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Transcranial Direct Current Stimulation in Schizophrenia

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Transcranial direct current stimulation (tDCS) is an upcoming treatment modality for patients with schizophrenia. A series of recent observations have demonstrated improvement in clinical status of schizophrenia patients with tDCS. This review summarizes the research work that has examined the effects of tDCS in schizophrenia patients with respect to symptom amelioration, cognitive enhancement and neuroplasticity evaluation. tDCS is emerging as a safe, rapid and effective treatment for various aspects of schizophrenia symptoms ranging from auditory hallucinations—for which the effect is most marked, to negative symptoms and cognitive symptoms as well. An interesting line of investigation involves using tDCS for altering and examining neuroplasticity in patients and healthy subjects and is likely to lead to new insights into the neurological aberrations and pathophysiology of schizophrenia. The mechanistic aspects of the technique are discussed in brief. Future work should focus on establishing the clinical efficacy of this novel technique and on evaluating this modality as an adjunct to cognitive enhancement protocols. Understanding the mechanism of action of tDCS as well as the determinants and neurobiological correlates of clinical response to tDCS remains an important goal, which will help us expand the clinical applications of tDCS for the treatment of patients with schizophrenia.

KEY WORDS: Transcranial direct current stimulation; Auditory hallucinations; Cortical plasticity; Schizophrenia.

INTRODUCTION

Antipsychotics have been the mainstay of treatment in schizophrenia since the introduction of chlorpromazine in 1952. The advent of antipsychotics has revolutionized the treatment of schizophrenia.[1] However, the conceptual paradigm for the treatment of schizophrenia has been largely unchanged since. Despite several attempts at theorizing schizophrenia as a disorder of neurotransmitters other than dopamine, there is no antipsychotic drug which does not have an anti-dopaminergic action.[2] Nonetheless, antipsychotics continue to be the cornerstone and the gold standard for treatment of schizophrenia; but for them, we might have been stuck in the era of custodial care with the occasional electroconvulsive therapy.[1] And yet, one cannot help but perceive an element of therapeutic stagnation—at least in terms of pharmacologic options, that has come to characterize the clinical management of this chronic disorder.[3] This gap in our care drives us toward discovering and/or inventing new modalities of treatment; along these lines, for the treatment of schizophrenia symptoms that do not respond to antipsychotic medication, a host of add-on pharmacological choices have been described.[4]

In this context, it is interesting to note that a series of recent observations have consistently demonstrated an immediate amelioration of persistent auditory verbal hallucinations in schizophrenia with transcranial direct current stimulation (tDCS). Application of tDCS for various psychiatric disorders including schizophrenia has been commented upon as an exciting area requiring further systematic exploration.[5] Interestingly, application of transcranial electrical brain stimulation for the treatment of severe mental disorders like psychosis dates back to 1870s.[6] Recently, there has been a re-emergent interest in the application of tDCS for the treatment of schizophrenia. In this review, we summarize the studies that have examined the effects of tDCS in schizophrenia patients. We identified these studies by performing a literature search in

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PubMed, PsycINFO and Google Scholar for published studies up until October 2013, with the following search terms and their combinations: transcranial direct current stimulation, tDCS, and schizophrenia.

MAIN DISCOURSE

Transcranial Direct Current Stimulation

tDCS is a noninvasive brain stimulation technique where direct current in the range of 0.5 to 2 mA is passed through the scalp by means of electrodes ranging in size, most commonly, from 25 to 35 cm^2 over designated areas of interest in an attempt to modulate the activity of specific brain region(s).[7-10] The historical roots of tDCS electrophysiology has been traced to the discovery of the biological effects of direct current; indeed, as early as two centuries ago, application of direct current to the scalp was possibly used to treat mental disorder.[11] It is an offshoot from techniques of electro-stimulation and electro-anesthesia, where direct current bias was reliably employed in the 1950s.[8] First clinical results using modern forms of tDCS were reported in the 1960s and 1970s motivated by the realization, in animal studies, that several minute long stimulation protocols had lasting changes on the cortical excitability.[8] Since then, tDCS has been explored for efficacy in a multitude of disorders ranging from pain to depression to post stroke recovery with varying levels of success.[12,13]

Though tDCS has been around for several decades, with regards to its application in treatment of schizophrenia, this therapeutic technique has had a rediscovery of sorts very recently, where it has been shown to have a relatively selective effect leading to rapid amelioration of auditory hallucinations in patients with schizophrenia (Table 1). Concurrently, researchers working on its effects on healthy individuals have been able to demonstrate stable, long lasting neuroplastic effects of this intervention in improving mathematical abilities.[14] These interesting developments have led to newer questions in the area of "neuroethics".[15,16] However, the debate on "neuroethics" is beyond the scope of this manuscript since the focus of this review is to critically evaluate the use of this emerging technique in patients with schizophrenia.

