Recent advances in noninvasive brain stimulation for schizophrenia

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Purpose of review
Noninvasive brain stimulation has emerged in the last three decades as a promising treatment for patients with antipsychotic-resistant symptoms of schizophrenia. This review updates the latest progress in the use of noninvasive brain stimulation to treat schizophrenia symptoms.

Recent findings
Several recently published randomized-controlled trials support a long-lasting clinical effect of stimulation techniques on schizophrenia symptoms. In addition, efforts have been made in recent months to improve efficacy through several optimization strategies. Studies have tested new parameters of stimulation, such as theta burst stimulation, and alternative cortical or subcortical targets and have reported encouraging results. New forms of electrical stimulations such as alternating and random noise stimulation, have also been studied and have shown clinical and cognitive usefulness for patients. Accelerated stimulation protocols, and prospects could arise with deeper stimulation strategies.

Summary
Using brain stimulation to treat symptoms of schizophrenia seems promising and the great flexibility of the stimulation parameters leaves much room for developing optimization strategies and improving its effectiveness. Further studies need to identify the optimal parameters to maximize response rate.

Keywords
brain stimulation, hallucinations, repetitive transcranial magnetic stimulation, schizophrenia, transcranial direct current stimulation

INTRODUCTION

Schizophrenia is a severe chronic mental disorder with a median lifetime risk of around 0.7% and accounting for a substantial part of the global burden of diseases (for a recent review, see [1▪▪]). Its clinical expression involves several symptoms that have been commonly clustered into positive symptoms, such as delusions and hallucinations, and negative symptoms, which include apathy, lack of motivation, social withdrawal, and speech poverty. First line treatments of schizophrenia rely on the use of antipsychotic medications. However, approximately 10–30% of patients show a poor or partial response to these treatments, emphasizing the need for a renewal in the therapeutic armamentarium of schizophrenia.

Noninvasive brain stimulation techniques have emerged in the last three decades as promising tools in the treatment of psychiatric disorders [2]. Among them, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are the most widely used. TMS consists of applying a magnetic field with an electromagnetic coil placed over the scalp with respect to a targeted cortical brain region. The magnetic field leads to a modulation of neuronal firing rate of the targeted area. The most common protocols propose to deliver multiple pulses repeated at a defined frequency (repetitive TMS – rTMS). The effects of rTMS on the neuronal excitability of the brain region located under the coil depend on frequency: rTMS delivered at low frequency ($\leq$1 Hz – LF-rTMS) can decrease cortical excitability [3], whereas rTMS delivered at high frequency ($\geq$5 Hz – HF-rTMS) can increase cortical excitability in the targeted brain areas [4].

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KEY POINTS

- In recent decades, noninvasive brain stimulation has emerged as a potential treatment for schizophrenia.
- Promising evidence is presented in the literature for using noninvasive brain stimulation techniques such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation in the treatment of hallucinations and negative symptoms of schizophrenia.
- The clinical use of noninvasive brain stimulation techniques in schizophrenia is supported by the guidelines developed by experts in the field who have assigned a level of evidence ranging from B (probable efficacy) to C (possible efficacy) depending on the targeted symptoms.
- New promising strategies are being developed to optimize the clinical effectiveness of noninvasive brain stimulation techniques through the use of new stimulation parameters and brain targets.
- Important questions need to be addressed in order to propose accurate and transferable clinical guidelines to apply.

tDCS consists of applying a low intensity direct current (from 1 to 3 mA) to the brain through at least two electrodes placed on the scalp. The current that flows from the anode to the cathode is supposed to reach the brain and induce polarity-dependent effects on cortical excitability. Namely, currents entering the brain at the anode site (i.e., anodal stimulation) are assumed to increase cortical excitability beneath the electrode by depolarizing neuronal resting membrane potentials, whereas currents exiting the brain at the cathode site (i.e., cathodal stimulation) are believed to decrease it by hyperpolarizing resting membrane potentials [5,6]. Local effects on cortical excitability last beyond the stimulation period for both rTMS [3,4] and tDCS [7]. In addition, acute and long-term local effects are not only observed on the excitability of the targeted cortical regions but also on the activity and connectivity of brain regions that are functionally connected to the area located under the stimulation site (long-scale effects) [8,9]. The effects can also reach deeper structure as revealed by an induced subcortical dopamine release following stimulation of the dorsolateral prefrontal cortex (DLPFC) [10,11].

