

Non-Invasive Brain Stimulation Does Not Improve Working Memory in Schizophrenia: A Meta-Analysis of Randomised Controlled Trials

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Abstract

Poor working memory functioning is commonly found in schizophrenia. A number of studies have now tested whether non-invasive brain stimulation can improve this aspect of cognitive functioning. This report used meta-analysis to synthesise the results of these studies to examine whether transcranial electrical stimulation (tES) or repetitive transcranial magnetic stimulation (rTMS) can improve working memory in schizophrenia. The studies included in this meta-analysis were sham-controlled, randomised controlled trials that utilised either tES or rTMS to treat working memory problems in schizophrenia. A total of 22 studies were included in the review. Nine studies administered rTMS and 13 administered tES. Meta-analysis revealed that compared to sham/placebo stimulation, neither TMS nor tES significantly improved working memory. This was found when working memory was measured with respect to the accuracy on working memory tasks (TMS studies: Hedges' $g = 0.112$, $CI_{95}:$ $-0.082, 0.305$, $p = .257$; tES studies Hedges' $g = 0.080$, $CI_{95}:$ $-0.117, 0.277$, $p = .427$) or the speed working memory tasks were completed (rTMS studies: Hedges' $g = 0.233$, $CI_{95}:$ $-0.212, 0.678$, $p = .305$; tES studies Hedges' $g = -0.016$, $CI_{95}:$ $-0.204, 0.173$, $p = .871$). For tES studies, meta-regression analysis found that studies with a larger number of stimulation sessions were associated with larger treatment effects. This association was not found for TMS studies. At present, rTMS and tES is not associated with a reliable improvement in working memory for individuals with schizophrenia.

Keywords Non-invasive brain stimulation · Repetitive Transcranial magnetic stimulation (rTMS) · Transcranial electrical stimulation (tES) · Schizophrenia · Working memory

Introduction

Working memory impairments are common in people with schizophrenia (Forbes, Carrick, McIntosh, & Lawrie, 2009; Heinrichs & Zakzanis, 1998). There is evidence indicating that the level of working memory impairment is related to functional outcomes in this group (Green, 1996; Green, Kern, & Heaton, 2004; Zaragoza Domingo, Bobes, Garcia-Portilla, Morralla & EPICOG-SCH Study Group, 2015). Given this, considerable research has been conducted to examine whether this aspect of cognitive functioning can be improved (Hasan, Strube, Palm, & Wobrock, 2016b; Marder, 2006; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). To date, psychotropic medications

have not been found to be effective in improving working memory (Manschreck & Boshes, 2007; Nielsen et al., 2015). Cognitive remediation therapy has also been examined, but appears to have a modest effect (Kambeitz-Illankovic et al., 2019; Wykes et al., 2011). More recently, non-invasive brain stimulation has been explored as a treatment option (Brunoni & Vanderhasselt, 2014; Hill, Fitzgerald, & Hoy, 2016; Jiang et al., 2019; Martin, McClintock, Forster, & Loo, 2016; Mervis, Capizzi, Boroda, & MacDonald, 2017). This report summarises research that has examined whether non-invasive brain stimulation can improve working memory in individuals with schizophrenia.

Working Memory in Schizophrenia

Working memory can be conceptualised as a memory system that temporarily stores and processes verbal and visuo-spatial information (Baddeley, 2003; D'Esposito, 2007). Functional neuroimaging studies have examined the neural activation patterns associated with working memory (Minzenberg,

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Laird, Thelen, Carter, & Glahn, 2009; Rottschy et al., 2012; Wager & Smith, 2003). From this research, the dorsolateral prefrontal cortex (DLPFC) has been identified as a key structure supporting working memory processes (Minzenberg et al., 2009; Rottschy et al., 2012; Wager & Smith, 2003). The evidence suggests that the DLPFC plays a role in manipulating verbal and visuo-spatial information by controlling attention, inhibiting interfering stimuli and integrating information (Barbey, Koenigs, & Grafman, 2013; D'Esposito & Postle, 2015; Lara & Wallis, 2015). Generally, the left hemisphere of the DLPFC shows lateralisation for verbal information, and the right for visuo-spatial information (Banich, 1998; Belger & Banich, 1998; Nagel, Herting, Maxwell, Bruno, & Fair, 2013; Reuter-Lorenz et al., 2000). However, when the demands of working memory are high during verbal and visuo-spatial tasks, bilateral activation is observed in the DLPFC to cope with task demands (Höller-Wallscheid, Thier, Pomper, & Lindner, 2017).

Poor working memory in schizophrenia has been linked to abnormal DLPFC activation (Callicott et al., 2003; Jiang et al., 2015; Minzenberg et al., 2009; Potkin et al., 2009; Royer et al., 2009). In schizophrenia, hypo-activation of the DLPFC during tasks of working memory is commonly reported in the literature (Minzenberg et al., 2009). Hypo-activation of the DLPFC appears to be related to encoding and the maintenance of information, especially as the number of items to be remembered increases (Anticevic, Repovs, & Barch, 2013; Metzack et al., 2012). Hyper-activation of the DLPFC has also been reported in schizophrenia (Callicott et al., 2003; Jiang et al., 2015; Potkin et al., 2009; Royer et al., 2009). Hyper-activation of the DLPFC is typically observed when participants with schizophrenia show working memory performance equivalent to healthy controls (Callicott et al., 2003; Jiang et al., 2015; Royer et al., 2009). The higher levels of DLPFC activation in this instance, likely reflects inefficient neural processing of the information (Callicott et al., 2003; Potkin et al., 2009).

The nature of working memory problems in schizophrenia has also been examined using electroencephalography (Barr et al., 2010; Basar-Eroglu et al., 2007; Chen et al., 2014; Haenschel et al., 2009). When neuronal populations fire synchronously, they generate brain waves or oscillations (Gandal, Edgar, Klook, & Siegel, 2012). This brain wave activity can be extracted from an electroencephalogram (Gandal et al., 2012). Evidence from this research suggests prefrontal neural oscillatory activity is atypical in schizophrenia, particularly in the gamma band frequency range (> 30 Hz) (Haenschel & Linden, 2011; Uhlhaas & Singer, 2010, 2015). Gamma oscillations are thought to have a key role in supporting working memory functions (Gandal et al., 2012; Haenschel & Linden, 2011; Uhlhaas & Singer, 2013). In schizophrenia, altered GABAergic neural transmission in the DLPFC, which is responsible for generating and modulating gamma activity, may

lead to impaired gamma oscillatory activity and to working memory deficits in this population (Chen et al., 2014; Lewis, 2000; Lewis, Curley, Glausier, & Volk, 2012; Sun et al., 2011).

In schizophrenia, a small number of studies have demonstrated that gamma oscillations are not optimally regulated during completion of working memory tasks. One finding in this area is that, gamma oscillatory power does not increase as the demands on short-term storage and processing also increase (Barr et al., 2010; Basar-Eroglu et al., 2007; Chen et al., 2014; Haenschel et al., 2009). For example, on the *n*-back task a sequence of targets is presented; the participant's task is to determine whether the target on a current trial is the same as the target presented 1, 2 or 3 (or more) trials ago. In healthy controls, gamma power increases as the distance between the target on the current and past trial increases (Barr et al., 2011; Basar-Eroglu et al., 2007). However, in schizophrenia, frontal gamma power remains high, regardless of the demands of the task (Barr et al., 2011; Basar-Eroglu et al., 2007). In addition to working memory tasks, gamma oscillations in schizophrenia are also atypical at rest and during other mental tasks, although findings are inconsistent across studies (Gandal et al., 2012; Uhlhaas & Singer, 2013).

Can Non-Invasive Brain Stimulation Improve Working Memory in Schizophrenia?

An outstanding question is whether non-invasive brain stimulation, specifically, transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES), over the DLPFC can improve working memory in individuals with schizophrenia (Brunoni & Vanderhasselt, 2014; Hill et al., 2016; Jiang et al., 2019; Mervis et al., 2017). TMS delivers brief, high-intensity magnetic pulses close to the surface of the scalp. This is facilitated through the use of a coil that induces electrical currents in a focal area underneath the region of the cortex stimulated (Hallett, 2007). The frequency of TMS pulses can have either an excitatory or inhibitory effect on the neural activity of the targeted brain region. Low frequency TMS (e.g., 1 Hz stimulation) can decrease excitability, while high frequency TMS (e.g., > 5 Hz stimulation) can increase excitability (Hallett, 2007). The application of repeated TMS pulses is referred to as repetitive transcranial magnetic stimulation (rTMS). Compared to a single pulse of TMS, rTMS is able to modulate neural activity beyond the stimulation period (Klömjai, Katz, & Lackmy-Vallée, 2015). Another form of rTMS is theta burst stimulation (TBS). This type of stimulation uses gamma frequency trains applied at a theta rhythm (Demeter, 2016).

In tES, a weak electrical current is administered to the brain via two or more electrodes, an anode and a cathode, that are placed on the scalp. The electrical current passes between the anode and cathode (Tortella et al., 2015). In transcranial direct

current stimulation (tDCS), an electrical current is administered at a constant rate over time (Antal & Paulus, 2013; Nitsche et al., 2008). In transcranial alternating current stimulation (tACS), an alternating current is applied to the brain with the goal of entraining neural oscillations at a given frequency range (Herrmann, Rach, Neuling, & Strüber, 2013). Compared to TMS, the weak electrical current from tES does not induce or inhibit action potentials in the underlying neuronal populations (Chase, Boudewyn, Carter, & Phillips, 2020). Instead, tES may modulate neural activity by influencing the direction of electrical fields, to induce a change in the resting trans-membrane potential at the site of stimulation, as well as between the electrodes (Rawji et al., 2018; Ye & Steiger, 2015). Anodal stimulation is typically associated with the enhancement of motor and cognitive functioning, whereas cathodal stimulation is associated with the inhibition of motor and cognitive functioning (Coffman, Clark, & Parasuraman, 2014). However, the effects of stimulation on neuronal excitability are nuanced by several factors, including cellular morphology, intensity of stimulation and electrode placement (Chase et al., 2020; Liu et al., 2018; Rawji et al., 2018; Ye & Steiger, 2015).

A potential factor influencing the effectiveness of non-invasive brain stimulation is the application of stimulation in a single session versus multiple sessions (Baumer et al., 2003; Cirillo et al., 2017; Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000; Monte-Silva et al., 2013). A single session of non-invasive brain stimulation can directly modulate neuronal activity to produce acute, but transient changes in brain excitability that typically last between 30 to 120 min post stimulation (Huang et al., 2017). However, to produce enduring changes in neuronal structure and connectivity, the changes in neuronal excitability need to be maintained over time (Cirillo et al., 2017; Monte-Silva et al., 2013). Therefore, the therapeutic effects of stimulation are more likely to occur after the application of multiple sessions (Baumer et al., 2003; Maeda et al., 2000; Monte-Silva et al., 2013). For example, a number of studies have demonstrated that consecutive sessions of non-invasive brain stimulation increase the magnitude and duration of the stimulation effect in the human motor cortex (Baumer et al., 2003; Maeda et al., 2000; Monte-Silva et al., 2013).

Past Meta-Analyses Examining the Effects of Non-Invasive Brain Stimulation on Working Memory in Schizophrenia

A number of studies have examined whether rTMS or tES can improve working memory in schizophrenia (Brunoni & Vanderhasselt, 2014; Hill et al., 2016; Jiang et al., 2019; Martin et al., 2016; Mervis et al., 2017). The rationale for using rTMS or tES to enhance working memory, follows research suggesting non-invasive brain stimulation can

modulate irregular gamma activity in schizophrenia (Barr et al., 2011; Hoy, Bailey, Arnold, & Fitzgerald, 2015). To date, data from research specifically examining the effects of rTMS and tES on working memory in schizophrenia has been summarised in three meta-analyses.

Mervis et al. (2017) used meta-analysis to summarise the results of four studies examining the effects of tDCS on working memory in schizophrenia. All studies included in the review, administered tDCS over the left DLPFC. This position was identified using 10–20 EEG system and placing the anodal electrode over F3. There is evidence suggesting that F3 and F4 correspond to the left and right dorsolateral prefrontal cortex respectively (Herwig, Satrapi, & Schonfeldt-Lecuona, 2003). The stimulation protocols did differ between studies. The number of sessions in which stimulation was administered varied from 1 to 28. The stimulation applied varied from 1 mA to 2 mA. Results from the meta-analysis revealed tDCS did not significantly improve working memory compared to sham stimulation. The average standardised mean difference was 0.23 (CI₉₅: -0.31, 0.77, $p = .411$).¹

In another meta-analysis, Martin et al. (2016) examined whether rTMS could improve working memory in schizophrenia. The meta-analysis summarised the findings from three studies. In these studies, the DLPFC was identified by placing the rTMS coil over F3/F4 in the 10–20 EEG system. Two studies used unilateral stimulation over F3 and one study used bilateral stimulation over F3/F4. Two studies used 10 Hz stimulation and one study used 20 Hz stimulation. Two studies administered rTMS over 15 sessions at a rate of 1000 pulses per session, and one study administered rTMS over 20 sessions at a rate of 1500 pulses per a session. Results from the meta-analysis showed that rTMS significantly improved working memory in schizophrenia when compared to sham stimulation. The average standardized mean difference was found to be 0.51 (CI₉₅: 0.18, 0.83, $p < .001$).

