale or item from a standardized psychiatric interview (i.e. PANSS or Brief Psychiatric Rating Scale	• Open trials • Insufficient data to calculate effect size • No sham control	N/A	N/A
Tranulis et al. 2008	MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials/1985–1 May 2006	AHRS, SAH, HCS, PSYRATS-AH, PANSS-AH	• Human experimental studies of rTMS • Treatment of AH • Diagnosis of SSD	• Not randomized • No placebo • Fewer than 3 treatment sessions • Lack of validated psychometric scale for AH • Coil placed other than over the left TPC • TMS not given at a low frequency	N/A	N/A
Freitas et al. 2009	Web of Science/up to July 2008	PANSS, SANS, SAPS, AHRS, HCS, SAH	• English language • Open, cross-over, or parallel study design • TMS applied for more than 1 session • Stabilization of psychotropics at least 4 weeks prior to treatment and maintained during treatment Negative symptoms: • High-frequency rTMS over L-DLPFC • PANSS-N or SANS used for outcome measure Positive symptoms: • Low-frequency rTMS over left TPC (specific criteria for locating TPC) • PANSS-P or SAPS used for outcome measure	• Single or paired pulse TMS • Did not meet inclusion criteria • Failure to report mean and standard deviation of outcome measures before and after treatment Negative symptoms: • Low-frequency rTMS • Bilateral or R-DLPFC • Non-specific outcome measures for negative symptoms Positive symptoms: • High-frequency on brain sites other than TPC • Non-specific outcome measures for positive symptoms	N/A	N/A

(Continued)

Table I. *(Continued)*.

Meta-analytical methods					Patient medication characteristics	
Major Depression						
Authors	Database / Period How about period searched / include	Primary outcome/ secondary outcome	Inclusion criteria	Exclusion criteria	Medication-resistant (#yes / #no / #N/A)	Medications at the start of rTMS (#stable/#unstable/ #off meds/#N/A)
Dlabac-de Lange et al. 2010	PubMed, Web of Science, EMBASE, 1985-July 2008	SANS, PANSS	• Parallel or cross-over design with sham • Diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder	• Cross-over studies with wash-out phase of less than 4 weeks • Insufficient information to calculate effect size • No sham control	N/A	N/A
Slotema et al. 2010	PubMed (1990-Oct 2008), Ovid MEDLINE (1990-Oct 2008), EMBASE Psychiatry (1997-Oct 2008), Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, PsycINFO (1990-Oct 2008)	N/A	• English language • Parallel, double-blind, randomized controlled parallel design using a sham condition • Diagnosis of psychiatric disorder in accordance with the DSM and or ICD criteria; not a 'narrow' diagnosis such as vascular depression • Sufficient data to calculate Hedges's g • Minimum of 3 studies for the psychiatric disorder • Minimum of 3 patients per study • If articles describe overlapping samples, the study with the largest sample size was included	N/A	'most studies included patients with medication resistant AVH'	N/A

AD = antidepressant; AH = auditory hallucinations; AHRS = Auditory Hallucination Rating Scale; AVH = auditory verbal hallucinations; BDI = Beck Depression Inventory; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression Severity of Illness Rating; DSM = Diagnostic and Statistical Manual; HAM-D = Hamilton Rating Scale for Depression; HCS = Hallucination Change Scale; ICD = International Classification of Diseases and Related Health Problems; L-DLPFC = left dorsolateral prefrontal cortex; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depression disorder; MT = motor threshold; N/A = information was not available; PANSS = Positive and Negative Syndrome Scale; PSYRATS = Psychotic Symptoms Rating Scale; RCT = randomized controlled trial; R-DLPFC = right dorsolateral prefrontal cortex; rTMS = repetitive transcranial magnetic stimulation; SAH = Scale for Auditory Hallucinations; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SD = standard deviation; SSD = schizophrenia spectrum disorders; TPC = temporo-parietal cortex; TRD = treatment-resistant depression.

