Chapter 7

Transcranial Magnetic Stimulation in Schizophrenia

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Abstract

Transcranial magnetic stimulation (TMS) is a method that can be used in neurophysiological research of schizophrenia and in the treatment of some symptoms or syndromes of this mental disorder. The most important indications for TMS (or repetitive TMS—rTMS) are the negative symptoms of schizophrenia and auditory hallucinations. Other less proven indications include cognitive deficit, especially working memory. This text summarizes general knowledge about (r)TMS and its use in schizophrenia. According to recent experiences, TMS is a very promising experimental and therapeutic method, but it needs further research for its optimized use.

Keywords: transcranial magnetic stimulation, TMS, rTMS, schizophrenia, negative symptoms, auditory hallucinations

1. Introduction

Transcranial magnetic stimulation (TMS) represents a relatively new method used in neurophysiological research, in which it helps to measure various cortical phenomena, including cortical inhibition, facilitation, and neuroplasticity. It is also used in the diagnosis and treatment of certain neuropsychiatric disorders. This method is a neurostimulation (neuromodulation) technique as is electroconvulsive therapy, vagal nerve stimulation, deep brain stimulation, transcranial direct current stimulation, and magnetic seizure therapy. Some neurostimulation techniques are invasive or semi-invasive; others, including TMS, are noninvasive [1, 2].

2. TMS principles, parameters and mechanism of action

The principle of the TMS method is based on Faraday's law of electromagnetic induction, formulated in 1831. This law states that around the primary coil through which a time-varying current is flowing, a changing magnetic field is created that is able to induce a secondary current in conductors found within its reach. A patient's brain may be one such conductor. The secondary current induced is, according to Lenz's law, in the direction opposing the primary current. During TMS, an insulated metal coil is placed over the patient's head that delivers a changing electrical current producing a changing magnetic field perpendicular to the current passing through the coil. Magnetic pulses may be administered individually (single-pulse TMS), or in pairs a few milliseconds apart (paired-pulse TMS), or repeatedly in a sequence or "train" lasting from seconds to minutes (repetitive transcranial magnetic stimulation or rTMS). The first two options are used primarily for research and diagnostic purposes; rTMS is used mainly in the treatment of certain neuropsychiatric disorders, including schizophrenia [1, 3].

Repetitive transcranial magnetic stimulation is defined by the number of pulses per second or by frequency in Hertz (Hz). The frequency is categorized as "low-frequency" ("slow") rTMS with 1 Hz or less and "high-frequency" ("fast") rTMS with more than 1 Hz (usually between 5 and 25 Hz). Another parameter of stimulation is its intensity expressed as the percentage of the individual resting motor threshold (MT). The motor threshold is defined as the minimal intensity of the stimulus able to produce muscle contraction in at least 5 of 10 successive trials (usually in one of the small muscles of the hand, e.g., the abductor pollicis brevis) when the stimulation is applied to the motor cortex. The most commonly used stimulation intensity varies between 80% and 120% of the individual resting motor threshold. Other stimulation parameters include the length of the train of pulses, the duration of the pause between them ("intertrain"), the total number of pulses administered during one session, the total number of individual sessions, the stimulation coil localization, the type of coil (the most commonly used type in rTMS is the "figure-of-eight coil"; there are also oval coils, conical coils etc.; the double cone coil is one of the most innovative types), and the coil's position, and orientation on the patient's head. The most frequent stimulation site is the dorsolateral prefrontal cortex (DLPFC). This stimulation site is usually defined as the location 5 cm rostral to the area of the motor cortex, the stimulation of which determines the resting motor threshold. Another method for the localization of the stimulation site uses the international system of EEG electrode placement 10/20; the most precise localization method is performed by stereotactic neuronavigation. An interesting modification of standard rTMS is pattern stimulation, with theta burst stimulation (TBS) as the most important [1–3].

Although the specific effect of rTMS on neurotransmission is not entirely clear, it has been proven repeatedly that high-frequency rTMS (10 to 20 Hz) increases brain excitability, and low-frequency rTMS (1 Hz and lower) decreases it. It has also been found that high-frequency rTMS applied over the left prefrontal cortex (PFC) increases brain perfusion, and thus the metabolism of this region, whereas low-frequency rTMS has the opposite effect [4].