Application of tDCS in Schizophrenia

Research on tDCS in schizophrenia has been in three largely distinct directions. Several case reports, and one randomized controlled trial (RCT) have tested its effectiveness in symptom reduction and its tolerability (Table 1). Other studies have evaluated the effect of tDCS on various cognitive faculties in the context of schizophrenia (Table 2). A third line of enquiry has utilized tDCS in conjunction with transcranial magnetic stimulation (TMS) as an investigative approach to evaluate neuroplasticity changes in patients with this disorder (Table 3). Insights gleaned from these enquiries in discussed below.

Safety of tDCS in Schizophrenia

A total of about 50 patients with schizophrenia have been reported in world literature to have received tDCS for therapeutic purposes (Table 1).[17-26] One consistent observation is that tDCS appears to be remarkably safe in the short and medium term. Though the long term safety of the technique is yet to be evaluated through systematic long term studies (although it is encouraging to note that the single case report of safe and effective domiciliary use of daily to twice-daily, domiciliary, 30-minutes, 1- to 3-mA tDCS sessions across nearly 3 years for the treatment of continuous, disabling, clozapine-refractory auditory hallucinations in schizophrenia)[21]; moreover, there has not been a single published report where tDCS had to be stopped for safety reasons. In addition, it is reassuring to note that the study in pediatric sample has not reported any significant problems either.[18] Even in a schizophrenia patient with a dermatological condition, tDCS could be applied safely on the region with vitiligo.[27] In many of the earlier reports, side effects that are reported have been mild itching and burning sensation, or mild but tolerable levels of pain at the electrode placement site. Studies involving controls have been equally comforting on the safety issue.[14]

tDCS in Schizophrenia: Clinical Impact

While the focus of most of the reports till date has been on hallucinations—the symptom cluster that has shown consistent improvement with tDCS—few reports also mention significant gains in negative symptoms. In the RCT by Brunelin *et al*.,[20] the effect size for improvement of negative symptoms was 1.07. Most reports present a picture of overall improvement in the patient's general state, including functioning as well as social interaction. Another interesting observation from our group has been the improvement in insight that has accompanied decrease in hallucinatory experiences.[22,23] With regard to cognitive symptoms, the three studies till date have been largely positive (Table 2).[28-30] While two of them have found a clear improvement in cognitive faculties,[29,30] the third observed improvement only in a subset of patients.[28] These

studies have only looked at select cognitive functions. Hemineglect bias (as evaluated by the line bisection studies) and defects in declarative memory are only two of the many cognitive deficits reported in patients with schizophrenia. Till the point when studies can demonstrate convincing improvement in a broad range of cognitive faculties, and these distill down to functional improvement in patients, one needs to be appropriately circumspect about