Table II. Summary of rTMS parameters and efficacy in meta-analytical studies.

Authors	Total studies/ total subjects	Stimulation site	Frequency (Hz)	Intensity (% MT)	Pulses per session	No. of sessions (days)	Weighted effect size	Significance of test of heterogeneity yes/no	Clinical response(s)
Major depression disorder									
McNamara et al. 2001	5/151	N/A	N/A	N/A	N/A	N/A	13.3	No	• rTMS appears to be beneficial in treating depression
Holtzheimer et al. 2001	12/264	L-DLPFC R-DLPFC	0.3–20	80–110		5–10	0.81	N/A	• rTMS was shown to be more beneficial than sham in treating MDD
Kozel et al. 2002	12/230	L-DLPFC	0.3–20	80–110	250–2000	5–10	0.53	No	• Clinical improvements in depression can be achieved by rTMS to the L-DLPFC
Burt et al. 2002	32/455 (9 were open-labelled)	Vertex Motor cortex 8 site TMS Bilateral L-DLPFC R-DLPFC	0.017–40	80–110	30–4800	1–15	Open 1.37; sham 0.67	Open: No; Sham: Yes	• rTMS is an effective methods of reducing depressive symptoms
Martin et al. 2003	14/324	L-DLPFC R-DLPFC	0.3–20	80–110	120–2000	5–10	−0.35	Yes	• Due to the poor quality of studies, insufficient data were obtained to determine whether rTMS is effective at treating depression
Couturier 2005	6/91	L-DLPFC	10–20	80–100	250–2000	5–10	−1.1	No	• rTMS was not more effective than placebo at treating MDD
Herrmann et al. 2006	33/877	L-DLPFC R-DLPFC	± 15[A]	80 to > 100	N/A	5 to > 10	0.65	Yes	• Active rTMS is more effective than sham at reducing symptoms of MDD (33.6% reduction of symptoms)
Gross et al. 2007	5/274	R-DLPFC: 20% 1 Hz; L-DLPFC: 40% 10, 15, 20 Hz; Bilateral: 40%		90–110	120–3000	10–16	0.76	No	• Effect sizes appear to be increasing compared to past meta-analyses of rTMS and depression (see Martin et al.) suggesting an improvement over the years of methodology and outcomes
Lam et al. 2008	24/1092	L-DLPFC: 1,8,10,17,20 Hz; R-DLPFC: 1 Hz; Bilateral: 15 Hz		80–120	N/A	5–20	0.48	Yes	• Active rTMS appears to be more effective at treating TRD than sham rTMS
Schutter 2009	30/1164	L-DLPFC	5–20	80–120	250–3000	5–20	0.39	No	• rTMS over the L-DLPFC is more effective than sham rTMS at reducing depression symptoms
Slotema et al. 2010	34/1383	L-DLPFC; R-DLPFC; Bilateral	0.3–20	80–100	120–3000	5–25	0.55	Yes	• rTMS is more effective than sham at treating depression
Schizophrenia									
Aleman et al. 2007	10/212	L TPC	1	80–100	N/A	4–10	0.76	Yes	• When compared to sham, rTMS applied to the left TPC is more effective at specifically reducing hallucinations in schizophrenia and not positive symptoms in general
Tranulis et al. 2008	10/232	L TPC	1	80–100	300–2000	4–10	0.514	No	• Low-frequency rTMS over the left TPC is more effective than sham at reducing medication-resistant AH
Freitas et al. 2009 **NegSym**	8/107	L-DLPFC	10–20	80–110	400–2000	5–20	0.27	No	• rTMS to the L-DLPFC is not statistically more effective than sham at reducing negative symptoms in schizophrenia
Freitas et al. 2009 **PosSym**	12/232	Left TPC	0.9–1	80–100	120–1200	4–15	PS: 0.17; AH: 1.04	PS: No; AH: Yes	• Low-frequency rTMS to the left TPC is not significantly better than placebo at reducing positive symptoms in schizophrenia
Dlabac-de Lange et al. 2010	9/213	L-DLPFC Right PFC Bilateral DLPFC	1–20	90–110	120–2000	10–20	0.43	Yes	• Effect size increased when studies stimulating at 1 Hz frequency were excluded ($d = 0.63$), and heterogeneity disappeared
Slotema et al. 2010 **NegSym**	7/148	Bilateral L-DLPFC R-DLPFC	1–20	90–110	120–2000	10–15	0.39	Yes	• When compared to sham, active rTMS over DLPFC, rTMS was not significantly better at improving NS. (This lack of significance may be attributed to a lack of studies)
Slotema et al. 2010 **PosSym**	7/189	T3P3; T4P4	1	80–100	300–1600	4–10	0.54	No	• When compared to sham, active rTMS over the TPC seems to be more effective at reducing medication-resistant AH

