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DOES TMS INFLUENCE VERBAL FUNCTION AND TREAT THE LANGUAGE DECLINE IN SCHIZOPHRENIA? FINDING ANSWERS VIA SYSTEMATIC REVIEW OF CURRENT RESEARCH

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SUMMARY

Background: *rTMS is an adequately safe intervention that is approved for treatment of various neuropsychiatric conditions. There is ongoing research on the application of rTMS for the treatment of resistant auditory verbal hallucinations (AVH) in schizophrenia (SZ), and also for alleviating negative and cognitive symptoms in patients with chronic SZ states. Language decline, as a part of thought, language and communication disorders, is one of the key symptoms of SZ, having a significant bearing on decreased social/interpersonal functioning of these patients. In this regard rTMS may be a promising treatment approach, while serving as an important research tool in the field of SZ studies. The aim of our present study was to compile and evaluate the existing data on whether rTMS affects verbal function in SZ patients, and if rTMS has any efficacy for the treatment of language disturbances in SZ spectrum disorders.*

Subjects and methods: *Our systematic search over the PubMed database revealed a total of 200 articles, of which 21 met criteria for inclusion in this analysis. We have reviewed in detail the study designs, inclusion and exclusion criteria, rTMS protocols and cognitive (in particular, speech/language domain) assessments reported in these articles.*

Results: *The 21 studies focused on two key topic clusters: (i) low-frequency rTMS treatment of AVH in SZ, and (ii) high-frequency rTMS treatment of negative and cognitive SZ symptoms. The majority of study participants presented with chronic and treatment-resistant states. Most of the low-frequency rTMS studies did not show any difference in verbal test measures in SZ in response to treatment. Less than a half of high-frequency rTMS studies reported a delayed positive effect on language cognitive domains in SZ. There were sporadic reports on dropouts associated with a decline in scores for auditory verbal learning tests.*

Conclusions: *Our systematic review found rTMS to be generally safe in relation to verbal/speech function, and suggested that verbal memory tests could serve as a measure of safety of this treatment procedure in SZ patients. Speech effects of rTMS have only been registered over long-term observation periods, such that time-frame which should be considered as an important factor for future studies. In our project "Innovative Neuropsychiatry Research Bank: Priority-2030" we plan to clarify (i) efficient rTMS protocols targeting neurocognitive improvement in SZ, and (ii) the cohort of SZ patients with a particular cognitive endophenotype and language profile amenable to treatment with rTMS, with a focus on language scores.*

Key words: *auditory verbal hallucinations - cognitive assessment - cognitive endophenotype - language disturbances - rTMS - schizophrenia - speech function - verbal fluency - verbal memory*

Abbreviations: *AVH - auditory verbal hallucinations; DLPFC – dorsolateral prefrontal cortex; RBANS - Repeatable* Battery *for the Assessment of Neuropsychological Status; rTMS - repetitive transcranial magnetic stimulation; SZ – schizophrenia; VLT / HVLT – verbal learning test / Hopkins verbal learning test*

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INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation method based on the principle of electromagnetic induction, which provokes altered neuronal activity of the targeted cortical brain regions (Tik et al. 2017). On the basis of the existing evidence, rTMS has been approved by the FDA for various neuropsychiatric conditions, such as a treatment resistant depression, obsessive-compulsive disorder, migraines with aura, as well as for smoking cessation, and other conditions (Cohen et al. 2022, Lefaucheur et al. 2020). The rTMS method has a notably good safety profile, with rapidly resolving minor effects such as headaches and local scalp pain at the stimulation site (Rossi et al. 2009). Serious adverse reactions are extremely rare (Lerner et al. 2019).

