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Treatments in context: transcranial direct current brain stimulation as a potential treatment in pediatric psychosis

Christopher N David, Judith L Rapoport, and Nitin Gogtay*

Child Psychiatry Branch, National Institute of Mental Health (NIMH), National Institutes of Health (NIH), Building 10, Room 3N202, 10 Center Drive, Bethesda, MD 20890, USA

Abstract

Childhood-onset schizophrenia is a chronic, severe form of schizophrenia, and is typically treatment resistant. Even after optimized pharmacotherapy, a majority (over 70%) of these pediatric patients present lasting psychotic symptoms and impaired cognition, necessitating the need for novel treatment modalities. Recent work in transcranial magnetic stimulation suggests moderate efficacy in symptom reduction in adult patients with schizophrenia; however, the transcranial magnetic stimulation treatment is cumbersome for this severely ill population. Transcranial direct current stimulation may provide a safe and effective adjuvant treatment for continued residual symptoms of schizophrenia.

Keywords

childhood-onset schizophrenia; pediatric psychosis treatment; transcranial direct current stimulation

What is childhood-onset schizophrenia?

Childhood-onset schizophrenia (COS) is a rare and severe form of illness defined by the onset of psychosis before 13 years of age [1]. Clinical and neurobiological continuity between the childhood- and adult-onset disorders has been shown with respect to premorbid risk factors [2–9], smooth pursuit eye tracking function [10], familial schizophrenia-spectrum disorders [11,12], neurocognitive measures [13,14] and anatomic brain imaging studies [15–17]. COS patients typically resemble the severe, chronic and treatment-refractory adult onset patients; however, the course is nonepisodic [18,19].

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*Author for correspondence: gogtayn@mail.nih.gov.

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Current pharmacological treatment

Medications remain the mainstay of treatment for controlling psychotic symptoms in COS. Partial response and a high incidence of side effects have been demonstrated in previous trials with typical antipsychotics [20].

Atypical antipsychotics have been the first line of treatment for pediatric schizophrenia populations. However, due to the severity and treatment resistance, the majority of the children end up on clozapine. A double-blind comparison of clozapine (mean dose: 176 ± 149 mg/day) and haloperidol (mean dose: 16 ± 8 mg/day) demonstrated clozapine's increased efficacy in the reduction of negative and positive schizophrenia symptoms [21]. A recent double-blind randomized controlled trial in COS patients has demonstrated clozapine's preferable clinical response profile when compared with olanzapine [22], and a recent study showed no difference in cortical-thickness development trajectory changes in COS patients on clozapine compared with olanzapine [23]. However, clozapine is also associated with significant side effects, including enuresis, tachycardia, hypertension and weight gain [22], as well as neutropenia [24] and akathisia [25].

Long-term outcomes & the need for additional treatment strategies

Long-term studies on chronic adult onset schizophrenia patients show that many patients continue to experience disabling symptoms in the form of positive symptoms, negative symptoms and impaired cognitive functioning (including social cognition). Studies suggest that negative symptoms are the most resistant to medication treatments [26,27] that followed specific neurocognitive function loss (including social cognition and working memory) [28].

The course of COS is chronic and nonepisodic, with at least half of the cases remaining severely impaired [29–31] and a substantial minority showing continued deterioration [29,31,32]. Previous work has highlighted the severity of their positive symptoms, with the vast majority experiencing auditory (90%) and visual hallucinations (80%), as well as the more exotic somatic/tactile (60%) and olfactory hallucinations (30%) as well [33]. Despite some clinical improvement, most pediatric patients continue to experience significant psychotic symptoms and marked neuro-cognitive impairment. Using recently proposed standardized remission criteria [34], at the time of discharge from the National Institute of Mental Health (NIMH; after 4–6 months of inpatient stay), 75% of COS patients continued to have significant positive and negative symptoms (as measured by SAPS and SANS scales); remission was seen in 14% [35]. Due to the partial efficacy response of current medications, it is crucial to continue exploring further treatment options that focus on improvement in individual functional and cognitive domains, rather than sole reliance on the singular, optimized pharmaceutical model [36].