AH = auditory hallucinations; L-DLPFC = left dorsolateral prefrontal cortex; N/A = information was not available; NS = negative symptoms; PFC = prefrontal cortex; PS = positive symptoms; R-DLPFC = right dorsolateral prefrontal cortex; rTMS = repetitive transcranial magnetic stimulation; T3P3 = midpoint between T3 and P3 using 10–20 EEG system; T4P4 = midpoint between T4 and P4 using 10–20 EEG system; TPC = temporo-parietal cortex. [A]Authors did not provide information about individual studies.

Schizophrenia

Meta-analytical methods and characteristics

Search criteria

For the five M-As on schizophrenia, the databases MEDLINE, Web of Science, and EMBASE were searched from as early as 1966 (47) until 2008 (24,48,49). All five M-As required that RCTs include a sham group. However, only one M-A required a specific diagnosis of schizophrenia as one of their inclusion criteria (47), while others included schizophrenia spectrum disorders or did not make any diagnostic specification (48,50).

Outcome measures

A wide range of scales were used to measure positive symptoms including, for example, the Positive and Negative Syndrome Scale (PANSS) (47–50), the Brief Psychiatric Rating Scale (BPRS) (47), the Auditory Hallucination Rating Scale (AHRS) (49,50), the Severity of the Auditory Hallucinations (SAH) (49,50), the Hallucination Change Scale (HCS) (49,50), the Psychotic Symptom Rating Scale–Auditory Hallucination Subscale (PSYRATS-AH) (49,50), and the Scale for the Assessment of Positive Symptoms (APS) (49). The Scale for the Assessment of Negative Symptoms (SANS) and PANSS were the scales used to quantify negative symptoms (48,49).

Reasons for excluding RCTs

Some RCTs were excluded from M-As mainly for the following reasons: rTMS was not the main therapeutic procedure employed (49), symptoms were not adequately measured (50), the lack of a sham condition (24), design other than double-blind (50), a wash-out phase <2 weeks (48), and lack of enough information to calculate ES (24).

Total number of RCTs and subjects included

Meta-analytical studies assessing rTMS for treating schizophrenia included far fewer RCTs than did those in MD. The total number of RCTs and subjects per M-A ranged, respectively, from 7 (24) to 12 (49), and from 107 (49) to 232 (49,50). Freitas and colleagues (49) reviewed the largest number of clinical trials ($n = 12$), albeit, unlike the other M-As, they also included open-label trials.

Pharmacological treatment pre-rTMS

The data on concomitant pharmacological therapy in the papers reviewed were sparse and uninformative. Surprisingly, stabilization of psychotropic dosage prior to rTMS treatment was required by only one M-A (49), which required stabilization of the dosage of psychotropics prior to rTMS treatment for either positive or negative symptoms. Another M-A reported that most patients included were medication-resistant; however, no further information was provided (24). Thus, data regarding patients' medication-resistance and/or the stable use of psychotropics at the start of rTMS therapy were limited in all five M-As.

