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REVIEW

Does Therapeutic Repetitive Transcranial Magnetic Stimulation Cause Cognitive Enhancing Effects in Patients with Neuropsychiatric Conditions? A Systematic Review and Meta-Analysis of Randomised Controlled Trials

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Abstract Repetitive transcranial magnetic stimulation (rTMS) is increasingly used as a therapeutic intervention for neuropsychiatric illnesses and has demonstrated efficacy for treatment of major depression. However, an unresolved question is whether a course of rTMS treatment results in effects on cognitive functioning. In this systematic review and meta-analysis we aimed to quantitatively determine whether a course of rTMS has cognitive enhancing effects. We examined cognitive outcomes from randomised, sham-controlled studies conducted in patients with neuropsychiatric conditions where rTMS was administered to the dorsolateral prefrontal cortex (DLPFC) across repeated sessions, searched from PubMed/MEDLINE and other databases up until October 2015. Thirty studies met our inclusion criteria. Cognitive outcomes were pooled and examined across the following domains: Global cognitive function, executive function, attention, working memory, processing speed, visual memory, verbal memory and visuospatial ability. Active rTMS treatment was unassociated with generalised gains across the majority of domains of cognitive functioning examined. Secondary analyses revealed a moderate sized positive effect for improved working memory in a small number of studies in patients with schizophrenia (k = 3, g = 0.507, 95 % CI = [0.183–0.831], $p < .01$). Therapeutic rTMS when administered to the DLPFC in patients with neuropsychiatric conditions does not result in robust cognitive enhancing effects.

Keywords Repetitive transcranial magnetic stimulation · Cognition · Neuropsychiatric · Working memory · Depression · Schizophrenia

Introduction

Since the advent of transcranial magnetic stimulation (TMS) in the mid 1990s, non-invasive brain stimulation methodologies have rapidly evolved to become both established neuroscientific tools for the investigation of brain functioning and innovative therapeutic approaches for a number of difficult-to- treat neuropsychiatric conditions. TMS involves the passing of strong, focal, time- varying magnetic pulses through the skull into underlying cortex, in which eddy currents are generated, depolarising neurons via electromagnetic induction. The technological development of TMS to allow for the delivery of multiple repeated strong magnetic pulses into the brain (i.e., repetitive transcranial magnetic stimulation (rTMS)) has proven to be a major advancement for neuropsychiatry, with rTMS now considered an efficacious and safe treatment option, particularly for patients with major depression (Lefaucheur et al. 2014). Despite its increasing clinical use, however, an unresolved question is if a course of rTMS treatment additionally results in effects on cognitive functioning. Thus, in this systematic review and meta-analysis we

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aimed to quantitatively determine whether a course of rTMS, given to the prefrontal cortex for treatment of neuropsychiatric disorders, has cognitive enhancing effects.

rTMS when given therapeutically for neuropsychiatric disorders is most commonly administered to the prefrontal cortex, specifically the dorsolateral prefrontal cortex (DLPFC), as this region is known to be structurally and functionally dysfunctional in a number of neuropsychiatric conditions, including major depression (Grimm et al. 2008; Khundakar et al. 2009) and schizophrenia (Meyer-Lindenberg et al. 2002; Weickert et al. 2009). Abnormal functioning in this region is considered to subserve poorer cognitive function in these conditions on tests of working memory (Marquand et al. 2008; Chen et al. 2014) and executive function (Harvey et al. 2004). rTMS stimulation administered in daily treatments over at least 2 weeks to either the left or right DLPFC has been shown to have antidepressant effects (O'Reardon et al. 2007; George et al. 2010; Berlim et al. 2013b, 2014). These effects are associated with structural changes through increased grey matter volumes in depression affected regions (Lan et al. 2016). Based on these positive findings in depression, therapeutic rTMS administered in a similar manner has additionally been explored in a number of other neuropsychiatric conditions, including schizophrenia (e.g., Wobrock et al. 2015) and obsessive compulsive disorder (OCD) (e.g., Sachdev et al. 2007), albeit with mixed results (Berlim et al. 2013a; Dougall et al. 2015). Whilst the mechanisms underlying therapeutic effects remains unclear, it is generally considered that these may result from cumulative functional changes within directly stimulated regions (e.g., increased regional cerebral blood flow, neurotransmitter levels; Noda et al. 2015) and/or changes in interconnected brain regions (e.g. Lan et al. 2016).

Interestingly, a single session of rTMS has been demonstrated to have acute cognitive enhancing effects. For example, high frequency rTMS when administered to task-related cortical regions immediately prior to task performance has been shown to improve response inhibition (Vanderhasselt et al. 2006), mental rotation (Klimesch et al. 2003) and confrontation naming (Cappa et al. 2002). These acute effects are consistent with regional cerebral blood flow increases shown during high frequency stimulation (Loo et al. 2003b) and increases in prefrontal gamma oscillatory activity immediately following stimulation (Barr et al. 2009). Proposed mechanisms for these site- specific cognitive enhancing effects have included neuronal priming, driving of oscillatory activity, and synaptic neuroplastic changes (Luber and Lisanby 2014). Given that the site of stimulation (i.e., DLPFC) frequently used for therapeutic rTMS is known to subserve multiple higher level cognitive functions including executive function, learning and memory, and working memory, and that repeated daily administration to this same region over several weeks has proven therapeutic effects, the possibility of cognitive enhancement following repeated rTMS administration remains an open question. Recent systematic reviews conducted in both mixed (Guse et al. 2010) and depressed samples (Serafini et al., 2015) indeed have suggested that rTMS has promising cognitive enhancing effects.

In the current systematic review and meta-analysis we aimed to delineate quantitatively whether rTMS treatment as typically applied therapeutically has cognitive enhancing effects. We chose to examine effects across domains of cognitive function, both to determine whether rTMS treatment has effects on particular cognitive abilities and to allow for collation of outcomes from different tests that measure the same abilities. The evidence evaluated was limited to randomised, sham- controlled clinical trials where rTMS was administered to the prefrontal cortex for the treatment of neuropsychiatric conditions, as it is in these clinical populations where the therapeutic use of rTMS has been most rigorously examined. Effects of repeated treatments over an acute treatment course were examined based on assessments performed before and at the end of the acute treatment period. We hypothesised that repeated rTMS administration to the prefrontal cortex would cause generalised improvement in fronto-executive cognitive abilities (i.e., executive function, working memory) subserved by the DLPFC.