3. TMS in neurophysiological research of schizophrenia

TMS with various single-pulse protocols and paired-pulse protocols is a useful tool for the assessment of physiology of the human motor system, including cortical excitability, inhibitory and excitatory mechanisms, conduction time, connectivity, and plasticity [5]. Moreover, Camprodon and Pascual-Leone [5] suppose that this tool has properties that we now need to understand across affective, behavioral, and cognitive circuits, to establish solid circuit-based models of neuropsychiatric diseases with the potential to affect clinical practice.

One of the phenomena, studied with TMS, is cortical inhibition. Cortical inhibition (CI) can be defined as a neurophysiological mechanism by which GABAergic interneurons influence the activity of other neurons. Several studies have identified CI impairment in schizophrenia. CI and CI impairment can be measured with a number of markers and protocols, including the cortical silent period (CSP). CSP measurement consists of a suprathreshold TMS pulse over the motor cortex paired with voluntary electromyographic activity, causing a cessation of muscle movement. The duration of this movement cessation is a measure of CI. It is thought that CSP measures $GABA_B$ inhibitory activity. Another CI marker is short-interval cortical inhibition (SICI). SICI measurement consists of a subthreshold conditioning TMS pulse preceding a suprathreshold pulse by several ms (1–5 ms). The amplitude of the motor-evoked potential (MEP) is then measured; it should be reduced by 50–90%. This marker is thought to measure $GABA_A$-mediated cortical inhibition [6–13]. Recent studies show that CI impairment can be improved with antipsychotics, especially clozapine, but also with quetiapine and risperidone [13–15]. Kaster et al. [13] suggested that the potentiation of $GABA_B$ may be a novel neurotransmitter mechanism that is involved in the pathophysiology and the treatment of schizophrenia. Another recent study found inhibitory deficits directly in the prefrontal cortex specific for schizophrenia using a combination of TMS and electroencephalography (EEG) [9]. Camprodon and Pascual-Leone [5] suppose that this multimodal combination of TMS and neuroimaging methods (EEG, magnetic resonance imaging, or positron emission tomography) can achieve TMS full potential—to measure the neurobiological effects of TMS even beyond the motor cortex.

4. Clinical application of TMS in schizophrenia

The most important use of TMS (or rTMS) is in the treatment of specific symptoms or syndromes of schizophrenia, especially negative symptoms and auditory hallucinations. Other less proven indications in schizophrenia include cognitive deficit, catatonic symptoms, obsessive-compulsive symptoms, and comorbid nicotine abuse (through the decrease of craving).

4.1. Negative symptoms

There is a consensus that the negative symptoms of schizophrenia include symptoms of affective flattening, alogia, avolition, social withdrawal, and anhedonia. The symptoms of

inattention, poverty of content of speech, and inappropriate affect are also often assigned in measuring scales mainly due to the clinical evaluation of the overall disorganization seen in patients with schizophrenia [16].

Severity of negative symptoms in schizophrenia is usually linked with worse functional outcomes, including specific relationships with impaired occupational functioning, household integration, social functioning, engagement in recreational activities, and quality of life [16—18].

Negative symptoms are often associated with hypofrontality and with a lack of dopamine in the prefrontal cortex [19, 20].

4.1.1. Effect of rTMS in the prefrontal cortex

Some authors have found that high-frequency rTMS could increase cortical excitability and the metabolic activity of targeted neurons [21, 22]. Prefrontal rTMS also modulates dopamine release in the dorsal striatum and in the nucleus accumbens in Wistar rats [23]. High-frequency rTMS of the DLPFC induces the release of dopamine in the ipsilateral nucleus caudatus in healthy volunteers, and it causes downregulation of the 5-HT2 receptors in the frontal cortex [24, 25].

The change of the expression of glutamic acid decarboxylase, which is the synthetic enzyme of the precursor of GABA, could be also modified by rTMS. This finding may be important because the severity of negative symptoms has been found to be inversely related to benzodiazepine receptor binding in the medial frontal region [26].

These findings have led to the hypothesis that high-frequency rTMS applied at the prefrontal cortex may be an effective treatment of negative symptoms in schizophrenia, and many studies were published on this topic.

4.1.2. Current results of rTMS in the treatment of negative symptoms

We summarize in this text the results from three meta-analyses and from recent articles that are not a part of the last meta-analysis by Shi et al. [27].