Schizophrenia (SZ) represents an important indication for rTMS use as second-line treatment, especially in cases of non-response to psychopharmacotherapy with antipsychotic medication. According to clinical guidelines, rTMS is effective at the 1a, 1b, and 2b levels of evidence (the Oxford Centre for Evidence-Based Medicine) for SZ treatment in relation to reduction of auditory verbal hallucinations (AVH), decrease in hypofrontality, and improvement of positive and negative symptoms (Lefaucheur et al. 2020). Of particular interest is the recognized capacity of rTMS to cause bidirectional physiological effects depending on the particular stimulation frequency (Brandt et al. 2021). Thus, low-frequency (e.g., 1 Hz) stimulation leads to reduced brain activation, which may be important in the context of treating positive symptoms of SZ (Boroojerdi

et al. 2000). Indeed, recent neurobiological findings suggest an association between AVH and abnormal hyperactivity in brain regions responsible for auditory perception and speech production (Chen et al. 2020). These areas, namely the left and right superior temporal cortex, left temporoparietal cortex, and Broca's area (Xie et al. 2021) may present specific targets for reducing the severity of AVH in SZ. Conversely, high-frequency rTMS (10-20 Hz) increases cortical excitability (Hasan et al. 2016), which might ameliorate aspects of impaired brain function. Current thinking suggests that downregulation of activity in the dorsolateral prefrontal cortex (DLPFC) has a link with cognitive (Barch & Ceaser 2012) and negative (Martino et al. 2007) SZ symptoms. The thought, language, and communication disorders of SZ are described within the primary negative and disorganization symptom cluster, which likely lead to secondary disturbances such as AVH, and which are related to the tendency for progressive worsening in social functioning over the course of the disorder (Andreasen 1979). Moreover, the core positive symptoms underlying the conspicuous manifestations of SZ also entail disruption of the language-mediated networks of meaning: (i) AVH (a disorder of speech perception), (ii) formal thought disorder (abnormal speech production running without feedback control), and (iii) delusions (the production of abnormal linguistic content) (Hinzen & Rosello 2015). In our opinion, language decline within the cognitive endophenotype of SZ spectrum disorders, such as indices of verbal fluency deficit, may serve as a dynamic marker of severity of the disorder. Language decline may also constitute a prognostic marker of the course of symptoms and interpersonal functioning, an index of the compensatory resources available for social adjustment, and an indicator of the efficacy of a treatment approach (Andreasen & Grove 1986, Smirnova et al. 2015, 2017, 2020).

In this review, we have focused on the literature reporting how different rTMS protocols affect verbal function of SZ patients, and potentially improve existing language disturbances as evaluated via verbal assessments. All of the brain regions noted above are variously implicated in speech and language functions (Hertrich et al. 2021, Xie et al. 2021). As such, one may reasonably expect that rTMS of these regions might rectify these disturbances. Tests of verbal fluency and verbal learning are easy and quick to perform, while presenting valid and sensitive objective indicators (Kreutzer et al. 2011, Larrabee 2000). There are many approaches for administering verbal tests in the present context. First, they can be used as a measure of safety in relation to cognitive function. Second, test results would help to distinguish the group of responsive patients who might significantly benefit from a rTMS procedure. Third, it would be useful for fundamental research and for the design of clinical trials to derive precise data on how language-related regions react to different types of rTMS stimulation. The aim of the current systematic review was to summarize and analyze the existing data on verbal test performance in the context of rTMS in SZ, with an emphasis on reports showing any significant effects on verbal function or language disturbances.

SUBJECTS AND METHODS

This systematic review was managed using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines and search strategy (Figure 1). The PICOS was formulated as: P – patients with schizophrenia spectrum psychotic disorders (schizophrenia and schizoaffective disorder), I – rTMS treatment, C – sham controls, O – changes in verbal aspects of cognitive functioning, S - all types of original research. The search in PubMed was conducted for the period from January 1st' 2000 till April 30th' 2022, and primarily involved the titles and abstracts of articles. The keyword list included "schizophrenia", "verbal/ language", "cognition" and "rTMS" and their alternatives in all possible combinations (see algorithm at the footnote of Figure 1).