Methods

We performed a systematic review and meta-analysis in accordance with the PRISMA guidelines (Liberati et al. 2009). A literature search was conducted in the following databases: Pubmed/MEDLINE, EMBASE (Ovid) and PsychINFO (Ovid). Articles were searched from the year 1995 (i.e., the first published pilot study of rTMS for depression (Kolbinger et al. 1995)) until 29 October 2015. The search terms were: 'repetitive transcranial magnetic stimulation' OR 'rTMS', AND 'neurocognition' OR 'neurocognitive performance' OR 'cognitive effects' OR 'cognitive' OR 'neuropsychological', AND 'randomized controlled trial' OR 'randomised controlled trial') OR 'controlled clinical trial' OR 'RCT' OR 'sham controlled'. These specific search terms were chosen to be broad enough to capture studies of rTMS conducted in clinical populations, regardless of diagnosis or site of stimulation, and specific enough to limit results to randomised controlled trials where cognitive outcomes were examined. Further, the bibliographies of published systematic reviews of the cognitive effects of rTMS were searched for additional studies (i.e., Guse et al. 2010; Dougall et al. 2015; Serafini et al. 2015), and we contacted study authors as needed to attain additional data. Results were limited to studies in humans and those published in English language.

Selection Criteria

Studies were required to meet the following inclusion criteria: 1) the study was conducted to examine rTMS treatment in a neuropsychiatric population; 2) the study involved the administration of multiple (at least 2) repeated stimulation sessions 3) the stimulation was administered only to the prefrontal cortex, and 4) sham stimulation was used as a comparator. Exclusion criteria were: 1) the therapeutic intervention targeted a primary neurodegenerative or neurological condition, substance use or personality disorder, 2) rTMS treatment was administered with concurrent training or during completion of any other task, and 3) stimulation was administered to a different region other than the prefrontal cortex. Included studies must also have used standardised cognitive test(s) with established psychometric properties, and reported post-acute treatment results (mean, SD, and Ns per condition).

Data Extraction

Following retrieval of studies, all review articles, conference abstracts and duplicates were removed. The title and abstracts for each study were then screened against the selection criteria by two authors (DM and JF). Full texts were screened in cases where the title and abstract provided insufficient information. All discrepancies were resolved by consensus. Where studies met all other inclusion criteria, but provided insufficient detail for reported outcomes, the corresponding authors were contacted to obtain missing data. Further, where multiple outcomes from the same cognitive test were reported (e.g., accuracy and reaction time), only the results from one outcome were analysed (see Table 1 for a description of all outcomes included in the analysis). The following additional study data were further extracted from included studies: neuropsychiatric condition, sample sizes for the active and sham conditions, frequency of stimulation sessions, site of stimulation (left, right or bilateral DLPFC), number of sessions, rTMS frequency, number of pulses/session, whether pharmacological treatment resistance was an inclusion criterion, age of participants in each condition, gender, duration of current illness, and other/comorbid diagnoses. All data were extracted by a single author (DM). Where studies included two active conditions, results from both active conditions were averaged and compared to sham for analysis. This was done in accordance with the analysis assumption for fixed effects models that the effect sizes would not vary according to rTMS stimulus parameters or other differences between studies. If standard errors were reported, standard deviations for outcome measures were calculated using the eq. $SD = SE \times \sqrt{N}$.

Statistical Analysis

The standardised mean difference (Hedge's g) was calculated for each outcome measure to minimise bias from small sample sizes (Deeks and Higgins 2010). Positive effect sizes indicated an advantage for the active stimulation condition. Scores for reaction times and errors were recoded such that a positive result indicated superior performance for the active treatment condition. Where multiple outcomes representing the same cognitive domain were reported from an individual study, or outcomes were reported from more than one active condition, the average of the respective effect sizes was calculated. Effect sizes were calculated to evaluate treatment effects of the following cognitive domains: global cognitive function, executive function, attention, working memory, processing speed, visual memory, verbal memory and visuospatial ability. For n back tasks, 0 and 1 back outcomes were analysed in the attention domain, and 2 and 3 back outcomes were analysed in the working memory domain, consistent with prior research showing that higher difficulty n back conditions are analogous to other working memory tasks (Haatveit et al. 2010). We analysed only cognitive domains where outcomes were available from at least three different studies. Effect sizes were adjusted for small sample bias through the inverse variance method and weighted and pooled using fixed effects models. Fixed effects models were chosen a priori so as to determine whether rTMS has effects on specific particular cognitive abilities from stimulating similar neurocircuitry across neuropsychiatric conditions, the high similarity between studies for the intervention in question (i.e., rTMS dose was individually titrated using similar methodologies, rTMS was focally administered to the left or right dorsolateral prefrontal cortex and administered daily over consecutive days) and to maximise statistical power. Due to possible heterogeneity in the fixed effects models, results for the main analyses were also repeated using random effects models. Homogeneity of each weighted effect size was tested using the Q statistic. Where pooled weighted effect sizes reached statistical significance according to the Z statistic ($p < .05$), secondary exploratory analyses examined weighted effect sizes for specific neuropsychiatric diagnoses where sufficient data were available. This variable was chosen for sub-group analysis based on differences in therapeutic efficacy for rTMS treatment between clinical conditions despite use of similar treatment parameters (see Table 2). Publication bias was examined using funnel plots and the Egger's test, and we used Review Manager software (version 5.3.5 for Macintosh) to assess risk of bias in randomised trials following published recommendations (Higgins et al. 2011). Analyses were conducted using SAS/STAT software Version 9.4 (SAS Institute Inc., Cary, NC).