Finally, a recent meta-analysis by Jiang et al. (2019) also examined whether rTMS could improve working memory in schizophrenia. This report summarised the results from seven studies that all administered rTMS over the DLPFC. Four studies used unilateral stimulation over F3, and three studies used bilateral stimulation over F3/F4. Five of the studies used 10 Hz stimulation and two used 20 Hz stimulation. The number of sessions in which stimulation was administered varied from 10, 15 and 20 sessions. The total pulses per a session varied from 1000 to 4000. Results from their meta-analysis showed that rTMS significantly improved working memory in schizophrenia relative to sham stimulation. The average standardized mean difference was found to be 0.34 (CI₉₅: 0.08, 0.59, $p = .009$).

¹ p value computed from confidence intervals.

The Current Meta-Analysis

In the current report, meta-analysis was used to further examine whether non-invasive brain stimulation can improve working memory in schizophrenia. This review had two aims. The first was to provide an update concerning the effects of tES and rTMS on working memory in this clinical group. The initial meta-analyses (Mervis et al., 2017) summarising the literature on the effects of tES on working memory in schizophrenia consisted of four studies. To our knowledge, more studies have since been published bringing the total to at least 13 (Chang, Kao, Chao, & Chang, 2019; Göder et al., 2013; Gomes et al., 2018; Hoy, Arnold, Emonson, Daskalakis, & Fitzgerald, 2014; Hoy, Whitty, Bailey, & Fitzgerald, 2016; Jeon et al., 2018; Lindenmayer et al., 2019; Nienow, MacDonald, & Lim, 2016; Palm et al., 2016; Papazova et al., 2018; Rassovsky et al., 2018; Schwippel et al., 2018; Smith et al., 2015). Similarly, for rTMS, at least nine studies have now been published (Barr et al., 2011, 2013; Francis et al., 2019; Guse et al., 2013; Hasan et al., 2016a; Mohr et al., 2006; Rabany, Deutsch, & Levkovitz, 2014; Zheng, Guo, Li, Li, & Wang, 2012; Zhuo et al., 2019). Most studies investigating the effects of non-invasive brain stimulation on working memory in schizophrenia typically have small sample sizes ($n < 20$), and are underpowered to detect potentially clinically important treatment effects. By pooling these studies using meta-analysis, these effects are more likely to be detected.

The second aim of this report was to use moderator analysis to undertake a “head-to-head test” comparing the efficacy of rTMS and tES to treat working memory in schizophrenia. Based on the meta-analyses undertaken so far, it seems that rTMS but not tES might be able to improve working memory in schizophrenia. However, it is not yet known whether this is still the case given more recent studies.

Method

Literature Search

Studies included in the meta-analysis were identified using MEDLINE, PsycINFO, CINAHL, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases. An initial search was conducted in September 2017 and then repeated in June 2019. The search syntax used to identify studies is presented in Appendix Tables 4, 5 and 6.

Selection Criteria

Studies were included in the meta-analysis if they met the following criteria. First, participants were required to have a

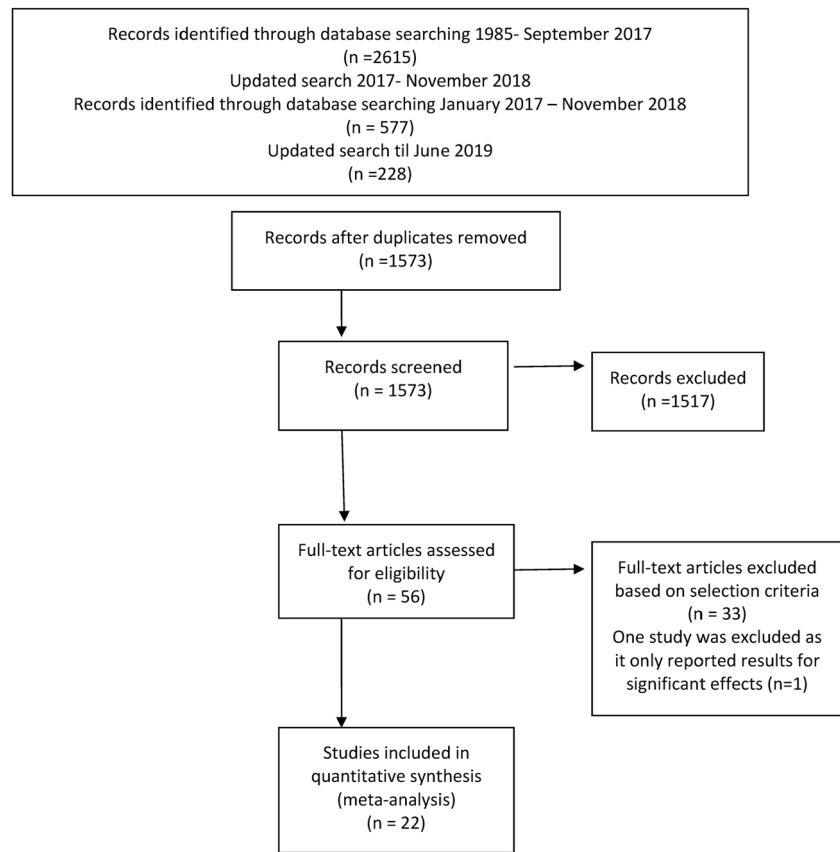
diagnosis of schizophrenia or schizoaffective disorder confirmed by a psychiatrist or using a structured diagnostic interview. Second, the study was required to have presented a working memory task that involved temporarily storing and processing verbal or non-verbal information. This included tasks such as the digit span task, *n*-back task, visuospatial working memory task, self-ordered pointing task (SOPT), Brief Assessment of Cognition (BACS), digit sequencing (Keefe et al., 2004), working memory tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition, 2019) and tasks from the MATRICS Consensus Cognitive Battery (MCCB) working memory domain (Kern et al., 2011; Nuechterlein et al., 2008). Studies using verbal fluency tasks (Dlabac-de Lange et al., 2015; Prikryl et al., 2012; Zheng et al., 2012) were excluded from the review since they do not specifically target working memory processes. Third, the study was required to have compared either rTMS or tES to sham stimulation. Fourth, rTMS or anodal tES needed to have been administered over the DLPFC. Only studies published in a peer-review journal were included. The studies could be published in any language.

A PRISMA flowchart showing the selection of studies included in the review is presented in Fig. 1. A total of 22 studies were identified and included in this review. Of this total, nine studies examined the effects of rTMS on working memory in schizophrenia (Barr et al., 2011, 2013; Francis et al., 2019; Guse et al., 2013; Hasan et al., 2016a; Mohr et al., 2006; Rabany et al., 2014; Zheng et al., 2012; Zhuo et al., 2019). All these studies used excitatory stimulation protocols. Three studies stimulated the DLPFC sequentially over F3 and F4 in a counterbalanced order (Barr et al., 2011, 2013; Francis et al., 2019). The remaining 13 studies administered tES as the intervention (Chang et al., 2019; Göder et al., 2013; Gomes et al., 2018; Hoy et al., 2014, 2016; Jeon et al., 2018; Lindenmayer et al., 2019; Nienow et al., 2016; Palm et al., 2016; Papazova et al., 2018; Rassovsky et al., 2018; Schwippel et al., 2018; Smith et al., 2015). For studies that administered tDCS, anodal stimulation over F3, F4 or over both F3 and F4 was used. Two studies administered tACS (Göder et al., 2013; Hoy et al., 2016).

Meta-Analytic Approach

Two sets of meta-analyses were undertaken in this review. The first examined the effects of tES and rTMS on accuracy measures of working memory. The second examined the effects of non-invasive brain stimulation on reaction times measured as participants completed a working memory task. For both accuracy and reaction time effect sizes, an overall meta-analysis was undertaken that combined the results of both rTMS and tES studies. The goal of these analyses was to determine

Fig. 1 PRISMA flowchart summarising study selection process



whether, overall, non-invasive brain stimulation improved working memory in schizophrenia. Additional meta-analyses were then conducted that summarised the results of rTMS and tES studies separately.

In the studies included in this review, working memory was measured using short-term recall tasks (e.g., digit span, Corsi blocks) or n -back tasks. One of the challenges synthesising effect sizes from n -back tasks was that not all studies used the same n -back ‘load.’ For example, Hoy et al. (2014) and Hoy et al. (2016) presented a 2-back task to participants. In the study by Barr et al. (2011), Papazova et al. (2018) and Schwippel et al. (2018), participants were presented with 1-, 2- and 3-back tasks. It could be that non-invasive brain stimulation is effective at high loads, but not low loads. To take this possibility into account, effect sizes from the n -back task were analysed using two methods. The first involved using meta-analysis to compute an average effect size based on all studies irrespective of the n -back load. The second involved undertaking separate meta-analyses that averaged effect sizes from n -back tasks with the same load. Specifically, meta-analyses were undertaken that averaged effect sizes from studies that administered 0-, 1-, 2 and 3-back tasks. For completeness, we report results at a specific n -back load even if only one effect size was available.

Effect Size Calculations

The results from each study were summarised using Hedges’ g . Specifically, from each study data from tables, figures, and results from statistical tests were extracted in order to compute Hedges’ g and its variance. For all but one study, Hedges’ g compared the change from baseline in working memory between the rTMS/tES and sham stimulation conditions. That is, the pre-post-test change in working memory functioning. To compute this effect size, both pre- and post-test data reported in each study were used. In one study, Hoy et al. (2014), only post-stimulation data were collected. For all studies, Hedges’ g was computed so that positive values indicated that rTMS/tES improved working memory, relative to sham stimulation. Negative Hedges’ g values indicated that working memory was superior following sham stimulation, compared to non-invasive brain stimulation.

The studies included in this review used either parallel ($k = 16$) or cross-over designs ($k = 6$; See Table 1). The tES studies comprised a combination of parallel and cross-over designs. All rTMS studies used parallel designs. In a parallel design, participants are randomly assigned to either stimulation or sham condition. For a cross-over design, participants complete both stimulation and sham conditions (Elbourne, Altman, Higgins, Curtin, & Vail, 2002). When computing an effect size using data extracted from a cross-over trial, the

Table 1 Summary of stimulation protocols and working memory assessment of included studies