Since neuroimaging studies have repeatedly reported dysregulation of brain activity in specific regions or functional networks, alteration of dopamine transmission and oscillations associated with symptoms of schizophrenia, noninvasive brain stimulation has thus been proposed as alternative therapeutic interventions in schizophrenia to normalize brain dysfunctions. Two main applications have been proposed: decreasing the hyperactivity of the temporo-parietal junction (TPJ) associated with auditory–verbal hallucinations; increasing the hypoactivity of the prefrontal cortex associated with negative symptoms, especially the left DLPFC (Fig. 1). Usually, noninvasive brain stimulation strategies have been proposed for patients with treatment-resistant or persistent symptoms, even

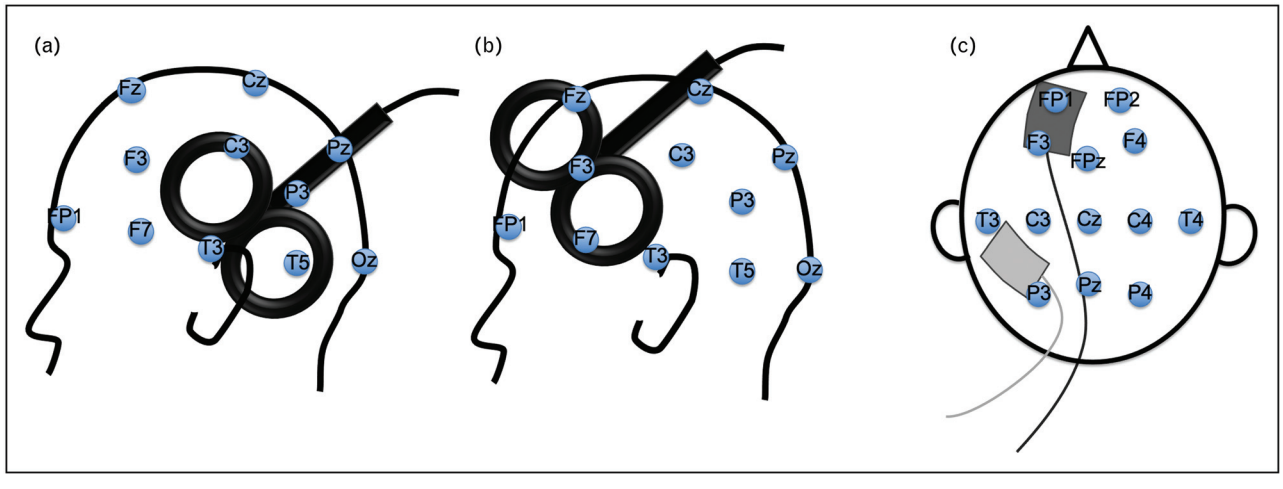

FIGURE 1. Illustration of common placements of rTMS coils (panel A for auditory verbal hallucinations and panel B for negative symptoms) and placements of tDCS electrodes (panel C for symptoms of schizophrenia, including auditory verbal hallucinations) to target symptoms of schizophrenia based on the 10/20 EEG electrode placement system. Panel c: dark grey electrode, anode; light grey, cathode. rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

those under antipsychotic medication at an adequate dose and duration.

Since the first publication of rTMS as a treatment for hallucinations in 1999 [12], there has been an exponential increase in the number of articles published on the interest of noninvasive brain stimulation for schizophrenia, both for clinical and fundamental purposes. In April 2022, the search equation [('rTMS OR tDCS') AND (schizophrenia)] yielded 299 hits in the PubMed database. Half of these have been published in the last 6 years, indicating the increased interest of the scientific community in these techniques. A recent meta-analysis including 208 randomized-controlled trials examined the efficacy of both rTMS and tDCS across all mental disorders and observed significant effect size for both techniques in various mental pathologies, including schizophrenia [13], further emphasizing the relevance of investigating the effectiveness of these techniques in the treatment of psychiatric diseases. Given the extensive literature on this topic, evidence-based guidelines have been published on the therapeutic use of rTMS and tDCS by groups of European and international experts in the field. These regularly updated guidelines are useful to help clinicians make decisions and avoid inappropriate applications.