The first meta-analysis reviewed eight double-blind studies and found that rTMS had a mild to moderate (d = 0.58) effect on alleviating the negative symptoms of schizophrenia [28]. The second meta-analysis evaluated nine double-blind studies with more than 200 enrolled patients [29]. When studies with any high-frequency stimulation of the left PFC were evaluated, the effect size of the treatment was low (d = 0.43); when the analysis included only studies with a 10 Hz frequency, the effect size of the treatment was intermediate (d = 0.63) [29]. The results of the third, most recent, meta-analysis suggest that rTMS is an effective treatment option for negative symptoms in schizophrenia. This meta-analysis included 16 studies. The moderators of rTMS on negative symptoms included duration of illness, stimulation frequency, stimulation intensity, and the type of outcome measures used (the effect size of rTMS on negative symptoms in sham-controlled trials was 0.80 as measured by the Scale for the Assessment of Negative Symptoms—SANS and 0.41 as measured by the Positive and Negative Syndrome Scale—PANSS) [27].

The authors of the third meta-analysis formulated some recommendations for the treatment of negative symptoms by rTMS based on the available results, which show that long-term stimulation (3 weeks or more) has a better effect than short-term stimulation. The best effect was with 10 Hz rTMS and 110% of individual MT. The number of pulses is also important—the effect is greater when the patient receives a higher number of pulses [27].

A recent study by Wobrock et al. included a sufficiently large sample (175 patients), but no statistically significant effect of rTMS was found in the improvement of negative symptoms in the active group compared with the sham group. The stimulation protocol was 15 sessions of 10 Hz stimulation of the left DLPFC, 110% MT, 5 s train and 30 s intertrain, and 15,000 pulses in the whole study. However, less-precise method was used for targeting the left DLPFC (the international system of EEG electrode placement 10/20, F3 electrode), and patients received a relatively small number of pulses, although the last meta-analysis indicated that a higher number of pulses have a better effect [30].

In another double-blind study, 117 patients with negative symptoms were randomized to a 20-day course of either active rTMS applied to the left DLPFC (it was targeted to 5 cm anterior to the point where maximum stimulation of the abductor pollicis brevis muscle was observed) or sham rTMS. The stimulation protocol was 10 Hz frequency, 4 s train and 56 s intertrain, 20 min each day, 80% MT, and 800 pulses per day. They reported that treatment with high-frequency rTMS for 6 weeks significantly improved negative symptoms in the active stimulation group as compared to the sham group. The decrease in negative symptoms persisted to the 6-month follow-up assessment [31].

Dlabac-de Lange et al. evaluated the effect of bilateral rTMS of DLPFC in schizophrenia patients with negative symptoms. The Tower of London (ToL) task during fMRI was used to measure the brain function of the DLPFC. The stimulation protocol was 10 Hz frequency, 15 sessions (divided into 3 weeks), 10 s train and 50 s intertrain, and 90% MT. Patients received 20 trains in one stimulation session. The brain activity in the right DLPFC and in the right medial frontal gyrus showed an increase in the active stimulation group after the stimulation, and the left posterior cingulate showed a decrease in brain activity after rTMS treatment of the DLPFC. No significant differences were found in task performance between the sham group and the active group after the treatment with rTMS. A significant difference was found in SANS but not in PANSS. The limits of the study can be seen in the localization of the DLPFC (targeted by F3 and F4 location from the EEG 10/20 system), in the small sample size (total of 24 patients) and in its heterogeneity, as there were significant differences between the active and sham groups at the beginning of the study [32].

4.1.3. New paradigms of rTMS in the treatment of negative symptoms

The authors of a recent study compared 96 patients who received 10 and 20 Hz, theta burst stimulation (TBS) and sham stimulation. The 10 Hz stimulation was only 80% MT at the beginning, and the intensity was gradually increased to 110% MT. Patients received 30 trains in one stimulation day, one stimulation interval was 5 s of the train and 30 s of the intertrain. The stimulation was divided into four weeks (20 stimulation sessions). The 20 Hz stimulation had the same stimulation parameters as the 10 Hz stimulation. In TBS, the basic train

had a frequency of 5 Hz, and the stimulation was given every 200 ms. Three single pulses (50 Hz) were embedded within each 5 Hz pulse, on 80% MT, and each session had 2400 pulses. The TBS group had significantly larger reductions in SANS and PANSS negative subscale scores than the 10 Hz group and the 20 Hz group, but there were no significant differences in the two scales between the 10 and 20 Hz groups. There was a reduction in the scores in the mentioned scales in all groups with active stimulation compared with the sham group stimulation [33].