Transcranial direct current polarization

Overview of transcranial direct current stimulation

Application of electrical current to the scalp to treat disorders of the brain and behaviors has been attempted for centuries [37]. The effects of applied electrical fields to alter cortical neuronal activity, both in isolated neuronal preparations *in vitro* and *in vivo* [38], have been

well established. The transcranial direct current stimulation (tDCS) procedure uses specific positioning of two electrodes to deliver a relatively weak, direct electrical current (most often 0.5–2 mA). Current is delivered through the anode, and after passing through neuronal tissue, passes out of the body via the cathode. A reverse current can be delivered by reversing the electrode arrangement (cathode on the head and anode on the body). Previous work has identified ways to finely tune electrical therapy treatment by varying the location and size of the electrodes [39,40]. tDCS has become an actively investigated method [41–43], with well-demonstrated benefits in improved memory (probably due to) neuronal excitability in healthy subjects [44–49], while investigation for its therapeutic use in clinical disorders continues in the recent literature [50,51].

Safety

Since the first clinical application of tDCS [52], several healthy subjects and patients have participated and received tDCS without adverse effects. Side effects of tDCS depend on the placement of the electrode, whether it is anodal or cathodal, the intensity of the stimulation, and the length of time the patient is treated [53]. In one recent large trial of tDCS of over 100 subjects and 500 sessions, none requested to stop the tDCS stimulation, with the largest complaint listed as mild tingling (70%), followed by a third of the sample describing slight itching and or fatigue. Headache (11%), nausea (3%) and insomnia (1%) were rare [53].

Safety has further been documented in several studies, including studies showing no evidence of neuronal damage induced by tDCS as evidenced by no detectable increase in levels of neuron-specific enolase (a sensitive marker of neuronal damage) [54–57]. McCreery *et al.* demonstrated that current densities below 25 mA/cm² do not induce brain tissue damage even after applying high-frequency stimulation over several hours [58], and most studies fall well below this limit.

In a prior NIMH study on healthy adult volunteers, Iyer *et al.* demonstrated the safety of tDCS applied at 1 and 2 mA for 20 min to normal subjects [59]. Two other recent studies have demonstrated the safety of 2 mA of cathodal tDCS for 20 min in patients with fibromyalgia [60] and Parkinson's disease [61]. Moreover, tDCS does not induce seizures, and cathodal tDCS may in fact have an anti-epileptic effect [53,62]. This study demonstrated, for the first time, the safety of tDCS in pediatric populations, with no adverse or notable events in the COS sample (n = 12) that underwent the procedure [63].

Mechanisms of action

The complexity of the brain leaves some uncertainty of the exact tDCS mechanism. A small DC is applied to the head over a targeted area of cerebral cortex while the function mediated by the targeted area is monitored for changes. The negative cathode allows electrical stimulation to leave the brain, with increased electron density in this region as current queues here to flow out of the brain into the rest of the circuit. The cathodal area is typically inhibited and the anodal area is activated [64].

In mammals, weak polarizing currents applied to the brain surface produce lasting changes in cortical evoked potentials and the activity of individual cortical neurons [65–67]. In

virtually all cases, surface-anodal polarization of the cortex increases the firing rates of spontaneously active cells, while surface-cathodal polarization has the opposite effect, downmodulating firing. The basis of the phenomenon of increased firing with anodal polarization was studied *in vivo* by Gartside, who inferred that the effect of polarization operated at the synaptic, rather than the system-dynamic, level, that is, via 'reverberating circuits' [68]. He also found that the effect of DC could be blocked by pretreatment with a variety of protein synthesis inhibitors, suggesting a mechanism with elements in common with natural synaptic plasticity [69].

