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Transcranial Magnetic Stimulation for Positive Symptoms in Schizophrenia: A Systematic Review

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Keywords
Schizophrenia · Positive symptoms · Auditory verbal hallucinations · Noninvasive brain stimulation · Transcranial magnetic stimulation

Abstract
Transcranial magnetic stimulation (TMS) has been proposed as a potential treatment add-on for positive symptoms in schizophrenia. To summarize the current evidence for its efficacy, we reviewed clinical trials from the last 20 years that investigated TMS for positive symptoms. We performed a search on the PubMed database for clinical trials that used TMS for the treatment of positive symptoms published in peer-reviewed journals. We excluded reviews, case reports, and opinion papers. Of the 30 studies included, the majority (n = 25) investigated auditory verbal hallucinations. Twelve studies found evidence for a positive treatment effect of TMS on positive symptoms, while 18 did not find enough evidence to conclude that TMS is effective for positive symptoms. However, the small sample size of the majority of studies is a limiting factor for the reliability of previous findings. In conclusion, evidence for an effect of TMS on positive symptoms was mixed. Since most of the studies were performed in patients with auditory verbal hallucinations, further research of TMS for other positive symptoms including thought disorder and delusions is warranted.

Introduction

Schizophrenia spectrum disorder is a severe mental illness with onset already in adolescence or early adulthood and manifestation throughout lifetime [1]. The presence of positive symptoms such as hallucinations, delusions, and disorganized speech are among the key symptoms to diagnose schizophrenia [2]. Despite considerable research, treatment remains unsatisfactory. In attempting to achieve more specificity in the search for treatment alternatives, single psychotic symptoms have been investigated [3–6]. The most prominent example is auditory verbal hallucinations. Occurring in up to 75% of patients with schizophrenia [7], auditory verbal hallucinations are one of the main symptom for a schizophrenia diagnosis

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[2]. Auditory verbal hallucinations are defined as false perceptions of voices and sounds in the absence of external stimuli. Despite the fact that hallucinations are not perceivable from an observer's perspective, the often commanding, intrusive, and violent nature of the voices can lead to reduced quality of life in patients [8] and in severe cases even to suicide [9].

The first-line treatment for positive symptoms such as auditory verbal hallucinations are second-generation antipsychotic drugs [10]. However, treatment with antipsychotics is often insufficient, and up to 30% of patients continue to suffer from treatment-resistant auditory verbal hallucinations [8]. Notably, such treatment resistance has been observed with both second-generation and first-generation antipsychotic drugs and is aggravated by the fact that antipsychotics are often accompanied by various side effects [11].

Transcranial magnetic stimulation (TMS) seems promising in this regard with its minimal risk profile [12]. Thus, adding TMS to the conventional treatment with antipsychotic drugs does not increase side effects but may enhance the chances of successfully treating positive symptoms.

Based on the principle of electromagnetic induction, TMS works through rapid changes in the magnetic field and induces an electric current in the cortex which in turn depolarizes neurons and elicits an action potential [13]. In general, two distinct applications of TMS can be distinguished: single pulse versus repetitive pulses. While single-pulse TMS is used in more experimental settings and to determine the motor threshold [14], repetitive-pulse TMS (rTMS) is used for various disorders, including major depressive disorder [15], obsessive-compulsive disorder [16], and schizophrenia spectrum disorders. The beneficial effects of rTMS in psychiatric disorders has been explained by short-term modulations of neuronal communication and subsequent changes in neuronal plasticity [17], also shown by changes in resting cerebral blood flow after rTMS [13, 18]. The neuromodulatory effects of TMS depend also on the applied frequency, such that low-frequency rTMS of 1 Hz is thought to inhibit cortical excitability under the coil, the time chosen for the interstimulus interval, and other factors [19].

Apart from traditional rTMS, protocols with other stimulation patterns have been developed, such as theta-burst stimulation (TBS) [14]. Compared with rTMS, TBS has the advantage of delivering powerful effects in a fraction of the time, and intermittent TBS has been shown to be noninferior to rTMS, at least in depression [20].

Of all positive symptoms, auditory verbal hallucinations are the most widely investigated symptom for the treatment with TMS. Hoffman et al. [21] were the first to propose an rTMS protocol with low-frequency stimulation (1 Hz) over the left temporoparietal cortex for the treatment of persistent auditory verbal hallucinations. The temporoparietal cortex is considered a central part of the language system [22], and targeting this region may thus inhibit the pathologically hyperactive language system and consequently reduce auditory hallucinations [23–26]. Further support for this hypothesis comes from a study that found hyperperfusion in the superior temporal gyrus before stimulation to be predictive for response to TMS [27].

Yet, despite a number of studies that replicated the original study by Hoffman et al. [21], 20 years later, evidence shows a heterogeneous picture. It remains a matter of debate whether TMS is effective for the treatment of auditory verbal hallucinations and other positive symptoms. Factors that might explain the heterogeneity of findings include differences in TMS protocols, such as frequency, duration, intensity, and stimulation location, as well as the patient population [19, 28–30]. Since the "level C" recommendation proposed by Lefaucheur et al. [19] that suggested that rTMS for auditory verbal hallucinations is "possibly effective or ineffective," a number of studies have been conducted that might provide more conclusive evidence. In addition, a small number of studies has shifted their focus from auditory verbal hallucinations to other positive symptoms such as delusions.