Efficacy

With respect to positive symptoms, the majority of M-As support the efficacy of active rTMS over sham when applied to the temporo-parietal cortex (TPC) in the context of auditory verbal hallucinations (AVH). Three of the four M-As concluded efficacy of the therapy compared to sham (24,47,49,50). Effect sizes for negative symptoms varied from 0.27 (49) to 0.43 (48), with notable increases in ES when analyses are restricted to the SANS as an outcome measure (48).

Evidence is building from meta-analyses to suggest an important role for duration of treatment for negative, but not positive, symptoms. However, the definitions underlying dichotomous comparisons have been inconsistent. With respect to positive symptoms, when considering RCTs with >5 sessions compared to those with <5 sessions, Aleman et al. (47) reported no significant change in ES (0.79 and 0.80, respectively). Yet, the recent M-A of negative symptom RCTs by Dlabač-de Lange et al. (48) compared ES of RCTs that had treatment durations <3 weeks with those that had durations ≥ 3 weeks. The mean ES was shown to be higher for those with longer treatment durations (0.58 versus 0.32).

Tolerability and side-effects

Side-effects from rTMS were only provided in two of the five M-As (24,50). Slotema and colleagues (24) compared side-effects with both high- and low-frequency rTMS for both positive and negative symptoms. The most common adverse effects were headaches for both positive (5.7%) and negative symptoms (10.3% for high-frequency rTMS and 12.5% for low-frequency rTMS of the DLPFC). Drop-out rates were only reported in one of the five M-As and were said to be low (50). More specifically, of the 10 RCTs reviewed by Tranulis and collaborators (50), only 4 had subjects who dropped out, with the highest attrition rate being 14%.

Site of stimulation

Positive symptoms: The left TPC was the most common site of stimulation in all M-As on the efficacy of rTMS for AVH.

Table III. Summary of effect sizes of the reviewed meta-analyses.

		Schizophrenia		
Reference	Major depression	Positive symptoms	Auditory hallucinations	Negative symptoms
Holtzheimer et al. 2001 (42)	0.81[a]	–	–	–
Kozel et al. 2002 (37)	0.53[b]	–	–	–
Burt et al. 2002 (39)	0.67[b]	–	–	–
Martin et al. 2003 (45)	0.35[c]	–	–	–
Couturier 2005 (40)	−1.1[c]	–	–	–
Herrmann et al. 2006 (41)	0.65[b]	–	–	–
Gross et al. 2007 (46)	0.76[a]	–	–	–
Lam et al. 2008 (43)	0.48[b]	–	–	–
Schutter et al. 2009 (44)	0.39[b]	–	–	–
Schutter et al. 2010 (38)	0.63[b]	–	–	–
Aleman et al. 2007 (47)	–	0.21[c]	0.76[b]	–
Tranulis et al. 2008 (50)	–	0.51[b]	–	–
Freitas et al. 2009 (49)	–	0.17[c]	1.04[a]	0.27[c]
Dlabac-de Lange et al. 2010 (48)	–	–	–	0.43[b]
Slotema et al. 2010 (24)	0.55[b]	–	0.54[b]	0.39[b]

[a]Large effect size = ≥ 0.65.
[b]Medium effect size = 0.36–0.65.
[c]Small effect size = ≤ 0.35.

Negative symptoms: On the other hand, the left DLPFC was the stimulation site for all M-As on negative symptoms. The right DLPFC (48) and the use of bilateral stimulation (24,48) were also described.

Frequency and intensity of stimulation

Positive symptoms: Frequencies ≤ 1 Hz were applied as a treatment for AVH in all M-As. Two of the four M-As on positive symptoms did not provide information on this subject (47,50). The intensity of rTMS for treating positive symptoms ranged between 80% and 100% of the resting motor threshold (24,47,49,50).