More recently, others working with weak anodal stimulation of the rat cortex in whole brains have found accumulation of calcium [70] and increased *c-Fos* expression [71], which appeared to be *N*-methyl-D-aspartate receptor dependent [72] after variable periods of exposure. While some of these changes appeared to persist for days, all were reversible. Thus, tDCS may offer a new valuable tool to modulate brain activity in a specific cortical region in a controlled manner and a tool for focal neuropharmacological delivery through neuronal stimulation and release of neurotransmitters [73,74].

In humans, when DC polarization (typically a current of 0.2–2 mA) is applied for 1–20 min over the motor cortex and motor-evoked potentials (MEPs) are measured as a probe for induced changes [55,56,75], the DC current can produce significant changes in corticospinal neuron excitability [55]. Moreover, the direction of change is dependent on the polarity of the current. When anodal polarization was applied to the motor cortex, MEPs were shown to have increased in size, while with the cathodal polarization the MEPs got smaller; after cessation of polarization, MEPs gradually returned to baseline levels. Effects were absent when electrodes were placed over nonmotor cortex, indicating a localized effect [55,56,75].

As there is a potential for possible unwanted excitability changes under reference electrodes in the brain, the use of extracephalic electrodes has increased in recent years [76–78]. A recent study of 12 healthy subjects by Moliadze *et al.* found the interelectrode distance to be negatively related to the magnitude and duration of induced after effects [79]. The only available study of tDCS used in children (further discussed below) used an extracephalic reference electrode and concluded its use to be well tolerated in the pediatric population [63]. The use of extracranial reference electrodes in the efficacy of tDCS is therefore still inconclusive and further work is required in the use of this method.

Cognitive & clinical benefits of tDCS

Recent studies have shown that DC polarization can enhance cognitive processes, particularly in the domains of learning and memory. In one of the earlier studies anodal tDCS of the primary motor area improved performance on the serial reaction time task; a test of implicit learning [80]. Subsequent studies have shown an array of cognitive benefits from tDCS stimulation. Kincses *et al.* have shown that anodal polarization of the left prefrontal cortex (PFC) accelerated the acquisition of implicit knowledge about a probabilistic relationship between sets of cues and outcomes [81]. PFC stimulation was also shown to improve response accuracy on a three-back task in healthy subjects [82] and Parkinson's patients [83]. Marshall *et al.* showed that anodal current to bilateral PFC,

applied during slow-wave sleep, enhanced word retention and mirror tracing skills acquired at earlier stages in their study [84]. A recent large (n = 103) study carried out at the NIH showed that left prefrontal anodal polarization significantly improved verbal fluency, whereas cathodal polarization showed no improvement [59]. The increasing literature on tDCS, particularly with behavioral effects on healthy participants, indicates definite excitatory effects on localized brain regions as well as motor function and control.

tDCS in neuropsychiatric conditions

In recent years, tDCS, along with transcranial magnetic stimulation (TMS), has reemerged as a method for transiently modulating or enhancing symptomatic outcome in major neuropsychiatric conditions [74]. Perhaps more important to their eventual clinical applications, tDCS studies have also suggested prolonged therapeutic efficacy, particularly in temporal, frontal and parietal areas [60,85].

Clinical applications have been reported for stroke patients using sham-controlled trials [62,86–90], as well as for use in neuropsychiatric disorders such as migraines [91], fibromyalgia [60], depression [92,93], epilepsy and tinnitus [94], although many of these are constrained by small sample limitations and have resulted in moderately weak effects [95,96]. Table 1 describes recent reviews of clinical applications of tDCS. Most studies remain small and frequently show inconsistent findings, thus necessitating the need for larger, double-blind, placebo-controlled studies.

Brain stimulation as treatment/augmentation in schizophrenia

The potential use of TMS and tDCS in clinical applications for the treatment of schizophrenia, particularly refractory cases, is a promising area for the literature to explore in upcoming years [63,74]. Repetitive TMS (rTMS) has been studied more in schizophrenia, but studies on rTMS to modulate auditory hallucinations have largely been positive, whereas efficacy for negative symptoms is equivocal [97]. On a practical level, rTMS requires large and costly equipment and more involved subject participation. This is typically difficult for more severely ill patients, such as COS subjects. tDCS offers a more mobile and practical solution due to the use of compact battery-powered equipment that is portable and thus can easily be used as an outpatient treatment with a trained administrator. tDCS, if effective, can also be a cheaper longer term treatment alternative [98]. Still, as Table 2 demonstrates, tDCS's application to the treatment of schizophrenia remains less studied and limited.