The cerebellum and cortico-thalamic-cerebellar circuit have also been included in the pathophysiology of schizophrenia. In patients with schizophrenia, some cerebellar dysfunctions were found, such as neurological soft signs, impaired eyeblink conditioning, procedural learning deficits, dyscoordination, abnormal posture, and poor cognitive performance. Resting state gamma activity is supposed to be a biomarker related to functional brain connectivity. One study tried to investigate the effect of cerebellar rTMS on resting state gamma activity. The efficacy of cerebellar rTMS was tested in 11 recent-onset schizophrenia patients who received 10 sessions of high-frequency rTMS to the midline cerebellum over a 2-week period. A significant decrease in negative symptoms and depression scores was observed after the rTMS treatment. Gamma spectral power in left frontal and temporal segments was reduced significantly after this treatment. In light of these preliminary results, cerebellar rTMS could be a useful innovation for the treatment of negative and affective symptoms in schizophrenia, but this has to be confirmed in further studies [34].

4.1.4. Negative symptoms and rTMS—summary

Recent guidelines state that high-frequency rTMS of the left DLPFC has a probable effect in the treatment of negative symptoms of schizophrenia (Level B evidence) [35].

A number of double-blind studies also proved a statistically significant decrease in the intensity of negative schizophrenia symptoms when current antipsychotic treatment was augmented with rTMS; the actual clinical significance of this procedure is disputed [4].

Another issue is represented by antipsychotic and other medication used in the treatment of patients with schizophrenia. According to some studies, this medication could negatively influence the activation induced by rTMS [36, 37].

rTMS represents a promising direction in the treatment of negative symptoms in schizophrenia, but it is necessary to improve current stimulation protocols (to use different frequencies in different areas, to investigate the effects of intensive stimulation protocols, and to investigate new targets such as the cerebellum).

4.2. Auditory hallucinations

Auditory verbal hallucinations (AVH), perceptions of voices in the absence of external stimuli, are a fundamental feature of mental illness and one of the characteristic symptoms of schizophrenia with high clinical importance [38]. AVH are reported by 50–70% of patients with schizophrenia, and in about 25–30% of patients, AVH are resistant to antipsychotic medication [39]. rTMS could be an additional therapeutic tool for AVH in schizophrenia [40].

4.2.1. Effect of rTMS on auditory hallucinations

The positive impact of rTMS on AVH can be seen in the inhibition of increased activity in the left temporoparietal cortex (TPC) (Broadmann area 40). This increased activity is repeatedly proven during hallucinations using brain imaging methods. This area is supposed to be involved in the perception of speech. The repeated stimulation of this area with a frequency of 1 Hz (low-frequency rTMS) induces a long-lasting decrease in the frequency and severity of medication-resistant AVH [41].

4.2.2. Current results of clinical studies and meta-analyses

The first study that applied rTMS as a therapeutic instrument for AVH was performed by Hoffman et al. in 1999. They postulated that low-frequency rTMS (1 Hz frequency) delivered to the left TPC would curtail auditory hallucinations by reducing the excitability of distributed neurocircuitry [39]. Since then several studies have been performed; some studies with positive results and others with negative results. All these studies were included in several meta-analyses.

The authors of the first meta-analysis observed a significant mean weighted effect size for rTMS versus sham stimulation, across 10 studies involving 212 patients ($d = 0.76$). The main outcome measure was the reduction in hallucinations as measured with appropriate psychometric rating scales. A typical hallucination rating scale is the Auditory Hallucinations Rating Scale (AHRS), which is a seven-item scale measuring frequency, reality, perceived loudness, number of different speaking voices, length of hallucinations (single words, phrases, sentences, or extended discourse), attentional salience (the degree to which hallucinations captured the attention of the patient), and distress level. When studies reported on multiple brain areas that were targeted with rTMS, only the left TPC was included. When only studies were included that used continuous stimulation (nine studies), the mean effect size increased to $d = 0.88$. To investigate whether the number of stimulation session would be an important variable, they compared studies with fewer than five stimulation sessions (four studies) to those with more than five stimulation sessions (six studies); there was no significant improvement. Two studies that included PANSS reported that rTMS had no significant effect on the PANSS positive subscale. Thus, the observed effect was specific to auditory hallucinations. There was no significant effect of rTMS on a composite index of general psychotic symptoms. The results provide support for the efficacy of the treatment in reducing the severity of AVH [42].