Negative symptoms: Although higher frequencies were more commonly used for treating negative symptoms of schizophrenia, two of the three M-As had frequencies ranging from 1 to 20 Hz (24,48). The intensity of rTMS for treating negative symptoms ranged between 80% and 110% of the resting motor threshold (24,48,49).

Number of treatment sessions and magnetic pulses per session

Positive symptoms: Treatment duration ranged from 4 days (47,49,50) to 15 days (49), while pulses per session ranged from 120 pulses (49) to 2,000 pulses (50).

Negative symptoms: Treatment duration was slightly longer for negative symptoms and ranged between 5 days (49) and 20 days (48). Pulses per session ranged between 120 pulses (24,48) and 2,000 pulses (24,48,49).

Discussion

Major depression

Overall, the search criteria, definition and implementation of sham condition, analysis, and outcome measures employed varied greatly between M-As. Despite this, the overwhelming majority of M-As support the efficacy of rTMS in MD. Clearly, the only M-As to conclude that rTMS for MD was not effective occurred during the infancy of this modality with pooled 'treatment-resistant' and non-resistant patients (45) or were characterized by over-restrictive inclusion criteria (40). Despite variability in the remainder of positive M-As, it is clear that M-As of rTMS in MD support the clinical utility of this therapeutic intervention. The discussion, therefore, is centred on estimates of efficacy and ES and the optimization of the stimulation.

We examined each M-A to determine whether particular RCTs (and their parameters) are associated with a lower efficacy of rTMS. An interesting dissociation was observed with several RCTs supporting rTMS compared to sham in some M-As, yet these same RCTs were found to be inconclusive or to favour sham in other M-As. Specifically, studies by Kimbrell et al. (52) and Loo et al. (53) resulted in low ES in several M-As (37,39,41,42,44,45). Yet, these two RCTs were also shown to have a high ES (favouring rTMS) in other M-As (37,43,45). More confusing still, results from two other RCTs (54,55) were also shown to have ESs favouring sham rTMS in some M-As (40,41,43–45) and controversially favour active rTMS in others (39,41,44).

These discordant findings can be explained, at least in part, by the variable statistical methods applied, and it is clear that analytical approach and choice of 'gold-standard' measures can radically affect the conclusions drawn. Although most M-As focused on weighted mean differences and standard mean differences, it has been argued that clinical response and remission may be a more appropriate measure of efficacy (43).

Outcome measures and patient characteristics

Various outcome measures were used to quantify symptoms in RCTs, including a number of versions of the HAM-D (e.g. the 17-, 21-, and 25-item). Although the HAM-D has been considered the 'gold standard' for the assessment of depressive symptoms, evidence has suggested that this scale presents with some psychometric limitations (56,57). It is worth noting that some trials with rTMS employing multiple scales demonstrated that subjects improved only on self-report Beck Depression Inventory scores without any changes on HAM-D scores (58), and therefore the therapy may greatly alleviate subjective depression despite the absence of change on the 'gold standard', a nuance not necessarily captured by the various M-A approaches.

In light of a large body of M-As supporting the therapeutic effect of rTMS over sham in MD, the issue of treatment resistance and its effect on ES quantification is currently a major limitation of clinical research in rTMS. Though there are no definitive consensual criteria for TRD (59), it is generally accepted that it corresponds to a failure of at least two antidepressants (ideally from two different pharmacological classes) in the current depressive episode. The inconsistent and superficial use of the 'medication-resistant' moniker with limited substantiation in the RCTs has certainly contributed to the loose conclusion that treatment resistance is not related to efficacy (44), despite the obviously limited, though significant, response and remission rates reported in the only M-A focused entirely on patients with TRD (43). Clearly, as a field, the clinical study of rTMS should exact higher standards of research design, patient characterization, and reporting in order to allow synthesis of data and permit meaningful assessment of the patient characteristics associated with efficacy.