Two recent tDCS studies in schizophrenia are notable for their preliminary findings in tDCS as a potential tool to reduce positive psychotic symptoms in this population. A 2011 pilot study was one of the first to suggest that tDCS could reduce Auditory Hallucination Rating Scale scores as well as other symptoms, as measured by the Positive and Negative Syndrome Scale, negative subscale scores and general psychopathology scores, for multiple months after the stimulation trial [99]. A recent follow-up study by this group highlighted that exposure to tDCS, relative to sham stimulation, resulted in significantly reduced auditory verbal hallucinations in a large (n = 30) schizophrenia sample, and Positive and Negative Syndrome Scale subscores were also marked by notable clinical improvement [100].

Despite notable efforts in this field to date, tDCS is still a relatively new and unestablished treatment modality. The shortcomings in assessing the current literature in tDCS use in schizophrenia, as in the case of any new methodology, are due to the variability in methodology such as electrode placement, amplitude of current and duration of current, which are yet to be established. Further standardization is needed through well-designed studies in schizophrenia and in other clinical psychiatric populations.

tDCS in COS

Most COS cases are treatment refractory, resulting in a disorder that is persistent, severe, disabling and resistant to pharmacologic treatment [14], which in turn requires nonpharmacological treatment alternatives that focus on residual psychosis or persistent cognitive deficits. Given the simplicity, low cost and ease of administration of tDCS, further study regarding its tolerability in the pediatric population is clearly warranted.

An early safety and tolerability tDCS study in this clinical population recently targeted bilateral frontal/temporal tDCS at a moderate dose (2 mA) and duration (20 min) in a pediatric population of COS patients [63]. While the treatment was well tolerated, sample size was small, and the study was not powered to detect a difference in efficacy between groups. In addition, antipsychotic medication may have altered cortical excitability in the study cohort, thereby preventing the functional effects of tDCS. This is supported by a previous study in which sulpiride, a dopamine antagonist, prevented the re-establishment of the excitability changes induced by tDCS [101]. Ultimately, however, the effects of antipsychotics, in particular clozapine (often used for treatment in this severe subsample of schizophrenia) on cortical excitability pre- and post-tDCS are unknown. Limitations in the sensitivity of the trial's measures resulted in a lack of significant effects, although with the completion of this pilot study future work is underway that uses more sensitive measures (e.g., diffusion-weighted MRI) to make such determinations. However, no clinical/symptomatic decompensation or worsening of psychotic/cognitive symptoms in relation to tDCS treatment occurred.

Expert commentary

While still new in the literature as a psychiatric treatment option relative to the current standing of studies on TMS, tDCS holds great promise as a new and alternative treatment method, particularly for pediatric clinical populations, due to the ease of administration and relative safety. Preliminary data in the NIMH COS cohort suggest that it is well tolerated even in clinically severe populations; an ongoing study will attempt to evaluate both the tolerability and efficacy (for cognitive benefits) of tDCS as 40-min duration. Many studies are exploring the neurocognitive effects of tDCS, and although the current literature is scarce to date, the next few years promise a number of randomized, double-blind controlled trial that will shed more quantitative light on the method's viability as a clinical treatment option. More pediatric studies, like the one at NIMH, are also necessary for both replication of tolerability as well as to establish efficacy parameters.

Five-year view

Given the tolerability in children from this study, a new double-blind placebo-controlled trial has begun to explore whether tDCS treatment for 40 min (at 2 mA) would enhance the efficacy of the treatment. Reviews of tDCS literature (Table 1) have established the safety of tDCS and highlighted that further work is needed in optimizing administrative procedures in current, duration and location for better understanding of the method's efficacy. Use of imaging techniques to further explore tDCS's efficacy are also underway; our group noted a reversal of magnetoencephalography patterns after tDCS exposure. Future work combining fMRI, magnetoencephalography and other imaging techniques may bring about further insight into what role in treatment this method may bring in future trials.