To summarize the current evidence for the efficacy of TMS for positive symptoms, we systematically reviewed the current body of literature including all clinical trials that investigated TMS with regard to positive symptoms. We contrasted the positive findings with the inconclusive findings and highlighted the factors that might promote efficacy of TMS. All the studies highlighted here have used TMS as an add-on to antipsychotic drug treatment. Although solid meta-analyses and reviews on TMS and auditory hallucinations have been published [19, 28, 31, 32], we aimed to provide an update of the current literature of clinical trials from the last 20 years and extend the focus on positive symptoms in general.

Methods

Search Strategy

We performed an electronic search via the NCBI PubMed database including studies until July 2018. We used the following key words for our search: rTMS; transcranial magnetic stimulation;

Table 1. Description of the TMS studies included

Authors, year	Design	Stimulation specifics					Study population				Effect	Class	Summary
		TMS	area	side	guided	frequency, Hz	symptoms	scale	*n* (F)	age, years			
Bais et al. [52], 2017	RCT	rTMS rTMS	TPJ TPJ	L B	No No	1 1	AVH AVH	AHRS AHRS	7 (3) 9 (5)	33.4±11.7 31.3±7.1	Yes Yes	B	Significant reduction in AVH after LF-rTMS over the left TPJ
Paillère-Martinot et al. [46], 2017	RCT	rTMS rTMS	STG MTG	L L	No No	1 1	AVH AVH	SAPS SAPS	15 (7) 15 (7)	32.1±6.79 32.1±6.79	No No	B	No evidence for the superiority of LF-rTMS over sham
Kimura et al. [63], 2016	RCT	rTMS	TPC	L	No	20	AVH	AHRS	16 (9)	44.6±10.5	No	B	No evidence for a positive effect of 4 sessions of HF-rTMS in reducing AVH vs. sham
Koops et al. [65], 2016	RCT	TBS	TPC	L	No	50	AVH	AHRS	37 (13)	38.0±15.0	No	A	No evidence for the superiority of TBS over sham reducing treatment-resistant AVH
Wobrock et al. [61], 2015	RCT	rTMS	DLPFC	L	No	10	Positive symptoms	PANSS	76 (14)	36.2±10.5	No	A	No evidence for the superiority of LF-rTMS over the DLPFC in reducing positive symptoms vs. sham
Bais et al. [53], 2014	RCT	rTMS rTMS	TPJ TPJ	L B	No No	1 1	AVH AVH	AHRS AHRS	16 (7) 15 (7)	37.2±14.9 33.9±9.2	No No	B	No evidence for the superiority of left-sided or bilateral LF-rTMS vs. sham in reducing AVH
Hoffman et al. [50], 2013	Crossover	rTMS	Wernicke	L vs. R	Yes	1	AVH	HCS	55 (28)	36.7±11.0	Yes	A	Significant reduction in AVH and overall clinical improvement after 15 sessions of LF-rTMS vs. sham
Kindler et al. [18], 2013	RCT	rTMS	TPC	L	Yes	1	AVH	PSYRATS	24 (7)	43.1±9.2	Yes	A	Significant reduction in AVH after rTMS vs. sham together with a decrease in CBF in the PAC
Blumberger et al. [56], 2012	RCT	rTMS Priming	TPC TPC	L L	No No	1 1	AH AH	PSYRATS PSYRATS	34 (NA) 34 (NA)	36.6±8.2 43.8±11.7	No No	A	No evidence for the superiority of priming rTMS and LF-rTMS over Heschl's gyrus vs. sham in reducing refractory AH
Jin et al. [66], 2012	RCT	αTMS αTMS	FC PC	B B	Yes Yes	2 2	Positive symptoms Positive symptoms	PANSS PANSS	41 (33) 41 (33)	37.3±14.0 37.3±14.0	Yes Yes	A	Significant reduction in positive symptoms after rTMS, independent of stimulating FC or PC, vs. sham

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Table 1 (continued)