Table 1 Cognitive variables included in the analyses

Cognitive domain	Cognitive variables	k
Global cognitive function	RBANS Total (scaled/raw)	2
	MMSE	6
	BNCE	1
	CAMCOG	1
Executive function	COWAT Letter	17
	COWAT Category	7
	Trail Making Test B	18
	Stroop (3/Interference)	13
	RAVENS Progressive Matrices	1
	WCST (Total Correct/Accuracy)	4
	WCST (Perseverative Errors)	1
	TAP Divided Attention (accuracy)	1
	Tower of London (Errors)	2
	RWT (Letter)	3
	RWT (Letter Switch)	1
	RWT (Category)	3
	RWT (Category Switch)	1
	WAIS Picture Completion	1
	WAIS Similarities	1
Attention	Digit Span Forward	9
	Nback accuracy (0 back)	1
	Nback accuracy (1 back)	2
	TAP Selective attention	1
	RBANS Attention (scaled)	1
Processing speed	Digit Symbol Substitution Test	8
	Trail Making Test A	15
	Stroop Colour	9
	Stroop Word	7
	Simple RT	1
	Choice RT	1
	Number Connection Task	1
Visual memory	BVMT-R (delayed recall) (scaled)	1
	VPAL Total Trials Completed	2
Verbal memory	RAVLT (Total 1-V)	6
	RAVLT (Delayed Recall)	3
	HVLT (Delayed Recall)	1
	VLMT (Total)	2
	WMS Logical Memory 2	1
	MVG (Total 1-V)	1
Visuospatial ability	Hooper Visual Organisation Test	1
	Judgement of Line Orientation	1
	RBANS Visuospatial (scaled)	1
Working memory	Digit Span Total (scaled/raw)	3
	Nback accuracy (3 back)	1
	Nback accuracy (2 back)	1
	Digit Span Backwards	8
	PASAT Total (raw)	1

BNCE = Brief Neurobehavioral Cognitive Examination; BVMT-R = The Brief Visuospatial Memory Test-Revised; COWAT = Controlled Oral Word Association Test; HVLT = Hopkins Verbal Learning Test; MMSE = Mini Mental Status Examination; MVG = Muenchner Verbaler Geaechtnistest; PASAT = Paced Auditory Serial Addition Test; RBANS = Repeatable Battery Assessment of Neuropsychological State; RAVLT = Rey Auditory Verbal Learning Test; RT = Reaction time; RWT = Regensburg Word Fluency Test; VPAL = Visual Paired Associate Learning; WAIS = Wechsler Adult Intelligence Scale; WCST = Wisconsin Card Sorting Test; WMS = Wechsler Memory Scale

Results

Our search criteria identified 351 references. Following removal of duplicates, reviews, and conference abstracts, this left 264 references for title/abstract review. Additional data was subsequently received from seven studies. Figure 1 summarises the search and selection process. A total of 30 studies were included in the quantitative analysis. Of the included studies, 18 were conducted in depressed patients, 8 in patients with schizophrenia, 2 in patients with posttraumatic stress disorder (PTSD), 1 in patients with obsessive compulsive disorder (OCD), and 1 in patients with panic disorder (PD). rTMS was administered at least once daily in every study (range 5–30 sessions). Twenty three studies involved administration of high frequency (5-30 Hz) LDLPFC rTMS, 2 involved low frequency (1 Hz) RDLPFC rTMS, and 7 involved bilateral DLPFC rTMS stimulation. A description of the treatment characteristics of the studies included in the analysis is outlined in Table 2.

Patient Characteristics

Table 3 shows the clinical and patient characteristics of the included studies. Across all studies, the mean age of participants across conditions ranged from 27 to 67 years and illness duration ranged from 0.4 to 41 years. For studies conducted in depressed patients, 10 of 18 studies were conducted in patients with treatment resistant depression. The mean duration of the current depressive episode across studies ranged from 0.35 to 8.5 years. Nine of 18 studies included patients with bipolar disorder, 2 studies included patients with Parkinson's disease, and 1 study included patients with stroke. For the studies in patients with schizophrenia, illness duration ranged from 7.5 to 25 years. Two of 8 studies included patients with schizoaffective disorder. For studies in patients with PTSD, illness duration ranged from 3.4 to 41 years. Single studies were included which examined effects in patients with OCD and PD/Agoraphobia.

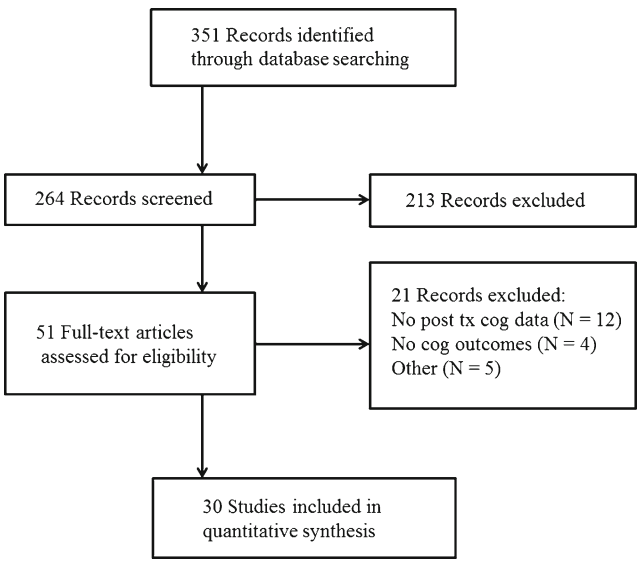

Fig. 1 Flowchart of search and study selection process

Quality Assessment

The quality of each included study was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials (Higgins et al. 2011). In brief, the Cochrane Collaboration's risk of bias assessment tool assesses five specific types of study biases including, selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and study personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting) (Higgins and Green 2008) The majority of studies had a low risk bias across most standard criteria including random sequence generation, blinding of participants, blinding outcome assessment, and incomplete outcome data. However, most studies had an unclear risk of bias for allocation concealment, and as expected based on published recommendations (Higgins et al. 2011), all studies showed unclear risk of bias for selective reporting of results (see Fig. 2).

Cognitive Domains

Global Cognitive Function

From 10 studies, outcomes from four measures of global cognitive function were extracted for analysis and included 314 participants. Results showed no difference in global cognitive test performance following acute active or sham rTMS treatment (see Fig. 3). This result remained unchanged using a random effects model.

Executive Function

From 25 studies, results from 15 different outcomes were analysed, which included a total of 768 participants. Results showed no difference in executive function performance following acute active or sham rTMS treatment (see Fig. 3). This result remained unchanged using a random effects model.