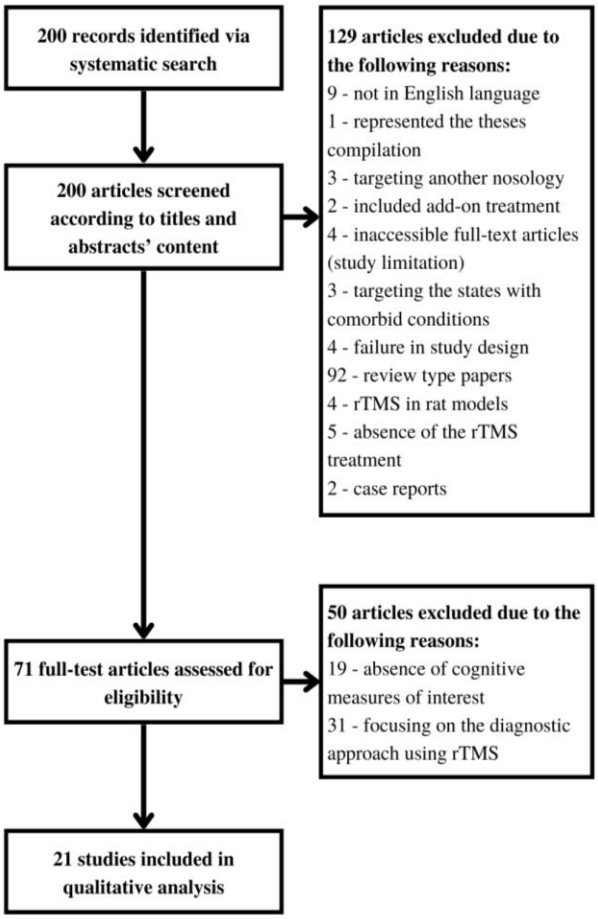

Figure 1. PRISMA flow diagram on the literature search algorithm of studies related to the rTMS effects on verbal function in schizophrenia

Table 1. Summary of rTMS protocols parameters and verbal tests applied in the studies of rTMS use in schizophrenia: low-frequency rTMS approach

References	Study design	N	Course duration	rTMS Protocol	Stimulation site	Verbal tests	Findings
d'Alfonso et al. 2002	Open-label non-controlled study	9	2 weeks (5 days per week; in total, 10 days)	1 Hz, 80 % MT, 20 min.	Left superior temporal gyrus	1. Rey Auditory-Verbal Learning Test (verbal memory) 2. Token Test, short form (verbal comprehension) 3. Verbal fluency	No significant effect.
McIntosh et al. 2004	Sham-controlled crossover study	16	9 days	1 Hz, 80 % MT, 4 to 8, 12 and 16 min on subsequent days. Each minute of stimulation was followed by 15 s pause.	Left temporo-parietal cortex	Auditory verbal learning test	No significant effect.
Hoffman et al. 2003	Double-Blind randomized, sham-controlled study	24	9 days	1 Hz, 90% MT, 8 minutes of stimulation on day 1, 12 minutes on day 2, and 16 minutes for the next 7 days (excluding weekends).	Left temporal and left parietal sites	1. California Verbal Learning Test 2. Controlled Oral Word Association Test 3. Semantic Fluency 4. Hopkins Verbal Learning Test as a discontinuation criterion	A margin-ally significant time by treatment group effect for the Hopkins Verbal Learning Test was detected in the follow-up phase, suggesting improvement in function.
Hoffman et al. 2005	Double-masked, sham-controlled, parallel design	51	9 days	1 Hz, 90% MT, 8 minutes of active/sham stimulation on Day I, 12 minutes of active/sham stimulation on Day II and 16 minutes of active/sham stimulation for the next seven days (excluding weekends).	Left temporal and left parietal sites	1. California Verbal Learning Test 2. Controlled Oral Word Association Test 3. Semantic Fluency 4. Hopkins Verbal Learning Test as a discontinuation criterion	No significant effect.
Fitzgerald et al. 2005	Double-blind, randomized, sham-controlled	33	2 weeks (5 days per week; in total, 10 days)	1 Hz, 90% MT (no further information).	Presumed site of the auditory temporoparietal cortex of the left hemisphere	1. Hopkins Verbal Learning Test 2. Verbal Fluency	No significant effect.

