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POSTGRADUATE THESIS

The efficacy of rTMS in treating auditory hallucinations in patients with schizophrenia or schizophrenia spectrum disorders. A systematic review

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Μεταπτυχιακή Διπλωματική Εργασία

Η αποτελεσματικότητα του επαναληπτικού διακρανιακού μαγνητικού ερεθισμού στην αντιμετώπιση των ακουστικών ψευδαισθήσεων σε ασθενείς με σχιζοφρένεια ή διαταραχές του φάσματος της σχιζοφρένειας. Μία συστηματική ανασκόπηση

Πατεράκη Γεωργία

Υπεβλήθη για την εκπλήρωση μέρους των απαιτήσεων για την απόκτηση του Μεταπτυχιακού Διπλώματος Ειδίκευσης «ΝΕΥΡΟΑΠΟΚΑΤΑΣΤΑΣΗ»

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ΠΑΤΕΡΑΚΗ ΓΕΩΡΓΙΑ

Πανεπιστήμιο Θεσσαλίας, Σχολή Επιστημών Υγείας, Τμήμα Ιατρικής, 2023

ΔΙΕΥΘΥΝΤΗΣ ΤΟΥ ΠΡΟΓΡΑΜΜΑΤΟΣ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

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ΕΥΧΑΡΙΣΤΙΕΣ

Με την ολοκλήρωση της διπλωματικής μου εργασίας, η οποία εκπονήθηκε στο πλαίσιο του προγράμματος μεταπτυχιακών σπουδών «Νευροαποκατάσταση» του Τμήματος της Ιατρικής του Πανεπιστημίου Θεσσαλίας, θα ήθελα να ευχαριστήσω όλους όσους συνέβαλαν στην ολοκλήρωση της.

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Πατεράκη Γεωργία

Abstract

Background: Auditory hallucinations (AH) are a symptom commonly found in schizophrenia and schizophrenia spectrum disorders. Although most cases respond well to antipsychotic medication, about 25% of patients remain resistant to treatment. The purpose of this systematic review was to collect the existing knowledge on the efficacy of repetitive transcranial magnetic stimulation (repetitive TMS, rTMS) in alleviating AH in patients with schizophrenia or schizophrenia spectrum disorders.

Methods: The PubMed Database was systematically searched by two independent researchers for studies assessing the efficacy of rTMS in AH among patients with schizophrenia or schizophrenia spectrum disorders. The reference lists of selected titles were also searched for additional publications. Studies were included according to established inclusion and exclusion criteria. Results were synthesized according to the target of stimulation and were then further grouped with regards to the rTMS approach used.

Results: A total of 28 randomized, sham-controlled studies were included in the final analysis. The majority of studies delivered rTMS over the left temporoparietal cortex, generating diverse results. The data over other regions were fairly limited thus, no strong conclusions can be yet drawn.

Conclusion: It is still unclear whether rTMS can prove beneficial in treating AH of patients with schizophrenia or schizophrenia spectrum disorders. Further research with randomized, double-blind, sham-controlled trials, employing the same TMS parameters is needed to assess the therapeutic value of rTMS paradigms.

Keywords: auditory hallucinations; schizophrenia; schizophrenia spectrum disorders; rTMS; systematic review;

Περίληψη

Σκοπός: Οι ακουστικές ψευδαισθήσεις είναι ένα σύμπτωμα που απαντάται συχνά στη σχιζοφρένεια και στις διαταραχές του φάσματος της σχιζοφρένειας. Μολονότι η πλειονότητα των περιπτώσεων ανταποκρίνεται καλά στην αντιψυχωσική αγωγή, περίπου το 25% των ασθενών παραμένουν ανθεκτικοί σε αυτή. Ο σκοπός αυτής της συστηματικής ανασκόπησης ήταν η συλλογή της υπάρχουσας γνώσης σχετικά με την αποτελεσματικότητα του επαναληπτικού διακρανιακού μαγνητικού ερεθισμού (repetitive TMS, rTMS) στην αντιμετώπιση των ακουστικών ψευδαισθήσεων σε ασθενείς με σχιζοφρένεια ή με διαταραχές του φάσματος της σχιζοφρένειας.

Μέθοδοι: Η βάση δεδομένων PubMed ερευνήθηκε συστηματικά από δύο ανεξάρτητους ερευνητές για μελέτες που αξιολογούν την αποτελεσματικότητα του rTMS στην αντιμετώπιση των ακουστικών ψευδαισθήσεων σε ασθενείς με σχιζοφρένεια ή διαταραχές του φάσματος της σχιζοφρένειας. Επιπλέον δημοσιεύσεις αναζητήθηκαν στις λίστες βιβλιογραφικών αναφορών των επιλεγμένων τίτλων. Οι μελέτες επιλέχθηκαν σύμφωνα με διαμορφωμένα κριτήρια ένταξης και αποκλεισμού. Τα αποτελέσματα συντέθηκαν σύμφωνα με τον στόχο της διέγερσης και ομαδοποιήθηκαν περαιτέρω σε σχέση με την προσέγγιση του rTMS που χρησιμοποιήθηκε.

Αποτελέσματα: Στην τελική ανάλυση συμπεριλήφθηκαν συνολικά 28 τυχαιοποιημένες, ελεγχόμενες με εικονική παρέμβαση μελέτες. Η πλειονότητα των μελετών εφάρμοσε rTMS στον αριστερό κροταφοβρεγματικό φλοιό, παράγοντας διφορούμενα αποτελέσματα. Τα δεδομένα για άλλες περιοχές ήταν περιορισμένα, επομένως δεν μπορούν ακόμη να εξαχθούν ασφαλή συμπεράσματα.

Συμπέρασμα: Δεν είναι ακόμη σαφές εάν το rTMS μπορεί να αποδειχθεί επωφελές στην αντιμετώπιση των ακουστικών ψευδαισθήσεων σε ασθενείς με σχιζοφρένεια ή με διαταραχές του φάσματος της σχιζοφρένειας. Απαιτείται περαιτέρω έρευνα με τυχαιοποιημένες, διπλά τυφλές, ελεγχόμενες με εικονική παρέμβαση δοκιμές χρησιμοποιώντας ίδιες TMS παραμέτρους για την αξιολόγηση της θεραπευτικής αξίας των rTMS πρωτοκόλλων.

Λέξεις-κλειδιά: ακουστικές ψευδαισθήσεις, σχιζοφρένεια, διαταραχές σχιζοφρενικού φάσματος, επαναληπτικός διακρανιακός μαγνητικός ερεθισμός, συστηματική ανασκόπηση

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INTRODUCTION

Auditory hallucinations (AH), are defined as the perception of sound in the absence of corresponding external stimuli (Blom, 2015). They can occur across a wide range of neuropsychiatric disorders and they are commonly found in the setting of schizophrenia and schizophrenia spectrum disorders. They typically occur in 50-70% of schizophrenic patients causing significant levels of distress. The first treatment option for auditory hallucinations is antipsychotic treatment which in the majority of cases, successfully relieves these symptoms; however, it may lead to severe physical or neurological side effects such as weight gain, diabetes, myocarditis and seizures (De Berardis et al., 2018; Schultz et al., 2007). Moreover, about 25% of AH cases remain resistant to antipsychotic treatment (Shergill et al., 1998). Hence, new therapeutic approaches are urgently needed.