Attention

From 12 studies, results from 5 different outcomes were analysed, with the analysis comprising 475 patients. Results showed no difference in attention performance following acute active or sham rTMS treatment (see Fig. 3). This result remained unchanged using a random effects model.

Table 2 Study treatment characteristics

Study	Group Active/Sham	Frequency of sessions	DLPFC Placement	No. of Sessions	Frequency Hz	Pulses per session
Depression						
Avery et al. (1999)	4/2	Daily	Left	10	10	1000
Blumberger et al. (2012)	26 (BL)/ 22 (UL)/ 20	Daily	Bilateral	15	1 then 10 (BL) 10 (UL)	1215 (BL) 1450 (UL)
Boggio et al. (2005)	13/12	Daily	Left	10	15	3000
Hausmann et al. (2004)	25(UL + BL)/13	Daily	Left and Bilateral	10	20	2000 (UL) 2600 (BL)
Holtzheimer et al. (2004)	7/8	Daily	Left	10	10	1600
Huang et al. (2012)	28/28	Daily	Left	10	10	800
Jorge et al. (2004)	10/10	Daily	Left	10	10	1000
Loo et al. (2001)	8/8	Daily	Left	10	10	1500
Loo et al. (2003a)	9/8	Daily	Bilateral	15	15	1800
Loo et al. (2007)	18/18	Twice Daily	Left	20	10	1500
McDonald et al. (2006)	20(L)/ 20(R)/ 11	Daily	Left and Right	10	10	1600
Mogg et al. (2007)	8/9	Daily	Left	10	10	2000
Moser et al. (2002)	9/10	Daily	Left	5	20	800
Mosimann et al. (2004)	15/9	Daily	Left	10	20	1600
Myczkowski et al. (2012)	8/6	Daily	Left	20	5	1250
Nadeau et al. (2014)	16(R)/ 18(L)/ 14	Daily	Left and Right	10	5	2000
Pal et al. (2010)	12/10	Daily	Left	10	5	600
Wajdik et al. (2014)	32/31	Daily	Left	15	10	1600
Schizophrenia						
Barr et al. (2013)	13/14	Daily	Bilateral	20	20	1500
Dlabac-de Lange et al. (2015b)	11/13	Twice daily	Bilateral	30	10	2000
Dlabac-de Lange et al. (2015a)	16/16	Twice daily	Bilateral	30	10	2000
Fitzgerald et al. 2008	12/8	Daily	Bilateral	15	10	2000
Guse et al. (2013)	13/12	Daily	Left	15	10	1000
Hasan et al. (2015)	28–48/ 36–52	Daily	Left	15	10	1000
Mogg et al. (2007)	8/9	Daily	Left	10	10	2000
Rollnik et al. (2000)	6/6	Daily	Left	10	20	800
PTSD						
Boggio et al. (2010)	10 (L)/ 10 (R)/ 10	Daily	Left and Right	10	20	1600
Watts et al. (2012)	10/10	Daily	Right	10	1	400
OCD						
Sachdev et al. (2007)	8/6	Daily	Left	10	10	1500
PD/Agoraphobia						
Deppermann et al. (2014)	22/22	Daily	Left	15	15	600 iTBS

OCD = obsessive compulsive disorder; PTSD = posttraumatic stress disorder; iTBS is intermittent theta burst stimulation