TMS studies	Trial design	Sample size	Intervention	Stimulation site (anode:cathode)	Stimulation frequency ^d (Hz)	Duration (pulses per a session) / (mins)	No. of sessions	WM Task/s	Outcome measures	Current density (mA/cm ²)
Barr et al. (2011)	Parallel	24	rTMS	F3 & F4 ^a	20	1500	1	1-back, 2-back, 3-back	Accuracy, Reaction Time	n/a
Barr et al. (2013)	Parallel	27	rTMS	F3 & F4 ^a	20	1500	20	1-back, 3-back	Accuracy, Reaction Time	n/a
Francis et al. (2019)	Parallel	19	rTMS	F3 & F4 ^a	20	1200	10	BACS digit sequencing	Accuracy	n/a
Guse et al. (2013)	Parallel	25	rTMS	F3	10	1000	15	0-back, 1-back, 2-back	Accuracy, Reaction Time	n/a
Hasan et al. (2016a)	Parallel	100	rTMS	F3	10	1000	15	DST forwards, DST backwards	Accuracy	n/a
Mohr et al. (2006)	Parallel	16	rTMS	F3	20	^b	10	DST forwards, DST backwards	Accuracy	n/a
Rabany et al. (2014)	Parallel	30	Deep rTMS	F3	20	^c	20	CANTAB WM	Accuracy	n/a
Zheng et al. (2012)	Parallel	80	rTMS, TBS	F3	rMTS = 10 & 20; TBS = 50.	rTMS = 1200 TBS = 10 mins	5	VSWM	Accuracy	n/a
Zhuo et al. (2019)	Parallel	60	rTMS	F3	20	2000	20	MCCB WM	Accuracy	n/a
Chang et al. (2019)	Parallel	60	tDCS	F3-FP1: T3-P3	0	20 mins	10	DST forwards, DST backwards	Accuracy	.057
Göder et al. (2013)	Crossover	14	tACS	F3/F4: M	0.75	25 mins	1	DST forwards, DST backwards	Accuracy	.015
Gomes et al. (2018)	Parallel	24	tDCS	F3: RCA	0	20 mins	10	MCCB WM	Accuracy	.080
Hoy et al. (2014)	Crossover	18	tDCS	F3: RSO	0	20 mins	1	2-back	Accuracy, Reaction Time	.029 & .057
Hoy et al. (2016)	Crossover	11	tDCS & tACS	F3: RSO	0 & 40	20 mins	1	2-back	Accuracy, Reaction Time	.057 & .029
Jeon et al. (2018)	Parallel	52	tDCS	F3:F4	0	30 mins	10	MCCB WM	Accuracy	.080
Lindenmayer et al. (2019)	Parallel	16	tDCS	F3-FP1: T3-P3	0	20 mins	40	MCCB WM	Accuracy	.057
Nienow et al. (2016)	Parallel	10	tDCS	F3: RSO	0	10 mins	28	2-back	Accuracy	.029
Palm et al. (2016)	Parallel	20	tDCS	F3: ROF	0	20 mins	10	SOPT	Accuracy	.057
Papazova et al. (2018)	Crossover	20	tDCS	F3: CDM	0	21 mins	1	1-back, 2-back, 3-back	Accuracy	.029 & .057
Rassovsky et al. (2018)	Crossover	37	tDCS	F3: RSO	0	20 mins	2	MCCB WM	Accuracy	.057
Schwippel et al. (2018)	Crossover	16	tDCS	F4: CDM	0	21 mins	1	1-back, 2-back, 3-back	Accuracy, Reaction Time	.029 & .057
Smith et al. (2015)	Parallel	29	tDCS	F3: RSO	0	20 mins	5	MCCB WM	Accuracy	.400

DST Digit Span Task, VFT Verbal Fluency Task, VSWM Visual Spatial Working Memory Task, CANTAB SWM Cambridge Neuropsychological Test Automated Battery Spatial Working Memory, BACS Digit Sequencing Brief Assessment of Cognition in Schizophrenia Digit Sequencing, SOPT Self-Ordered Pointing task, MCCB WM/MA TRICS Consensus Cognitive Battery (MCCB) Working Memory Domain, M mastoids, RCA right contralateral area, RSO contralateral supraorbital, ROF right orbitofrontal, CDM contralateral deltoid muscle

Total sample size reflects participants that completed the study and were included in the analysis. ^a Bilateral sequential stimulation, counterbalanced administration. ^b Authors indicate that stimulation was applied over a 20 min period. ^c Each session consisted of 42 two-second trains, divided by 20-s inter-train intervals. ^d Stimulation frequency of a direct current expressed as 0 Hz

correlation between scores from sham and stimulation conditions needs to be taken into account, as they are from the same participants. In a parallel design, scores from sham and stimulation conditions are treated as independent, since they are from different participants. Given differences in the dependency of the data between parallel design and cross-over studies, separate sets of equations were used to compute Hedges' *g* and variance for these different designs.

Equations for Computing Effect Sizes for Parallel and Cross-over Trials Computing Hedges' *g* for parallel- and cross-over trials involved standardising the change in scores from baseline, by the pooled standard deviation of changes for stimulation and sham conditions. Then a correction factor, notated as *J*, is applied to the standardised mean difference (SMD) and variance. The correction is needed because, the standardised mean difference overestimates the population effect size when sample sizes are small (Hedges & Olkin, 1985). For example, when the sample size is 20, the standardised mean difference overestimates the population effect by 4% (Durlak, 2009). The correction factor *J* corrects the standardised mean difference using the study's sample size. Given that the sample sizes of most of the studies included in this meta-analysis were typically between 10 and 20, Hedges' *g* was considered the most appropriate effect size for this meta-analysis to avoid overestimating treatment effects. Equations (1) and (2) were used to compute Hedges' *g* and variance for parallel trials respectively and, Eqs. (3) and (4) for computing the corresponding values for cross over trials.

$$\text{SMD (Parallel Trials)} = \left(\frac{\Delta M_{Stimulation} - \Delta M_{Sham}}{\sqrt{\frac{(n_{Stimulation}-1)\Delta S_{Stimulation}^2 + (n_{Sham}-1)\Delta S_{Sham}^2}{n_{Stimulation} + n_{Sham} - 2}}} \right) \quad (1)$$

, Hedges' *g* = SMD × *J*

$$\text{Variance } g = \left(\frac{n_{Stimulation} + n_{Sham}}{n_{Stimulation} \times n_{Sham}} + \frac{SMD^2}{2(n_{Stimulation} + n_{Sham})} \right) \times J^2 \quad (2)$$

SMD (Cross Over Trials)

$$= \left(\frac{\Delta M_{Stimulation} - \Delta M_{Sham}}{\sqrt{\frac{S_{difference}}{2(1-r)}}}} \right), \text{ Hedges' } g$$

$$= \text{SMD} \times J \quad (3)$$

$$\text{Variance } g = \left(\frac{1}{n_{pairs}} + \frac{SMD^2}{2 \times n_{pairs}} \right) \times J^2 \quad (4)$$

Where:

$\Delta M_{Stimulation} / \Delta M_{Sham}$ = Change in working memory score from baseline following rTMS/tES/sham stimulation. For

Hoy et al. (2014), $\Delta M_{Stimulation}$ and ΔM_{Sham} comprised post-stimulation data.

$n_{Stimulation} / n_{Sham}$ sample size for rTMS/tES/sham conditions.
 n_{pairs} total number of pairs in cross-over trial.
 $\Delta S_{Stimulation} / \Delta S_{Sham}$ Standard deviation of the change score between baseline and rTMS/tES/sham.
 $S_{difference}$ Standard deviation of the differences scores between rTMS/tES and sham conditions in cross over trials.

$$J = \left(1 - \frac{3}{4df-1} \right)$$

r correlation between rTMS/tES and sham change scores.

For 12 studies, the data required to compute Hedge's *g* were obtained from descriptive statistics or results from statistical tests (Francis et al., 2019; Hasan et al., 2016a; Hoy et al., 2014, 2016; Lindenmayer et al., 2019; Mohr et al., 2006; Nienow et al., 2016; Palm et al., 2016; Rabany et al., 2014; Smith et al., 2015; Zheng et al., 2012; Zhuo et al., 2019). However, for the remaining 10 studies (Barr et al., 2011; Barr et al., 2013; Chang et al., 2019; Gomes et al., 2018; Guse et al., 2013; Hoy et al., 2014; Jeon et al., 2018; Papazova et al., 2018; Rassovsky et al., 2018; Schwippel et al., 2018) the necessary information needed to compute the change in standard deviation needed (i.e., ΔS for parallel trials and $S_{difference}$ for cross-over trials) for Eqs. 1 or 3 was not available. For these studies, this value was imputed using Eq. 5. However, to compute Eq. 5, the correlation between baseline and stimulation (i.e., pre-post-test) scores is required. This value was not presented in these studies. At present there is no universally agreed upon method for dealing with this missing correlation value in meta-analysis. This value must therefore be estimated (Pearson & Smart, 2018). For this report, following Follmann, Elliott, Suh, and Cutler (1992), the correlation was conservatively set at 0.5.

$$SD_{change} = \sqrt{S_{Baseline}^2 + S_{Stimulation}^2 - (2 \times r_{baseline,stimulation} \times S_{Baseline} \times S_{Stimulation})} \quad (5)$$

Where:

$r_{baseline, stimulation}$ correlation between baseline and stimulation scores.
 $S_{Baseline}$ standard deviation of baseline scores.
 $S_{Stimulation}$ standard deviation of stimulation (i.e., tES, rTMS, sham) scores.

For six cross-over trials, insufficient information was reported to compute Eq. 3 (Göder et al., 2013; Hoy et al., 2014, 2016; Papazova et al., 2018; Rassovsky et al., 2018; Schwippel et al., 2018). This was because the correlation between scores from stimulation and sham conditions was not available (notated as r in Eq. 3). This is a common issue associated with the meta-analysis of cross-over trials (Curtin, Altman, & Elbourne, 2002; Elbourne et al., 2002). To overcome this problem, the value of this correlation was estimated. For this meta-analysis the correlation between stimulation and sham change from baseline scores was therefore set at zero. That is, it is assumed scores in the stimulation and sham conditions are independent. This value has been used in a previous meta-analysis of cross-over trials (Jennings, Davies, Higgins, Anzures-Cabrera, & Broadley, 2012).

Types of Tasks Used to Measure Working Memory The studies included in this meta-analysis assessed working memory using either n -back or short-term recall tasks (see Table 1). On n -back tasks, performance can be measured using accuracy and reaction times. Thus, separate effect sizes were computed for accuracy and reaction time data. For accuracy data, positive Hedges' g values indicated that rTMS/tES was associated with higher accuracy scores compared to sham stimulation. Negative Hedges' g values indicated sham stimulation was associated with higher accuracy scores compared to rTMS/tES. For reaction time data, positive Hedges' g values indicated that non-invasive brain stimulation was associated with faster reaction times compared to sham stimulation. Negative Hedges' g values indicated sham stimulation was associated with faster reaction times compared to rTMS/tES.

A total of 13 studies (see Table 1) used short-term recall tasks to measure the effects of stimulation on working memory (Chang et al., 2019; Francis et al., 2019; Göder et al., 2013; Gomes et al., 2018; Hasan et al., 2016a; Jeon et al., 2018; Lindenmayer et al., 2019; Mohr et al., 2006; Palm et al., 2016; Rabany et al., 2014; Smith et al., 2015; Zheng et al., 2012; Zhuo et al., 2019). Common to these tasks is that participants were asked to recall an increasing string consisting of digits, letters or a visuo-spatial sequence. For these studies, working memory performance was measured only in terms of accuracy. That is, the number of items correctly recalled. For studies using these short-term recall tasks, positive Hedges' g values indicated rTMS/tES was associated with recalling a larger number of elements (i.e., digits, letters, visuo-spatial sequenced) compared to sham stimulation. Negative Hedges' g values indicated sham stimulation was associated with recalling a larger number of elements compared to rTMS/tES. All individual effect sizes computed from each study are available for download via the Open Science Framework platform (https://osf.io/3darh/?view_only=f2df690695e248628546a9c586f94612).

Studies with Multiple Outcomes or Multiple Comparisons For five studies, the effects of non-invasive brain stimulation were reported using multiple outcomes (Barr et al., 2011, 2013; Chang et al., 2019; Göder et al., 2013; Mohr et al., 2006). For example, in two studies, the results from an n -back task were reported separately for target and non-target trials (Barr et al., 2011, 2013). In another, results were reported separately for word and picture versions of the n -back task (Nienow et al., 2016). For two studies assessing working memory using a digit span task, results were presented separately for forward and backward trials (Chang et al., 2019; Göder et al., 2013) and in one study, results were presented from verbal and non-verbal variants of the task (Mohr et al., 2006). For these studies, a composite effect size was created. Specifically, separate effect sizes and variances were first computed for each outcome variable and then, an average effect size and variance was computed.

Three studies compared two stimulation interventions to a single sham group. In the study by Zheng et al. (2012), the effects of rTMS at 10 Hz and 20 Hz on working memory were compared to a single sham stimulation group. Hoy et al. (2014) compared the effects of 1 mA and 2 mA tDCS to a single sham stimulation group. Also, Hoy et al. (2016) compared the effects of tDCS and tACS to a single sham stimulation group. For these studies, it was decided to compute separate effect sizes for each different TMS/tES protocols. For example, in the study by Zheng et al. (2012), separate effect sizes were computed that compared the effectiveness of 10 Hz to sham stimulation and 20 Hz to sham stimulation. One limitation with this approach is that summary data from the same sham group are treated as an independent sample, which in turn leads to an underestimation of the standard error when undertaking meta-analysis. However, since this process was undertaken for only three studies, with relatively small sample sizes, the effect on the standard error of the meta-analysis was negligible.

Meta-Analytic Procedures

Study level effect sizes were averaged using a random effects model (Borenstein, Hedges, Higgins, & Rothstein, 2011; Hedges & Olkin, 1985). For all meta-analyses, alpha was set at .05 (two-tailed). Additionally, the amount of 'true' heterogeneity or systematic influences between study level effect sizes was measured using the I^2 statistic (Thompson & Higgins, 2002). This statistic summarises, as a percentage, differences in study level effect sizes that are due to systematic influence. In this meta-analysis we interpreted I^2 values according to the guidelines outlined by Thompson and Higgins (2002) whereby values of 25%, 50% and 75% correspond to low, moderate and high levels of heterogeneity respectively.