Transcranial magnetic stimulation (TMS) is a safe and relatively painless, non-invasive brain stimulation technique that generates brief magnetic fields when an electric current passes through an electromagnetic coil placed over the scalp (Burke et al., 2019). These magnetic fields are capable of inducing electric currents in the brain which, depending on their frequency, may have inhibitory (≤ 1 Hz) or excitatory (> 1 Hz) effects (Aleman, 2013). When TMS is applied repetitively in trains (repetitive TMS, rTMS) it has the capacity of inducing changes in the neurons that can outlast the stimulation period, thus it has gathered increasing interest as a potential treatment strategy for the symptomatic relief of several disorders, including AH in schizophrenia and schizophrenia spectrum disorders. There is evidence for TMS therapeutic application in neurological and psychiatric disorders (Aloizou et al., 2021, Petsani et al. 2021, Ntakou et al., 2022, Pateraki et al, 2022).

Theta-burst stimulation is a recently developed form of rTMS which involves the application of 3 bursts of high-frequency (50 Hz) stimulation, with an interburst interval of 200 ms (5 Hz, 80% AMT). It can be applied either continuously or with an intermittent pattern; when TBS is administered continuously (cTBS) (i.e. 300 pulses over 20 seconds or 600 pulses over 40 seconds) it has been shown to induce strong inhibitory effects, whereas when TBS is applied with an intermittent pattern (intermittent TBS, iTBS) (i.e. 30 pulses of TBS applied in 2 seconds, repeated every 10 seconds for a total number of 600 pulses) excitatory effects have been observed (Huang et al., 2005).

The purpose of this systematic review was to gather the existing knowledge on the use of rTMS in the alleviation of AH in patients with schizophrenia or schizophrenia spectrum disorders and determine whether it can prove beneficial in this context.

MATERIALS AND METHODS

Study Search

A systematic review was conducted based on the recommended Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines.

The PubMed Database was searched with the following string: ((TMS) OR (Transcranial Magnetic Stimulation) OR (RTMS) OR (Repetitive Transcranial Magnetic Stimulation)) AND ((Schizophrenia) OR (Schizoaffective disorder)) AND (Auditory Hallucinations). No restrictions with regards to language, publication date, or any other were applied. Titles and abstracts were screened by two independent researchers in order to find relevant articles. For the selected titles, full-text articles were retrieved and reference lists of each were searched for additional publications.

Eligibility Criteria

Studies that fulfilled the following criteria were considered for inclusion:

- Sham-controlled trials of repetitive transcranial magnetic stimulation
- Patients with a primary diagnosis of schizophrenia or schizophrenia spectrum disorder diagnosed according to standardized criteria (e.g. DSM-IV, ICD-10)
- At least one auditory hallucination-specific assessment is reported (e.g. the Auditory Hallucinations Rating Scale (AHRS), or the Auditory Hallucination Subscale of the Psychotic Symptom Rating Scale (AH-PSYRATS))

Studies that met the following exclusion criteria were not carried out further in the analysis:

- The study is not in accordance with a parallel type of study design, nor with a crossover one
- Data on patients with schizophrenia or schizophrenia spectrum disorder provided cumulatively with other disorders

Evaluation of Risk of Bias

The revised version of Cochrane Risk of Bias Tool 2.0 (RoB 2.0) was used for the evaluation of the risk of bias of each study. In RoB 2, a fixed set of signaling questions is used to assess the methodological characteristics in each of the following domains that bias could stem from: (1) Randomization process, (2) Deviations from the intended intervention, (3) Missing outcome data (4) Measurement of the outcome (5) Selection of the reported result. For crossover studies, an extra set of questions is used to evaluate bias arised from period and carryover effects (Domain S). After responding to each set of questions, each of the aforementioned domains is classified as "High Risk", "Some Concerns", or "Low Risk". Finally, the study is assigned an overall risk of bias which is based on the sum of all the aforementioned domains.

Data Extraction

The following information were extracted from each study:

Authors and year of publication, study design, number of participants, TMS protocol, nature of sham stimulation, timepoints of assessment, AH rating scales used, AH outcome.

Reporting of Data

Studies were categorized according to the region that was used as the target of active stimulation. In cases where real stimulation was performed in more than one area, the study was mentioned in all corresponding sections. Articles were further grouped according to the TMS protocol used (e.g. LF-rTMS, HF-rTMS, cTBS). A brief description of each study was generated (including the number of patients, the patients' diagnosis, TMS parameters, number of sessions, scale of assessment of AH and AH outcome) followed by a brief commentary.

RESULTS

Study selection

The full search strategy appears in Figure 1. Literature search in the PubMed Database generated 196 results, 110 of which were excluded as they were deemed irrelevant for the purpose of this review. Of the remaining 86 studies, 1 full-text article could not be retrieved. Articles were individually screened for adherence to the established inclusion and exclusion criteria. Based on the eligibility criteria, 26 case-studies, 20 clinical trials that did not include a sham group, and 6 studies that evaluated datasets of patients that were already included in another study were excluded. Moreover, 2 were study protocols, 1 study did not include diagnostic criteria, 1 study did not report auditory hallucinations separately to other positive symptoms, 1 study had a retrospective design and 1 study was not in accordance with either a parallel or a crossover design. Thus, 27 studies were included and 1 more study was detected from screening of the reference lists of relevant articles. In total, 28 studies were included in the final analysis.