The second meta-analysis included ten studies with 232 patients. All these studies used low-frequency rTMS of the left TPC on patients with schizophrenia and treated and measured medication-resistant AVH. They extracted outcomes from several scales for assessing AVH: Hallucination Change Scale (HCS), Auditory Hallucinations Rating Scale (AHRS), Severity of Auditory Hallucinations (SAH scale), Psychotic Symptom Rating scale—Auditory Hallucinations Subscale (PSYRATS-AH), and Positive and Negative Syndrome Scale—Auditory Hallucinations Item (PANSS-AH). The HCS seems more sensitive to rTMS effects on AVH, while most studies using AHRS reported negative results. The authors observed significant effect size (Hedges' $g = 0.514$) [43].

The third meta-analysis was performed by Freitas et al. [28]. The authors specifically analyzed the effect on auditory hallucinations in seven sham-controlled studies and found a large and significant effect size for the sham-controlled studies (1.04; p = 0.002). They observed the need for individual assessment of the functional anatomy of hallucinations, using hallucination-activation maps obtained either by PET or fMRI, and stereotaxically determined the stimulation site following individual fMRI detection of inner speech regions instead of less sophisticated approach including coil position using the international 10/20 EEG electrode system in TP3 site, which might enhance TMS efficacy [43]. A critical finding in a study by Hoffman et al. concerned the discrepancy between the fMRI-guided TPC sites used in their trial and the standard TP3 which had little to no overlap [44]. Moreover, in a study by Sommer et al., five of the seven patients undergoing functional guided rTMS had predominant right-sided hallucinatory activity and were therefore stimulated over the right TPC [28, 45].

Another three meta-analyses were published by Slotema et al. [41, 46, 47]. According to the first one, with seven randomized controlled trials and 189 patients included, rTMS was superior to sham treatment, with a mean weighted effect size of 0.54 [46]. The second meta-analysis included 17 studies. The mean weighted effect size of rTMS directed at the left temporoparietal area was 0.44. But the effect of rTMS was no longer significant at one month of follow-up care (according to five studies with a follow-up assessment of at least one month) [47]. The most recent meta-analysis by Slotema included 19 studies with a total number of 548 patients. The mean weighted effect size for the treatment of auditory hallucinations was 0.44. No significant mean weighted effect size was found for the severity of psychosis. For patients with medication-resistant auditory hallucinations, the mean weighted effect size was 0.45. Repetitive transcranial magnetic stimulation applied at the left temporo-parietal area with a frequency of 1 Hz yielded a moderate mean weighted effect size of 0.63, indicating the superiority of this paradigm. Various other paradigms failed to show superior effects. rTMS applied at the right temporo-parietal area was not superior to sham treatment. The authors concluded that rTMS, especially when applied at the left temporo-parietal area with a frequency of 1 Hz, is effective for the treatment of auditory hallucinations, including for patients with medication-resistant hallucinations [41]. The limitation of all rTMS studies is the placebo, because of the difficulty of reproducing the noise and the scalp sensation (including superficial muscle contractions) of the active treatment. The initial method of producing a placebo effect was to tilt the coil at 45° or 90°. However, this method clearly unmasks it to patients who were previously treated with rTMS or for those in a crossover design. The more recent methods involve using a completely similar sham coil. Another significant limitation of these studies is the concomitant pharmacotherapy in all subjects. Several pharmacological treatments may interfere with treatment response, by modifying cortical excitability, by preventing the transsynaptic transmission of rTMS, or by interfering with the cerebral plasticity effects induced by rTMS [43].