Notes: N - Sample size (N of patients); AVHs - Auditory Verbal Hallucinations; CI - Confidence interval; DLPFC - Dorsolateral prefrontal cortex; FDR - False discovery rate; LFL - low frequency, left-sided stimulation; MCCB - MATRIX Consensus Cognitive Battery; MT - Motor threshold; PGI-MS -Postgraduate Institute Memory Scale; RBANS - Repeatable *Battery* for the Assessment of Neuropsychological Status

Table 1. Continues

References	Study design	N	Course duration	rTMS Protocol	Stimulation site	Verbal tests	Findings
Oh et al. 2011	Preliminary study	10	15 sessions, 3 weeks	40 trains, beginning every 30 s: 20 trains of 10 Hz rTMS at MT 100%,3 s duration and 20 trains of 1 Hz r TMS at MT 80%.	10 Hz to left DLPFC 1 Hz to left temporoparietal cortex	Korean versions of the Auditory Verbal Learning Test	The fourth and fifth trials and the total scores showed a significant increase (Z = −2.041, p = 0.041; Z = −2.251, p = 0.024; and Z = −2.201, respectively; p = 0.028).
Blumberger et al. 2012	Blinded,sham-controlled study	51	20 sessions, 5 days per week; 4 weeks	1st group: LFL rTMS at an intensity of 115% RMT for 20 min; 2nd group:10 min of 6 Hz (twenty 5 s trains with 25 s inter-train interval) at 90% RMT followed by 10 min of 1 Hz stimulation at 115% RMT, 20 min of stimulation in total; 3rd group: sham stimulation.	Heschl's gyrus	RBANS, Language domain	No significant effect.
Hoffman et al. 2013	Double-Blind randomized, sham-controlled study	83	15 sessions; 5 days per week: 1st 5 days – W or rW 2nd 5 days – the opposite side 3rd 5 days - the site associated with greater percent improvement in AVHs. If no site produced greater improvement, stimulation returned to W. After unmasking patients randomized to the active group were offered five more rTMS sessions; patients randomized to the sham group were offered unmasked rTMS following the same schedule.	1 Hz, 90% MT, 960 pulses/session.	Wernicke's area and its right homologue (W or rW)	Hopkins Verbal Learning Test	No significant effect.
Xie et al. 2021	Shizophrenia vs. Controls	63	15 successive days	1 Hz, 110% MT, 10 s, with 5 s interval with 60 trains.	Left temporoparietal junction	MCCB, Verbal learning subtest	Significant improvement (FDR correction, $p<0.05$) in verbal learning (29.60±12.60 vs. 39.60±12.24, $p=0.035$).
Gupta et al. 2021	Adjuvant rTMS vs. no rTMS	39	10 sessions, 5 days per week; 2 weeks	1 Hz, 100% MT, one continuous 20 min train.	Left temporo-parietal zone	PGI-MS	No significant difference.

Notes: N - Sample size (N of patients); AVHs - Auditory Verbal Hallucinations; CI - Confidence interval; DLPFC - Dorsolateral prefrontal cortex; FDR - False discovery rate; LFL - low frequency, left-sided stimulation; MCCB - MATRIX Consensus Cognitive Battery; MT - Motor threshold; PGI-MS -Postgraduate Institute Memory Scale; RBANS - Repeatable *Battery* for the Assessment of Neuropsychological Status

Table 2. Summary of rTMS protocols parameters and verbal tests applied in the studies of rTMS use in schizophrenia: high-frequency rTMS approach