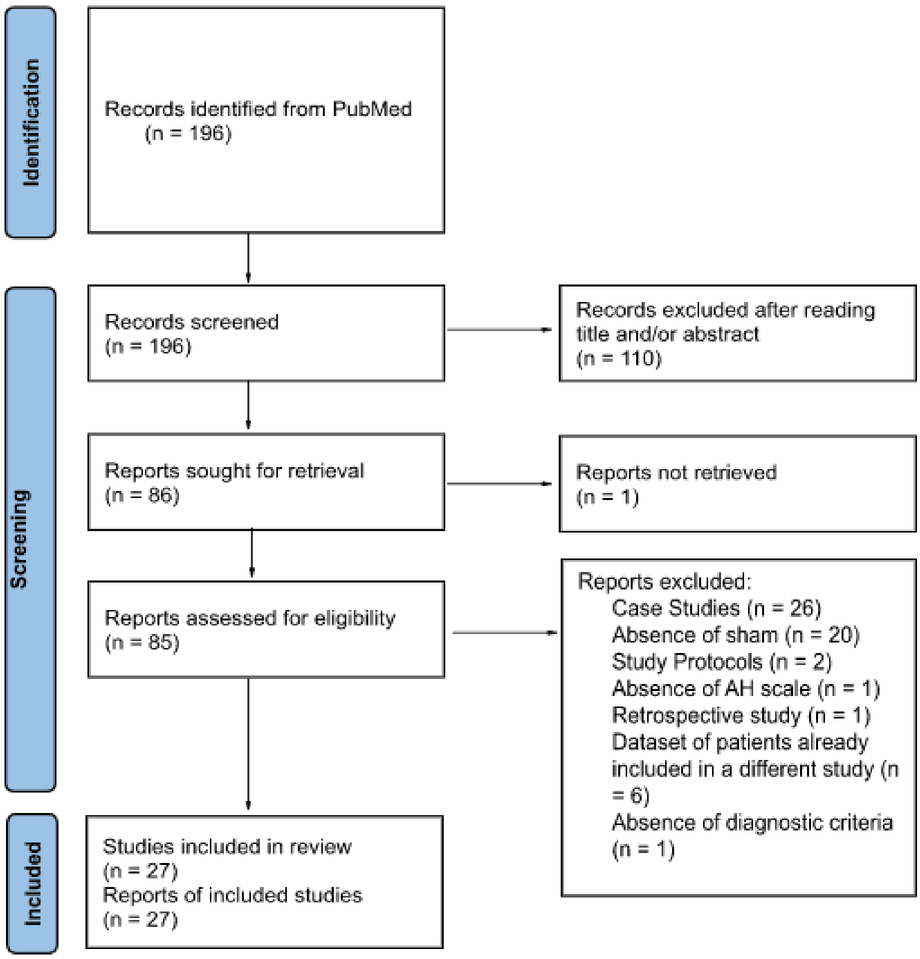

Figure 1: Complete research strategy in the PubMed Database

Study Characteristics

Of the 28 studies included in the final analysis, 18 had a parallel design and 10 had a crossover design. The majority (n=22) employed LF-rTMS (1 Hz), two studies delivered HF-rTMS (20 Hz), two cTBS (50 Hz), one deep TMS (1 Hz) and one used both LF- and HF-rTMS in different arms. Stimulation sites included the left temporoparietal cortex (n=20), the right temporoparietal cortex (n=4), the bilateral temporoparietal cortex (n=3), Broca's area (n=1), bilateral Broca's area (Broca's area and right homologous region) (n=1), Wernicke's area (n=1), right homologous to Wernicke's region (n=1), the Heschl's gyrus (n=1) and the left superior temporal gyrus (n=1).

Moreover, one was fMRI-guided to the site of maximal activation as detected during an AH episode, two were fMRI-guided over the most activated areas during a language task and one targeted 3 to 6 areas that exhibited the most AH-related prominent activation, again indicated by fMRI. The variable motor threshold (MT) varied greatly between the protocols, ranging from 80 to 115% MT. The number of sessions also was highly heterogeneous between the studies ranging from 1 to 24. All studies used a figure-of-8 coil, except for the study that employed deep TMS, where H1 coil was used. The characteristics of all included studies can be found in

APPENDIX

Table 1: Characteristics of studies investigating rTMS over the LTP Table 2: Characteristics of studies investigating rTMS over the RTP Table 3: Characteristics of studies investigating rTMS over the Bilateral TP and Table 4: Characteristics of studies investigating alternative areas and protocolsof the

APPENDIX grouped together according to the region used as the target of stimulation.

Risk of bias of included studies

Out of 28 included studies, 15 had a high risk of bias and 13 were labeled as "Some concerns". The methodological limitation most commonly found (n=21) was the lack of information of a pre-specified analysis plan (Domain 5) (n= 23), followed by whether the randomized allocation remained concealed until participants were assigned to interventions (Domain 1) (n=21).

SYNTHESIS OF THE RESULTS

RTMS over the LTP

Low-frequency stimulation

Gathering neuroimaging findings have demonstrated a hyperactivation in the left temporoparietal cortex (LTP) in patients experiencing AH. Hence, it seems plausible that the administration of protocols inducing inhibitory effects, such as low-frequency rTMS, could prove beneficial in alleviating AH. The first study to pioneer this intervention was conducted by Hoffman et al. (1999) with a crossover design. Three patients with schizophrenia or schizoaffective disorder received either active rTMS (1 Hz, 80% MT) or sham over the LTP. For clinical assessment of AH, a narrative description was provided at the time of admission to the hospital which was used as a baseline measure and was assigned the score of 10. The morning after each session, a reassessment was conducted generating a severity rating of the AH, with 0 corresponding to no AH. The improvement in AH following real stimulation was greater than that of sham and in 2 out 3 cases even outlasted the treatment for at least 2 weeks (Hoffman et al., 1999). These results were later replicated in another crossover study with a slightly bigger sample size. More specifically, the administration of 4 sessions of either sham or active LF-rTMS (1 Hz, 80% MT) in 12 patients with schizophrenia or schizoaffective disorder (2:1 ratio) led to a significant amelioration solely in the active stimulation group (Hoffman et al., 2000). Contradicting results were observed however in a later study employing identical TMS parameters. McIntosh et al. (2004) enrolled 16 patients in a crossover study and delivered 4 sessions of LF-rTMS (1 Hz, 80% MT) over the LTP. Clinical assessment of AH was conducted using the Hallucination Item of Positive and Negative Syndrome Scale (PANSS-P3) as well as a 10-point Likert scale rated in the same way as described above. As opposed to previous findings, no significant differences were detected between the two stimulation conditions (McIntosh et al., 2004). Interestingly, when Chibbaro et al. (2005) delivered 4 sessions of real LF-rTMS (1 Hz, 90% MT) or sham over the LTP of 16 patients with paranoid schizophrenia, a significant improvement was detected in both groups. However the real group demonstrated a significantly better change compared to sham at the follow-up assessments, with the last evaluation being performed 2 months after stimulation cessation (Chibbaro et al., 2005).

Moving on, Hoffman et al. (2005) extended the treatment duration and delivered 9 sessions of either sham or real LF-rTMS (1 Hz, 90% MT) over 9 consecutive weekdays in fifty patients with a primary diagnosis of schizophrenia or schizoaffective disorder. In this double-blind parallel study, assessment was conducted at baseline and 24 hours following stimulation at days 3, 6 and 9 using the Hallucination Change Scale (HCS) and the Auditory Hallucinations Rating Scale

(AHRS). A significant decrease in HCS was produced in both groups however, HCS scores in the active group were found to be significantly lower at Days 6 and 9 compared to sham. With regards to the AHRS, no significant alterations were observed except for the subitem of frequency in the active group (Hoffman et al., 2005). In a crossover study published in the same year by Poulet et al. (2005), 10 patients diagnosed with schizophrenia and medication-resistant AH received 10 sessions (twice a day for 5 days) of sham or real stimulation (1 Hz, 90% MT) over the LTP. Assessment of AH was conducted on a daily basis during the trial with the AHRS and then 30, 60, and 90 days after treatment cessation. AHRS scores in the active group were found significantly improved compared to sham and in 5 out 7 labeled as "responders" (≥20% improvement in AHRS scores compared to baseline), were maintained for at least 2 months (Poulet et al., 2005). In line with these, encouraging results were also obtained in a double-blind, parallel study conducted by Brunelin et al. (2006). Twenty-four patients with schizophrenia were randomly assigned to receive sham or active stimulation (1 Hz, 90% MT) twice a day for 5 successive days. Ten sessions of rTMS led to a significant amelioration in the AHRS scores of the active group, whereas sham remained unaltered (Brunelin et al., 2006).

In a randomized, controlled trial conducted by Fitzgerald et al. (2005) 32, of 33 patients enrolled, with a primary diagnosis of schizophrenia or schizoaffective disorder were assigned to receive 15 minutes of either real or sham rTMS (1 Hz, 90% RMT) for 10 consecutive weekdays. AH were assessed using the HCS, the auditory hallucinations subscale of the Psychotic Symptoms Rating Scales (PSYRATS-AH) and PANSS-P3. None of the aforementioned scales demonstrated a significant improvement, except for the variable of the PSYRATS-AH "loudness of voices" (Fitzgerald et al., 2005).