This review presents the state of the literature and the latest advances in the development of noninvasive brain stimulation interventions for the management of symptoms of schizophrenia, with a focus on rTMS and tDCS techniques.

RECENT EVIDENCES FOR CLINICAL EFFICACY OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

According to the more recent guidelines on the use of rTMS published in 2020 by European experts, a possible efficacy (level C evidence) of LF-rTMS on the left TPJ was proposed for the treatment of auditory verbal hallucinations and HF-rTMS on the left DLPFC for negative symptoms [14▪▪]. Although LF-rTMS for hallucinations retained the same level of evidence as in the previous 2017 guidelines, it is interesting to note that due to the publication of recent negative findings, the level of evidence for HF-rTMS for negative symptoms was reduced from level B (probable efficacy) to level C, highlighting the need for large randomized-controlled trials and regular guideline updates. No recommendations were made for HF-rTMS for hallucinations and for HF-rTMS on a site other than the DLFPC for negative symptoms.

Since the publication of the last guidelines, new randomized-controlled trials have been conducted investigating alternative stimulation sites and proposing optimization of stimulation parameters, mainly for negative symptoms.

For instance, investigating new target of stimulation, the effects of targeting the dorsomedial prefrontal cortex bilaterally with HF-rTMS (10 Hz) were recently studied in an MRI-guided randomized-controlled trial including 15 patients who received active stimulation and 14 who received sham stimulation [15▪▪]. Targeting the dorsomedial prefrontal cortex was made possible by the use of a butterfly coil that consists of two large circular coils forming an obtuse angle and allows deeper brain targets to be reached. A significant improvement in negative symptoms was observed after 20 sessions of active HF-rTMS applied bilaterally to the dorsomedial prefrontal cortex, compared to sham. Although limited by a relatively small sample size and a high heterogeneity in response patterns, this study highlights that, as was the case for depression [16], the dorsomedial prefrontal cortex may also be an appropriate target in patients with prominent negative symptoms.

Strategies of optimization of the stimulation parameters have also been developed. In order to decrease the duration of stimulation sessions and obtain larger and more sustainable clinical effects [11], shorter duration rTMS protocols, such as the so-called theta burst stimulation (TBS), have been proposed. TBS consists in applying bursts containing three pulses at 50 Hz repeated at 200-ms intervals for 2 s (i.e., at 5 Hz, theta frequency) either continuously (cTBS) or intermittently (iTBS, e.g., TBS delivered during 2 s every 10 s). cTBS and iTBS show opposite effects on cortical excitability: iTBS increases, whereas cTBS decreases neuronal firing [17].

A recent double-blind randomized-controlled trial reported the clinical benefit of iTBS applied over the left DLPFC on negative symptoms in schizophrenia [18▪]. Patients received 20 sessions of iTBS (two sessions per working day for 2 weeks), with each session lasting less than 10 min (990 pulses). A significant reduction of 26% was observed in the active group compared to the sham group 6 months after the end of the stimulation protocol, suggesting a delayed beneficial effect of noninvasive brain stimulation. Clinical improvements were accompanied by an increase in functional connectivity between the left DLPFC and the right midbrain, including the ventral tegmental area, supporting the role of dopamine transmission and frontal cortex activity and connectivity in the pathophysiology of negative symptoms. Although these findings suggest potential clinical interest for iTBS for negative symptoms of schizophrenia, direct comparisons with conventional rTMS protocols are needed, as has been developed in the field of depression [19].

A recently published study protocol aims to precisely estimate the noninferiority of iTBS treatment compared to conventional HF-rTMS for the treatment of negative symptoms in schizophrenia [20]. This ongoing study constitutes an important step toward establishing iTBS as an alternative treatment for negative symptoms.

Finally, another recent study combining two optimization strategies targeted the cerebellar vermis area VII-B with MRI-guided iTBS. The choice of the cerebellum as a target for the treatment of schizophrenia symptoms was supported by the literature, including neuroimaging studies that reported the involvement of the cerebellum in the negative symptoms of schizophrenia within a frontocerebellar network [21]. Although a significant biological effect of 10 sessions of active iTBS was observed using resting-state functional connectivity analyses, these improvements did not translate into clinical benefits and there was no significant superiority of active stimulation over sham stimulation [22]. This study did not replicate previous promising findings reporting the clinical efficacy of iTBS over the cerebellar vermis for negative symptoms of schizophrenia [23] claiming for further studies.