References	Study design	N	Course duration	rTMS Protocol	Stimulation site	Verbal tests	Findings
Holi et al. 2004	Double-blind, sham-controlled study	22	2 weeks, 10 sessions	10 Hz, 100% MT, 20 trains of 5 s stimulation, 30 s apart	Left DLPFC	As a part of MMSE	No significant effect.
Mogg et al. 2007	Double-blind randomized controlled pilot study	17	consecutive 10 days course	10 Hz, 110% MT, inter-train interval of 50 s and 20 trains	Left DLPFC	1. COWAT 2. HVLT	COWAT - no significant effect. HVLT - significant group difference at the two-week follow-up assessment (t=2.75, df = 12, p=0.02) with the real group having a score of 2.6 points (95% CI=0.53 to 4.6) better than the sham group.
Fitzgerald et al. 2008	Double-blind randomized controlled study	20	3-weeks, 5 days per week	10 Hz, 110% MT, 1000 pulses to each hemisphere daily	Bilateral PFC	COWAT	No significant effect.
Dlabac-de Lange et al. 2014	Multicenter, double-blind randomized, sham-controlled study	32	3 weeks, 15 sessions	10 Hz, 90% MT, 20 trains of 10 s with an inter-train interval of 50 s	Bilateral DLPFC	1. Dutch version of the Rey Auditory Verbal Learning Test 2. Verbal Fluency Test	A significant improvement of semantic verbal fluency was found in the active group (n=10) compared with the sham group (n=9) up to 4 weeks follow-up (p=0.006, F=9.31).
Hasan et al. 2013	Multicenter, double-blind randomized, sham-controlled study	156	3 weeks, 15 sessions	10 Hz, 110% MT, 20 trains with 50 stimuli per train, 30 second intertrain interval	Left DLPFC	1. Rey Auditory Verbal Learning Test 2. Regensburg Word Fluency Test	No significant effect.
Francis et al. 2018	Pilot double-blind, sham-controlled study	7	2 weeks, 10 sessions	20 Hz, 110% MT, 30 trains, 20 pulses per train, inter-train interval of 30 s	Left and right DLPFCs	BACS (Verbal Fluency and Verbal Memory)	Significant improvement in Semantic and Letter Fluency (LSE = 10.33, p=0.014) compared to baseline at the two-week follow-up, but not at the treatment endpoint visit.
Zhuo et al. 2019	Randomized, double-blind, sham-controlled trial	60	20 sessions	20 Hz, 90% MT, 100 trains with 20 stimuli per train, 9 s intertrain interval	Left DLPFC	1. MCCB – verbal learning subtest 2.Animal Fluency 3. Hopkins Verbal Learning Test – Revised	No significant effect.
Guan et al. 2020	Pilot double-blind, sham-controlled randomized study	56	5 days per week, 8 weeks	20 Hz, 110% Mt, 64,000 stimuli/course	Left DLPFC	RBANS, Language domain	No significant effect.
Xiu et al. 2020	Double-blind, sham-controlled	120	40 sessions, 8 weeks	1st group: 20 Hz 2nd group 10 Hz 110% MT, 40 3 s trains with a 27 s inter-train interval	Left DLPFC	RBANS, Language domain	Repeated-measures ANOVA suggested a significant interaction of group-by-time effect on language index ($F_{(4,97)}$=56, p=0.002; Bonferroni corrected p<0.05) and a significant time effect ($F_{(4,97)}$=6.6, p<0.01; Bonferroni corrected p<0.01), but not significant in group effect ($F_{(4,97)}$=0.83, p=0.44). Language index ($F_{(1,48)}$=5.5, p=0.02; effect size = 0.75; Bonferroni corrected p>0.05) was significantly higher in the 10 Hz rTMS group compared with the 20 Hz rTMS group at 6-month follow-up.
Voineskos et al. 2020	Randomized, double-blind, sham-controlled trial	82	20 sessions, 4 weeks	20 Hz, 90% MT, 25 stimulation trains of 30 stimuli, inter-train interval of 30 s	Bilateral DLPFC	MCCB, Verbal learning subtest	No significant effect.
Wen et al. 2021	Pilot double-blind sham-controlled randomized study	52	5 days per week, 20 sessions	10 Hz, 110% MT, 4 s with 26 s interval	Left DLPFC	RBANS, Language domain	No significant group and/or time effect. PANSS negative symptom scores was negatively correlated with RBANS language scores in the real stimulation group (p=0.046).

Notes: N - Sample size (N of patients); ANOVA - Analysis of Variance; BACS - Brief Assessment of Cognition in Schizophrenia; CI - Confidence interval; COWAT - Controlled Oral Word Association Test; DLPFC - Dorsolateral prefrontal cortex; HVLT - Hopkins Verbal Learning Test; MCCB - MATRIX Consensus Cognitive Battery; MMSE - Mini-Mental State Examination; MT - Motor threshold; RBANS - Repeatable *Battery* for the Assessment of Neuropsychological Status; *PANSS - Positive and Negative Syndrome Scale*

RESULTS

The systematic search initially revealed 200 articles, which underwent primary screening (titles and abstracts analysis), and further secondary stages of screening according to the elaborated exclusion criteria. This included identifying studies that entailed only cognitive assessments without verbal tests, or administration of the n-back test only (see Figure 1 for detail). According to the PICOS standards, we selected 21 full-length articles for detailed analysis, which were subdivided into two major topic clusters: (i) studies of low-frequency (1Hz) rTMS for treatment of persistent AVH in SZ (Table 1), and (ii) studies of high-frequency (10-20 Hz) rTMS targeting negative and cognitive SZ symptoms (Table 2). As such, cognitive effects would have been registered in the latter studies as the primary outcome of therapy. One study (Oh & Kim 2011) combined both approaches (Table 1).