Table 1. Studies using tDCS for symptom reduction in patients with schizophrenia

Study	Design	tDCS methodology	Key findings
Homan *et al.*, 2011[17]	Case report; single patient	• Unilateral cathodal stimulation over Wernicke's area; anode kept over right supraorbital area • 1 mA current with 35 cm^2 electrodes • 5 minutes sessions for 10 consecutive days	• Prominent reduction in auditory hallucinations and total psychopathology scores • Decrease in regional blood flow in BA 41/42 44/45 and 22 as measured by arterial spin labeling • Persistence of improvement at 6 weeks follow up
Mattai *et al.*, 2011[18]	Double blind sham controlled design; 12 adolescent patients	• Bilateral anodal DLPFC or bilateral cathodal superior temporal gyrus stimulation; active or sham • 2 mA with 25 cm^2 electrodes • 10 sessions of 20 minutes each over two weeks (weekdays only)	• tDCS was well tolerated in children with schizophrenia • No serious adverse events during the study
Brunelin *et al.*, 2012[19]	Open label trial; two patients	• Anodal left DLPFC and cathodal left TPC stimulation • 2 mA current strength • 20 minutes sessions twice a day separated by at least 3-hours for 5 consecutive working days	• Promising reduction in both auditory hallucination and overall symptoms severity • Efficacy appeared immediately after stimulation sessions and was maintained or increased over three months
Brunelin *et al.*, 2012[20]	Randomized double-blind controlled trial; 30 patients	• Anodal left DLPFC and cathodal left TPC stimulation • 2 mA current strength with 35 cm^2 electrodes • 20 minutes sessions twice a day separated by at least 3-hours for 5 consecutive working days	• "Robust" reduction in both auditory hallucination as well as overall symptoms severity • Persistence of beneficial effect on hallucinations for up to 3 months • Large effect size, immediate improvement onset
Andrade, 2013[21]	Case report; single patient	• Cathode midway between T3 and P3, and anode over the F3 site • 1- to 3-mA with 25 cm^2 electrodes • Daily to twice-daily for 30-minutes on domiciliary basis for nearly three years	• First report in literature of the safe and effective use of domiciliary tDCS • Noteworthy overall improvement in clinical status • Maintenance tDCS shown to maintain acute tDCS-induced improvements
Rakesh *et al.*, 2013[22]	Case report; single patient	• Anodal left DLPFC and cathodal left TPC stimulation • 2 mA current strength with 35 cm^2 electrodes • 20 minutes sessions twice a day separated by at least 3-hours for 5 consecutive working days	• First description of tDCS monotherapy resulting in immediate and complete cessation of auditory hallucinations • Improvement in insight noted, facilitating re-initiation of maintenance antipsychotic medication
Shivakumar *et al.*, 2013[23]	Case report; single patient	• Anodal left DLPFC and cathodal left TPC stimulation • 2 mA current strength with 35 cm^2 electrodes • 20 minutes sessions twice a day separated by at least 3-hours for 5 consecutive working days	• First description of add-on treatment with tDCS in a patient with schizophrenia during the acute phase • Rapid and complete cessation of auditory verbal hallucinations • Remarkable improvement in insight
Shiozawa *et al.*, 2013[24]	Case report; single patient	• Cathode over the right and anode over the left DLPFC • 2 mA current strength with 35 cm^2 electrodes • 20 minutes tDCS sessions for 10 consecutive days	• First description of tDCS for catatonia • Improvement in symptoms in spite of lack of response to several antipsychotics and ECT • Rapid response
Shiozawa *et al.*, 2013[25]	Case report; single patient	• Anode over left DLPFC and cathode over left occipital area for the first ten sessions and over left TPC for the subsequent 10 sessions after a rest period of 5 days • 2 mA current strength with 35 cm^2 electrodes • 20 minutes tDCS sessions over 15 days with 5 rest days (day 6 – day 10)	• First description of visual hallucinations improving with tDCS • Concurrent improvement in auditory hallucinations as well as other positive symptoms like delusions
Palm *et al.*, 2013[26]	Case report; single patient	• Anode over the left DLPFC, cathode over the contralateral supraorbital region • 2 mA current strength • 20 minutes sessions for 10 days within 2 weeks	• Large improvement in both positive and negative symptoms • Reduction in resting state functional connectivity in the anterior part of the default mode network

tDCS, transcranial direct current stimulation; DLPFC, dorsolateral prefrontal cortex; TPC, temporoparietal cortex; BA, Brodmann area; ECT, electroconvulsive therapy.

Table 2. Studies using tDCS for enhancement of cognition in patients with schizophrenia

Study	Design	tDCS methodology	Key findings
Vercammen *et al.*, 2011[28]	Case-control study, 20 subjects in each group	• Anodal over left DLPFC, cathode over the contralateral supraorbital ridge • 2 mA current strength with 35 cm^2 electrodes • One active and one sham session per subject each lasting 20 minutes	• Whole sample results do not show significant improvement in probabilistic association learning in patients with schizophrenia • A subset of patients improved with active tDCS, especially those who have greater cognitive reserve at baseline
Ribolsi *et al.*, 2013[29]	Case control study with four groups: schizophrenia patients, unaffected relatives, patients with unipolar depression, and healthy controls 15 schizophrenia patients got tDCS	• Anode over right PPC and left PPC in 2 different sessions at an interval of 7 days, cathode over the contralateral shoulder • 1 mA with 35 cm^2 electrodes over 10 minutes	• Partial correction of lack of leftward bias in line bisection task in patients with schizophrenia with right PPC tDCS • No change in performance of mental number line task after tDCS to either left or right PPC
Göder *et al.*, 2013[30]	14 patients; active vs. sham	• Bilateral electrodes at frontolateral locations F3 and F4 and mastoids • Current oscillated between 0 and 300 μA, 8 mm diameter electrodes • Stimulation started 10 minutes after subjects entered stage 2 sleep. 5 blocks of 5-minutes tDCS separated by 1-minute free intervals	• tDCS well tolerated during sleep • Significant improvement in declarative memory • Significantly more positive mood in the morning

tDCS, transcranial direct current stimulation; DLPFC, dorsolateral prefrontal cortex; PPC, posterior parietal cortex.

the potential utility of this technique in ameliorating cognitive symptoms. Sample sizes in all these studies are modest but they open up an interesting possibility of helping patients with their cognitive symptoms. These findings, although preliminary, are quite exciting and make one wonder whether tDCS adaptively modulates certain critical component(s) in the pathophysiology of schizophrenia.