In a parallel, double-blind study 39 patients with schizophrenia were randomly allocated to receive sham stimulation, or real stimulation (1 Hz, 100% RMT) over the LTP, or real stimulation over the right temporoparietal cortex (RTP) once a day for 10 days. The AHRS measured at baseline, at day 5 and at day 10 of stimulation revealed no significant differences between the 3 groups (Lee et al., 2005). In accordance with these, Jandl et al. (2006) recruited 16 patients with schizophrenia or schizoaffective disorder and medication-resistant AH in a crossover, double-blind randomized controlled trial (RCT). Of those, 14 patients received rTMS (1 Hz, 100% MT) over the LTP, over the RTP, or sham rTMS for 5 consecutive days. Assessment took place after each session and then 1, 2 and 4 weeks after treatment cessation using the PSYRATS-AH. The means sum score of PSYRATS-AH did not demonstrate significant improvement in any group. However, in the left stimulation group 5 subjects were labeled as complete or partial responders (defined as a 30% and 50% decrease of the PSYRATS-AH respectively) as opposed to sham where none of the patients was identified as a responder (Jandl et al., 2006). The superiority of active versus sham stimulation was also failed to be reported in a study conducted by Saba et al. (2006). Sixteen patients diagnosed with paranoid schizophrenia were randomly allocated to receive 10 sessions of sham or active LF-rTMS (1 Hz, 80% MT). PANSS-P3 scores which were assessed at baseline and following the last session demonstrated a significant improvement in both active and sham groups (Saba et al., 2006). Negative results were also generated in a double-blind, pilot study with a longer treatment duration (de Jesus et al., 2011). In this parallel study, 17 patients with refractory schizophrenia were enrolled and were randomly allocated to receive 20 sessions (over a four-week time span) of active (1 Hz, 90% MT) or sham rTMS. Clinical evaluation of AH, which was conducted with the AHRS, demonstrated no significant improvement of active compared to sham. Somewhat surprising results were obtained when Van Lutterveld et al. (2012) enrolled 24 patients with a primary diagnosis of schizophrenia, schizoaffective disorder, or psychosis not otherwise specified (NOS). Patients were randomly assigned to receive one session of stimulation (1 Hz, 90% MT) over the LTP, RTP or sham, in a crossover study, with a one-week washout period. Clinical assessment of AH, which was performed with the HCS and the AHRS before and after each session, revealed significant improvement in all groups. Interestingly, the improvement observed in the HCS of the sham group was found to be significantly greater than that of the left group (van Lutterveld et al., 2012).

Bais et al., 2014 enrolled 51 patients diagnosed with schizophrenia and medication-resistant AH who were randomly allocated to one of three treatment arms: (i) LF-rTMS (1 Hz, 90% RMT) over the LTP, (ii) LF-rTMS over the temporoparietal area (TP) bilaterally and (iii) sham stimulation over the LTP, performed twice a day for six days. AH severity was assessed using the AHRS and Positive and Negative Affect Scale (PANAS) adapted for hallucinations. Twelve sessions of active or sham stimulation led to a significant reduction in mean AHRS and PANAS scores of all groups, with LF-rTMS over the LTP failing to demonstrate any superiority compared to the others (Bais et al., 2014). In a more recent randomized, controlled trial 10 patients with schizophrenia were enrolled and assigned to receive 10 daily sessions of stimulation (1 Hz, 90% RMT) of either the LTP or the vertex (control group). The PSYRATS-AH, which was used for the evaluation of the AH and was performed at baseline and following the last stimulation session, revealed no significant differences between real and control groups (Aubonnet et al., 2020).

In a different LF-rTMS paradigm, Gornerova et al. (2023) randomly allocated 19 patients with schizophrenia in an active (0.9 Hz, 100% MT) or sham stimulation over the LTP for 10 consecutive workdays. AHRS revealed a significant improvement in the active group as opposed to sham (Gornerova et al., 2023).

Lastly, the efficacy of low-frequency deep TMS has also been evaluated in the same context. Rosenberg et al. (2012) enrolled 18 patients with schizophrenia and administered deep TMS (1 Hz, 110% MT) for 10 consecutive days. AH were assessed at baseline and after the last rTMS sessions using the AHRS. The results obtained referred only to 10 out of 18 patients, given the fact that 8 patients (4 in each group) dropped out before completion of the treatment. In the subset of patients that completed the study, no significant differences were reported between the two stimulation conditions (Rosenberg et al., 2012).

To sum up, the efficacy of low-frequency stimulation protocols over the LTP remains controversial up to date. Earlier studies have produced somewhat encouraging results paving the way towards extensive testing of low-frequency paradigms which however, failed to consistently report improvement in AH. This incongruence in findings could be partly attributed to the high heterogeneity characterizing the rTMS protocols. Indeed, different TMS paradigms varied greatly in terms of motor threshold, nature of sham stimulation, treatment duration and number of stimuli. Therefore, although these results suggest that LF-rTMS protocols that target the LTP might be beneficial in this context, larger studies, with definitive rTMS approaches are needed in order for safe conclusions to be drawn.

Alternative stimulation paradigms

Given the inconsistent findings generated by the administration of low-frequency stimulation §protocols over the LTP, Kimura et al. (2016) aimed to investigate whether a high-frequency stimulation protocol over the same region would prove more beneficial in the treatment of AH. Hence, an RCT with a parallel design was conducted, where 30 patients with schizophrenia and medication-resistant AH, were randomly allocated to receive either sham or real HF-rTMS (20 Hz, 80% RMT) twice a day for 2 successive days (day 1 and day 2). Assessment was conducted with the AHRS and scores were obtained at baseline, and at days 3, 10, 17 and 31. No significant alterations were observed in any of the aforementioned evaluations for neither group (Kimura et al., 2016).

In a different stimulation paradigm, Koops et al., (2016) administered continuous theta-burst stimulation (cTBS), which is known to induce inhibitory effects, over the LTP to explore its efficacy in the alleviation of AH (Koops et al., 2016). More specifically, 64 patients diagnosed with schizophrenia, schizoaffective disorder, schizophreniform disorder, or psychosis NOS were treated with 10 sessions (twice a day for 5 successive days) of sham or real cTBS (60 seconds stimulation train with a 3-pulse burst at 50 Hz repeated every 200ms) at 80% MT. At the end of the trial, both groups demonstrated significantly reduced AHRS scores compared to baseline and no significant main effect for the treatment group was observed (Koops et al., 2016).

To our knowledge, these are the only sham-controlled stimulation protocols, other than LF-rTMS, that have been applied over the LTP. Albeit the above protocols failed to demonstrate an amelioration in AH, no safe conclusions can be reached given the paucity of relevant studies.

RTMS over the RTP

As mentioned, in the section RTMS over the LTP, Lee et al. (2005) in the sham-controlled trial also included a group who received LF-rTMS over the RTP. Albeit, AHRS scores failed to reveal any significant differences between the 3 groups, the right stimulation was found more improved in the sub-item of attentional salience compared to sham, demonstrating a trend towards significance (Lee et al., 2005).