Mixed-effects moderator analysis (Borenstein et al., 2011) was used to undertake a "head-to-head test" comparing the

efficacy of rTMS and tES to treat working memory in schizophrenia. That is, whether there was a significant difference in the average effect sizes from rTMS studies compared to tES studies. Mixed-effects moderator analysis was undertaken using Comprehensive Meta-Analysis Software 2.0. Finally, exploratory random effects meta-regression (Thompson & Higgins, 2002) was undertaken to examine the effects of different stimulation protocols on effect sizes.

Risk of Bias

The risk of bias was assessed using the Cochrane Collaboration's Risk of Bias Tool (Higgins & Altman, 2008). This tool assesses whether a study is at high, low or unclear risk of selection bias, performance bias, detection bias, attrition bias and reporting bias in intervention studies.

Publication Bias

For each meta-analysis, publication bias was assessed using Egger's Test (Egger, Davey Smith, Schneider, & Minder, 1997). This test assesses publication bias on the basis of the distribution of effect sizes around the weighted average effect size. In the absence of publication bias, effect sizes are expected to be symmetrically distributed around the weighted average effect size. When publication bias is present, effect sizes are asymmetrically distributed around the weighted average effect size. For example, effect sizes reporting null or negative effects may be missing from the distribution. The extent the distribution of effect sizes is asymmetrically distributed was formally tested using Egger's Test (Egger et al., 1997). A significant result indicates the effect sizes are asymmetrically distributed and publication bias may be present.

Results

Methodological Characteristics of Included Studies

Table 1 presents a summary of the methodological characteristics of the studies included in this review. Seven studies administered rTMS, one study administered both rTMS and theta burst stimulation (TBS), and one study administered rTMS using a deep TMS coil. The sample sizes ranged from 16 to 100 participants. For six rTMS studies, stimulation was administered over the F3 electrode position in the EEG 10–20 system. In three studies, rTMS was administered bilaterally and sequentially over both F3 and F4 electrode positions with the order of administration counterbalanced. Pulses were delivered at 10 Hz, 20 Hz or 50 Hz. There was some variability with respect to the number of pulses administered per session as well as the number of sessions participants completed.

In 13 studies tES was administered. Eleven studies administered tDCS, one study administered tACS and one study administered both tDCS and tACS. The sample sizes ranged from 10 to 60 participants. For 12 of the tES studies, anodal stimulation was applied over the F3 electrode. For one study, anodal stimulation was applied over the F4 electrode. The cathode was most commonly placed on the contralateral supraorbital or orbitofrontal area. In two studies, the cathode was placed over the temporo-parietal junction, midway between the T3 and P3 electrode. One study placed the cathode over the F4 electrode. The stimulation intensity varied from 1 mA or 2 mA. In two studies tACS was applied. There was variability in the number of sessions participants completed, this ranged from a single session to 40 sessions.

Across all studies working memory was most commonly assessed using variants of the *n*-back or digit span tasks. With respect to the *n*-back tasks, 0–1-, 2- and 3-back versions of the tasks were administered. On these tasks, participants are asked to indicate whether a presented visual or auditory stimulus matches a previously displayed item shown *n*-previous positions. In two studies working memory was assessed using variants of the digit span task in which participants aim to temporarily remember a string of digits or spatial locations.

Summary of Participant Characteristics of Studies Included in the Meta-Analyses

Table 2 shows participant characteristics of the studies included in this review that examined the effects of rTMS and tES on working memory in schizophrenia. Of the nine studies using rTMS, the average age of the participants was 39.76 years ($SD = 10.82$). Of the total sample, 20% were female. The Positive and Negative Syndrome Scale (PANSS) was used in all studies as a clinical measure of symptom severity at baseline. The PANSS total score was reported in the majority of studies except for Barr et al. (2013), Mohr et al. (2006) and Rabany et al. (2014). The mean PANSS total score for the intervention group was 65.95 ($SD = 12.57$). The mean PANSS total score for the control 'sham' group was 66.41 ($SD = 11.10$). In all studies participants were treated with antipsychotic medication. Most studies except for Barr et al. (2011), Barr et al. (2013) and Mohr et al. (2006) reported that participants remained on a stable dose of antipsychotic medications for the duration of the trial.

Of the 13 tES studies included, the average age of participants was 41.21 years ($SD = 7.30$). Of the total sample, 30% were female. Most studies provided a measure of the PANSS total score, except for Nienow et al. (2016) and Rassovsky et al. (2018) who assessed clinical severity using the Brief Psychiatric Rating Scale. For the tES studies that used a parallel study design, the mean PANSS score for the intervention group was 78.11 ($SD = 6.67$) and 76.41 for the control group ($SD = 7.31$). For the studies that used a cross-over design, the

Table 2 Summary of participants from each study included in the review

s	Age, Sample Size, & Gender				PANSS Positive				PANSS Negative				PANSS Total			
	Intervention Group		Control Group		Intervention Group		Control Group		Intervention Group		Control Group		Intervention Group		Control Group	
	M	SD	Total n	Female n	M	SD	Total n	Female n	M	SD	M	SD	M	SD	M	SD
Barr et al. (2013)	41.2	12.0	13	6	49.0	12.4	14	3	13.4	4.7	12.2	4.5	15.5	6.3	.	.
Francis et al. (2019)	23.4	3.1	9	2	22.3	3.1	10	2	10.3	3.0	10.0	3.7	14.7	5.1	45.1	8.5
Guse et al. (2013)	37.0	.	13	3	36.0	.	12	3	15.3	4.4	11.9	3.1	23.3	2.2	81.7	11.9
Hasan et al. (2016a)	36.4	10.6	77	11	35.5	9.0	79	22	14.2	4.4	13.0	3.7	25.2	3.8	80.0	15.7
Mohr et al. (2006)	35.3	9.2	8	1	32.8	6.3	8	3
Rabany et al. (2014)	33.1	11.3	20	7	35.9	11.0	10	2
Zheng et al. (2012) (10 Hz)	56.5	7.4	19	0	55.6	5.8	17	0	11.7	4.4	12.2	4.2	23.3	4.9	22.8	5.1
Zheng et al. (2012) (20 Hz)	56.8	5.4	19	0	55.6	5.8	17	0	11.1	4.5	12.2	4.2	22.0	4.8	22.8	5.1
Zheng et al. (2012) (TBS)	56.4	9.3	18	0	55.6	5.8	17	0	12.9	5.4	12.2	4.2	23.6	5.4	22.8	5.1
Zhuo et al. (2019)	29.0	7.4	33	11	30.6	8.3	27	8	14.2	3.4	15.3	2.7	21.7	3.4	22.6	3.8
Chang et al. (2019)	46.4	10.3	30	16	42.2	10.3	30	17	15.8	5.1	14.9	3.9	19.7	4.7	18.4	4.4
Göder et al. (2013)	33.0	8.0	14	45.0	.
Gomes et al. (2018)	39.2	9.3	12	2	33.8	12.1	12	5	16.3	3.1	13.3	3.2	23.8	5.6	21.7	8.4
Hoy et al. (2014)	42.2	11.0	18	6	17.6	7.4	.	.	15.8	4.3	68.1	18.0
Hoy et al. (2016)	43.3	10.0	11	6	15.2	4.8	.	.	12.4	3.0	60.3	13.4
Jeon et al. (2018)	40.0	9.4	26	13	39.9	12.4	28	15	20.3	6.6	18.1	5.8	23.2	7.0	21.5	6.1
Lindenmayer et al. (2019)	.	.	15	2	81.5	7.5
Nienow et al. (2016)	61.5	6.0	10	.	61.0	2.8
Palm et al. (2016)	38.4	12.9	10	5	34.1	10.7	10	0	10.0	3.9	10.7	4.1	24.0	5.4	25.1	4.1
Papazova et al. (2018) 1 mA	36.6	10.6	20	5	13.0	2.7	.	.	12.9	3.1	52.7	7.8
Papazova et al. (2018) 2 mA	37.7	10.8	20	4	15.5	5.0	.	.	14.9	5.3	60.4	16.3
Rassovsky et al. (2018)	42.7	8.6	38	12
Schwippel et al. (2018) 1 mA	32.0	7.5	16	4	10.5	4.2	.	.	16.6	8.6	51.9	15.5
Schwippel et al. (2018) 2 mA	37.3	11.3	16	5	13.8	5.1	.	.	14.3	6.8	51.3	14.8
Smith et al. (2015)	46.8	11.1	17	3	44.9	9.9	16	6	67.9	20.0

Barr et al. (2011) excluded as separate data for the intervention and control groups was not provided

mean PANSS score was 55.66 ($SD = 7.69$). All participants were treated with antipsychotic medication. All studies except for Gomes et al. (2018), Papazova et al. (2018) and Smith et al. (2015) reported that clients remained on a stable dose of antipsychotic medications.

The Effect of Non-Invasive Brain Stimulation on Accuracy in Schizophrenia

Figure 2 presents a forest plot showing the results of the meta-analyses examining the effect of tES and TMS on working memory. The first notable trend to emerge from the analyses is that all results were non-significant. Neither rTMS or tES were found to reliably improve working memory in schizophrenia, with respect to accuracy. This result was found for short-term recall and *n*-back tasks. Results from Egger’s test was not significant for all meta-analyses. Thus, publication bias does not appear to be leading to an over-estimation of effect sizes.

Another trend to emerge from these meta-analyses is that in almost all instances, the I^2 statistic was close to zero for the rTMS studies. This indicates that despite differences in participant characteristics and stimulation protocols noted above, there appears to be no detectable systematic influence on study-level effect sizes. That is, at present it seems that differences in individual study effect sizes can be attributed to random error (i.e., chance rather than by the influence of one or more independent/predictor variables). However, for the tES

studies, there does appear to be one or more systematic influences affecting the magnitude of effect sizes. This is reflected by the small-to-medium levels of heterogeneity observed for the working memory outcome measures. This indicates that differences between study level effect sizes for tES studies may not only be due to chance or random error.

The next set of analyses tested whether tES was superior to rTMS with respect to improving accuracy scores on working memory tasks in schizophrenia. The results from mixed-effects moderator analysis revealed no significant differences between rTMS and tES effect sizes. Specifically, the average effect size computed from ‘All Tasks’ ($Q(1) = 0.052, p = .820$), ‘short-term recall tasks’ ($Q(1) = 0.001, p = .971$), ‘*n*-Back (all loads)’ ($Q(1) = 0.003, p = .960$), ‘1-Back’ ($Q(1) = 0.238, p = .625$), ‘2-Back’ ($Q(1) = 3.019, p = .082$) and ‘3-Back’ ($Q(1) = 0.395, p = .530$) were all non-significant.

The Effect of Non-invasive Brain Stimulation on Reaction Times in Schizophrenia

Figure 3 presents results from meta-analyses examining the effects of non-invasive brain stimulation on reaction times. All effect sizes were from *n*-back tasks. In all cases, the average effect size was not found to be significant. This result was found when effect sizes were averaged across all loads from the *n*-back as well as at specific *n*-back loads. Another trend to note in Fig. 3 is that for all analyses the I^2 statistic was zero.