Table 3 Study clinical and patient characteristics

Study			Active 1 rTMS			Active 2 rTMS			Sham rTMS		
	TR	Age, Mean (SD)	M/F	Duration Current Ep (Years) M (SD)	Age, Mean (SD)	M/F	Duration Current Ep (Years) M (SD)	Age, Mean (SD)	M/F	Duration Current Ep (Years) M (SD)	Other diagnoses
Depression											
Avery et al. (1999)	Y2	44.3(10.1)	0/4	7 (3.56)	N/A	N/A	N/A	45 (7.07)	1/1	8.5 (4.95)	BP (A1 = 1)
Blumberger (2012)	Y2	58 (12.5)	12/14	-	48.9 (13.4)	10/12	-	45.8 (13.4)	6/14	-	-
Boggio et al. (2005)	N	-	-	-	N/A	N/A	N/A	-	-	-	PD (all patients)
Hausmann et al. (2004)	N	47.3 (13.3)	6/6	-	45.2 (11.9)	5/8	-	47 (11.3)	4/9	-	BP (A1 = 2, A2 = 2, Sh = 2)
Holtzheimer et al. (2004)	Y2	40.4 (8.5)	3/4	-	N/A	N/A	N/A	45.4 (4.9)	5/3	-	-
Huang et al. (2012)	N	32.8 (7.28)	9/19	0.82 (0.24)	N/A	N/A	N/A	31.4 (7.29)	8/20	0.81 (0.25)	-
Jorge et al. (2004)	Y2	63.1 (8.1)	6/4	0.39 (0.35)	N/A	N/A	N/A	66.5 (12.2)	5/5	0.35 (0.19)	Stroke (all patients)
Loo et al. (2001)	N	45.7 (14.7)	-	0.61 (0.22)	N/A	N/A	N/A	50.9 (14.7)	-	1.04 (0.64)	BP (3 total)
Loo et al. (2003a)	Y1	54.9 (18.0)	3/9	0.93 (0.79)	N/A	N/A	N/A	48.4 (10.9)	4/6	1.31 (0.81)	BP (A1 = 2, Sh = 1)
Loo et al. (2007)	N	49.8 (2.5)	9/10	1.03 (0.69)	N/A	N/A	N/A	45.7 (15)	11/8	0.87 (0.63)	BP (A1 = 3, Sh =1)
McDonald et al. (2006)	Y3	49.0 (–)	7/18	-	49 (–)	16/9	-	54 (–)	7/5	-	BP (A1 = 5, A2 = 0, Sh =3)
Mogg et al. (2008)	N	55 (18)	13/16	1.46 (0.73)	N/A	N/A	N/A	52 (15.5)	9/21	1.52 (0.64)	-
Moser et al. (2002)	Y1	60.5 (3.4)	5/5	-	N/A	N/A	N/A	60.9 (2)	5/5	-	Dysthymia (A1 = 2, Sh = 0)
Mosimann et al. (2004)	Y2	60 (13.4)	10/5	1.3 (2)	N/A	N/A	N/A	64.4 (13)	4/5	2.2 (2.8)	BP (A1 = 4, Sh = 0)
Myczkowski et al. (2012)	N	29.6 (6.37)	0/8	-	N/A	N/A	N/A	(7.15)	0/6	-	BP (A1 = 3, Sh = 2)
Nadeau et al. (2014)	Y2	48.5 (10.8)	7/9	-	46.7 (15.3)	4/14	-	41.9 (14.1)[a]	5/2	-	BP (A1 = 2, A2 = 0, Sh = 0)
Pal et al. (2010)	N	68.5[b]	6/6	-	N/A	N/A	N/A	67.5[b]	5/5	-	PD (all patients)
Wajdik et al. (2014)	Y2	44.3 (10.3)	14/21	2.34 (1.37)	N/A	N/A	N/A	44.2 (9.7)	17/16	2.19 (1.41)	-
Schizophrenia				Illness (Years)			Illness (Years)			Illness (Years)	
Barr et al. (2013)	N	41.2 (12.0)	7/6	18.6 (11.7)	N/A	N/A	N/A	49 (12.4)	11/3	24.5 (16.2)	-
Dlabac-de Lange et al. (2015b)	N	40.7 (12.6)	10/1	16 (10.7)	N/A	N/A	N/A	30.8 (8.9)	9/4	7.5 (7.71)	-
Dlabac-de Lange et al. (2015a)	N	41.8 (11.6)	14/2	15.7 (10.1)	N/A	N/A	N/A	32.3 (9.7)	12/4	9.92 (8.92)	SA (A1 = 1, Sh = 0)
Fitzgerald et al. (2008)	Y2	37.2 (10.4)	10/2	-	N/A	N/A	N/A	33.2 (9.8)	6/2	-	SA (A1 = 2, Sh = 2)
Guse et al. (2013)	N	37 (–)	10/3	-	N/A	N/A	N/A	36 (–)	9/3	-	-
Hasan et al. (2015)	N	36.2 (10.5)	62/14	-	N/A	N/A	N/A	34.9 (9.1)	56/25	-	-
Mogg et al. (2007)	N	50.8 (14.5)	7/1	25 (16.7)	N/A	N/A	N/A	33.6 (9.8)	9/0	9 (7.9)	-
Rollnik et al. (2000)	N	-	8/4	-	N/A	N/A	N/A	-	8/4	-	-
PTSD											
Boggio et al. (2010)	N	47.1 (12.1)	3/7	4.18 (4.16)	40.7 (13.7)	4/6	4.12 (4.61)	45.9 (11.5)	2/8	3.42 (4.48)	-
Watts et al. (2012)	N	54 (12.3)	1/9	38.2 (14.1)	N/A	N/A	N/A	57.8 (11.8)	1/9	41.3 (13.8)	-
OCD											
Sachdev et al. (2007)	Y2	29.5 (9.9)	3/7	12.6 (7.5)	N/A	N/A	N/A	35.8 (8.2)	5/3	12.3 (5.4)	-

Table 3 (continued)

Study		Active 1 rTMS				Active 2 rTMS				Sham rTMS			
	TR	Age, Mean (SD)	M/F	Duration Current Ep (Years) M (SD)	Age, Mean (SD)	M/F	Duration Current Ep (Years) M (SD)	Age, Mean (SD)	M/F	Duration Current Ep (Years) M (SD)	Other diagnoses
PD/Agoraphobia											
Deppermann et al. (2014)	N	37.6 (–)	9/13	7.67 (–)	N/A	N/A	N/A	36.3 (–)	8/14	7 (–)	-

TR is pharmacological treatment resistance; Y1–3 indicates one to three failed adequate pharmacological treatments; N indicates treatment resistance not an inclusion criterion; BP is bipolar disorder; PD is Parkinson's disease; SA is schizoaffective disorder. [a] Data for Left Sham rTMS only. [b] median values

Processing Speed

A total of 20 studies were included in the analysis with 7 different outcomes compiled from a total of 641 participants. There was no difference in processing speed performance between the active and sham rTMS conditions (see Fig. 4). This result remained unchanged using a random effects model.

Visual Memory

Outcomes were analysed from 3 studies that included 2 different outcome measures and 84 participants. Results showed no visual memory performance difference between active and sham rTMS (see Fig. 4). This result remained unchanged using a random effects model.

Verbal Memory

Fourteen studies were included with outcomes analysed from 6 different outcome measures, with a total of 285 participants. There was no verbal memory performance difference between active and sham rTMS (see Fig. 4). This result remained unchanged using a random effects model.

Visuospatial Ability

Three studies were included which used three different outcome measures and had a total of 94 participants. Results showed no visuospatial ability performance differences between active and sham rTMS (see Fig. 4). This result remained unchanged using a random effects model.

Working Memory

From 13 studies, outcomes from 5 measures comprising 460 participants were analysed. These results showed a statistically significant advantage for active rTMS compared to sham for improvement in working memory performance (see Fig. 5.). This effect was at trend level statistical significance using a random effects model ($g = 0.208$, 95 % CI = [−0.030–0.446], $p = 0.09$). Figure 6 shows the funnel plot for the effect sizes reported from the individual studies, which due to asymmetry, indicated potential risk of publication bias. This was not supported, however, by the results of the Egger's test ($p = 0.43$). Secondary analyses conducted to examine specific effects in studies with depressed participants showed that by only including studies in patients with depression, the advantage of active rTMS was no longer significant ($k = 9$, $g = 0.087$, 95 % CI = [−0.154–0.328], $p = 0.48$). However, for results of studies conducted only in patients with schizophrenia ($k = 3$, $g = 0.507$, 95 % CI = [0.183–0.831], $p < 0.01$)