Stimulation target and parameters

Most M-As required RCTs to administer rTMS to the wide expanses corresponding to the 'prefrontal cortex' (37,42) or, more specifically, to the DLPFC, but there are no clear fractures in ES between those M-As that limited their analyses to left, right, or bilateral DLPFC stimulation. Concerns have been raised regarding the most common site of stimulation, the left DLPFC (40,41,44,46). Although some evidence has suggested that the left DLPFC may be an appropriate target in MD (60–64), it is an expansive brain region, only one component of an extensive neural network (65), and there are no conclusive data suggesting that this area is the optimal location.

Moreover, currently available data with respect to the clinical utility of rTMS over the DLPFC in MD must be interpreted in the context of a growing literature questioning current methods for localizing DLPFC (40,41). Although the '5-cm rule' (66) has been commonly used throughout the years, it has been increasingly criticized (40,41,67). Newer methods including neuronavigation have recently been implemented to help locate more precisely the site of stimulation for each participant (68). More accurate placement of the coil over the DLPFC may help increase the efficacy of rTMS (69).

Some evidence suggests that the efficacy of rTMS may improve with increasing stimulus intensities (70). However, not all RCTs applying higher rTMS stimulation intensities have demonstrated larger ES (53). Indeed, Herrmann and Ebmeier (41) demonstrated that increased stimulation intensities may not necessarily increase the efficacy of rTMS in MD. They compared weighted mean ES for a variety of stimulation intensities and demonstrated that ES were largest at 100% of resting motor threshold compared to infra- or supra-threshold stimulation. As such, to increase homogeneity of future RCTs, designs should adhere to a stimulation intensity ≥ 100% of the resting motor threshold unless a safety or necessary parameter variant renders this impossible or impractical.

Similarly, more treatment sessions seem to favour improvements in outcome for MD, yet RCTs with longer treatment duration do

not consistently yield the largest ES (71). Though one RCT demonstrated a nearly linear effect of the total number of treatment sessions and improvements in depressive symptoms (72), the only commonality between M-As was that most RCTs with treatment durations of 10 days or less had lower ES (43,44,46). Therefore, it is clear that the standard of care should be to administer rTMS in excess of 10 sessions.

Future research and upcoming questions for meta-analyses

The role and utility of future M-As of rTMS in MD will have at the crux their ability to synthesize and integrate RCTs differentiating left versus right versus bilateral stimulation and evolving stimulation parameters. Some data suggest that low frequency may be more effective when treating MD (73). More specifically, previous studies have shown that when high-frequency rTMS (20 Hz) was directly compared to low-frequency rTMS (5 Hz) and sham rTMS a greater number of patients in the low-frequency rTMS group were responders (> 50% decrease in HAM-D scores). Yet, the current review suggests that large ES can be achieved in studies applying either high- or low-frequency rTMS and does not support one over the other (74,75). As the available data grow, future M-As must begin the task of synthesizing more homogeneous samples in order best to decorticate differences in efficacy and optimize treatment.

Moreover, the task before future M-As will be compounded by the introduction of novel targets (76). Already, preliminary data involving single administration of rTMS support the antidepressant properties of right parietal rTMS and its capability to modulate the prefrontal-parietal circuit in emotional functioning (77). Novel targets will become far more accessible as the technological limitations restricting the depth of stimulation are solved. With the recently developed deep transcranial magnetic stimulation (DTMS) H1 coil, magnetic fields can be induced at depths up to 3 cm (23,78), and preliminary open-labelled studies and RCTs in the traditional DLPFC target have found DTMS to be a safe and effective method for decreasing depressive symptoms (79,80). Effectively doubling the depth of stimulation will allow the exploration of additional targets, and it behoves the rTMS community to synthesize such data carefully in order to determine the most efficacious targets.

Schizophrenia

While the M-As on rTMS in schizophrenia broadly support its efficacy in decreasing both positive and negative symptoms, this must be cautiously evaluated in light of the small number of RCTs driving these M-As. Indeed, the addition of a single large RCT, such as the recent well-conducted and methodologically rigorous negative study in AVH that is not included in any of the M-As (81), has the potential rapidly and considerably to alter such conclusions. This is clearly an area requiring and deserving of additional research in order to flesh out the potential role of rTMS in schizophrenia.