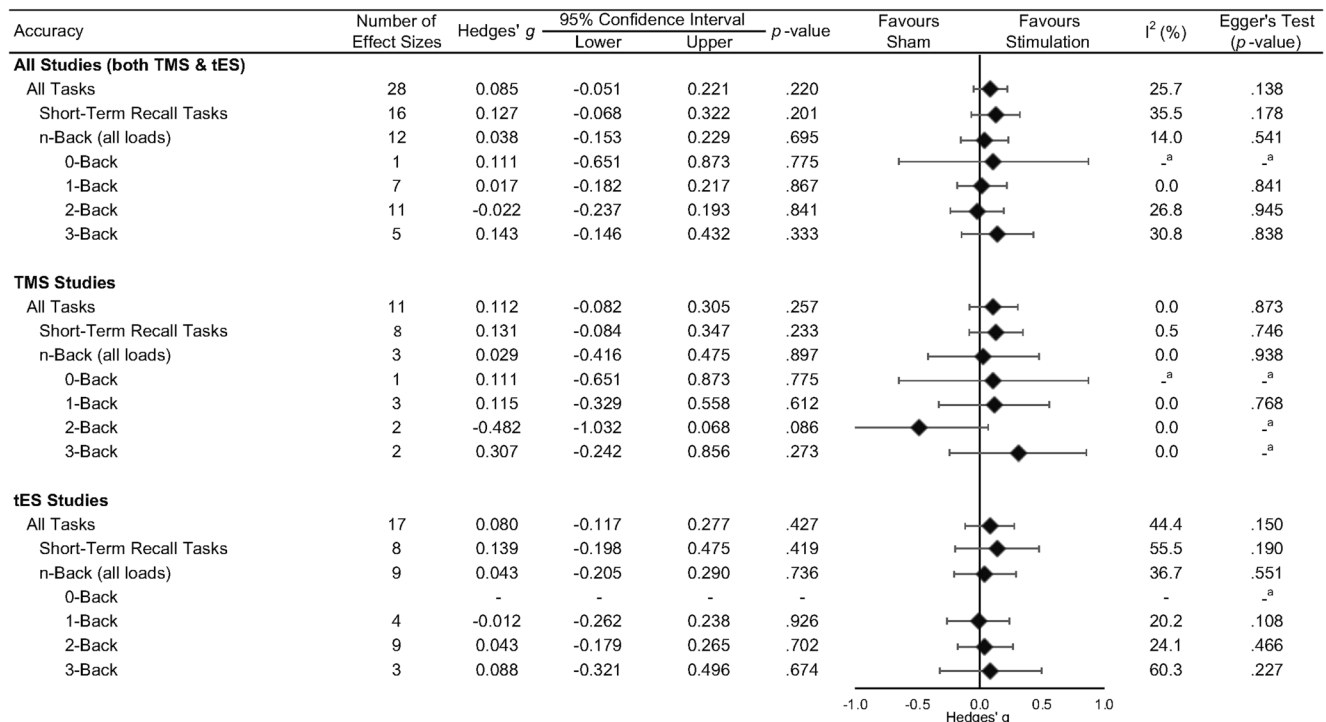


Fig. 2 Meta-analyses examining the effect of non-invasive brain stimulation on accuracy data. ^aInsufficient number of studies to undertake Egger’s Test. * $p < .05$

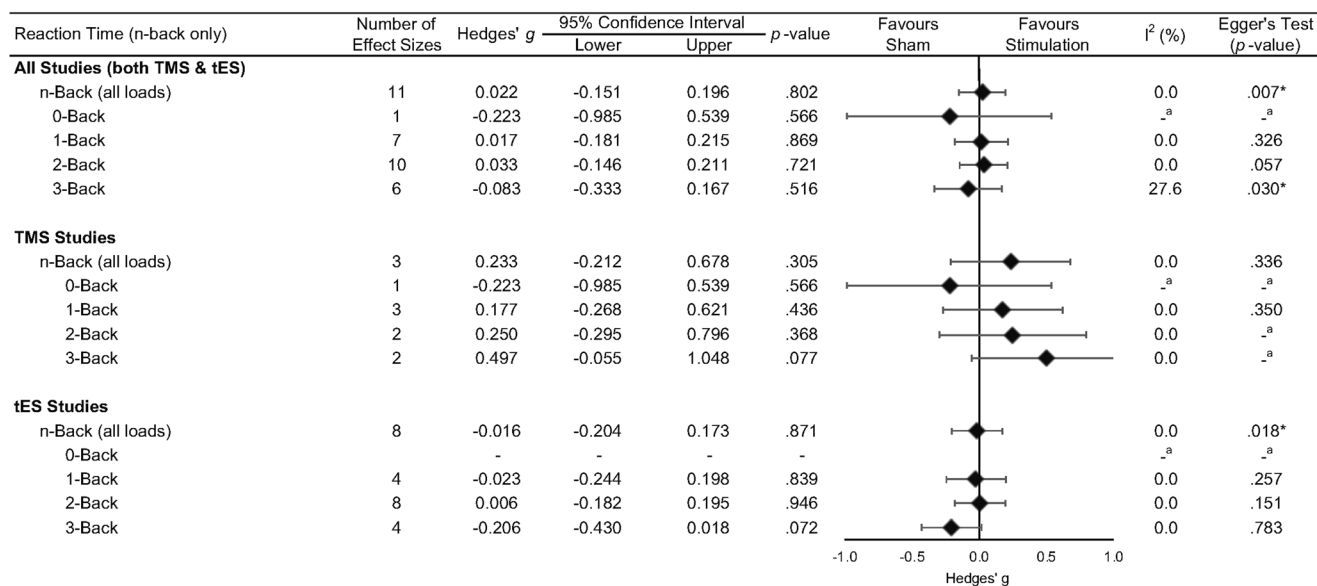


Fig. 3 Meta-analyses examining the effect of non-invasive brain stimulation on reaction time data. ^aInsufficient number of studies to undertake Egger's Test. * $p < .05$

This indicates differences in study level effect sizes can be best explained with respect to random error. For reaction times, publication bias does not appear to be leading to an overestimation of effect sizes. With the exception of three meta-analyses, the results of Egger's tests were not significant. To estimate the effect of this bias on the significant Egger's test results, an unbiased estimate of these average effect sizes was computed using Duval and Tweedie's (2000) trim-and-fill method. In each case the unbiased estimate yielded a comparable result to the observed value (Unbiased Estimate: All Studies, *n*-Back (all loads): Hedges' $g = -.047$, $p = .568$; All studies, 3-Back: Hedges' $g = -.040$, $p = .657$; tES Studies *n*-Back (all loads): Hedges' $g = -.087$, $p = .318$). Thus, publication bias does not appear to be leading to an over-estimation of effect sizes.

The results from mixed-effects moderator analysis revealed no significant differences between rTMS and tES effect sizes on *n*-Back (all loads) ($Q(1) = 1.015$, $p = .314$), 1-Back ($Q(1) = 0.621$, $p = .431$) and 2-Back ($Q(1) = 0.687$, $p = .407$). However, on the 3-Back ($Q(1) = 5.352$, $p = .021$), the average effect size from TMS studies was significantly larger compared to tES studies.

Using Meta-Regression to Examine the Influence of Stimulation Protocols on Effect Sizes

The next set of analyses examined the effect of varying stimulation protocols on study level effect sizes. As noted previously, Table 1 showed considerable variability with respect to the stimulation protocols in the rTMS and tES studies. For example, for both rTMS and tES studies, differences were present in relation to the type of stimulation (rTMS, deep

rTMS, TBS, tDCS, tACS), stimulation site, intensity of the stimulation, duration and number of sessions. Meta-regression was used to test whether one or more of these variables was related to study-level differences in effect sizes.

Separate meta-regression analyses were undertaken for rTMS and tES studies. For rTMS studies, separate meta-regression analyses tested whether (1) the type of rTMS used (rTMS, Deep rTMS, TBS), (2) stimulation site (bilateral vs. unilateral), (3) stimulation frequency, (4) number of pulses or the (5) number of stimulation sessions, predicted study level effect sizes. For tES studies, we tested whether (1) the type of tES (tDCS vs tACS), (2) stimulation site (bilateral vs. unilateral), (3) stimulation frequency, (4) current density, (5) stimulation duration, (6) stimulation frequency or the (7) number of sessions, predicted effect sizes. The study-level values for each of these predictor variables is presented in Table 1. The outcome variable used in each study were study level effect sizes. For each study, where applicable, effect sizes were averaged across reaction time and accuracy, as well as across different spans from the *n*-back task. The results from the meta-regression analyses are summarised in Table 3. The only significant result found was that the number of test sessions for tES studies predicted effect sizes. For illustrative purposes, this result is shown in Fig. 4. For this analysis, the positive beta value indicates studies with more stimulation sessions, observed larger positive effect sizes.

Sensitivity Analyses: The Effect of Correlation Assumptions on Meta-Analyses

As noted in methods, for a number of studies, assumptions needed to be made about the magnitude of the correlation

Table 3 Results from meta-regression analyses examining the effects of stimulation protocols on study level effect sizes

Study Type/Predictor Variable	Slope (beta)	R ²	Q _{model}	Q _{residual}	df	p value
TMS Studies						
Type of TMS [†]						
rTMS vs. TBS ^a	-0.245	0.060	0.44	6.82	1,8	.509
rTMS vs. Deep rTMS ^b	0.125	0.016	0.11	6.82	1,8	.743
Stimulation site: (bilateral vs. unilateral) ^c	0.014	0.000	0.00	7.40	1,9	.970
Stimulation Frequency (Hz)	0.266	0.071	0.52	6.88	1,9	.470
Number of pulses per session	-0.389	0.151	1.03	5.77	1,6	.310
Number of stimulation sessions	-0.598	0.358	2.65	4.75	1,9	.104
tES Studies						
Type of tES (tDCS vs tACS)						
Bilateral vs. unilateral stimulation						
F3 vs. Bilateral Stimulation ^d	0.229	0.052	0.88	16.00	1,13	.347
F4 vs. Bilateral Stimulation ^e	-0.309	0.096	0.07	0.66	1,3	.792
F3 vs F4 ^f	0.266	0.071	1.15	15.12	1,12	.284
Stimulation Frequency (Hz)	-0.219	0.048	0.91	18.16	1,15	.340
Current Density (mA/cm ²)	0.285	0.081	1.55	17.52	1,15	.213
Stimulation Duration	0.065	0.004	0.08	18.99	1,15	.778
Number of stimulation sessions	0.526	0.276	5.27	13.80	1,15	.022*

[†] Insufficient studies to compare TBS (*k* = 1) and Deep rTMS (*k* = 1). ^{a,b,c,d,e,f} Predictor variable was dummy coded (0,1) in analyses. ^a rTMS = 1, TBS = 0; ^b rTMS = 1, Deep rTMS = 0; ^c Bilateral Stimulation = 1, Unilateral stimulation = 0; ^d F3 = 1, Bilateral Stimulation = 0, ^e F4 = 1, Bilateral Stimulation = 0; ^f F3 = 1, F4 = 0

between (1) pre-post test scores and (2), stimulation and sham scores. For 10 studies, the correlation between pre-post test scores was fixed at 0.5. For six tES cross-sectional studies, the correlation between sham and stimulation scores was set at 0.0. The impact of using these correlation values on the meta-analyses was tested by re-running the meta-analysis and systematically varying correlation values. For the pre-post-test correlation, meta-analyses were re-run with the correlation values of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7,

0.8 and 0.9. For the stimulation and sham scores correlation used to compute effect sizes for cross-over studies, meta-analyses were run using values of 0.0, 0.5 and 0.9. Sensitivity analyses were run separately for rTMS and tES studies and also for accuracy and reaction time data. The results are presented in Fig. 5. The key result to note from this figure is that the average effect sizes remain stable and all meta-analyses returned a non-significant result irrespective of the correlation value.

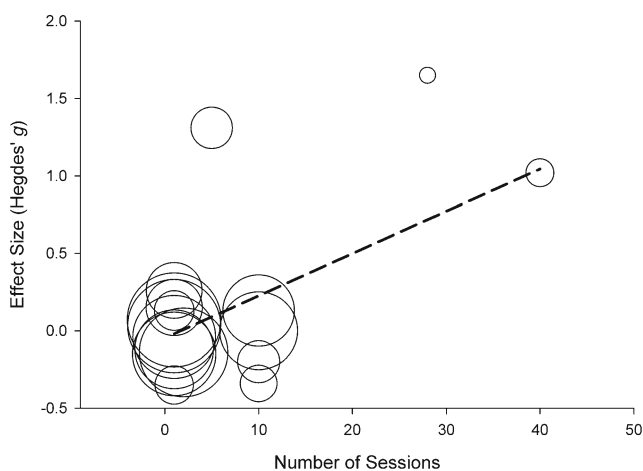


Fig. 4 Scatterplot showing the association between the number of stimulations sessions and study level effect sizes for tES study. Broken line shows the regression line computed using parameters estimated from the meta-regression analyses. The size of the data points in the figure reflect the weight of the effect sizes in the model

Results from the Risk of Bias Assessment

Results from the assessment of bias using Cochrane Collaboration’s Risk for rTMS and tES studies are presented in Figs. 6 and 7 respectively. Amongst rTMS studies and tES studies, high or unclear risk was commonly assessed for selection, performance and reporting bias.

Discussion

This report summarised research examining the effectiveness of non-invasive brain stimulation for improving working memory in schizophrenia. The meta-analyses presented in this report summarised results from 22 studies representing data from 737 participants across different measures of working memory. Three key findings emerged. First, the evidence does not indicate that rTMS or tES improves working memory in schizophrenia.