Authors, year	Design	Stimulation specifics					Study population				Effect	Class	Summary
		TMS	area	side	guided	frequency, Hz	symptoms	scale	*n* (F)	age, years			
Slotema et al. [45], 2011	RCT	rTMS	TPC	L	Yes	1	AVH	AHRS	42 (6)	38.0±9.6	No	A	No superiority of fMRI-guided LF-rTMS over the left TPC vs. unguided TMS and sham
Cordes et al. [60], 2010	RCT	rTMS	DLPFC	L	No	2	Positive symptoms	PANSS	18 (4)	34.3±9.7	No	B	No evidence for the superiority of LF-rTMS (left DLPFC) to reduce positive symptoms vs. sham
Loo et al. [48], 2010	Crossover	rTMS rTMS	TC TC	L R	No No	1 1	AH AH	AHRS AHRS	18 (6) 18 (6)	33.8±12.2 33.8±12.2	No No	C	No difference in symptom severity after LF-rTMS of left vs. right TC and sham
Vercammen et al. [57], 2010	RCT	rTMS	TPJ	L	No	1	AVH	PANSS	9 (5)	38.9±13.2	Yes	C	Significant reduction in AVH after LF-rTMS (left TPJ) vs. sham with connectivity changes of the target area
Bagati et al. [39], 2009	RCT	rTMS	TPC	L	No	1	AH	PSYRATS	20 (NA)	29.4±7.3	Yes	A	Significant improvement in AH after LF-rTMS (left TPC) vs. sham
Vercammen et al. [51], 2009	RCT	rTMS rTMS	TPJ TPJ	L B	No No	1 1	AVH AVH	AHRS AHRS	24 (6) 24 (6)	33.8±14.2 33.8±9.3	Yes Yes	A	LF-rTMS over the TPJ was superior to bilateral rTMS or sham in reducing AH
Rosa et al. [43], 2007	RCT	rTMS	TPC	L	No	1	AH	AHRS	6 (2)	29.8±8.4	No	B	No evidence for the superiority of LF-rTMS as add-on to clozapine in reducing AH vs. sham
Jandl et al. [49], 2006	Crossover	rTMS rTMS	TPC TPC	L R	No No	1 1	AH AH	PSYRATS PSYRATS	14 (5) 14 (5)	36.3±13.7 36.3±13.7	No No	B	No evidence of LF-rTMS of the left or right STG in reducing AVH vs. sham
Saba et al. [44], 2006	RCT	rTMS	TPC	L	No	1	AH, delusions	PANSS	8 (NA)	30.7±8.0	No	B	No evidence for the superiority of LF-rTMS over sham
Chibbaro et al. [40], 2005	Non-randomized	rTMS	TPC	L	No	1, 6	AH	SAH	8 (3)	39.1±10.8	Yes	C	Significant long-term reduction in AH after LF-rTMS vs. sham
Fitzgerald et al. [41], 2005	RCT	rTMS	TPC	L	No	1	AH	HCS	17 (NA)	NA	No	B	No evidence for the superiority of active LF-rTMS vs. sham

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Table 1 (continued)

Authors, year	Design	Stimulation specifics					Study population				Effect	Class	Summary
		TMS	area	side	guided	frequency, Hz	symptoms	scale	*n* (F)	age, years			
Hoffman et al. [37], 2005	RCT	rTMS	TPC	L	No	1	AH	HCS	27 (9)	35.1±11.9	Yes	A	Significant reduction in AVH after LF-rTMS vs. sham stimulation moderated by hallucination frequency
Lee et al. [47], 2005	RCT	rTMS rTMS	TPC TPC	L R	No No	1 1	AH AH	AHRS AHRS	13 (5) 12 (5)	41.3±10.3 39.7±6.9	Yes Yes	B	Significant reduction in AH after LF-rTMS both over the left and the right TPC vs. sham
Hajak et al. [59], 2004	Non-randomized	rTMS	DLPFC	L	No	2	Positive symptoms	BPRS	10 (8)	37.9±7.7	No	C	Trend for worsening of positive symptoms after HF-rTMS vs. sham
Holi et al. [55], 2004	Crossover	rTMS	DLPFC	L	No	10	Positive symptoms	PANSS	11 (NA)	38.5±10.4	No	C	No evidence for superiority of left prefrontal LF-rTMS vs. sham
McIntosh et al. [42], 2004	Crossover	rTMS	TPC	L	No	1	AH	HCS	16 (9)	35.9±10.9	No	B	No evidence for the superiority of LF-rTMS in reducing AVH vs. sham
Schönfeld-Lecuona et al. [54], 2004	Crossover	rTMS	Broca, STG	L	Yes	1	AVH	PSYRATS	12 (7)	40.0±NA	No	B	No evidence for the superiority of LF-rTMS over sham
Hoffman et al. [38], 2003	RCT	rTMS	TPC	L	No	1	AH	HCS	12 (5)	35.8±12.1	Yes	B	Significantly reduced AVH after LF rTMS vs. sham, especially regarding frequency and attentional salience
Hoffman et al. [36], 2000	Crossover	rTMS	TPC	L	No	1	AH	PANSS	12 (2)	41.8±8.6	Yes	C	Superiority of LF-rTMS of the TPC in reducing AVH vs. sham
Hoffman et al. [21], 1999	Crossover	rTMS	TPC	L	No	1	AH	PANSS	3 (1)	40.7±NA	Yes	C	Significant reduction in AVH after LF rTMS vs. sham with near total cessation of AVH for <2 weeks ($n = 2$)

Evidence for an effect is defined as any statistical evidence that the treatment supplied a positive and significant effect on positive symptoms. AH, auditory hallucinations; AHRS, AH Rating Scale [38]; AVH, auditory verbal hallucinations; CBF, cerebral blood flow; DLPFC, dorsolateral prefrontal cortex; F, female; FC, frontal cortex; HCS, Hallucination Change Score [50]; HF, high frequency: LF, low frequency; MTG, middle temporal gyrus; *n*, number of patients in the treatment group; NA, not available; PAC, primary auditory cortex; PANSS, Positive and Negative Syndrome Scale [72]; PC, parietal cortex; PSYRATS, Psychotic Symptom Rating Scale [73]; RCT, randomized controlled trial; rTMS, repetitive transcranial magnetic stimulation; SAH, Scale for AH [40]; SAPS, Scale for the Assessment of Positive Symptoms [74]; STG, superior temporal gyrus; TC, temporal cortex; TPC, temporoparietal cortex; TPJ, temporoparietal junction. Class: A, randomized trials with a sample size ≥20 patients in the treatment group; B, randomized trials with a sample size <20 patients in the treatment group; C, trials that did not randomize patients to the study groups.