When 14 patients were randomized to receive active (1 Hz, 100% MT) or sham stimulation over the LTP or RTP in a double-blind, crossover RCT, no significant beneficial effect in AH was obtained from neither of the aforementioned conditions (Jandl et al., 2006). In similar vein, Saba et al. (2006) also failed to detect a significant improvement in PANSS-P3 following 10 sessions of LF-rTMS (1 Hz, 80% MT) over the LTP, RTP or sham of 16 patients with paranoid schizophrenia (Saba et al., 2006). In a crossover RCT, 24 patients received sham or active LF-rTMS (1 Hz, 90% MT) over the LTP or RTP and reported significant improvement in all groups (van Lutterveld et al., 2012).

Collectively, these 4 studies do not support the use of stimulation over the RTP for AH improvement; however, reports are still fairly limited to reach a strong conclusion.

RTMS over the Bilateral TP

Kim et al., (2014) enrolled 24 patients diagnosed with schizophrenia or schizoaffective disorder and persistent AH, in a crossover RCT. Patients were randomly assigned to one of the following treatment groups: (i) LF-rTMS (1 Hz, 100% MT) over the bilateral TP, twice a day (once for each side, 3 hours apart) for 5 days, (ii) HF-rTMS (20 Hz, 100% MT) over the bilateral TP, twice a day for 3 days and (iii) HF-rTMS (20 Hz, 100% MT) to Broca’s area and its right homologue twice a day for 3 days. Assessment was performed at baseline, 24 hours after the stimulation on Day 1 and Day 3 or 5 (for LF-rTMS) using the AHRS and HCS. All groups demonstrated a significant decrease over time in both scales; however, no superior effect of any of the active TMS paradigms was found superior to sham (Kim et al., 2014). As previously mentioned, Bais et al. (2014) enrolled 51 patients with a primary diagnosis of schizophrenia and randomly allocated them to receive LF-rTMS (1 Hz, 90% RMT) over the LTP, LF-rTMS over the bilateral TP or sham stimulation over the LTP. For bilateral TP, stimulation was performed over the LTP for 10 minutes and then was shifted to the RTP for 10 additional minutes. Based on the AHRS and PANSS adapted for hallucinations scores, bilateral stimulation was not superior to either the LTP or sham (Bais et al., 2014). Encouraging results were generated in a more recent parallel RCT, where cTBS was employed. In this study, 59 patients with schizophrenia were randomly assigned in a real or sham stimulation group. In total, 20 sessions of cTBS were applied over the bilateral temporoparietal cortex (twice a day, once for each hemisphere, 5 days a week for 2 weeks). Active stimulation led to a significant amelioration in all scales used to assess the severity of AH, namely PSYRATS-AH, AHRS and positive symptoms of PANSS (Tyagi et al., 2022).

To our knowledge, only the aforementioned studies have explored the efficacy of stimulation over the bilateral temporoparietal cortex in a randomized, sham-controlled manner. Negative results were obtained from studies incorporating LF- or HF-rTMS paradigms; however, cTBS seems to be more promising in this context.

Other Areas/Protocols

One of the protocols explored in the randomized, sham-controlled study by Kim et al. (2014) (RTMS over the Bilateral TP) included the delivery of HF-rTMS (20 Hz, 100% MT) over Broca's area and its right homologue (located at the crossing between T3-Fz and F7-Cz for the left hemisphere and crossing between T4-Fz and F8-Cz for the right) twice a day for 3 days. With regards to AH, no significant improvement was reported between active stimulation and sham (Kim et al., 2014).

In an earlier study, researchers sought to investigate whether the application of LF-rTMS over individually-determined, fMRI-guided regions would be more efficacious in the alleviation of AH compared to sham. In this crossover study, 11 patients with paranoid schizophrenia and medication-resistant AH received active stimulation (1 Hz, 90% MT) above the left superior temporal gyrus (STG) (BA 22, 41/42) corresponding to the left primary auditory cortex, the Broca's area (BA 44/45) and control stimulation over the parieto-occipital region, in a randomized order. Each stimulation protocol was performed once a day for 5 consecutive days, with a 2-days wash out period. In 4 out of 11 patients, regions of interest were fMRI-guided, whereas in the remaining 7 structural MRI in conjunction with a neuronavigation system was used. Assessment of hallucination severity was conducted twice a day using items from the Haddock self-rating scale. Disappointingly, no significant differences were reported between the three stimulation conditions. Only a trend for improvement was exhibited in 4 patients of the left STG; interestingly, these were the same patients who underwent fMRI for target localization (Schönfeldt-Lecuona et al., 2004).

In an interesting, crossover study conducted by Hoffman et al. (2007) 16 patients with schizophrenia or schizoaffective disorder and intermittent or continuous hallucinations were enrolled and received sham and/or active LF-rTMS (1 Hz, 90% MT) in a randomized order. The first 5 patients received a 3-day block of sessions of stimulation over each one of the 3 identified most prominent cortical sites (activation maps were generated for intermittent hallucinators and Wernicke's referenced correlation maps for continuous hallucinators, based on fMRI data) and a sham stimulation condition. Clinical assessment of AH was conducted using an individualized HCS at baseline and after each 3-day block. For the remaining patients (n=11), the protocol was modified in order for up to 6 sites (and a sham site) to be stimulated; at first, two days of real stimulation were performed over one of the six most prominent cortical sites or over the sham site and HCS was assessed. If HCS revealed an at least 10% reduction, two more sessions were performed over the same area (active or sham); if not, stimulation was carried on over the next site. This process was repeated until either 24 sessions of active stimulation were delivered or the six most prominent cortical sites received active stimulation. Based on the HCS assessment, the only region that demonstrated a significantly greater improvement in AH over sham was the LTP. Improvement was also observed in 3 out of 5 patients that received stimulation over the right or left primary auditory cortex. However, negative results were obtained following stimulation of more anterior sites in STG or of sites anterior to Wernicke's area. With regards to stimulation over Broca's area, results were in accordance with the previous reports, as no consistent improvement was observed (Hoffman et al., 2007). In a larger RCT 51 patients with a primary diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder or psychosis NOS were randomly assigned to one of the three treatment arms: (i) real stimulation (1 Hz, 90% MT) over the LTP, (ii) real stimulation (same parameters) fMRI-guided over the site with the maximal activation during an AH or, (iii) sham stimulation for 15 consecutive weekdays. When results were limited to the subset of patients afflicted by schizophrenia, no significant improvement was reported between active (fMRI-guided and not) and sham stimulation (no other data were reported separately) (Slotema et al., 2011).

FMRI findings have associated AH with increased activity in Wernicke's area as well as its right homologous regions. In an RCT conducted by Hoffman et al. (2013), 83 patients with schizophrenia or schizoaffective disorder were assigned to a real (1 Hz, 90% MT) or sham intervention group, with a 2:1 ratio. Patients received 3 blocks of 5-sessions with initial stimulation sites either Wernicke's area or its right homologous region located via structural MRI (1:1 ratio). Stimulation was then shifted to the next site for the 2nd 5-session block. And lastly, a 3rd 5-session block was performed to the site which generated the greater results according to the HCS (in case of no difference, Wernicke's area was chosen as the site of the 3rd block stimulation). Assessment was conducted at baseline and after each 5-session block with the HCS and AHRS. Following the 1st block of stimulation, when analyses were performed for the whose MT could consistently be detected, two interesting findings were observed; patients with low-salience AH were significantly more improved when stimulation was performed over the Wernicke's area whereas, patients with high-salience AH were significantly more improved when stimulation was performed over the right homologous region, relative to sham. Following 15 sessions of rTMS, the only variable significantly improved in active compared to sham stimulation was frequency. When the analysis was limited to patients whose MT could be consistently detected, HCS of the active group was also found significantly reduced compared to sham (Hoffman *et al.*, 2013).