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Key issues

- Treatment-refractory psychiatric populations present a unique challenge to the development and use of effective treatment approaches.
- Following previous work on transcranial magnetic stimulation and its clinical efficacy, transcranial direct current stimulation (tDCS) is quickly becoming a new highly investigated target for its properties as a potentially viable clinical stimulation method.
- Pilot studies have indicated that tDCS is well tolerated in even the most sensitive and difficult psychiatric, pediatric populations.
- While some are currently underway, additional studies are necessary using tDCS in double-blind randomized controlled trials with psychiatric populations.

Table 1

Summary of recent reviews discussing transcranial direct current stimulation efficacy.

tDCS articles (n)	Modality/pathology	Safety/tolerability	Observed efficacy evidence	Further study recommended?	Comments	Ref.
2 studies	PD and dystonia	Safe Well tolerated	Yes	Yes	Polarity-dependent effect on corticospinal motor excitability in PD patients Anodal stimulation resulted in a robust increase of corticospinal excitability, cathodal stimulation slightly decreased it Increase in the M1 excitability after anodal tDCS was marginally correlated with motor function	[102]
5 studies	Stroke recovery	Safe Well tolerated	Yes	Yes	tDCS is capable of modulating the excitability of targeted brain regions by altering neuronal membrane potentials Anodal stimulation increases cortical excitability in the stimulated brain tissue, while cathodal stimulation decreases it Corresponding behavioral effects have been seen if the behavior tested draws on the region that is stimulated If replicated, tDCS may become an important adjunct therapy in routine rehabilitative procedures in acute and chronic stroke settings	[103]
3 studies	MDD	Safe Well tolerated	Yes	Yes	Antidepressive effect of prefrontal tDCS Effects appear to be comparable with antidepressant medication, occur early and are stable for 2–6 weeks Appears to enhance learning and cognitive processing	[104]
6 studies	MDD	Safe Well tolerated	Unclear	Yes	Evidence not strong to support tDCS as a constant in the therapeutic modalities for depression Needs further parameter optimization for current, location and duration	[51]
29 TMS/tDCS 5 with tDCS	AD	Safe Well tolerated	Preliminary	Yes	Preliminary evidence for therapeutic utility of TMS/tDCS in AD	[105]
10 studies	Major depression	Safe Well tolerated	Yes	Yes	Active tDCS was found to be more effective than sham tDCS for the reduction of depression severity	[106]
15 motor studies 19 cognitive studies	Motor and cognitive functional domains	Safe Well tolerated	Yes	Yes	Anodal and cathodal electrodes: same effect sizes for motor functions but cognitive function results can be affected	[43]
3 studies	AD	Safe Well tolerated	Preliminary	Yes	Benefits of tDCS and rTMS in AD patients Effects short-lived and were not replicated after longer-duration interventions	[107]
14 studies	Corticomotor excitability and motor function in subjects with	Safe Well tolerated	Yes	Yes	A-tDCS improved motor learning in stroke patients	[108]

tDCS articles (n)	Modality/pathology	Safety/tolerability	Observed efficacy evidence	Further study recommended?	Comments	Ref.
	stroke vs healthy individuals stroke vs healthy individuals					

MDD: Major depression disorder; PD: Parkinson's disease; rTMS: Repetitive TMS; tDCS: Transcranial direct current stimulation; TMS: Transcranial magnetic stimulation.

Table 2

Recent transcranial direct current stimulation studies in schizophrenia.