Nevertheless, in reviewing the available M-As of rTMS in schizophrenia, rTMS seems to be effective and more successful at alleviating positive symptoms than negative symptoms; however, this may in part be due to the limited number of studies investigating the effects of rTMS on the latter, as well as the difficulties attributed to treating negative symptoms (82). Also, in the spectrum of psychotic symptoms, the available M-As suggest that individual symptoms and subtypes could serve as outcome measures. Specifically, rTMS appears to be more effective if only considering AVH as opposed to a global positive symptom construct (49).

Given the small number of M-As, varying methods applied in M-As in schizophrenia and chronic psychotic disorders likely played a significant role in the heterogeneous results, with the inclusion of open-labelled studies in some (49) and loosening diagnostic inclusion criteria in others (48). This is clearly an area that is still developing and rapidly growing, and should learn from the lessons of M-As in MD to move quickly towards more homogeneous RCTs in order clearly to establish the efficacy and role of rTMS in psychotic disorders.

A similar concern relates to the measures used in RCTs forming the foundation of M-As. While multiple testing concerns encourage succinct and targeted measurement, those studies that have provided numerous measures have revealed that some tools appear to be more sensitive at detecting the effects of rTMS in psychotic disorders. Notably, the SANS appears to be more sensitive at detecting negative symptom changes during rTMS treatment than the PANSS (48). Indeed, M-As implementing the SANS were shown to have higher ES when compared to those using the PANSS (0.73 and 0.35, respectively). Particular attention should be paid to the specific instruments employed, their validity, and the corresponding clinical significance of change on these measures.

It is unfortunate that patient characteristics are seldom addressed in M-As of rTMS in schizophrenia. Preliminary data indicate that patients with lower PANSS scores at baseline may respond better to rTMS in comparison to more severely ill patients (49). Similarly, in schizophrenia the term 'treatment resistance' usually refers to patients with prominent positive symptoms who do not respond to at least two antipsychotic treatments (83), yet it has been acknowledged that negative symptoms tend to persist as well (84–88). As this issue is seldom addressed in the M-As on schizophrenia reviewed in the current paper, it is difficult to predict, on the basis of the current literature, which individuals will likely respond to rTMS.

Stimulation target and parameters

With regard to positive and negative symptoms in schizophrenia, it remains unclear which brain regions should be ideally targeted by rTMS (48–50). The most commonly modulated site for positive symptoms was the left TPC, an area that has been associated with the neural basis of AVH (89–91). Many M-As encouraged the use of neuronavigation in order to locate more precisely the area(s) of stimulation (49,50). It is interesting and telling that studies employing stereotactically guided rTMS in order to accurately locate Broca's area or the superior temporal gyrus (92), including the aforementioned recent large negative trial (81), have not found support for this target in reducing auditory hallucinations.

This raises important challenges, for our knowledge of impaired neural circuitry in schizophrenia is still evolving, and therefore positive trials may have instead targeted a different or more diffuse area potentially more appropriate as a target for rTMS. However, other brain regions such as the frontal lobe (90,93) have been also shown to play a role in AVH (94,95). With respect to negative symptoms, anatomical deficits have been documented in the medial frontal areas (96), anterior cingulate (97), and medial temporal lobe (98). Accordingly, an issue with regard to these proposed sites of stimulation is their depth within the brain. As previously mentioned, rTMS may not be able to modulate these deeper brain regions likely implicated in negative symptoms, a challenge that may be solved with the advent of DTMS, a technology with preliminary efficacy support in schizophrenia (23).