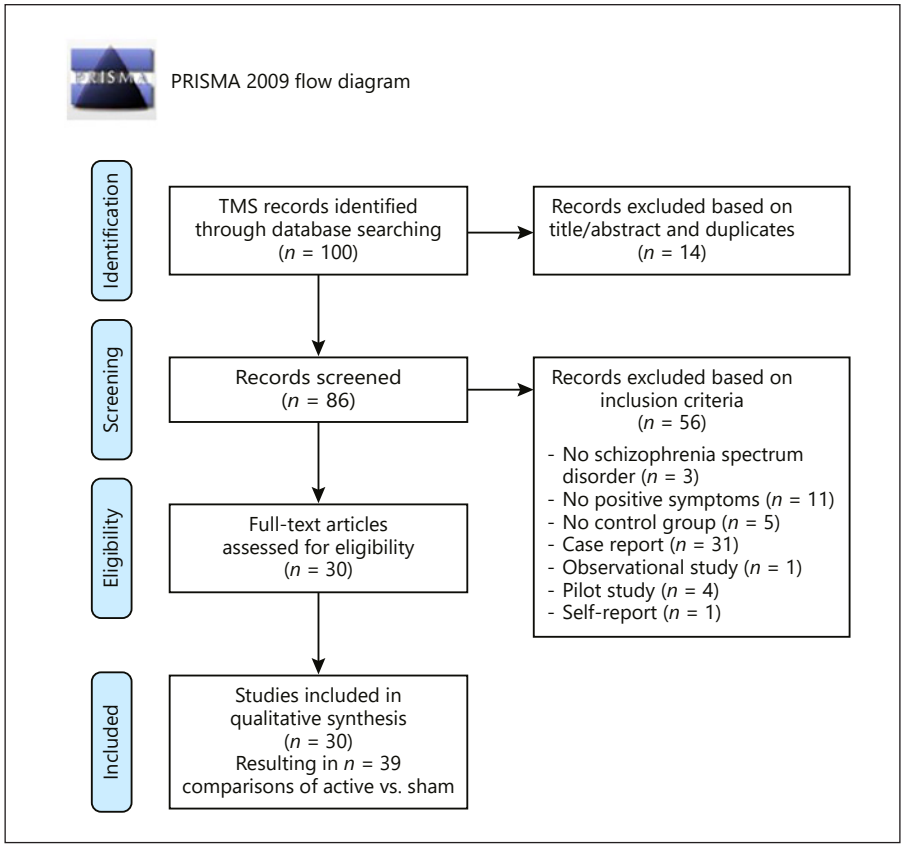

Fig. 1. PRISMA flow diagram [33]. This flow diagram shows the process of searching, screening, and including the final studies ($n = 31$).

TMS; psychosis; schizophrenia; positive symptoms; auditory hallucinations; thought disorder; delusions; hallucinations; thinking; and disorganization.

Selection Criteria

We conducted a systematic review and included studies that met the following inclusion criteria: (1) application of TMS, (2) comparison to a sham group, (3) patients with positive symptoms and a diagnosis of schizophrenia spectrum disorder, (4) age <18 and >65 years, (5) original articles and clinical trials, (6) no case reports, case series, and opinion papers, (7) no studies including participants with substance disorders who were not abstinent during the study period, and (8) no non-English studies.

Recorded Variables

We recorded the following variables: number of participants for the treatment or the experimental group, type of symptoms experienced, type of study design, patient diagnosis, stimulation target, stimulation hemisphere, whether neuronavigation was used, and whether evidence for an effect was found. Evidence for a positive effect was defined as a statistically significant improvement in positive symptoms after treatment with TMS compared with sham, while not enough evidence for a positive effect referred to studies that found no difference between active and sham stimulation (Table 1). Further, we classified the studies included according to the following criteria: (A) trials that used randomization for group assignment and had a sample size ≥20 patients in the treatment group, (B) trials that used randomization for group assignment but had a sample size <20 patients in the treatment group, and (C) trials that did not randomize patients to the study groups.

We adhered to the PRISMA guidelines [33] in the way that 2 independent researchers (T.M. and H.A.) conducted the literature search, screened the articles included, eliminated duplicates, decided whether the article met the inclusion criteria, and extracted all relevant data from the final articles. Their independent searches were compared by S.W., and discrepancies were investigated and resolved by discussion with S.W.

Results

We identified a total of 100 studies that investigated the effects of TMS on positive symptoms in schizophrenia. Of those, 69 studies had to be excluded (Fig. 1); 30 studies remained that fulfilled the inclusion criteria. As some of the included studies investigated more than one active stimulation compared with sham stimulation, 39 comparisons of active TMS with sham were considered.