N	Target region	Design/intensity/ statistics	Duration (min)	Outcome	*ES	Reported side effects	Comments	Study
21 SZ or schizo-affective	Anodal tDCS – left DLPFC Cathodal—contralateral supraorbital ridge	Active stimulation participants received 2 mA tDCS Two blocks of the weather prediction test consisting of 75 trials each with a 3-min break between blocks Sham: 30 s of active stimulation at the beginning of the 5-min interval immediately prior to task onset Repeated measures ANOVA on the cumulative mean percentage correct over 15 trial blocks	5 min prior to task onset Continued for another 15 min until task completion	No significant main effect of active tDCS compared with sham conditions or significant trial block by condition interaction Anodal tDCS to the DLPFC did not appear to improve probabilistic association learning SZ Results from the variance comparison suggested that a subgroup of responders may exist in the active tDCS condition	Significant main effect of trial block, $F(1.8, 35) = 5.51$; $p < 0.01$	NA	Demonstrated for the first time that probabilistic association learning may be modulated by prefrontal tDCS in some people with schizophrenia Greater variation in the active relative to sham conditions suggested that a subgroup may be present that was more responsive to tDCS treatment Further sample stratification can identify those SZ patients who may benefit from tDCS	[109]
21 SZ patients 21 matched healthy controls	Right first dorsal interosseus muscle as identified by TMS Other electrode was located contralaterally above the right orbit	Continuous current flow cathodal tDCS (motor cortex electrode) – intensity of 1 mA to produce long-lasting excitability changes (up to 1 h) in the human motor cortex	9	Cathodal tDCS failed to reduce motor-evoked potential amplitudes in schizophrenia patients, indicating abolished LTD-like plasticity SZ patients had a prolonged GABA(B)-dependent CSP at baseline tDCS failed to modulate the duration of CSP in the patient group, although they presented an elevated resting motor threshold at baseline in	NA	RMT elevated in schizophrenia patients at baseline, but did not change after cathodal tDCS in either group	First <i>in vivo</i> assessment of glutamate-dependent LTD-like cortical plasticity Evidence for a specific plasticity deficit in schizophrenia patients, which might be associated with a hyperglutamatergic state. May reflect a reduced signal-to-noise ratio and a disturbed filter function in schizophrenia patients	[110]

N	Target region	Design/intensity/ statistics	Duration (min)	Outcome	*ES	Reported side effects	Comments	Study
12 participants with COS	Anode-bilateral DLPFC (n = 8) Cathode-bilateral superior temporal gyrus (n = 5)	Double blind 2 mA of active treatment or sham treatment (with possibility of open active treatment), for a total of ten sessions (2 weeks)	20	iDCS well tolerated in the COS population with no serious adverse events occurring during the study	NA	Mild discomfort, transient redness, fatigue, tingling, itching	First study to demonstrate that a 20-min duration of 2 mA of bilateral anodal and bilateral cathodal DC polarization to the DLPFC and STG was well tolerated in a pediatric population. No behavioral changes noted due to small sample size. Work is ongoing	[63]
2 SZ patients with refractory AH	Anodal iDCS+DLPFC Cathodal iDCS+TPC	2 mA twice a day with a 3-h interval, for five consecutive working days	2	1st patients: large reduction in AHRs scores, improvement in other schizophrenic symptoms (PANSS, negative subscale scores and general psycho- pathology scores) 3 months after stimulation sessions	NA	No adverse events Transient mild tingling or a slight itching	Clinical efficacy evident immediately after stimulation sessions and maintained/continued 3 months post-treatment Possible treatment for auditory hallucinations and overall symptoms in refractory SZ patients	[99]
18 SZ 18 HC	Left primary motor cortex (M1) Studied effects on the nonstimulated right M1 cortex	Three-way ANOVA; assumption of time- specific and hemispheric-specific effects of iDCS To produce long-lasting excitability changes (up to 1 h), a constant current was applied with an intensity of 1 mA; MEPs were recorded before iDCS and 5 min after stimulation	9	Reduced LTD-like plasticity in schizophrenia patients, which is in line with our prior results of dysfunctional LTD-like plasticity Smaller left hemisphere MEPs smaller after stimulation compared with the right hemisphere in schizophrenia patients present	Significant effect of time (F(1, 34) = 8.027; p = 0.008)	None	Schizophrenia display reduced LTD-like plasticity following iDCS at the site of stimulation and abolished LTD-like plasticity on the nonstimulated side when compared with healthy controls Additional evidence for a reduced plasticity response in the stimulated hemisphere of schizophrenia patients	[111]
68 SCZ patients Subgroup of 15 SCZ,	Right PPC and the left PPC Reference cathode electrode was placed	Anodal stimulation over right PPC and the left PPC in two different sessions (1 mA) at an interval of 7 days, while the reference cathode electrode was	10–20	Only right parietal iDCS altered SCZ scores on LB with a partial correction of their	'Condition' effect (F _{1,14} = 46.166, p < 0.0001, = 0.77) 'Condition' ×	NA	Confirm the existence of reduced lateralization in SCZ, suggesting specific impaired	[112]