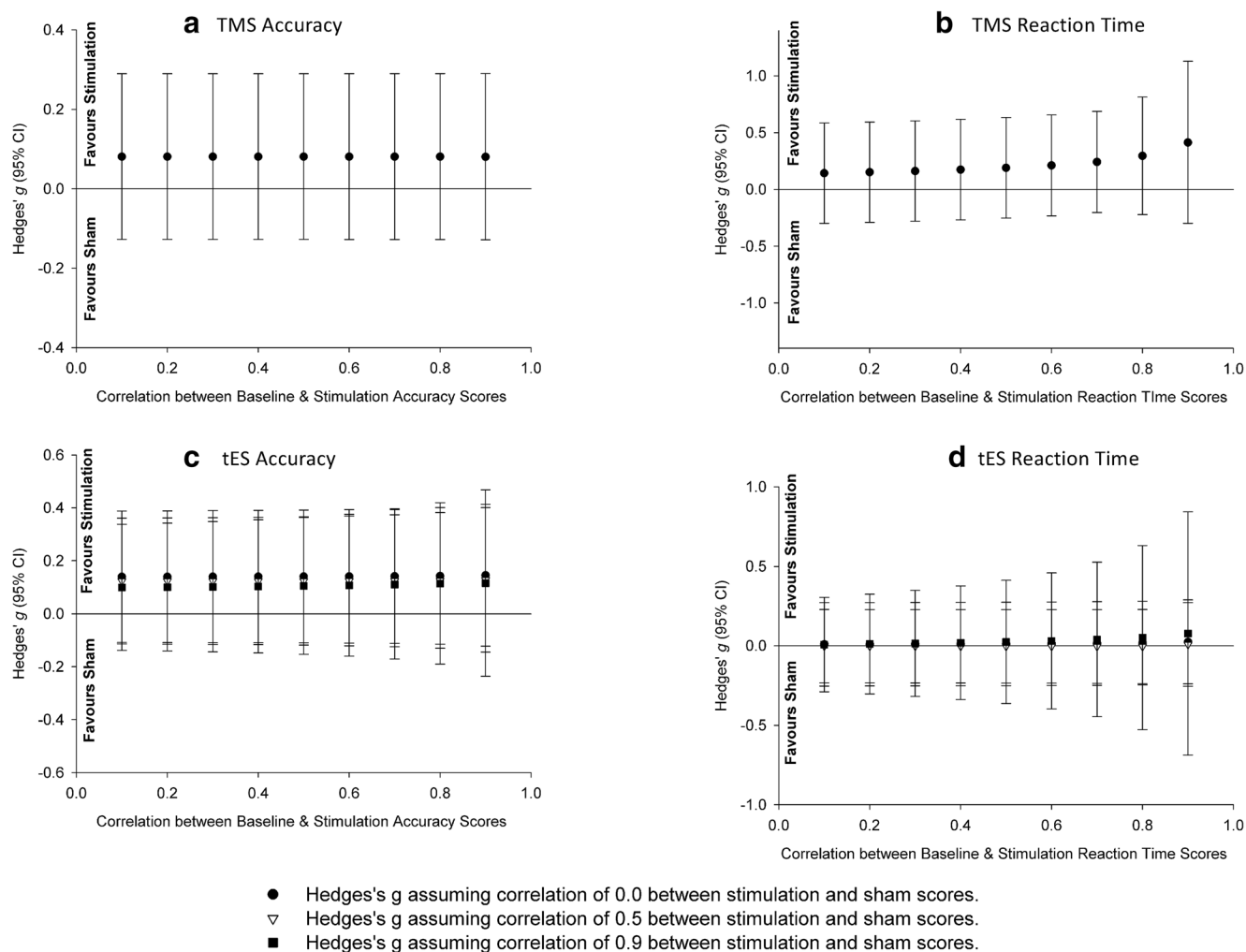
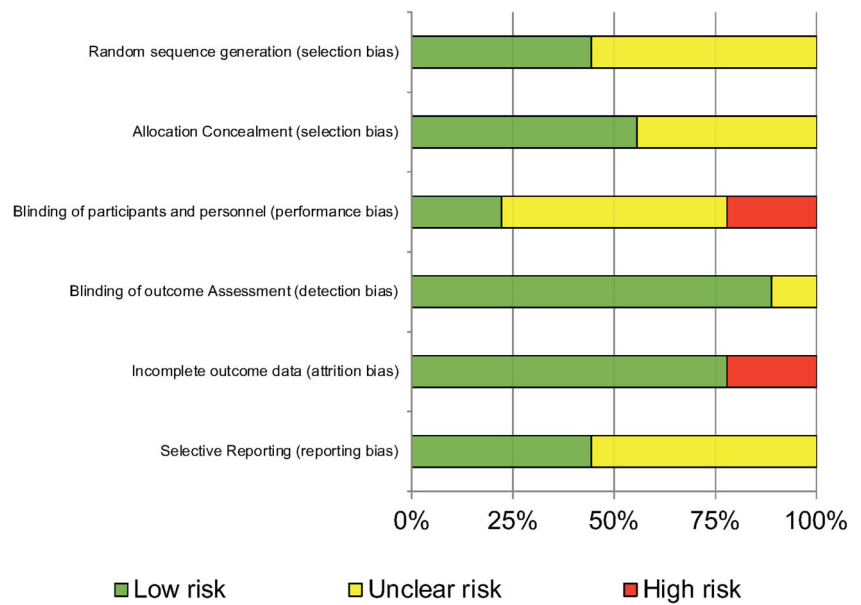


Fig. 5 Results from sensitivity analyses examining effects of assumptions about correlations between scores on meta-analyses

This interpretation of the results is forwarded from multiple analyses that examined the effect of non-invasive brain stimulation on different tasks and outcome variables (i.e., accuracy & reaction time). In all cases non-significant treatment effects were observed. In addition, unlike previous meta-analysis, attempts were made to take into account correlated data structures arising from pre-post-test designs and cross-over trials. Even when different correlation values were examined (see Fig. 5), meta-analyses were still non-significant. Second, head-to-head tests did not find evidence that rTMS was more effective at treating working memory compared to tES. The one exception was that for reaction times on the 3-back task. The effect size for rTMS was found to be larger compared to the tES effect sizes. Finally, meta-regression analysis largely indicated that different rTMS and tES stimulation protocols were not systematically influencing effect sizes. However, one meta-regression analysis indicated that, for tES studies, there was a positive association between the number of stimulation sessions and effect sizes. Overall, the results of this review indicate that, at present, neither rTMS or tES improves working memory in schizophrenia.

Results from the meta-analyses showing tES does not improve working memory in schizophrenia are consistent with the preliminary findings of Mervis et al. (2017). Their meta-analysis summarised the results of four tDCS studies. Overall, tDCS was not found to have a significant treatment effect. The current report replicated this result even when synthesising results from 13 studies. However, in the current report, small to moderate degrees of systematic influence were found for the meta-analyses examining the effect of tES on accuracy scores. This result indicates that differences between study level effect sizes are not attributable to random error. Meta-regression analyses revealed that tES studies with more stimulation sessions, were associated with larger treatment effects. That is, applying electrical stimulation to the DLPFC over multiple sessions appears to enhance the therapeutic effects of tES. This finding might suggest that to improve working memory via non-invasive brain stimulation, changes in neural structure and connectivity is required. This in turn requires multiple stimulation sessions (Baumer et al., 2003; Maeda et al., 2000; Monte-Silva et al., 2013). In terms of the number of sessions required, it is noted that in the study by

Fig. 6 Results from the assessment of bias for rTMS studies. A summary plot is presented that illustrates the percentage of bias for the rTMS studies included in the meta-analysis. The summary plot is colour coded to represent the percentage of low risk, unclear risk or high risk of bias in the following areas, selection bias, performance bias, detection bias, attrition bias and reporting bias



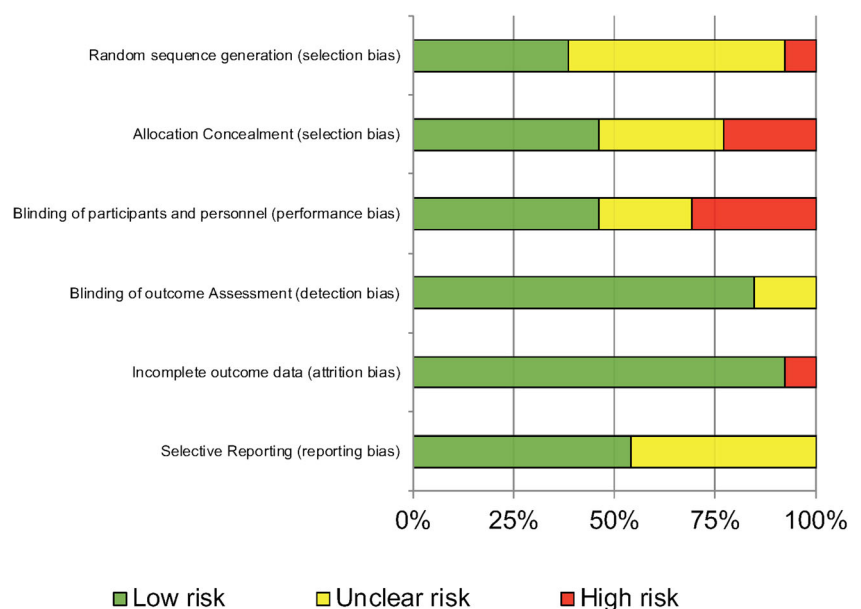
Lindenmayer et al. (2019), participants completed 40 tDCS sessions. That study also observed the largest positive effect size on working memory in schizophrenia. To improve working memory in this clinical group using tDCS, 40 or more sessions may therefore be required.

Our finding that rTMS does not improve working memory in schizophrenia is not consistent with the meta-analyses presented by Martin et al. (2016) and Jiang et al. (2019). In the review by Jiang et al. (2019), which was based on seven studies, rTMS was found to significantly improve working memory. One explanation for the difference in findings may relate to the tasks included in the meta-analysis. Jiang et al. (2019) included studies in their meta-analyses that did not specifically assess working memory. One study included in their review assessed general intelligence

(Mittrach et al., 2010). Three studies included in the review assessed the effects of the stimulation on tasks that are typically associated with the assessment of declarative memory (Dlabac-de Lange et al., 2015; Mogg et al., 2007; Wölwer et al., 2014). These tasks largely depend on the hippocampus and temporal lobes (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). Given this, the results of Jiang et al. might provide new evidence that rTMS can be effective for improving declarative memory functioning in schizophrenia.

Another finding to emerge from the current meta-analyses of rTMS studies was the absence of systematic influences on study level effect sizes. The I^2 value for accuracy and reaction time data was repeatedly found to be 0%. This value was also found by Jiang et al. (2019). This indicates at least for two

Fig. 7 Results from the assessment of bias for tES studies. A summary plot is presented that illustrates the percentage of bias for the tES studies included in the meta-analysis. The summary plot is colour coded to represent the percentage of low risk, unclear risk or high risk of bias in the following areas, selection bias, performance bias, detection bias, attrition bias and reporting bias



meta-analyses, the differences in study findings can be attributed to random error. This result was further confirmed by the meta-regression analyses undertaken in this report, which showed that various stimulation protocols did not predict study effect sizes. However, one avenue for further research might be to examine the number of rTMS sessions on working memory outcomes. As noted above, for tES studies, the number of stimulation sessions was positively related to effect sizes. This result was not found for TMS studies. It could be more TMS sessions are required to improve working memory. As noted above, in the tES literature, 40 stimulation sessions were associated with the largest improvement in working memory. In the rTMS literature reviewed as part of this report, the maximum number of stimulation sessions administered to participants was 20 (see Table 1). It could be that rTMS might also be able to improve working memory in schizophrenia, but substantially more stimulation sessions are needed to modify the neural networks that support this memory system.

An additional aim of this review was to directly compare the effectiveness of tES and rTMS interventions. Results from the moderator analyses revealed non-significant differences between average effect sizes from rTMS and tES studies, for most accuracy and reaction time outcome variables. For these variables, there is insufficient evidence to indicate that rTMS or tES are associated with a superior treatment effect. The one exception to this trend was observed for reaction time effect sizes from 3-back tasks. For this one outcome variable, rTMS was associated with a greater improvement compared to tES. However, this result should be interpreted with caution. Results from the meta-analysis showed that for tES studies, the average effect size for reaction times from 3-back tasks was negative and approached statistical significance (Hedges' $g = -.206$, $p = .072$; See Fig. 3). For TMS studies, a large positive effect size that was also close to significance was observed (Hedges' $g = .497$, $p = .077$). It is difficult to determine whether the significant moderator result was due to superior working memory performance following sham tES, or the positive treatment effects associated with rTMS. This is further compounded by the small number of studies/effect sizes that were represented in this analysis ($k = 2$ for rTMS studies and $k = 4$ for tES studies). The superiority of rTMS or tES will need to be investigated in future research.