4.2.3. Auditory hallucinations and rTMS—summary

The results of all of these meta-analyses show that 1 Hz rTMS applied at the left temporo-parietal area is effective in the treatment of auditory hallucinations (even in treatment-resistant

patients), but the effect is of a relatively short duration (shorter than in patients with depressive disorder). In the trials covered in the meta-analysis by Slotema et al. [47], the effect of rTMS on AVH was no longer significant at the one-month follow-up visit. This short duration of the effect of rTMS is a matter of concern. A daily treatment of 2–4 weeks with a small treatment effect combined with a short duration may call into question its utility as a meaningful treatment for patients troubled by persistent symptoms [47]. The treatment of other positive symptoms with rTMS is ineffective. Recent guidelines state that low-frequency rTMS of the left TPC has a possible effect in the treatment of auditory hallucinations (Level C evidence); for other paradigms (high-frequency rTMS or continuous theta burst stimulation—cTBS), there are no recommendations [35].

4.3. Other indications

The treatment of other symptoms, syndromes, and comorbid conditions in patients with schizophrenia is less proven. Some studies focused on the cognitive effects of rTMS in schizophrenia. Their results were heterogeneous. A meta-analysis included four studies of high-frequency rTMS at the DLPFC and its effect on working memory. The authors concluded that rTMS significantly improved all measures of working memory performance [48]. But a recent study failed to prove a superior effect of rTMS over sham stimulation in the improvement of various cognitive domains in 156 schizophrenia patients with predominant negative symptoms [49]. Recent guidelines state no recommendations for the treatment of cognitive deficit in schizophrenia [35].

Three case studies described rTMS in the treatment of catatonic symptoms in patients with schizophrenia—the improvement in two cases was rapid and sufficient; the last case was negative [50].

A similar situation was seen in the treatment of obsessive-compulsive symptoms associated with schizophrenia. Two case studies with positive results were published, but the effect was only transient, and a recent pilot study had negative results [51, 52].

TMS offers an interesting option for the treatment of comorbid misuse of alcohol, nicotine, and other psychotropic substances. Two studies proved the effect of high-frequency rTMS at the left DLPFC on the reduction in cigarette consumption in patients with schizophrenia [53, 54].

TMS could also influence other less specific symptoms which are presents in schizophrenia as well as in other mental disorders, such as attention deficit or impulsiveness.

5. Future directions

It is possible to distinguish between two categories of factors associated with the efficacy of rTMS in schizophrenia: (1) clinical factors and (2) factors associated with rTMS, especially stimulation parameters.

Clinical factors include heterogeneity of symptoms of schizophrenia treated with rTMS, especially negative symptoms. Prikryl et al. analyzed negative symptoms influenced with

rTMS using five domains of SANS (affective flattening/blunting, alogia, avolition/apathy, anhedonia, and impaired attention). The stimulation improved all domains, except for alogia [4]. To improve the results with rTMS, the definition and the prediction of responders are needed. This could be achieved using markers of impaired cortical inhibition and neuroplasticity—especially when TMS (with the potential to measure cortical inhibition and its changes) and EEG or other neuroimaging methods (MRI, fMRI, SPECT, PET) are combined. Tikka et al. described significant correlation between the reduction in negative and depressive symptoms in patients with schizophrenia and the reduction in gamma spectral power in left frontal and temporal segments after cerebellar rTMS. The authors suggest resting state gamma spectral power in frontal and temporal regions for a biomarker of treatment response [55]. Homan et al. described that responders were robustly differentiated from nonresponders to rTMS by the higher regional blood flow in the left superior temporal gyrus before treatment for AVH. The authors conclude that resting perfusion measurement before treatment might be a clinically relevant way to identify possible responders and nonresponders to rTMS [56].

The optimization of stimulation parameters is another important issue. New stimulation targets (for example, the cerebellum or anterior cingulate), better and more precise methods of stimulation coil placement (stereotactic navigation), new coil types (double cone coil, maybe H-coils for deep TMS), stimulation frequency (individual frequency), intensity, number of pulses (higher number of pulses), and the number of stimulation sessions (intensive stimulation) are also subjects of current research. This research can provide data for new and innovative stimulation paradigms, which are needed for a more robust clinical effect of TMS in schizophrenia.

6. Conclusion

TMS is a very promising research and therapeutic method for patients with schizophrenia. It is a useful tool for researching cortical inhibition and neuroplasticity. The most important application of TMS (or rTMS) is in the treatment of some symptoms or syndromes, especially negative symptoms (high-frequency rTMS at the left DLPFC) and auditory hallucinations (low-frequency rTMS at the left TPC), and maybe even cognitive deficit. The results of clinical studies are promising, but further research is needed to optimize the treatment results.

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