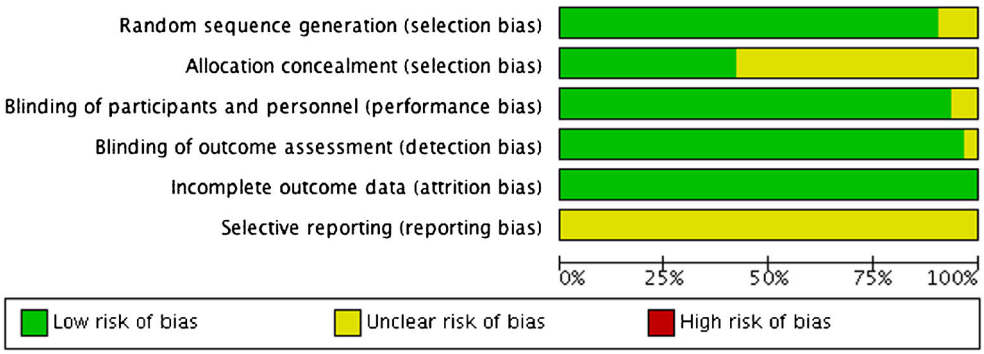

Fig. 2 Summary plot showing assessment of risk of bias

there was a moderate sized effect favouring active rTMS relative to sham (see Fig. 5). This effect remained statistically significant when this analysis was repeated excluding the study by Guse et al. (2013), as this study included the same participants as the Hasan et al. (2015) study (i.e., k = 2, g = 0.458, 95 % CI = [0.105–0.811], $p = 0.01$).

Discussion

To the best of our knowledge, this is the first meta-analysis to quantitatively assess whether an acute course of therapeutic rTMS administered to the prefrontal cortex has cognitive enhancing effects in patients with neuropsychiatric conditions.

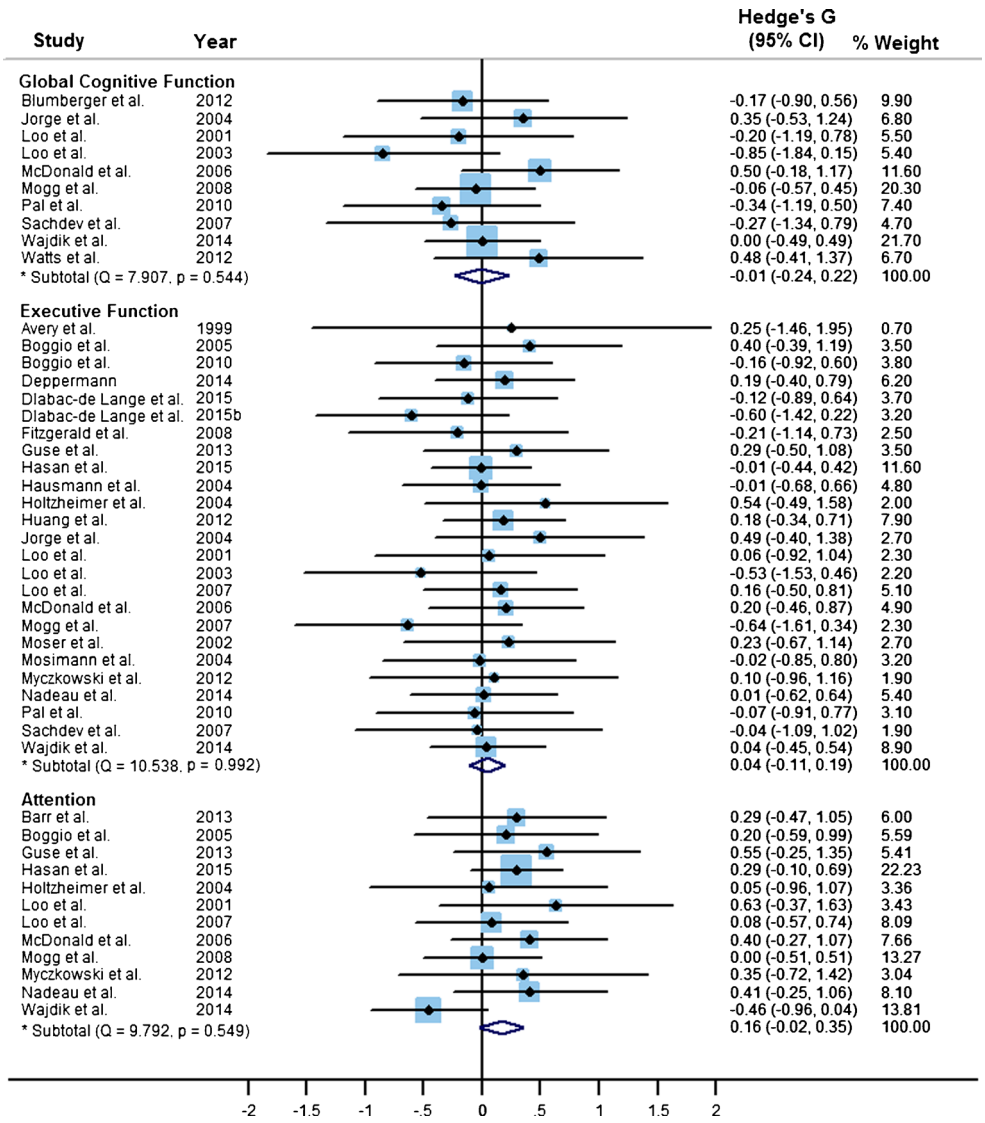

Fig. 3 Forest plots for effects of rTMS on global cognitive function, executive function and attention