Limitations and Avenues for Future Research

The results from this review indicate that at present, the evidence does not indicate non-invasive brain stimulation can reliably improve working memory in schizophrenia. Additionally, for the rTMS studies in particular, there does not appear to be a particular stimulation protocol that optimally improves working memory in this group. For the rTMS studies the I^2 values were consistently low. A low I^2 can be interpreted to indicate that systematic influences may be present, but not detectable in the meta-

analysis. This issue may have arisen because of the small sample sizes associated with most all studies. To overcome this problem, multiple studies with larger sample sizes will be required. Given the difficulty recruiting and testing individuals with schizophrenia for non-invasive brain stimulation research, multi-site randomised controlled trials may be more appropriate. Additional considerations about whether other stimulation protocols that vary in their focality, length of treatment, intensity, frequency and number of treatments and inter-treatment intervals will also need to be investigated in future research.

Another issue that needs to be taken into account in future research arises from the assessment of bias undertaken in this report. Overall, the included studies were assessed to be at high risk of selection and performance bias. Most commonly, the randomisation procedure was not outlined and the personnel administering the stimulation were not blinded to the treatment condition. These types of bias are a concern in meta-analyses should significant treatment effects have been observed. This is because selection and performance bias may lead to an overestimation of treatment effects (Higgins & Altman, 2008).

A final limitation of this report is that the majority of studies used rTMS and tDCS over the DLPFC to modulate working memory in schizophrenia. In this review, only two studies used tACS, one study used deep rTMS and one study used TBS. Other forms of non-invasive brain stimulation were included in the search syntax (e.g. single pulse TMS, transcranial random noise stimulation, high definition tDCS) but no studies using these other variants of stimulation were identified for inclusion in the analyses. Therefore, the finding of the current review does not rule out that other forms of stimulation might improve working memory in this clinical population.

Conclusions

The meta-analyses indicate that rTMS and tES when applied over the DLPFC are not associated with a reliable improvement of working memory in schizophrenia. This interpretation of the results was forwarded from multiple meta-analyses that all revealed non-significant treatment effects. There is also insufficient evidence to suggest whether rTMS or tES is superior as a treatment for working memory problems. An interesting finding to emerge from this report is that increasing the number of stimulation sessions might lead to greater treatment effects. However, this was only observed for the tES studies. Due to an absence of systematic influence on study level effect sizes for the rTMS studies, it is unclear whether particular stimulation protocols are able to have a greater effect on working memory functioning. Additional research investigating the effects of different stimulation protocols using larger sample sizes is needed.

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Appendix 1

Table 4 Search syntax for Medline, PsycINFO & CINAHL

	Titles	Abstracts	Keywords
transcranial direct current stimulation	(TI transcranial direct current stimulation) OR	(AB transcranial direct current stimulation) OR	(KW transcranial direct current stimulation) OR
transcranial direct current stimulat*	(TI transcranial direct current stimulat*) OR	(AB transcranial direct current stimulat*) OR	(KW transcranial direct current stimulat*) OR
transcranial DC stimulation	(TI transcranial DC stimulation) OR	(AB transcranial DC stimulation) OR	(KW transcranial DC stimulation) OR
transcranial DC stimulat*	(TI transcranial DC stimulat*) OR	(AB transcranial DC stimulat*) OR	(KW transcranial DC stimulat*) OR
tDCS	(TI tDCS) OR	(AB tDCS) OR	(KW tDCS) OR
transcranial alternating current stimulation	(TI transcranial alternating current stimulation) OR	(AB transcranial alternating current stimulation) OR	(KW transcranial alternating current stimulation) OR
transcranial alternating current stimulat*	(TI transcranial alternating current stimulat*) OR	(AB transcranial alternating current stimulat*) OR	(KW transcranial alternating current stimulat*) OR
tACS	(TI tACS) OR	(AB tACS) OR	(KW tACS) OR
transcranial random noise stimulation	(TI transcranial random noise stimulation) OR	(AB transcranial random noise stimulation) OR	(KW transcranial random noise stimulation) OR
transcranial random noise stimulat*	(TI transcranial random noise stimulat*) OR	(AB transcranial random noise stimulat*) OR	(KW transcranial random noise stimulat*) OR
tRNS	(TI tRNS) OR	(AB tRNS) OR	(KW tRNS) OR
transcranial N5 electric* current*	(TI transcranial N5 electric* current*) OR	(AB transcranial N5 electric* current*) OR	(KW transcranial N5 electric* current*) OR
transcranial N5 electric* stimulat*	(TI transcranial N5 electric* stimulat*) OR	(AB transcranial N5 electric* stimulat*) OR	(KW transcranial N5 electric* stimulat*) OR
transcranial N5 brain stimulat*	(TI transcranial N5 brain stimulat*) OR	(AB transcranial N5 brain stimulat*) OR	(KW transcranial N5 brain stimulat*) OR
noninvasive N5 electric* current*	(TI noninvasive N5 electric* current*) OR	(AB noninvasive N5 electric* current*) OR	(KW noninvasive N5 electric* current*) OR
non-invasive N5 electric* current*	(TI non-invasive N5 electric* current*) OR	(AB non-invasive N5 electric* current*) OR	(KW non-invasive N5 electric* current*) OR
noninvasive N5 electric* stimulat*	(TI noninvasive N5 electric* stimulat*) OR	(AB noninvasive N5 electric* stimulat*) OR	(KW noninvasive N5 electric* stimulat*) OR
non-invasive N5 electric* stimulat*	(TI non-invasive N5 electric* stimulat*) OR	(AB non-invasive N5 electric* stimulat*) OR	(KW non-invasive N5 electric* stimulat*) OR
noninvasive N5 brain stimulat*	(TI noninvasive N5 brain stimulat*) OR	(AB noninvasive N5 brain stimulat*) OR	(KW noninvasive N5 brain stimulat*) OR
non-invasive N5 brain stimulat*	(TI non-invasive N5 brain stimulat*) OR	(AB non-invasive N5 brain stimulat*) OR	(KW non-invasive N5 brain stimulat*) OR
transcranial stimulat*	(TI transcranial stimulat*) OR	(AB transcranial stimulat*) OR	(KW transcranial stimulat*) OR
transcranial current*	(TI transcranial current*) OR	(AB transcranial current*) OR	(KW transcranial current*) OR
noninvasive stimulat*	(TI noninvasive stimulat*) OR	(AB noninvasive stimulat*) OR	(KW noninvasive stimulat*) OR
noninvasive current*	(TI noninvasive current*) OR	(AB noninvasive current*) OR	(KW noninvasive current*) OR
non-invasive stimulat*	(TI non-invasive stimulat*) OR	(AB non-invasive stimulat*) OR	(KW non-invasive stimulat*) OR
non-invasive current*	(TI non-invasive current*) OR	(AB non-invasive current*) OR	(KW non-invasive current*) OR
atDCS	(TI atDCS) OR	(AB atDCS) OR	(KW atDCS) OR
a-tDCS	(TI a-tDCS) OR	(AB a-tDCS) OR	(KW a-tDCS) OR
ctDCS	(TI ctDCS) OR	(AB ctDCS) OR	(KW ctDCS) OR
c-tDCS	(TI c-tDCS) OR	(AB c-tDCS) OR	(KW c-tDCS) OR
stDCS	(TI stDCS) OR	(AB stDCS) OR	(KW stDCS) OR
s-tDCS	(TI s-tDCS) OR	(AB s-tDCS) OR	(KW s-tDCS) OR
sotDCS	(TI sotDCS) OR	(AB sotDCS) OR	(KW sotDCS) OR
so-tDCS	(TI so-tDCS) OR	(AB so-tDCS) OR	(KW so-tDCS) OR
HDtdcs	(TI HDtdcs) OR	(AB HDtdcs) OR	(KW HDtdcs) OR
transcranial magnetic stimulation	(TI transcranial magnetic stimulation) OR	(AB transcranial magnetic stimulation) OR	(KW transcranial magnetic stimulation) OR
transcranial magnetic stimulat*	(TI transcranial magnetic stimulat*) OR	(AB transcranial magnetic stimulat*) OR	(KW transcranial magnetic stimulat*) OR
TMS	(TI TMS) OR	(AB TMS) OR	(KW TMS) OR
repetitive transcranial magnetic stimulation	(TI repetitive transcranial magnetic stimulation) OR	(AB repetitive transcranial magnetic stimulation) OR	(KW repetitive transcranial magnetic stimulation) OR
repetitive transcranial magnetic stimulat*	(TI repetitive transcranial magnetic stimulat*) OR	(AB repetitive transcranial magnetic stimulat*) OR	(KW repetitive transcranial magnetic stimulat*) OR
rTMS	(TI rTMS) OR	(AB rTMS) OR	(KW rTMS) OR
deep transcranial magnetic stimulation	(TI deep transcranial magnetic stimulation) OR	(AB deep transcranial magnetic stimulation) OR	(KW deep transcranial magnetic stimulation) OR
deep transcranial magnetic stimulat*	(TI deep transcranial magnetic stimulat*) OR	(AB deep transcranial magnetic stimulat*) OR	(KW deep transcranial magnetic stimulat*) OR
dTMS	(TI dTMS) OR	(AB dTMS) OR	(KW dTMS) OR
theta burst stimulation	(TI theta burst stimulation) OR	(AB theta burst stimulation) OR	(KW theta burst stimulation) OR
theta burst stimulat*	(TI theta burst stimulat*) OR	(AB theta burst stimulat*) OR	(KW theta burst stimulat*) OR
TBS	(TI TBS) OR	(AB TBS) OR	(KW TBS) OR
navigated brain stimulation	(TI navigated brain stimulation) OR	(AB navigated brain stimulation) OR	(KW navigated brain stimulation) OR
navigated brain stimulat*	(TI navigated brain stimulat*) OR	(AB navigated brain stimulat*) OR	(KW navigated brain stimulat*) OR
navigated transcranial magnetic brain stimulation	(TI navigated transcranial magnetic brain stimulation) OR	(AB navigated transcranial magnetic brain stimulation) OR	(KW navigated transcranial magnetic brain stimulation) OR
navigated transcranial magnetic brain stimulat*	(TI navigated transcranial magnetic brain stimulat*) OR	(AB navigated transcranial magnetic brain stimulat*) OR	(KW navigated transcranial magnetic brain stimulat*) OR

Table 4 (continued)

	Titles	Abstracts	Keywords
theta-burst stimulation	(TI theta-burst stimulation) OR	(AB theta-burst stimulation) OR	(KW theta-burst stimulation) OR
theta-burst stimulat*	(TI theta-burst stimulat*) OR	(AB theta-burst stimulat*) OR	(KW theta-burst stimulat*)
schizophrenia	(TI schizophrenia) OR	(AB schizophrenia) OR	(KW schizophrenia) OR
schizo*	(TI schizo*) OR	(AB schizo*) OR	(KW schizo*) OR
schizoaffective disorder	(TI schizoaffective disorder) OR	(AB schizoaffective disorder) OR	(KW schizoaffective disorder) OR
schizoaffect*	(TI schizoaffect*) OR	(AB schizoaffect*) OR	(KW schizoaffect*) OR
psychosis	(TI psychosis) OR	(AB psychosis) OR	(KW psychosis) OR
psychotic disorder	(TI psychotic disorder) OR	(AB psychotic disorder) OR	(KW psychotic disorder) OR
first episode psychosis	(TI first episode psychosis) OR	(AB first episode psychosis) OR	(KW first episode psychosis) OR
first-episode psychosis	(TI first-episode psychosis) OR	(AB first-episode psychosis) OR	(KW first-episode psychosis) OR
chronic schizophrenia	(TI chronic schizophrenia) OR	(AB chronic schizophrenia) OR	(KW chronic schizophrenia) OR
chronic psychosis	(TI chronic psychosis) OR	(AB chronic psychosis) OR	(KW chronic psychosis)