Together, a total of 803 patients (females: $N = 279$) received active TMS. Note that the exact count for females

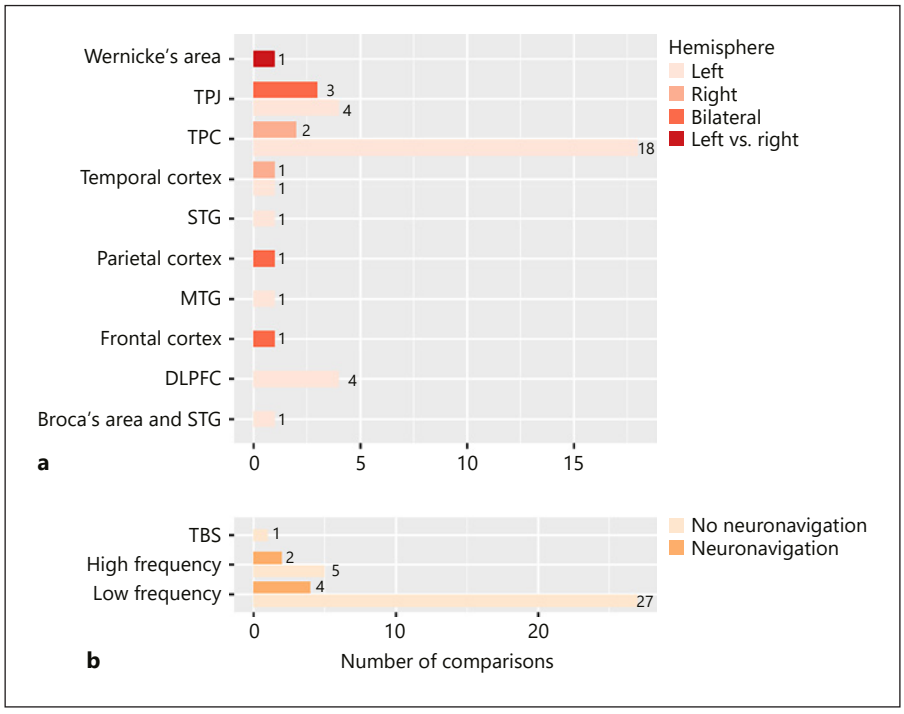

Fig. 2. Bar charts illustrate the frequency of transcranial magnetic stimulation (TMS) protocol parameters. **a** Target area and hemisphere. This bar chart shows the number of studies that stimulated one of the following target areas: dorsolateral prefrontal cortex (DLPFC), middle temporal gyrus (MTG), parietal cortex, superior temporal gyrus (STG), temporoparietal cortex (TPC) or junction (TPJ), and temporal cortex. The hemisphere stimulated was in most cases the left side, in some the right side, in some bilateral; 1 study defined the side individually in each patient, and 1 study investigated the difference between the left and the right hemisphere. **b** Stimulation frequency and use of neuronavigation. The majority of the studies stimulated with low frequency (≤1 Hz) while only few stimulated with high frequency (≥5 Hz) or theta-burst stimulation (TBS, with 50 Hz). Regarding neuronavigation, only 6 studies used guided TMS.

and males was not available for 6 comparisons. All patients in the studies included met criteria for schizophrenia spectrum disorder according to DSM-IV [34] or DSM-5 [2]. The mean age of those included ranged from 29.4 to 44.6 years of age (M = 36.53, SD = 2.48). All included studies investigated TMS as an add-on to antipsychotic treatment, with 31 (79.5%) of the comparisons doing so in patients with medication-resistant auditory verbal hallucinations.

The stimulation targets varied across the comparisons. In particular, 1 (2.6%) comparison targeted Broca's area, 4 (10.3%) the dorsolateral prefrontal cortex, 1 (2.6%) the middle temporal gyrus, 1 (2.6%) the parietal cortex, 1 (2.6%) the superior temporal gyrus, 2 (5.1%) the temporal cortex, 20 (51.3%) the temporoparietal cortex, 7 (18.0%) the temporoparietal junction, and 1 (2.6%) Wernicke's area (Fig. 2a). Also, protocols varied with regard to the targeted hemisphere: the majority (30; 76.9%) of the comparisons targeted the left hemisphere, 3 (7.7%) the right hemisphere, 1 (2.6%) compared stimulation of the left with the right hemisphere, and 5 (12.8%) stimulated bilaterally (Fig. 2a).

We categorized stimulation frequency into low frequency (≤1 Hz) and high frequency (≥ 5 Hz) based on Siebner and Rothwell [35]. Of the comparisons, 31 (79.5%) used low-frequency rTMS and 7 (17.9%) high-frequency rTMS; 1 (2.6%) study used TBS (Fig. 2b). Of the 39 comparisons, only 6 (15.4%) used neuronavigation (Fig. 2b).

As a result, 17 (43.6%) comparisons found TMS on average superior to sham with a significant decrease in positive symptoms, while 22 (56.4%) found not enough evidence for a difference between active TMS and sham (Fig. 3). Note that 7 (17.9%) comparisons were done in studies that did not use a randomization procedure to assign patients to the study groups.

Low-Frequency TMS

rTMS

The first rTMS protocol for positive symptoms in schizophrenia was introduced by Hoffman et al. [21] for patients suffering from medication-resistant auditory verbal hallucinations over 20 years ago. In a double-blind, crossover trial, 3 patients received low-frequency rTMS of the temporoparietal cortex once a day for 5 days and sham treatment for another week. Symptom severity decreased and remained reduced for 2 weeks [21]. Following this promising result, Hoffman et al. [38] conducted a series of studies with larger samples [36, 37] and an extended treatment for 9 instead of 5 days. In all studies, symptom severity of auditory verbal hallucinations was reduced after active rTMS compared with sham. Effects