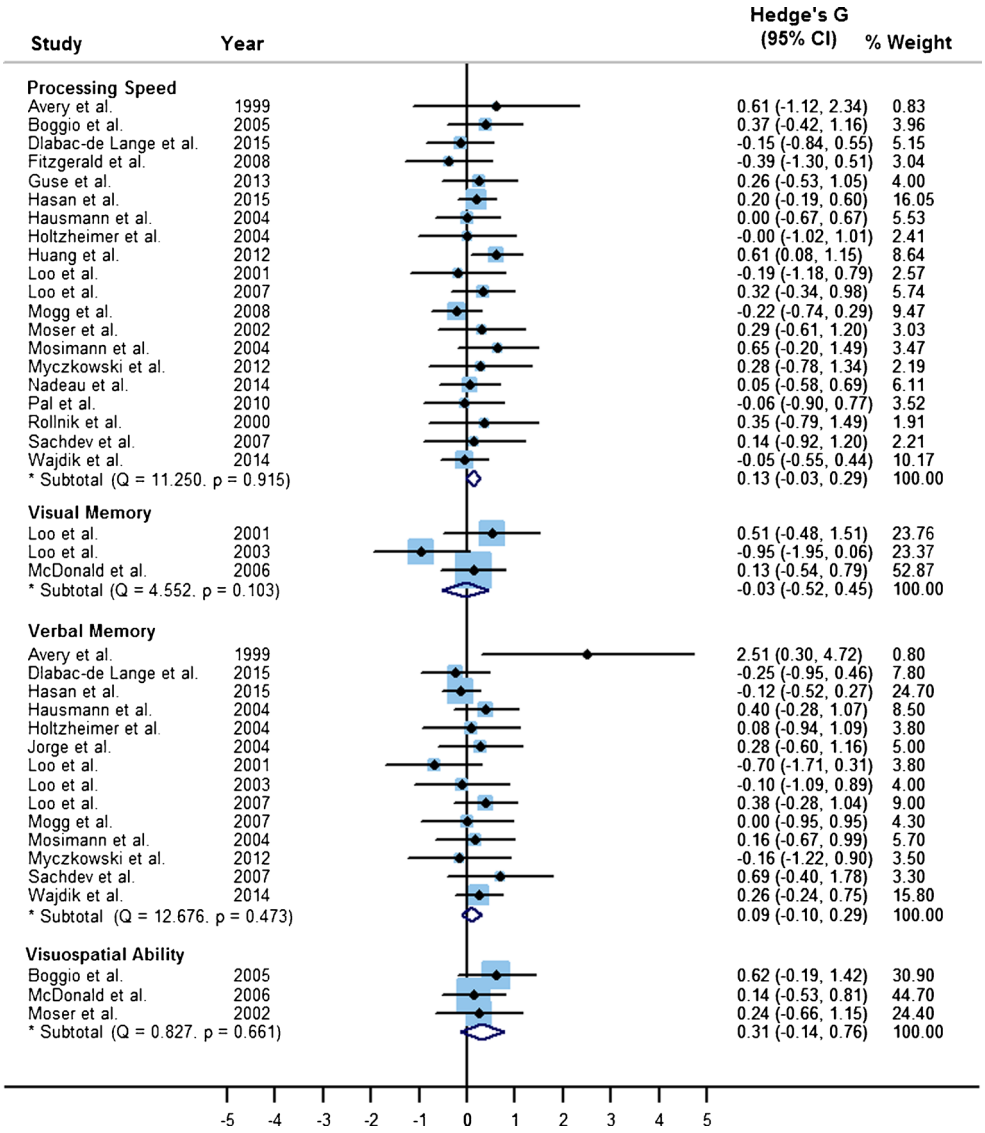

Fig. 4 Forest plots for effects of rTMS on processing speed, visual memory, verbal memory and visuospatial ability

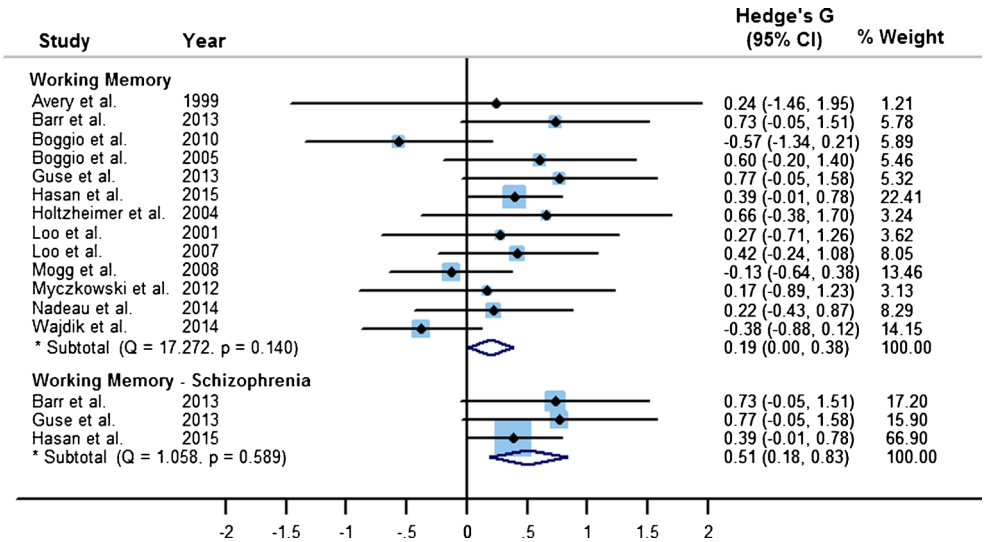

Fig. 5 Forest plots of effects of rTMS on working memory

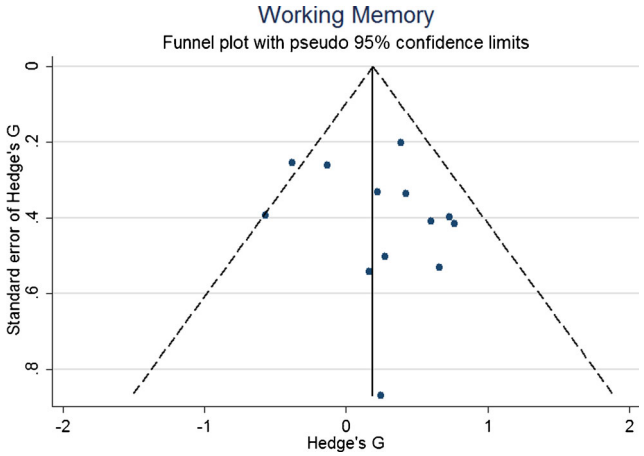

Fig. 6 Funnel plot for working memory outcomes

The majority of studies included in this meta-analysis showed a low risk of bias across most risk criteria as outlined by the Cochrane Collaboration (Higgins et al. 2011). Across the majority of cognitive domains analysed, results showed no overall effect of active rTMS treatment for enhancing cognition, with the exception of a small sized effect for improvement in working memory. Secondary exploratory analyses revealed that this advantage was specific to a small number of studies in patients with schizophrenia.