RECENT EVIDENCES FOR CLINICAL EFFICACY OF TRANSCRANIAL ELECTRICAL STIMULATION

Compared to the literature on rTMS, only a few studies have examined the clinical value of tDCS for schizophrenia. However, the latest evidence-based guidelines for the clinical use of tDCS proposed a level B evidence for frontotemporal tDCS (with the anode placed over the left prefrontal cortex and the cathode over the left TPJ) to reduce auditory-verbal hallucinations in schizophrenia [24▪▪]. No level of evidence was proposed for tDCS to reduce negative symptoms, mainly due to the lack of studies with large effect sizes specifically designed to investigate this effect as a primary outcome. However, since the publication of these guidelines, two large randomized-controlled trials have been published, including 100 [25] and 60 [26] patients with schizophrenia, respectively. Both studies reported the clinical efficacy of active tDCS over sham in reducing negative symptoms with either a frontotemporal (anode over the DLPFC coupled to the cathode over the TPJ) or bi-anodal (2 anodes over the right and left DLPFC) tDCS electrode montage. One may note that this improvement was observed directly at the end of tDCS treatment in the study using bifrontal tDCS [26] while the other found efficacy of frontotemporal tDCS only 6 weeks after the end of treatment [25]. The reduction in negative symptom was maintained during the 3-month follow-up period in both studies. Thus, it is likely that future guidelines will recommend tDCS also for negative symptoms with a level B of evidence.

Optimization strategies have also been proposed in the field of electrical stimulation. For example, other forms of current have been used, such as transcranial alternating current stimulation (tACS), which consists in applying a low-intensity alternated sinusoidal current oscillating at a specific frequency. tACS is suggested to modulate brain oscillations by entraining endogenous oscillations in a frequency-dependent way [27]. A recent review examined the first findings of the efficacy of tACS in psychiatry [28▪]. Only 7 publications focused on schizophrenia, including case reports, open-label studies, and randomized-controlled trials. The results of these studies are difficult to summarize as tACS was administered in different frequency bands and different clinical and cognitive outcomes were evaluated. Nevertheless, promising applications are expected, since all studies reported significant results despite heterogeneous protocols, and characterization of adequate stimulation parameters and long-term effects need to be investigated in further studies. In this line, a recent double-blind randomized-controlled trial that included 36 patients with schizophrenia investigated the clinical effects of 10 sessions of in-phase frontoparietal theta-tACS (6 Hz) while the patients were simultaneously engaged in a working memory task during stimulation [29▪▪]. Theta-tACS was delivered on the left DLPFC and the left TPJ with 0° phase difference using two 4 × 1 high definition (HD) electrode montages with two synchronized stimulators at each site. A greater reduction in negative symptoms was observed at the end of the 10 stimulation sessions in the active group (−13.8%) compared to the sham group (−3.8%). This recent study proposes several optimization strategies: the use of HD stimulation (with 10 electrodes of 1 cm radius) instead of the two classical 7 × 5 cm electrodes, which has the potential for more precise and longer-lasting effects than conventional tDCS [30], the use of theta-tACS delivered in phase (instead of the classical DC stimulation) and the combination between stimulation and cognitive task in order to control the brain state during stimulation. The rationale for using in-phase stimulation, that is, stimulating both the left prefrontal and parietal sites at 6 Hz, was to facilitate frontoparietal synchronization. The rationale for combining stimulation and a cognitive task is that an already activated neuronal network will be more responsive to external electrical stimulation than an inactive network [31]. Therefore, the combination of tACS and cognitive tasks appears to be a promising

avenue for optimizing noninvasive brain stimulation.

Finally, also in an effort to find the optimal parameters for a better response to stimulation, the use of transcranial random noise stimulation (tRNS) has recently emerged. tRNS consists in applying a low-intensity current oscillating at random frequencies, typically in a range between 0 and 1000 Hz, but frequencies can be divided in two ranges of low frequency-tRNS (from 0.1 Hz to 100 Hz), and high frequency-tRNS (from 101 to 640 Hz). tRNS may show greater efficiency than other transcranial electrical stimulation techniques [32], allegedly through stochastic resonance, that is, amplification of a signal by adding noise. To date, only few case reports and only one pilot randomized-controlled trial have investigated the clinical interest of tRNS in the treatment of symptoms in schizophrenia [33▪▪,34,35]. The results are encouraging: clinical improvements have been observed, accompanied by increased insight, which is a crucial factor in the management of the disorder. A large randomized-controlled trial investigating the impact of tRNS on schizophrenia symptoms is in progress and will allow us to better evaluate the effectiveness of this new stimulation tool [36▪].