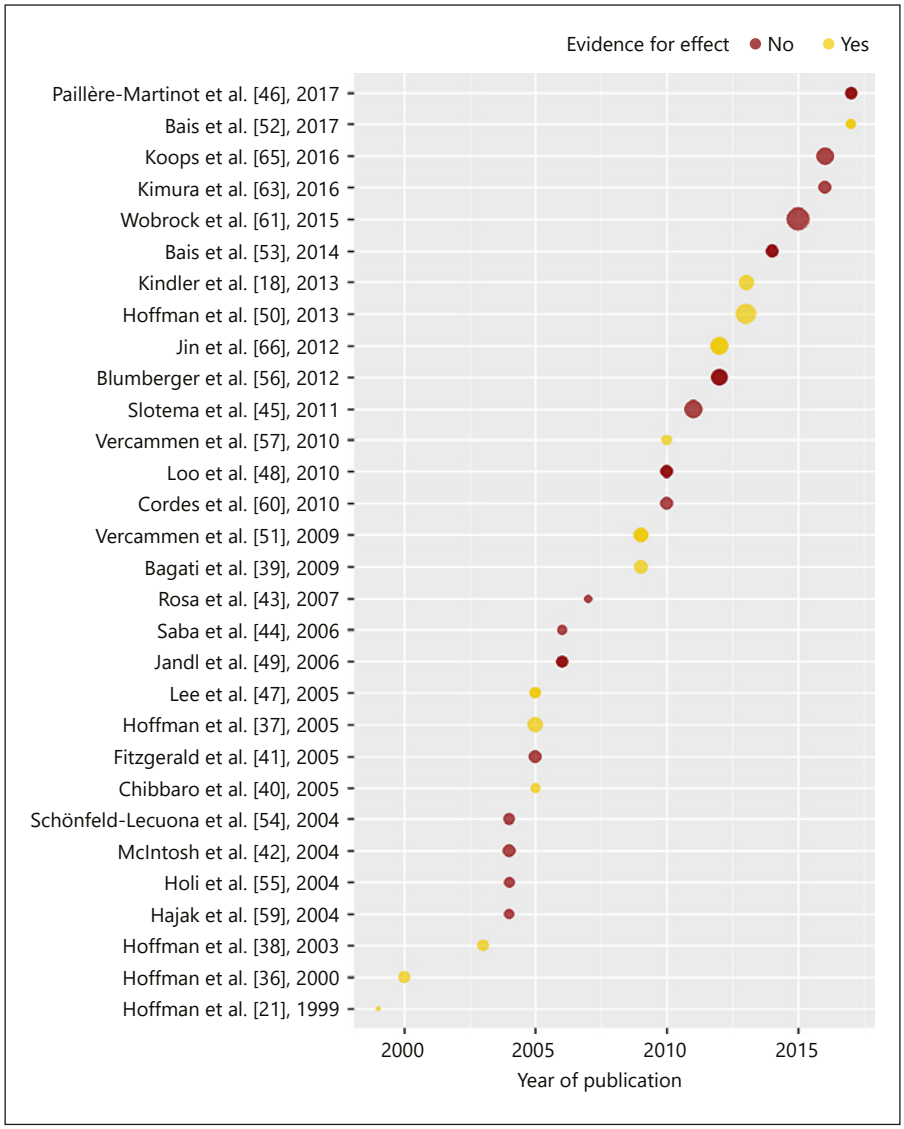

Fig. 3. Evidence for an effect. The bubble plot shows that 12 studies found evidence for a positive effect suggesting that TMS is superior to sham, while 18 found not enough evidence to conclude that TMS is superior to sham. Note that the size of the bubbles is relative to the sample size of the treatment group. Of the 39 comparisons, 27 (69.2%) had a sample size <20 patients in the treatment group.

lasted up to 15 weeks in half of the patients. Following these promising results, Bagati et al. [39] used the same protocol in 20 patients, Chibbaro et al. [40] in 16 patients, and Fitzgerald et al. [41] in 17 patients. All replicated the positive findings and found a significant reduction in auditory verbal hallucinations and positive symptoms, which lasted up to 8 weeks in the case of Chibbaro et al. [40].

Yet, a number of studies did not replicate these positive findings. Using the initially proposed protocol by Hoffman et al. [38], McIntosh et al. [42] (in a crossover trial) and Rosa et al. [43] (in a randomized controlled trial, RCT) reported a reduction in auditory verbal hallucinations, however, in both the active and sham group. This is in line with the findings of Saba et al. [44], who used the initial protocol in 8 patients with delusions and auditory hallucinations. Interestingly, this is the only study that investigated the effects of rTMS explicitly also on delusions so far. Yet, the authors found no evidence for a beneficial effect of rTMS. Moreover, one of the largest RCTs so far [45] included 3 groups: (1) rTMS group with individually defined stimulation target, (2) rTMS group with temporoparietal cortex stimulation, and (3) sham group. For the individual assessment of the target region, Slotema et al. [45] used functional MRI (fMRI) to calculate the area with the highest hallucinatory activation. Yet, neither stimulation of the temporoparietal cortex nor of the individually defined targets was superior to sham stimu-

lation. In line with this, a recent study by Paillère-Martinot et al. [46] showed that individual localization with fMRI and a language recognition task did not lead to a better result. In fact, a reduction in hallucinations was present in both the treatment and the sham group, providing evidence against the efficacy of rTMS for auditory verbal hallucinations.