The literature on rTMS in schizophrenia remains too scant to draw firm conclusions regarding a set of optimized stimulation parameters. However, RCTs resulting in large ES in favour of rTMS,

both for positive and negative symptoms, employed a minimum intensity of 90% of the resting motor threshold (99,100). Based on our conceptual framework of schizophrenia, supported by fMRI characterization of hallucinations, the inhibitory stimulation frequency of 1 Hz has been used in studies of positive symptoms, though this will certainly hinge on the neurocircuitry targeted and may not necessarily be appropriate. In the context of negative symptoms, those studies with the highest ES used frequencies of 10 Hz or 15 Hz (101). It remains difficult to synthesize the data with respect to stimulation parameters, and stimulation paradigms should be planned with sound neuroanatomical and neurophysiological understanding guiding decision-making.

The data with respect to treatment duration for psychotic symptoms are somewhat more consistent, however. For positive symptoms, being mindful of the limited number of RCTs (12), there does not appear to be a dose-dependent increase in ES with more treatment sessions (47). However, with regard to negative symptoms, the only M-A that has shown a significant therapeutic effect of rTMS had a higher range of treatment sessions (48). Accordingly, RCTs with treatment durations of less than 3 weeks (102,103) had lower ES when compared to those lasting longer than 3 weeks (104–106). Yet, somewhat at odds with this conclusion, it does not appear that a higher number of total pulses per rTMS treatment is necessarily better, for neither positive nor negative symptoms of schizophrenia.

Limitations

A potential source of bias in any review is a failure to retrieve a comprehensive sample of studies (107). In this respect, our decision to focus on published reviews, though considered necessary when investigating such a broad subject area, might have limited the comprehensiveness of our literature review and result in certain risks of bias and error. Furthermore, we have been reliant on the authors of reviews accurately reporting the findings from the primary studies they have synthesized. Additionally, although heterogeneity amongst the patient samples (e.g. in terms of severity and duration of illness, and type, dosage, and duration of pharmacotherapy) and inconsistent methods of treatment delivery and control comparisons for rTMS may have important methodological implications, they are not always effectively taken into consideration by systematic reviews.

Another methodological issue highlighted by this meta-review is the extensive duplication of systematic reviews and M-As. A failure to account for overlapping study samples has the potential to over-emphasize the strength of the evidence supporting a particular topic. However, whilst variance amongst duplicate reviews may be attributable to individual statistical analyses techniques and sensitivity parameters employed, it may also, in part, be a consequence of the varying combination of primary studies. Finally, formal appraisals of the methodological quality of included studies were not always conducted and/or presented by the individual M-As, and, as a result, review findings did not always prioritize stronger evidence from methodologically robust studies over weaker evidence from less robust ones.

Overall, although some of the limitations mentioned above may be attributed, at least partially, to our approach to scoping and assessing the literature, they may also have arisen because clear quantifiable evidence capable of substantially resolving uncertainties in the field of psychiatric neuromodulation is not yet available. Nevertheless, we believe that meta-reviews are relevant because they summarize the research evidence, identify gaps in the literature, and endeavour to explain the reasons for discordant conclusions between systematic reviews and M-As.

Conclusions

Meta-analytical studies are crucial for providing information on the efficacy of rTMS for both MD and schizophrenia. Overall, M-As in MD overwhelmingly support its efficacy, with individual ES estimations being clearly influenced by the choice of outcome measures and/or by patient characteristics (including treatment resistance). The literature on rTMS for schizophrenia is far more tenuous, with a small number of RCTs comprising a limited number of patients driving the M-As of both positive and negative symptoms. While the literature is expanding and the incremental influence of each successive RCT remains high in this field, the available M-As suggest that rTMS may be a promising therapy for both positive and negative symptoms of schizophrenia. However, illness characteristics (including treatment resistance) have not been adequately accounted for and must be addressed in future RCTs. The necessary evolution of knowledge syntheses of rTMS in MD and schizophrenia will be to focus on RCTs addressing optimized stimulation target(s) and/or parameters in more homogeneously defined clinical populations.

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