In a study conducted by Paillère-Martinot et al. (2017), 27 patients with schizophrenia or schizoaffective disorder and medication-resistant AH were randomly assigned to receive 10 sessions of active (1 Hz, 100% MT) or sham rTMS over a language perception area, identified by fMRI during a language recognition task. In 14 patients the language perception area was located at the superior temporal gyrus (STG), whereas in the remaining 13 the middle temporal gyrus was identified. AH severity was assessed using the hallucination subscale of the Scale for the Assessment for Positive Symptoms (SAPS) and AHRS. With regards to the stimulation condition, no significant differences were reported between the two however, when patients experiencing external AH were compared to those experiencing internal AH improvement in the 1st was significantly greater compared to the last, regardless of stimulation condition (Paillère-Martinot et al., 2017).

In a more recent study, Dollfus et al. (2018) enrolled 74 patients with schizophrenia or schizoaffective disorder of whom 59 completed the trial and randomly assigned them to receive 4 sessions (twice a day for 2 days) of either active (20 Hz, 80% RMT) or sham rTMS over the site that demonstrated the maximal activation during a language task as indicated by fMRI. In all cases, the area of interest was located at the crossing between the projection of the ascending branch of the left lateral sulcus and the left superior temporal sulcus. AH were evaluated using the AHRS at baseline, following the 2nd stimulation session and then at days 7, 14, 21 and 30. Primary outcome of the study was the percentage of patients demonstrating a greater than 30% reduction in AHRS scores, obtained from two consecutive assessments. Disappointingly, the primary outcome did not differ significantly between the 2 groups. However, the percentage of patients demonstrating a >30% AHRS decrease was found to be significantly different in active compared to sham at days 1 and 14 (Dollfus et al., 2018).

Blumberger et al. (2012), aimed to explore whether the incorporation of priming in a low-stimulation paradigm would optimize the efficacy in alleviating AH in patients with schizophrenia or schizoaffective disorder. Fifty-one patients with refractory AH were randomly allocated to receive 20 sessions of real or sham rTMS over the Heschl's gyrus, which has demonstrated increased activation during AH (Dierks et al., 1999; van de Ven et al., 2005). Patients in the active stimulation groups received LF-rTMS either with or without priming. In patients assigned to the priming group 10 minutes of 6 Hz (90% RMT) preceded the administration of 10 minutes of 1 Hz (115% RMT). No-priming group received 20 minutes of LF-rTMS (1 Hz, 115% RMT). The severity of AH was evaluated using the PSYRATS-AH, AHRS and HCS at baseline, weekly and one month after treatment cessation. No significant differences were found between the three stimulation conditions (Blumberger et al., 2012).

The number of studies exploring rTMS over more specific sites and especially via the use of neuroimaging techniques is still fairly limited and scarce findings are reported with regards to each region individually.

DISCUSSION

A systematic search and analysis were conducted summarizing the currently available data on the efficacy of sham-controlled studies employing rTMS, deep TMS and cTBS in alleviating AH in patients with schizophrenia or schizophrenia spectrum disorders. The initial search in the PubMed database yielded 196 results, 27 of which were included in this analysis. One study identified from a different source was also included. The majority of studies investigating the efficacy of rTMS in the treatment of AH have employed LF-rTMS paradigms. LF-rTMS (=< 1 Hz) is believed to induce inhibitory effects in the stimulated area by exerting LTD-like alterations in the underlying neurons. Considering that AH have been associated with increased activity and deficits in inhibitory circuits, it seems plausible that LF-rTMS could prove beneficial in this context. Early evidence postulated that the left temporoparietal cortex is a potential culprit in the pathophysiology of AH given its hyperactivation in patients with schizophrenia experiencing AH (Shergill et al., 2000; Silbersweig et al., 1995). Those findings prompted early researchers to perform low-frequency stimulation paradigms over this area. To date, numerous studies have examined the efficacy of rTMS over the LTP primarily via the use of low-frequency rTMS protocols, with only two studies investigating HF-rTMS and cTBS in this context, yielding diverse results. Among the included studies that targeted the LTP (RTMS over the LTP), only 7 studies reported a positive outcome compared to sham. This inconsistency in reports is of no surprise, given the considerable heterogeneity between the studies in TMS parameters (intensity, treatment duration, number of stimuli).

Moreover, in the vast majority of studies, LTP was determined as the region halfway between T3 and P3, according to the International 10-20 EEG coordinates (Klem et al., 1999). Although cost-effective, this standardized targeting method has been associated with an inter-individual variability (Koessler et al., 2009; Scrivener and Reader, 2022) which could lead to inaccurate site determination; taking into account earlier evidence demonstrating a proportional association between TMS' effects and the stimulation-to-target distance (Cohen et al., 1990; Fadini et al., 2009) it is of great importance to use personalized targeting methods, such as brain imaging techniques, in order to optimize rTMS' efficacy.

Moving on, the RTP has also been incriminated in the manifestation of AH; indeed, an earlier study observed an activation during AH which was more predominant over the right hemisphere. Thus, 4 studies chose the RTP as the target of stimulation, whereas 3 studies applied stimulation over both LTP and RTP, bilaterally. Out of 4 studies exploring the former, all included low-frequency (1 Hz) stimulation paradigms but only one reported a mild positive outcome. In bilateral TP, two studies used LF-rTMS generating negative results whilst one reported a significant improvement following active cTBS, suggesting it might be of higher therapeutic value.

AH have been associated with speech perception and language processing areas (Shergill et al., 2000; Silbersweig et al., 1995), therefore some studies have also evaluated the delivery of stimulation over speech-related areas, either fMRI-guided or not. Two studies have applied LF-rTMS over Broca's area (one of which fMRI-guided) and one more study has delivered HF-rTMS over Broca's area and its right homologous region (bilateral Broca's), none of which demonstrated improvement in AH severity. When Wernicke's and right homologous region were stimulated successively in three alternating 5-sessions blocks, only hallucination frequency was found significantly reduced. Additionally, the stimulation of Heschl's gyrus either with or without priming also failed to generate positive results.

Lastly, two studies have employed fMRI-guided paradigms for the delivery of LF-rTMS over the sites exhibiting maximal AH-related activity, one of which demonstrated a significant improvement when stimulation was applied over the LTP.

In conclusion, rTMS has demonstrated a potential clinical utility in AH for patients with schizophrenia or schizophrenia spectrum disorders; however, given an important amount of studies reporting otherwise no strong conclusions can be yet drawn. In order to further elucidate this, more sham-controlled, ideally multi-center RCTs should be designed with more definitive rTMS approaches for the optimized stimulation paradigms to be detected.