TOWARD ACCELERATED PROTOCOLS TO MAXIMIZE EFFICIENCY IN SHORTER TIME FRAMES

Considerable effort has been made to reduce the financial and time burdens associated with noninvasive brain stimulation treatments, including the development of shorter protocols such as TBS protocols [18▪]. It was also proposed to provide a higher number of stimulation sessions per day, ranging from one per day in conventional use of HF-rTMS for depression to 2 per day with LF-rTMS or frontotemporal tDCS for hallucinations [37,38], and up to a higher number of sessions per day in the recent application of the so-called accelerated protocols [39]. Accelerated protocols were first deployed in depression, where rapid significant clinical effects were reported [40,41]. Following this trend, we recently reported the safety and the efficacy of delivering 5 sessions of tDCS per day for two days in a patient with treatment-resistant schizophrenia [42▪].

To go even further in the optimization of parameters, we could be guided by what has been recently reported in the field of depression. Cole and collaborators have developed a challenging randomized-controlled trial with three optimization tracks: the individualized targeting of the DLPFC region based on resting-state functional MRI and identified as the most functionally anticorrelated with the subgenual anterior cingulate cortex; the use of an accelerated protocol with 10 sessions per day for 5 consecutive days; the application of a higher overall pulse dose of stimulation (90 000 pulses in total) in shorter sessions through the use of iTBS (approximately 10 min) [43▪]. This protocol induced a large antidepressant effect with a remission rate of approximately 80% in the active group compared to 13% in the sham group. A protocol of this type represents a significant clinical opportunity for patients in emergency or hospital settings due to its high efficacy and rapidity of action.

DEEP BRAIN STIMULATION IN SCHIZOPHRENIA

Due to technical limitations of current available noninvasive brain stimulation techniques that do not reach such deep regions, only surface cortical brain areas have been targeted so far. However, targeting deeper areas has been a topic for discussion in recent years [44▪▪]. To date, a case report has investigated the efficacy of deep brain stimulation of the pars reticula substantia nigra through an implanted electrode in a patient with schizophrenia and has described a stable clinical improvement [45]. A randomized-controlled pilot trial investigated the impact of deep brain stimulation of the subgenual anterior cingulate cortex or the nucleus accumbens, a subcortical region in which excessive dopamine activity has been described in schizophrenia, and concluded the efficacy and safety of deep brain stimulation in eight patients with medication-resistant schizophrenia [46]. In addition to the lack of sufficient evidence, the generalization of deep brain stimulation for the treatment of schizophrenia is limited by its invasive nature, which requires a surgical intervention and ethical discussion on the ability of patients with schizophrenia to give full informed consent with respect to their lack of insight into the illness. We have recently seen the emergence of a new tool with clear potential for the treatment of neuropsychiatric diseases that should allow us to stimulate deep areas without altering the functioning and physical integrity of the brain regions located above: the transcranial ultrasound neuromodulation (for a complete review of this technique in humans, see [47]). It would therefore counteract difficulties associated with deep brain stimulation and widen the field of possibilities for the use of noninvasive brain stimulation.

CONCLUSION

rTMS and tDCS have demonstrated efficacy for the treatment of negative symptoms and auditory

hallucinations in patients with schizophrenia. However, how these tools are meaningful and transferable into clinical settings is still under debate since inconsistent results were observed and a significant proportion of patients do not respond to noninvasive brain stimulation. Future studies should aim to identify predictive markers of response to help identify patients who are most likely to respond. Before translation to the clinical setting, efforts should be made when proposing clinical guidelines to accurately describe the stimulation parameters to apply in terms of stimulation frequency, intensity, total number of sessions, number of sessions per day, and stimulation location (and how to appropriately stimulate the correct region).

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Conflicts of interest

There are no conflicts of interest.

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