While robust therapeutic effects of rTMS have been demonstrated, particularly for major depression, it has remained an open question in the field whether treatment has concomitant cognitive enhancing effects. Unfortunately, the current findings from aggregated data extracted from 30 controlled clinical trials showed no overall effect for active rTMS compared to sham across the majority of cognitive domains tested, including executive functioning, attention, and verbal memory, cognitive abilities known to be subserved by the stimulated brain region (i.e., DLPFC). These results therefore have two main implications: first, that repeated rTMS treatment does not cause generalised upregulation of DLPFC functioning, and second, that any potential cognitive enhancing changes due to rTMS may be neuropsychiatric disorder or ability/task specific.

The DLPFC is known to be integral to multiple executive functions, including verbal generativity (Gaillard et al. 2000), set-shifting (Moll et al. 2002) and response inhibition (Vanderhasselt et al. 2006), as well as working (Cabeza and Nyberg 2000; Mull and Seyal 2001) and verbal memory (Nikolin et al. 2015). These cognitive abilities were examined by the majority of the studies included in this current meta-analysis. The failure to find a generalised cognitive enhancing effect across any of these specific cognitive domains is therefore suggestive that repeated rTMS administration does not cause broader upregulation of DLPFC functioning. This finding may have potential important implications for the understanding of the mechanisms underlying rTMS's therapeutic effects, which remain poorly understood. Specifically, rTMS's therapeutic mechanisms (e.g., antidepressant effects) may be independent to broader cognitive changes. This finding is consistent with the results from a retrospective analysis of four rTMS studies in depressed patients which similarly found a dissociation between cognitive and therapeutic outcomes; namely, that cognitive changes across the full treatment course were not associated with therapeutic effects, however, early cognitive changes in visual memory during the treatment course predicted subsequent therapeutic outcomes (Hoy et al. 2012). Therefore, whilst there appears to be a direct lack of association between cognitive and therapeutic outcomes, the possibility that rTMS related cognitive enhancement occurs across a separate time-course independent of therapeutic effects cannot be ruled out at this stage. Further, over the last decade it has become increasingly recognised that accurate targeting of rTMS within the DLPFC is critical for therapeutic efficacy, particularly for treatment of depression (Fitzgerald et al. 2009; Fox et al. 2012; Herbsman et al. 2009; Johnson et al. 2013). Functional neuroimaging research has further identified specific subregions of the DLPFC to be parts of functionally distinct distributed connected networks, including the frontoparietal and default mode networks (Yeo et al. 2011; Opitz et al. 2015), which highlights the potential importance for regional specificity and accurate rTMS targeting. Thus, given the importance of rTMS targeting within the DLPFC in relation to therapeutic outcomes, the potential for associations with more highly specific cognitive abilities or functions that are regionally and/or network specific (e.g., emotion regulation functions of the DLPFC) also remains a possibility.

Interestingly, the only domain where a significant cognitive enhancing effect was found was for working memory, with this advantage found only in a small number of studies in patients with schizophrenia. In contrast to depression, trait cognitive deficits in patients with schizophrenia are known to be far more robust with large- sized generalised deficits apparent from onset of illness, with worse deficits in the domains of verbal memory and processing speed (Mesholam-Gately et al. 2009; Schaefer et al. 2013). Neuroimaging studies have similarly implicated dysfunction in specific dorsal and ventral regions related to poorer verbal memory functioning (Ragland et al. 2009; Rimol et al. 2010; Ragland et al. 2015). For working memory specifically, rTMS stimulation when administered to the LDLPFC during task performance in healthy participants (i.e., in an inhibitory paradigm) impaired performance (Mull and Seyal 2001), implicating an important functional role of this region. Conversely, rTMS administered immediately prior to performance in an intermittent theta-burst pattern, a modified rTMS approach that involves the application of very high frequency rTMS (i.e., 50 Hz) in an excitatory paradigm, improved performance post

stimulation in healthy volunteers (Hoy et al. 2015). Similar performance enhancing effects on working memory were additionally seen with stimulation applied during task performance in a healthy sample using transcranial direct current (tDCS) (Nikolin et al. 2015), another facilitatory non-invasive brain stimulation method demonstrated to have cognitive enhancing effects (Brunoni and Vanderhasselt 2014; Coffman et al. 2014). The current finding of a positive effect of multiple rTMS sessions for enhancing working memory performance in patients with schizophrenia therefore suggests potential benefits of repeated stimulation sessions when applied to this clinical population. Future studies are required to replicate this finding.

Limitations to the current analysis include that data from different cognitive tests were aggregated for analysis for each cognitive domain (e.g., executive functioning), which may have limited specificity for the examination of cognitive effects, and that effects were examined across studies which included different neuropsychiatric populations using heterogeneous rTMS parameters and stimulation site targeting methodologies. Nevertheless, despite this potential heterogeneity in outcomes and studies, we note that effect sizes between studies were homogenous, the tests for heterogeneity were negative, and that there was no evidence found for publication risk bias. Furthermore, the effect of heterogeneity would be to reduce power to detect positive findings and our primary aim was to investigate *robust* effects across commonly accepted cognitive domains which nonetheless are more likely to be evident using fixed effects models. Other limitations include the inclusion of a small number of studies conducted in patients with OCD, PTSD, and PD which potentially precluded the potential to conduct sub-group analyses in these populations, and that included articles were restricted to those written in the English language.

In conclusion, the results from this first quantitative meta-analytic examination of the cognitive effects of therapeutic rTMS from a large number of randomised controlled clinical trials found no robust effect of active rTMS across multiple different cognitive domains. However, an isolated positive effect was observed for improved working memory performance in a small number of studies conducted in patients with schizophrenia, indicating the possibility for specificity of effects in this clinical population. Future controlled studies are required to replicate this effect before rTMS to improve cognition in this population is recommended as a clinical treatment. Future research is further required to determine whether rTMS treatment has more highly specific cognitive effects (e.g., for specific executive abilities, or on specific tasks).

Compliance with Ethical Standards

Conflict of Interest Author Martin declares that he has no conflict of interest. Author McClintock has received research support from the NIH/NIMH (K23 MH087739) and has received honoraria for teaching from TMS Health Solutions. Author Forster declares that she has no conflict of interest. Author Loo has received equipment on loan from the Neuronetics company.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in studies conducted by the authors.

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