N	Target region	Design/intensity/ statistics	Duration (min)	Outcome	*ES	Reported side effects	Comments	Study
parietal tDCS	over the contralateral shoulder	placed over the contralateral shoulder Tested whether MNL performance may be influenced by tDCS over both the left and right PPC		lack of leftward bias No change in SCZ performance either after right PPC tDCS. No difference in performance on MNL between SCZ and HS	'parietal stimulation' interaction effect ($F_{1,14} = 19.603$, $p = 0.0005$, $\eta^2 = 0.58$)		functioning of the right parietal lobe Changes in the performance observed on LB tasks in SCZ could be due to an increase in the neural activity of the right PPC induced by tDCS	
30 SZ	Anode: left dorsolateral prefrontal cortex Cathode: left temporoparietal cortex	Active 2-mA tDCS or sham stimulation twice a day on five consecutive weekdays	20	Auditory verbal hallucinations significantly reduced by tDCS relative to sham stimulation PANSS symptoms also notably improved	Mean hallucination amelioration: $d = 1.58$; 95% CI: 0.76-2.40 Positive and negative symptom improvement: ($d = 0.98$; 95% CI: 0.22-1.73)	None	Beneficial effects on reducing hallucination symptomatology lasted for 3 months	[100]

N	Target region	Design/intensity/ statistics	Duration (min)	Outcome	*ES	Reported side effects	Comments	Study
18 SZ patients 18 control subjects	Motor-cortical electrode placed over right first dorsal interosseus muscle as identified by TMS Other electrode placed contralaterally above right orbit	Researchers sought long-lasting excitability changes (up to 1 h), applied constant current of 1 mA, to understand relationship plasticity of interhemispheric connectivity and nonfocal LTD-like plasticity in schizophrenia via application of excitability-diminishing cathodal tDCS	9	On stimulated hemisphere: cathodal tDCS increased RMTs in both groups and decreased MEP sizes in healthy controls to a greater extent compared with schizophrenia patients	After stimulation, healthy controls showed no difference in the MEP sizes between hemisphere (t = 1.731; df = 17; p = 0.102), while SZ patients demonstrated higher MEP values on the right hemisphere (t = 2.654; df = 17; p = 0.017) Significant difference after stimulation between groups on the left (t = 2.041; df = 34; p = 0.049) and right hemispheres (t = 2.244; df = 34; p = 0.031; but no difference at baseline)	NA	Support other findings of reduction in LTD-like plasticity within schizophrenia patient samples, potential link in schizophrenia-specific neuropathology between interhemisphere connectivity and cortical plasticity	[111]

AHRS: Auditory Hallucination Rating Scale; COS: Childhood-onset schizophrenia; CSP: Cortical silent period; DC: Direct current; DLPFC: Dorsolateral prefrontal cortex; ES: Effect size; *ES: Significant effect size; LTD: Long-term depression (of neuronal plasticity/response); MEP: Motor-evoked potential; NA: Not available; PANSS: Positive and Negative Syndrome Scale; PPC: Posterior parietal cortex; RMT: Resting motor threshold; SZ: Schizophrenia populations/patients; tDCS: Transcranial direct current stimulation; TMS: Transcranial magnetic stimulation.