The hemisphere over which TMS was applied was another element that varied between protocols. While the majority of studies targeted the left hemisphere, following the example of the initial studies [36–38], Lee et al. [47] were among the first to compare the effects of rTMS of the left versus the right temporoparietal cortex. The authors found a significant reduction in auditory verbal hallucinations in both rTMS groups independently of the hemisphere to which rTMS was applied. This is in line with 3 crossover trials that compared the laterality of the target for the temporal cortex [48], the temporoparietal cortex [49], and Wernicke's area [50]. All found not enough evidence for the superiority of left- versus right-hemisphere stimulation. Similar effects were reported by Vercammen et al. [51], who used low-frequency rTMS of the left temporoparietal cortex twice daily for 6 days and compared this with bilateral stimulation. The authors found a significant reduction in the frequency of auditory verbal hallucinations in patients who had received rTMS over the left hemisphere. Interestingly, the patients who received bilateral rTMS reported less emotional responsiveness to the hallucinations. In contrast, 2 RCTs comparing left-hemisphere to bilateral stimulation [52, 53] of the temporoparietal junction in patients with medication-resistant auditory verbal hallucinations found no significant improvement in hallucination severity, independent of the hemisphere targeted.

Apart from the target site, the target area was also an element that varied between protocols. The temporal cortex, with the temporoparietal junction in particular, was the most commonly targeted area [33, 39, 44, 46, 54], especially in hallucination studies. Yet, Schönfeldt-Lecuona et al. [54] stimulated a group of patients with chronic, medication-resistant auditory verbal hallucinations for 5 days with low-frequency rTMS and targeted the superior temporal gyrus and Broca's area based on the hyperactivation that the pretreatment fMRI revealed. Neither targeting the superior temporal gyrus nor Broca's area reduced positive symptoms significantly compared with sham stimulation. Also, Holi et al. [55] stimulated the left dorsolateral prefrontal cortex with 10 Hz for 10 days and found an improvement in positive symptoms, but this was also true for sham-treated patients.

In addition to varying the above-discussed parameters of TMS protocols, further variations have been tested. One such variation was a priming pulse of 6 Hz before the actual stimulation, suggested by Blumberger et al. [56]. The rationale was to enhance the physiological effect of low-frequency rTMS by priming the brain with a single pulse of a slightly higher frequency. Using this protocol, the authors found no superiority of the priming protocol over the conventional low-frequency rTMS protocol or sham therapy in 54 patients with medication-resistant auditory hallucinations.

As a side note, 1 study investigated brain changes after TMS using fMRI. Vercammen et al. [57] investigated the hypothesized decreased connectivity between the left temporoparietal junction and the bilateral amygdala and anterior cingulate in relation to auditory verbal hallucinations [58]. After treating the left temporoparietal junction of 18 patients for 6 days with 1-Hz rTMS, functional connectivity was increased between the left temporoparietal junction and right insula. Interestingly, connectivity was decreased between the left temporoparietal junction and the left anterior cingulate in patients who received sham. The authors concluded that rTMS had an effect on functional connectivity of the left temporoparietal junction, but the relation to clinical outcome needs further investigation.

High-Frequency rTMS

Of the 39 comparisons, 8 were performed to assess high-frequency rTMS for the treatment of positive symptoms. Among the first studies that used high-frequency rTMS with 10 Hz were Hajak et al. [59]. The authors stimulated the left dorsolateral prefrontal cortex of 10 patients with a schizophrenia spectrum diagnosis. Yet, after the 10-day treatment, a trend to worsening of positive symptoms was observed while negative symptoms had significantly improved. Note that patients were not randomized to the study groups. In line with this finding were the results of the RCT by Cordes et al. [60]. The authors found not enough evidence for a beneficial effect of rTMS on positive symptoms. In contrast, Wobrock et al. [61] used the same protocol but stimulated 5 days for 3 weeks. This relatively large study focused primarily on negative symptoms with positive symptoms as a secondary outcome. The authors reported that positive symptoms improved significantly after 21 days in the rTMS group compared with the sham group. However, a closer look at the results shows that both the active as well as the sham group had the same outcome score on day 21 with the only difference being a higher baseline score in the active group. It

is rather unlikely that an analysis of covariance (the most sensitive way to analyze RCTs [62]) would have found evidence for a treatment effect here, which is why we did not count this study as showing evidence for TMS efficacy. Last, Kimura et al. [63] used an even higher frequency: the authors stimulated with 20 Hz in 4 sessions over 2 days but found no positive effect on auditory verbal hallucination severity.

Theta-Burst Stimulation

TBS was introduced as a novel stimulation pattern of TMS in the treatment of refractory auditory verbal hallucinations. From a clinical perspective, TBS has the advantage of being much shorter with an application duration of only 44 s compared with 15 min with the conventional 1-Hz rTMS protocol, yet the same number of pulses [64]. Koops et al. [65] were the first to investigate the application of continuous TBS compared with sham in a large sample of 71 patients with schizophrenia suffering from auditory verbal hallucinations. Patients received 10 stimulations of continuous TBS with 60-s trains consisting of 3 pulse bursts at 50 Hz repeated every 200 ms. The authors found that the severity of auditory verbal hallucinations was reduced in both the active and the sham group, indicating no specific benefit of continuous TBS over sham stimulation.