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APPENDIX

Table 1: Characteristics of studies investigating rTMS over the LTP

Authors, Year	**Study Design**	**Diagnosis**	**No. of Patients**	**TMS Protocol**	**Target**	**No. of sessions**	**Sham**	**Time of Assessments**	**AH Assessment**	**AH outcome**	**Risk of bias**
(Hoffman *et al.*, 1999)	Cross-over	SCH, SAD	3	1 Hz, 80% of MT	T3P3	4	Coil tilted 45°	Baseline and each morning after each TMS session	Individualized RS	Greater reduction following active stimulation	High

(Hoffman *et al.*, 2000)	Cross-over	SCH, SAD	12	1 Hz, 80% of MT	T3P3	4	Coil tilted 45°	Baseline and the morning after each TMS session and undefined follow up after trials, last follow up 2 months after last rTMS session	Individualized RS	Significant reduction after active compared to sham stimulation p<0.006)	High
(McIntosh *et al.*, 2004)	Cross-over	SCH, SAD, SCP	16	1 Hz, 80% MT	T3P3	4	Coil tilted 45°	At baseline and at the end of weeks 1 and 2	PANSS-P3 and a 10-point Likert scale to measure the intensity of AH	No significant difference between real and sham groups	Some concerns
(Chibbaro *et al.*, 2005)	Parallel	SCH	16	1 Hz, 90% RMT	T3P3	4	Coil tilted 45◦	At baseline, after the 4th session and the 1st, 2nd, 3rd and 4th, 6th, 8th week after rTMS	A composite scale that assesses the severity of AH	Significant improvement in both real (p=0.001) and sham (p=0.01) groups, with the real group reporting a significantly better change when compared to sham group from the 1st week follow-up (p=0.03) to the 8th (p=0.0000)	Some concerns
(Fitzgerald *et al.*, 2005)	Parallel	SCH, SAD	32	1 Hz, 90% RMT	T3P3	10	Coil tilted 45°	At baseline, after 5 and 10 treatment sessions and after 10 active treatment sessions if they initially received sham stimulation	HCS, PSYRATS-AH, PANSS-P3	No significant improvement in either group except for the variable of the PSYRATS hallucination subscale "loudness of voices" (Significance at a level between 0.01 and 0.05)	Some concerns

(Hoffman *et al.*, 2005)	Parallel	SCH, SAD	50	1 Hz, 90% MT	T3P3	9	Coil tilted 45°	At baseline and 24 hours following Day 3, 6 and 9	HCS, AHRS	HCS: Significantly lower for the active group compared to sham at Day 6 (p=0.015) and at Day 9 (p=0.01). AHRS: The only variable significantly improved was frequency (p<0.0001) solely in the active group	Some concerns
(Lee *et al.*, 2005)	Parallel	SCH	39	1 Hz, 100% RMT	T3P3	10	Coil tilted 90º	At baseline, on Day 5 and on Day 10	AHRS	No significant difference of active compared to sham	Some concerns
(Poulet *et al.*, 2005)	Cross-over	SCH	10	1 Hz, 90% MT	T3P3	10	Sham coil	At baseline, daily during the trial and 30, 60, and 90 days after the end of the trial.	AHRS	Significant improvement of active group compared to sham; In 5 out of 7 responders scores remained improved for at least 2 months	Some concerns
(Brunelin *et al.*, 2006)	Parallel	SCH	24	1 Hz, 90% MT	T3P3	10	Sham coil	At baseline and after rTMS sessions	AHRS	Significantly reduced AHRS score in active compared to sham	Some concerns
(Jandl *et al.*, 2006)	Cross-over	SCH, SAD	14	1 Hz, 100% MT	T3P3	5	Coil tilted 45º	At baseline and after each stimulation and after 1, 2 and 4 weeks after treatment cessation	PSYRATS-AH	No significant difference in the mean sum score; five responders in the left stimulation group, none in sham	High
(Saba *et al.*, 2006)	Parallel	SCH	16	1 HZ, 80% MT	T3P3	10	Sham coil	At baseline and after the last TMS treatment session	PANSS-P3	No significant main effect for treatment group.	High

(de Jesus *et al.*, 2011)	Parallel	SCH	17	1 Hz, 90% MT	T3P3	20	Coil tilted 45º	At baseline, at day 7, 14, 21, 28 and day 60	AHRS	No significant improvement of active compared to sham	High
(Rosenberg *et al.*, 2012)	Parallel	SCH	10	1 Hz, 110% MT	4.5 cm posteriorly of the left motor cortex and 6.5 cm laterally towards the left shoulder of the patient	10	Sham coil	At baseline and within 24 hours after the last session	AHRS	No significant differences between real and sham groups	High
(van Lutterveld *et al.*, 2012)	Cross-over	PNOS, SCH, SAD	24	1 Hz, 90% MT	T3P3	1	Centro-occipital cortex	Before and after each session	HCS, AHRS	Significant improvement in all scales in all of the 3 groups. Significantly greater improvement in HCS in the sham group compared to the left group	Some concerns
(Bais *et al.*, 2014)	Parallel	SCH	47	1 Hz, 90% RMT	T3P3	12	Sham coil	At baseline, immediately after treatment, 4 weeks and 3 months after treatment cessation	AHRS, PANAS for hallucinations	No significant main effect for the treatment group.	Some concerns
(Kim *et al.*, 2014)	Cross-over	SCH or SAD	23	1 Hz, 100% MT or 20 Hz, 100% MT	T3P3	6 or 10	Coil tilted 45º	At baseline, 24 hours after the stimulation on Day 1 and Day 3 or 5 (only for LF)		Active stimulation was not significantly greater than sham	Some concerns
(Kimura *et al.*, 2016)	Parallel	SCH	30	20 Hz, 80% RMT	T3P3	4	Sham coil	At baseline, at Day 3, Day 10, Day 17 and Day 31 (Day 1 was defined as the day of the first stimulation session)	AHRS	No significant difference in active versus sham group	Some concerns
(Koops *et al.*, 2016)	Parallel	SCH, SAD, PNOS, SCP	64	cTBS (50 Hz, 80% MT	T3P3	10	Sham coil	At baseline, at the end of the treatment and one month after the last treatment	AHRS, PSYRATS-AH	Significantly reduced PSYRATS-AH (p=0.002) and AHRS (p<0.001) in	High

										both (real and sham) groups. No significant main effect for the treatment group	
(Aubonnet *et al.*, 2020)	Parallel	SCH	10	1 Hz, 100% RMT	T3P3	10	Vertex	At baseline and one week after completing the 10 sessions	PSYRATS-AH	No significant differences between the 2 groups	High
(Gornerova *et al.*, 2023)	Parallel	SCH	19	0.9 Hz, 100% MT	T3P3	10	Coil tilted 90°	At baseline and after the 1st and 2nd week of stimulation	AHRS	Significant improvement of active compared to sham (p=0.014)	Some concerns

SCH: Schizophrenia, SAD: Schizoaffective disorder, SCP: Schizophreniform, BD: Bipolar disorder, PNOS: Psychosis not otherwise specified
T3P3: midway between T3 and P3, according to the International 10-20 EEG coordinates
RS: Rating Scale, PANSS-P3: Hallucination Item of the Positive and Negative Syndrome Scale, HCS: Hallucination Change Scale, PSYRATS-AH: Auditory Hallucinations of The Psychotic Symptom Rating Scale, AHRS: Auditory Hallucinations Rating Scale, PANAS: Positive and Negative Affect Scale