Study sample and design

Studies sample sizes ranged from 7 to 156 SZ patients, to a total of 1003 patients across all of the studies included in the analysis. Only one study had specifically recruited patients in the initial phase of SZ manifesttations, whereas the remainder of the studies was carried out in populations of patients with a long duration of illness, which is consistent with the description of chronic negative and/or treatment-resistant positive symptoms as a key indication for rTMS administration. Seven studies considered the dynamics in cognitive parameters as being one of the key treatment outcomes, whereas six studies focused on the negative symptoms as the main target of interest. Nine papers investigated the efficacy of rTMS in SZ patients with refractory positive symptoms, mainly AVH, and studied changes in cognition as a secondary outcome or as a measure of safety. Three of these studies used the Hopkins Verbal Learning Test (HVLT) for in-treatment monitoring of cognitive functioning (Hoffman et al. 2003, 2005, McIntosh et al. 2004). Most of the studies were clinical research projects, except for one article that aimed to measure structural and functional brain alterations following upon rTMS (Xie et al. 2021).

Verbal cognition assessments

The most frequently used tests applied across the rTMS studies in SZ were (i) the verbal learning test (VLT) (n=11 studies) in its different modifications, and (ii) the verbal fluency test (n=7), respectively, and also (iii) the controlled word association test (n=4). Complex cognitive assessment, which incorporates precise language measurements, was used in several studies, in particular, (i) MATRIX Consensus Cognitive Battery (MCCB), including the verbal learning test (n=3 studies), (ii) Repeatable *Battery* for the Assessment of Neuropsychological Status (RBANS), including the language domain (n=4), and (iii) BACS, including verbal memory and fluency tests (n=1). One study also used the Mini-Mental State Examination (MMSE), and another study introduced a less-widely employed Postgraduate Institute Memory Scale (PGI-MS), in which the components were reported to be verbal assessments.

Verbal cognition outcomes

Three studies on rTMS for the treatment of refracttory AVH reported an increase in cognitive functioning, including positive VLT dynamics, whereas another seven studies did not report any such changes. Hence, in all ten of these studies, there was an agreement that rTMS was safe with respect to cognitive functioning in SZ. Most studies of this group did not specify quantitative indicators, but merely stated that were no significant differences in verbal performance of SZ patients upon treatment. Two studies reported single dropout cases, which were associated with a prominent decrease in HVLT scores (Hoffman et al. 2005, 2013).

Data on cognitive enhancement in SZ upon a course of rTMS, as measured by total test scores, remains contradictory. Seven studies did not show any significant changes in verbal test scores, and four studies revealed a minor improvement in the treated patients (Tables 1, 2). One study showed significant treatment effects in the language domain of RBANS (Xiu et al. 2020), whereas another study failed to detect any significant time-to-group interactions, but did note a negative correlation between PANSS negative symptom scores and RBANS language scores relative to baseline (Wen et al. 2021). One study reported an improvement in HVLT scores (Mogg et al. 2007), and two studies identified positive effects of rTMS on verbal fluency test measures in SZ patients (Dlabac-de Lange et al. 2015, Francis et al. 2019). All four of the studies reporting these significant effects emphasized that the positive effects were only evident at the follow-up examination (Dlabac-de Lange et al. 2015, Francis et al. 2019, Mogg et al. 2007), or were more prominent with increasing period of observation (Xiu et al. 2020). One study highlighted that relatively positive dynamics in the active rTMS group emerged due to the contrast with worsening cognitive function in SZ controls (Francis et al. 2019).

DISCUSSION

After screening the 200 recent articles selected via the above-mentioned keywords in PubMed, we identified 21 papers meeting the full criteria of our topic of interest. Thus, we can conclude that this topic is not currently considered as a key object for fundamental research in rTMS, despite its promising potential, given the long-established consensus that progressive thought, language, and communication impairments are a central aspect of the clinical description of SZ and its associated decline in social functioning (Andreasen 1979,

DeLisi 2001, Hunzen & Rossello 2015). We suggest that the rTMS studies, including verbal assessments, represent an important tool for diagnostics (Iter et al. 2018), prognostication (Bedi et al. 2015) and treatment (Joyal et al. 2016), but might also be a matter of research interest for examining basic aspects of the neurobiology of SZ (Nagels & Kircher 2016).