αTMS

Neuronavigation is possible by means of fMRI but also by means of electroencephalography (EEG). In particular, using α-waves detected by EEG can be used to guide rTMS. The rationale is that setting the stimulus rate of rTMS individually at each patient's intrinsic peak α-frequency induces a resonant EEG response that enhances synchronization and reduces symptoms. Jin et al. [66] used α-EEG-guided rTMS in a randomized, double-blind, sham-controlled trial in 4 groups: (1) frontal αTMS, (2) partial αTMS, (3) frontal sham, and (4) parietal sham. The frequency was individualized, ranging from 8 to 13 Hz. Interestingly, both the frontal and parietal α-EEG-guided TMS group showed significantly reduced positive symptoms and general psychotic symptoms compared with both sham groups.

Discussion

The current study systematically reviewed clinical trials that investigated TMS for positive symptoms in schizophrenia. We found that the majority of studies used rTMS in auditory verbal hallucinations, with half of the comparisons indicating a superiority of active over sham stimulation. However, with a few exceptions, the studies used small samples, making it difficult to draw strong conclusions.

Besides the small sample sizes, the follow-up time of each study might have been too short to determine any long-term clinical improvement or positive symptom reduction. Future research should aim at designing RCTs with large enough samples [67] to detect clinically relevant effects of rTMS on positive symptoms.

The studies reviewed here have shown the abundance of research done to further investigate the initial finding by Hoffman et al. [21]. Using the same rTMS parameters, 11 comparisons replicated and reproduced the positive findings of the initial study [21]. These comparisons showed a robust reduction in auditory verbal hallucinations when compared with sham. In addition to these 11 comparisons, another 5 found evidence for a beneficial effect of TMS over sham stimulation with protocols diverging from the initial one. However, one has to keep in mind that these 16 comparisons showing positive effects did so in very small samples. Of those, 7 investigated 12 patients or less, whereas only 1 study [61] included a sample of 55 patients in the active group. In contrast, of the 22 studies that found no evidence for an effect of active rTMS and clinical reduction in positive symptoms, 17 comparisons had small sample sizes ($n < 20$). However, a small sample size study with a nonsignificant finding does not implicate no effect. Limitations and biases can be present in smaller samples leading to caveats of a true effect. For example, a study with low statistical power has a smaller chance of detecting a true effect, but it is less well appreciated that low power also reduces the likelihood that a statistically significant outcome reflects a true effect [67].

Due to the lack of consistent replication, research has focused on modifications to the original protocol for auditory verbal hallucinations. With regard to the stimulation target, the superior temporal gyrus, middle temporal gyrus, Wernicke's area, Broca's area, frontal and parietal cortices, and the dorsolateral prefrontal cortex were all alterations to the initial target of choice. Stimulation targets did not seem to produce any robust findings as the studies had mixed outcomes on positive symptom reduction – some showing positive effects and some producing no significant differences. In addition, differences in stimulation laterality have also been tested, with overall inconsistent results. Together, this suggests that the stimulation of different target regions was not effective in re-

ducing auditory verbal hallucinations or positive symptoms in general.

To help increase specificity of stimulation, the use of neuronavigation has been investigated. Hoffman et al. [37] demonstrated the usefulness of neuronavigation with regard to coil placement and its effect on auditory verbal hallucinations, targeting Wernicke's area and right homologous. Interestingly, a reduction in the hallucination frequency had an apparent positive effect in the treatment group compared with the sham group [37]. Nevertheless, there is not enough evidence to indicate a superiority of neuronavigation over conventional stimulation protocols.

With respect to stimulation frequency, most studies looking at high-frequency rTMS have not shown efficacy in the reduction of auditory verbal hallucinations or positive symptoms in general. Still, the introduction of TBS has provided a promising way to use shorter stimulation durations. However, in terms of efficacy, the 1 study included in this review [65] suggested that TBS was not superior to sham.

The majority of the studies assessed the effects of TMS on auditory hallucinations with only 1 study focusing specifically on delusions [44]. The authors found no evidence for a beneficial effect of TMS on delusions and hallucinations. One explanation for this could be that high-frequency stimulation is needed to reach deeper brain areas involved in the phenomenon of delusions [44, 68].

Overall, evidence for the efficacy of TMS in the treatment of positive symptoms is mixed irrespective of the variation in TMS parameters. However, this does not mean that there is heterogeneity in the way individual patients respond to TMS. This common believe, when based on the observations from RCTs, is problematic [69], and the estimation of individual treatment responses requires appropriate designs [70] and modeling [71].

Some limitations merit comment. It was beyond the scope of this review to quantitatively assess the studies. A few authoritative reviews and meta-analyses do exist [19, 28, 31, 32] and have indicated effect sizes for auditory hallucinations in the range of mild to moderate. Yet, we summarized previously published findings in a comprehensive synthesis and with descriptive statistics. Further, one third of the studies used a subscale of the Positive and Negative Syndrome Scale (PANSS [72]) to assess auditory verbal hallucinations. Using a general instead of a symptom-specific questionnaire limits the precise assessment of the respective symptom and might not be sensitive enough to capture subtle changes in symptom severity.

In conclusion, evidence for an effect of rTMS on positive symptoms was mixed, and rTMS cannot be recommended as an add-on treatment of positive symptoms at this point. Since most of the studies were performed in patients with auditory verbal hallucinations, further research on rTMS for other positive symptoms, including delusions and thought disorder, is warranted.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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Author Contributions

All authors agreed on the studies included. T.M. and H.A. screened the studies and extracted the data. T.M. and S.W. wrote the first draft. All authors contributed to and approved the final manuscript version.

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