Table 2: Characteristics of studies investigating rTMS over the RTP

Authors, Year	**Study Design**	**Diagnosis**	**No. of Patients**	**TMS Protocol**	**Target**	**No. of sessions**	**Sham**	**Time of Assessments**	**AH Assessment**	**AH outcome**	**Risk of bias**
(Lee *et al.*, 2005)	Parallel	SCH	39	1 Hz, 100% RMT	T4P4	10	Coil tilted 90°	At baseline, on Day 5 and on Day 10	AHRS	No significant differences between the three groups	Some concerns
(Jandl *et al.*, 2006)	Cross-over	SCH, SAD	14	1 Hz, 100% MT	T4P4	5	Coil tilted 45°	At baseline and after each stimulation and after 1, 2 and 4 weeks after treatment cessation	PSYRATS-AH	Significant difference (p=0.018) in feature "response to treatment"	High
(Saba *et al.*, 2006)	Parallel	SCH	16	1 HZ, 80% MT	T4P4	10	Sham coil	At baseline and after the last TMS treatment session	PANSS-P3	No significant difference between groups	High
(van Lutterveld *et al.*, 2012)	Cross-over	PNOS, SCH, SAD	24	1 Hz, 90% MT	T4P4	1	Centro-occipital cortex	Before and after each session	HCS, AHRS	Significantly greater improvement in HCS in sham group compared to left group	Some concerns

SCH: Schizophrenia, SAD: Schizoaffective disorder, PNOS: Psychosis not otherwise specified
T4P4: midway between T4 and P4, according to the International 10-20 EEG coordinates
AHRS: Auditory Hallucinations Rating Scale, PSYRATS-AH: Auditory Hallucinations of The Psychotic Symptom Rating Scale, PANSS-P3: Hallucination Item of the Positive and Negative Syndrome Scale, HCS: Hallucination Change Scale

Table 3: Characteristics of studies investigating rTMS over the Bilateral TP

Authors, Year	Study Design	Diagnosis	No. of Patients	TMS Protocol	Target	No. of sessions	Sham	Time of Assessments	AH Assessment	AH outcome	Risk of bias
(Bais *et al.*, 2014)	Parallel	SCH	47	1 Hz, 90% RMT	T3P3 and T4P4	12	Sham coil	At baseline, immediately after treatment, 4 weeks and 3 months after treatment cessation	AHRS, PANAS for hallucinations	No significant difference between groups	Some concerns
(Kim *et al.*, 2014)	Cross-over	SCH or SAD	23	1 Hz, 100% MT or 20 Hz, 100% MT	T3P3 and T4P4	6 or 10	Coil angled 45º	Prior to initiation, 24 hours after the stimulation on Day 1 and Day 3 or 5 (only for LF)	AHRS, HCS	No significant difference between groups	Some concerns
(Tyagi *et al.*, 2022)	Parallel	SCH	59	cTBS (50 Hz, 80% RMT)	T3P3 and T4P4	20	Sham coil	At baseline, at the end of the treatment and 2 weeks after the last treatment	AHRS, PSYRATS-AH, PANSS-PS	Significant group*time interaction (p<0.001) in both scales	High

SCH: Schizophrenia, SAD: Schizoaffective disorder
T3P3: midway between T3 and P3, according to the International 10-20 EEG coordinates, T4P4: midway between T4 and P4, according to the International 10-20 EEG coordinates
AHRS: Auditory Hallucinations Rating Scale, PANAS: Positive and negative Affect Scale, PSYRATS-AH: Auditory Hallucinations of The Psychotic Symptom Rating Scale, PANSS-PS: Positive Symptoms of Positive and Negative Syndrome Scale

Table 4: Characteristics of studies investigating alternative areas and protocols

Authors, Year	Study Design	Diagnosis	No. of Patients	TMS Protocol	Target	No. of sessions	Sham	Time of Assessments	AH Assessment	AH outcome	Risk of bias
(Schönfeldt-Lecuona *et al.*, 2004)	Cross-over	SCH	11	1 Hz, 90% MT	Broca's area, left STG (fMRI or structural MRI)	5	Midline parieto-occipital region	Twice per day	Haddock self-rating scale	No significant improvement of active stimulation compared to sham	High
(Hoffman *et al.*, 2007)	Cross-over	SCH, SAD	16	1 Hz, 90% MT	Most prominent sites (fMRI)	Ranging from 12 to 24	Coil tilted 45º	At baseline and after each 3-day block	HCS	Significantly greater improvement of LTP versus sham (p=0.009) and anterior temporal regions (p=0.028)	High

(Slotema *et al.*, 2011)	Parallel	SCH, SAD, BD, Psychosis NOS	51	1 Hz, 90% MT	T3P3 or site of maximal hallucinatory activity during an AH (fMRI)	15	Coil angled 90°	At baseline, at the end of the first, second, and last week as well as 3 months after the end of the rTMS trial	AHRS	Analyses limited to SCH: Active (i.e fMRI-guided and not) not superior to sham	High
(Blumberger *et al.*, 2012)	Parallel	SCH, SAD	51	Priming: 6 Hz, 90% RMT and 1 Hz, 115% RMT No Priming: 1 Hz 115% RMT	Heschl's gyrus (structural MRI)	20	Coil angled 90º	At baseline, weekly and one month after treatment cessation	PSYRATS-AH, AHRS, HCS	No significant improvement	High
(Hoffman *et al.*, 2013)	Cross-over	SCH, SAD	83	1 Hz, 90% MT	Wernicke's area, right homologous (structural MRI)	15	Coil angled 45º	At baseline and after each 5-session block	HCS, AHRS	Only hallucination frequency significantly improved in active versus sham following 15 sessions	High
(Kim *et al.*, 2014)	Cross-over	SCH or SAD	23	20 Hz, 100% MT	Broca's area and right homologous (crossing between T3-Fz and F7-Cz for the left hemisphere and crossing between T4-Fz and F8-Cz for the right)	6	Coil angled 45º	Prior to initiation, 24 hours after the stimulation on Day 1 and Day 3 or 5 (only for LF)	AHRS, HCS	Active stimulation was not significantly greater than sham	Some concerns
(Paillère-Martinot *et al.*, 2017)	Parallel	SCH, SAD	27	1 Hz, 100% MT	Language perception area (fMRI)	10	Sham coil	At baseline and on the last TMS treatment day	Hallucination Subscale of SAPS, AHRS, PSYRATS to assess specific AVH characteristics	No significant difference between groups	Low

(Dollfus *et al.*, 2018)	Parallel	SCH, SAD	59	20 Hz, 80% RMT	Area of maximal language task-evoked activation (fMRI)	4	Sham coils	At baseline, after day 1 of rTMS, after day 2 of rTMS and at days 7, 14, 21 and 30	AHRS	No significant difference in the percentage of responders between active and sham groups except for Day 14 (p=0.016)	High

SCH: Schizophrenia, SAD: Schizoaffective disorder, BD: Bipolar disorder, PNOS: Psychosis not otherwise specified
T3P3: midway between T3 and P3, according to the International 10-20 EEG coordinates
HCS: Hallucination Change Scale, AHRS: Auditory Hallucinations Rating Scale, PSYRATS-AH: Auditory Hallucinations of The Psychotic Symptom Rating Scale, SAPS: Scale for the Assessment for Positive Symptoms