We emphasize that the target areas of stimulation for rTMS treatment of SZ are closely connected with speech function. The hypothesis underlying the purported efficacy of low-frequency rTMS for treating refractory AVH is based on the clinical research findings of increased activation in SZ patients of left temporoparietal and superior temporal cortex, these being areas with a primary association with speech perception (Lennox et al. 2000). DLPFC, another target zone for rTMS in SZ, is recognized to be involved in pragmatic processing, which might be depicted as a basal aspect of language (Hertrich et al. 2021). On the other hand, even simple tests of verbal fluency can be deeply investigated in different aspects related to impaired and declining mental functioning and neural network disruption in SZ (Smirnova et al. 2017). To our mind, this is the point of departure for experimentally establishing the association between rTMS-related treatment dynamics of language impairments in SZ patients and their underlying neurobiological defects, which manifest in different cognitive endophenotypes. Of all the clinical studies conducted to date, not one has been focused specifically on speech/ verbal functioning or language disturbances in SZ, although the majority of cognitive assessment procedures somehow involved language-associated measurements.

Most of the SZ studies failed to demonstrate a significant improvement in response to the rTMS treatment, and several studies demonstrated improvements of small effect size. When any positive changes were registered in a SZ sample, these effects in the first instance involved changes in verbal test performance. Consequently, in clinical practice, the wide range of possible cognitive assessments in SZ might be reduced to a narrow focus on verbal memory/learning or verbal fluency tests. A prognostic assignment of a subgroup of rTMS-responsive SZ patients might then be enabled using a simplified assessment procedure. Another important finding arising from the reported positive results concerns the temporal delay of the benefits from rTMS, and the direct positive correlation between duration of the post-treatment observation period and the extent of cognitive enhancement in SZ patients. As such, the benefits may be derived from long-term plastic changes in cortical functioning rather than acute perturbations. Returning to the issue of safety, the relevant studies concurred in concluding that the rTMS treatment did not worsen cognitive functioning in SZ patients. However, there were a number of dropout cases associated with significant decreases in HVLT scores (Hoffman et al. 2003, 2005, McIntosh et al. 2004). A possible explanation for those observations is that some subset of SZ patients may be particularly sensitive to the procedure, or that there was a failure to control some parameters related to the rTMS application.

CONCLUSIONS

Our literature survey shows that reports of altered or improved verbal functioning in SZ patients in response to rTMS are mainly represented by clinical trials rather than fundamental research projects. Specific types of rTMS stimulation protocols are suggested for the treatment of either AVH, negative, or cognitive symptoms. All of the investigated protocols were safe with respect to cognitive functioning, though there were some cases of significant decline in verbal memory in SZ patients due to as yet unestablished reasons. The majority of the studies demonstrated that verbal measures did not improve significantly in response to the rTMS treatment. Those studies that did report improvements in cognition were based on verbal assessments across the entire group of investigated cases, and showed a significant delay to onset of the positive benefits. Thus, it is possible that many studies may have missed the later developing improvements in cognitive function. Results of the present research could inform the design of future studies. In brief, we can hypothesize that it should be possible in the future (i) to resolve a subcohort of SZ patients with a particular cognitive endophenotype and language profile who would respond best to the rTMS treatment, and (ii) to specify the variables for optimizing the rTMS protocol so as to target the neurocognitive impairments, including language decline, in SZ spectrum disorders.

Limitations of the study

We did not conduct a quantitative meta-analysis due to the heterogeneity of SZ patients' groups, the variety of treatment protocols applied and evaluation methods used.

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Contribution of individual authors:

Tatiana I. Shishkovskaia & Daria Smirnova formulated the primary hypothesis.

Tatiana I. Shishkovskaia managed the literature search and wrote the first draft of the manuscript, which has been revised by Arseny J. Gayduk & Daria Smirnova in detail, completed for the final version and approved for submission.

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