Table 5 Search syntax for EMBASE

	Titles	Abstracts	Keywords
transcranial direct current stimulation	(transcranial direct current stimulation:ti,ab) OR	(AB transcranial direct current stimulation) OR	(KW transcranial direct current stimulation) OR
transcranial direct current stimulat\$	(transcranial direct current stimulat\$:ti,ab) OR	(AB transcranial direct current stimulat\$) OR	(KW transcranial direct current stimulat\$) OR
transcranial DC stimulation	(transcranial DC stimulation:ti,ab) OR	(AB transcranial DC stimulation) OR	(KW transcranial DC stimulation) OR
transcranial DC stimulat\$	(transcranial DC stimulat\$:ti,ab) OR	(AB transcranial DC stimulat\$) OR	(KW transcranial DC stimulat\$) OR
tDCS	(tDCS:ti,ab) OR	(AB tDCS) OR	(KW tDCS) OR
transcranial alternating current stimulation	(transcranial alternating current stimulation:ti,ab) OR	(AB transcranial alternating current stimulation) OR	(KW transcranial alternating current stimulation) OR
transcranial alternating current stimulat\$	(transcranial alternating current stimulat\$:ti,ab) OR	(AB transcranial alternating current stimulat\$) OR	(KW transcranial alternating current stimulat\$) OR
tACS	(tACS:ti,ab) OR	(AB tACS) OR	(KW tACS) OR
transcranial random noise stimulation	(transcranial random noise stimulation:ti,ab) OR	(AB transcranial random noise stimulation) OR	(KW transcranial random noise stimulation) OR
transcranial random noise stimulat\$	(transcranial random noise stimulat\$:ti,ab) OR	(AB transcranial random noise stimulat\$) OR	(KW transcranial random noise stimulat\$) OR
tRNS	(tRNS:ti,ab) OR	(AB tRNS) OR	(KW tRNS) OR
transcranial adj5 electric\$ current\$	(transcranial adj5 electric\$ current\$:ti,ab) OR	(AB transcranial adj5 electric\$ current\$) OR	(KW transcranial adj5 electric\$ current\$) OR
transcranial adj5 electric\$ stimulat\$	(transcranial adj5 electric\$ stimulat\$:ti,ab) OR	(AB transcranial adj5 electric\$ stimulat\$) OR	(KW transcranial adj5 electric\$ stimulat\$) OR
transcranial adj5 brain stimulat\$	(transcranial adj5 brain stimulat\$:ti,ab) OR	(AB transcranial adj5 brain stimulat\$) OR	(KW transcranial adj5 brain stimulat\$) OR
noninvasive adj5 electric\$ current\$	(noninvasive adj5 electric\$ current\$:ti,ab) OR	(AB noninvasive adj5 electric\$ current\$) OR	(KW noninvasive adj5 electric\$ current\$) OR
non-invasive adj5 electric\$ current\$	(non-invasive adj5 electric\$ current\$:ti,ab) OR	(AB non-invasive adj5 electric\$ current\$) OR	(KW non-invasive adj5 electric\$ current\$) OR
noninvasive adj5 electric\$ stimulat\$	(noninvasive adj5 electric\$ stimulat\$:ti,ab) OR	(AB noninvasive adj5 electric\$ stimulat\$) OR	(KW noninvasive adj5 electric\$ stimulat\$) OR
non-invasive adj5 electric\$ stimulat\$	(non-invasive adj5 electric\$ stimulat\$:ti,ab) OR	(AB non-invasive adj5 electric\$ stimulat\$) OR	(KW non-invasive adj5 electric\$ stimulat\$) OR
noninvasive adj5 brain stimulat\$	(noninvasive adj5 brain stimulat\$:ti,ab) OR	(AB noninvasive adj5 brain stimulat\$) OR	(KW noninvasive adj5 brain stimulat\$) OR
non-invasive adj5 brain stimulat\$	(non-invasive adj5 brain stimulat\$:ti,ab) OR	(AB non-invasive adj5 brain stimulat\$) OR	(KW non-invasive adj5 brain stimulat\$) OR
transcranial stimulat\$	(transcranial stimulat\$:ti,ab) OR	(AB transcranial stimulat\$) OR	(KW transcranial stimulat\$) OR
transcranial current\$	(transcranial current\$:ti,ab) OR	(AB transcranial current\$) OR	(KW transcranial current\$) OR
noninvasive stimulat\$	(noninvasive stimulat\$:ti,ab) OR	(AB noninvasive stimulat\$) OR	(KW noninvasive stimulat\$) OR
noninvasive current\$	(noninvasive current\$:ti,ab) OR	(AB noninvasive current\$) OR	(KW noninvasive current\$) OR
non-invasive stimulat\$	(non-invasive stimulat\$:ti,ab) OR	(AB non-invasive stimulat\$) OR	(KW non-invasive stimulat\$) OR
non-invasive current\$	(non-invasive current\$:ti,ab) OR	(AB non-invasive current\$) OR	(KW non-invasive current\$) OR
atDCS	(atDCS:ti,ab) OR	(AB atDCS) OR	(KW atDCS) OR
a-tDCS	(a-tDCS:ti,ab) OR	(AB a-tDCS) OR	(KW a-tDCS) OR
ctDCS	(ctDCS:ti,ab) OR	(AB ctDCS) OR	(KW ctDCS) OR
c-tDCS	(c-tDCS:ti,ab) OR	(AB c-tDCS) OR	(KW c-tDCS) OR
stDCS	(stDCS:ti,ab) OR	(AB stDCS) OR	(KW stDCS) OR
s-tDCS	(s-tDCS:ti,ab) OR	(AB s-tDCS) OR	(KW s-tDCS) OR
so-tDCS	(so-tDCS:ti,ab) OR	(AB so-tDCS) OR	(KW so-tDCS) OR
HDtdcs	(HDtdcs:ti,ab) OR	(AB HDtdcs) OR	(KW HDtdcs) OR
HD-tdcs	(HD-tdcs:ti,ab) OR	(AB HD-tdcs) OR	(KW HD-tdcs) OR
transcranial magnetic stimulation	(transcranial magnetic stimulation:ti,ab) OR	(AB transcranial magnetic stimulation) OR	(KW transcranial magnetic stimulation) OR
transcranial magnetic stimulat\$	(transcranial magnetic stimulat\$:ti,ab) OR	(AB transcranial magnetic stimulat\$) OR	(KW transcranial magnetic stimulat\$) OR
tms	(tms:ti,ab) OR	(AB tms) OR	(KW tms) OR

Table 5 (continued)

	Titles	Abstracts	Keywords
repetitive transcranial magnetic stimulation	(repetitive transcranial magnetic stimulation:ti,ab) OR	(AB repetitive transcranial magnetic stimulation) OR	(KW repetitive transcranial magnetic stimulation) OR
repetitive transcranial magnet stimulat\$	(repetitive transcranial magnet stimulat\$:ti,ab) OR	(AB repetitive transcranial magnet stimulat\$) OR	(KW repetitive transcranial magnet stimulat\$) OR
rtms	(rtms:ti,ab) OR	(AB rtms) OR	(KW rtms) OR
deep transcranial magnetic stimulation	(deep transcranial magnetic stimulation:ti,ab) OR	(AB deep transcranial magnetic stimulation) OR	(KW deep transcranial magnetic stimulation) OR
deep transcranial magnetic stimulat\$	(deep transcranial magnetic stimulat\$:ti,ab) OR	(AB deep transcranial magnetic stimulat\$) OR	(KW deep transcranial magnetic stimulat\$) OR
dtms	(dtms:ti,ab) OR	(AB dtms) OR	(KW dtms) OR
theta burst stimulation	(theta burst stimulation:ti,ab) OR	(AB theta burst stimulation) OR	(KW theta burst stimulation) OR
theta burst stimulat\$	(theta burst stimulat\$:ti,ab) OR	(AB theta burst stimulat\$) OR	(KW theta burst stimulat\$) OR
tbs	(tbs:ti,ab) OR	(AB tbs) OR	(KW tbs) OR
schizophrenia	(schizophrenia:ti,ab) OR	(AB schizophrenia) OR	(KW schizophrenia) OR
schizo\$	(schizo\$:ti,ab) OR	(AB schizo\$) OR	(KW schizo\$) OR
schizoaffective	(schizoaffective:ti,ab) OR	(AB schizoaffective) OR	(KW schizoaffective) OR
schizoaffect\$	(schizoaffect\$:ti,ab) OR	(AB schizoaffect\$) OR	(KW schizoaffect\$) OR
psychosis	(psychosis:ti,ab) OR	(AB psychosis) OR	(KW psychosis) OR
psychotic disorder	(psychotic disorder:ti,ab) OR	(AB psychotic disorder) OR	(KW psychotic disorder) OR
first episode psychosis	(first episode psychosis:ti,ab) OR	(AB first episode psychosis) OR	(KW first episode psychosis) OR
first-episode psychosis	(first-episode psychosis:ti,ab) OR	(AB first-episode psychosis) OR	(KW first-episode psychosis) OR
chronic schizophrenia	(chronic schizophrenia:ti,ab) OR	(AB chronic schizophrenia) OR	(KW chronic schizophrenia) OR
chronic psychosis	(chronic psychosis:ti,ab) OR	(AB chronic psychosis) OR	(KW chronic psychosis) OR

Table 6 Search syntax for CENTRAL

transcranial direct current stimulation	(transcranial direct current stimulation)	or
transcranial direct current stimulat*	(transcranial direct current stimulat*)	or
transcranial DC stimulation	(transcranial DC stimulation)	or
transcranial DC stimulat*	(transcranial DC stimulat*)	or
tDCS	(tDCS)	or
transcranial alternating current stimulation	(transcranial alternating current stimulation)	or
transcranial alternating current stimulat*	(transcranial alternating current stimulat*)	or
tACS	(tACS)	or
transcranial random noise stimulation	(transcranial random noise stimulation)	or
transcranial random noise stimulat*	(transcranial random noise stimulat*)	or
tRNS	(tRNS)	or
transcranial NEAR/5 electric* current*	(transcranial NEAR/5 electric* current*)	or
transcranial NEAR/5 electric* stimulat*	(transcranial NEAR/5 electric* stimulat*)	or
transcranial NEAR/5 brain stimulat*	(transcranial NEAR/5 brain stimulat*)	or
noninvasive NEAR/5 electric* current*	(noninvasive NEAR/5 electric* current*)	or
non-invasive NEAR/5 electric* current*	(non-invasive NEAR/5 electric* current*)	or
noninvasive NEAR/5 electric* stimulat*	(noninvasive NEAR/5 electric* stimulat*)	or
non-invasive NEAR/5 electric* stimulat*	(non-invasive NEAR/5 electric* stimulat*)	or
noninvasive NEAR/5 brain stimulat*	(noninvasive NEAR/5 brain stimulat*)	or
non-invasive NEAR/5 brain stimulat*	(non-invasive NEAR/5 brain stimulat*)	or
transcranial stimulat*	(transcranial stimulat*)	or
transcranial current*	(transcranial current*)	or
noninvasive stimulat*	(noninvasive stimulat*)	or
noninvasive current*	(noninvasive current*)	or
non-invasive stimulat*	(non-invasive stimulat*)	or
non-invasive current*	(non-invasive current*)	or
atDCS	(atDCS)	or
a-tDCS	(a-tDCS)	or
ctDCS	(ctDCS)	or
c-tDCS	(c-tDCS)	or

Table 6 (continued)

transcranial direct current stimulation	(transcranial direct current stimulation)	or
stDCS	(stDCS)	or
s-tDCS	(s-tDCS)	or
sotDCS	(sotDCS)	or
so-tDCS	(so-tDCS)	or
HDtdcs	(HDtdcs)	or
HD-tdcs	(HD-tdcs)	or
transcranial magnetic stimulation	(transcranial magnetic stimulation)	or
transcranial magnetic stimulat*	(transcranial magnetic stimulat*)	or
TMS	(TMS)	or
repetitive transcranial magnetic stimulation	(repetitive transcranial magnetic stimulation)	or
repetitive transcranial magnetic stimulat*	(repetitive transcranial magnetic stimulat*)	or
rTMS	(rTMS)	or
deep transcranial magnetic stimulation	(deep transcranial magnetic stimulation)	or
deep transcranial magnetic stimulat*	(deep transcranial magnetic stimulat*)	or
dTMS	(dTMS)	or
theta burst stimulation	(theta burst stimulation)	or
theta burst stimulat*	(theta burst stimulat*)	or
theta-burst stimulation	(theta-burst stimulation)	or
theta-burst stimulat*	(theta-burst stimulat*)	or
TBS	(TBS)	or
navigated brain stimulation	(navigated brain stimulation)	or
navigated brain stimulat*	(navigated brain stimulat*)	or
navigated transcranial magnetic brain stimulation	(navigated transcranial magnetic brain stimulation)	or
navigated transcranial magnetic brain stimulat*	(navigated transcranial magnetic brain stimulat*))
	AND	
schizophrenia	(schizophrenia)	or
schizo*	(schizo*)	or
schizoaffective	(schizoaffective)	or
schizoaffect*	(schizoaffect*)	or
psychosis	(psychosis)	or
psychotic disorder	(psychotic disorder)	or
first episode psychosis	(first episode psychosis)	or
first-episode psychosis	(first-episode psychosis)	or
chronic schizophrenia	(chronic schizophrenia)	

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