Effectiveness of tDCS on Auditory Hallucinations in Schizophrenia

With regard to clinical effectiveness, following features make tDCS quite distinctive and appealing as a novel therapeutic technique:

(i) Rapid onset of action: Most reports till date appear to suggest that clinical improvement begins quite early, in some cases just after the first couple of sessions of tDCS.[19,22-24]

(ii) The persistence of response is another factor that most reports concur on. A five to ten day session can be expected to provide sustained improvement for two to three months. This is, perhaps, the most favorable aspect of treatment with tDCS, enabling patients to achieve symptom control which is not only fast but also long lasting. This opens up many therapeutic avenues and possibilities and is likely to increase the acceptability of treatment as a whole.

(iii) Considering the fact that most of these reports have looked at patients who have been on antipsychotics for a long time without appreciable response, the quantum of improvement is quite striking. The effect size reported in the only RCT by Brunelin *et al*.[20] was 1.58, almost thrice the usual effect sizes with antipsychotic medication.

Of course, any discussion on the size of the effect has to be tempered by the knowledge that potential publication bias might operate to inflate apparent effect sizes during the initial periods whenever a new treatment is introduced.[31] The same enthusiasm had greeted the introduction of TMS on the clinical scene with large effect sizes being reported initially. But over time it has fallen; the current understanding is that it is actually close to 0.3.[32] Hence, one has to wait for studies with larger samples to get a true estimation of the impact tDCS has on symptoms of schizophrenia.

tDCS as an Investigative tool for Schizophrenia

The investigative potential of tDCS to understand the pathogenesis schizophrenia has been tapped by the series of research publications over the last two years; these research works have demonstrated altered neuroplasticity in

Table 3. Studies using tDCS to evaluate neuroplasticity in patients with schizophrenia

Study	Design	tDCS and experimental methodology	Key findings
Hasan *et al.*, 2011[33]	Case control study, 22 patients, 22 controls	• Anode over the representational field of the right dorsal interosseus muscle (FDI) (left primary motor cortex), cathode over right orbit • 1 mA with 35 cm^2 electrodes for 13 minutes • TMS-generated motor evoked potential (MEP) parameters studied pre- and post-tDCS	• All schizophrenia patients demonstrated reduced cortical inhibition • Multi-episode schizophrenia patients showed significantly reduced long-term-potentiation-like plasticity compared to recent-onset schizophrenia patients and healthy controls
Hasan *et al.*, 2012[34]	Case control study, 21 patients, 21 controls	• Cathode over the representational field of the right FDI muscle as identified by TMS (left primary motor cortex), anode over right orbit • 1 mA with 35 cm^2 electrodes for 9 minutes • TMS-generated MEP parameters studied pre- and post-tDCS	• Cathodal tDCS failed to reduce MEP amplitudes in patients, indicating abolished long term depression (LTD)-like plasticity • Patients had a prolonged $GABA_B$-dependent cortical silent period at baseline and tDCS failed to modulate its duration in patients
Hasan *et al.*, 2012[35]	Case control study, 18 patients, 18 controls	• Cathode over the representational field of the right FDI muscle as identified by TMS (left primary motor cortex), anode over right orbit • 1 mA with 35 cm^2 electrodes for 9 minutes • TMS-generated MEP parameters studied pre- and post-tDCS	• Cathodal tDCS increased resting motor thresholds (RMT) in both groups and decreased MEP in controls to a greater extent compared to patients on the stimulated hemisphere • RMTs increased and MEP decreased only in the control group on the non-stimulated hemisphere
Hasan *et al.*, 2013[36]	Three groups, 15 patients, 12 first degree relatives (FDR), 20 controls	• Cathode over the representational field of the right FDI muscle as identified by TMS (left primary motor cortex), anode over right orbit • 1 mA with 35 cm^2 electrodes for 9 minutes • TMS-generated MEP parameters studied pre- and post-tDCS	• Both FDR and patients showed abolished motor-cortical LTD-like plasticity of the stimulated hemisphere • Plasticity abolished in patients and reversed in FDR on the non-stimulated hemisphere
Nawani *et al.*, 2013[37]	Case report; single patient	• Anodal left DLPFC and cathodal left TPC stimulation • 2 mA current strength with 35 cm^2 electrodes • 20 minutes sessions twice a day separated by at least 3-hours for 5 consecutive working days • EEG based N100 amplitude during an auditory oddball paradigm before and after tetanic stimulation used as a marker of neuroplasticity	• Significant increase in the Δ-N100 (difference between post tetanic and pre-tetanic N100 amplitude) after tDCS – indicating correction of an impaired plasticity state • Improvement in Δ-N100 accompanied by marked clinical improvement with respect to the intensity of auditory hallucinations
Hasan *et al.*, 2013[38]	Case Control Study; 9 patients and 9 healthy controls	• Unilateral tDCS (cathode left M1, anode right supraorbital) compared with bilateral tDCS (cathode left M1, anode right M1) • TMS-generated MEP parameters studied pre- and post-tDCS	• Healthy subjects showed a reduction of left M1 excitability following unilateral tDCS on the stimulated left hemisphere and an increase in right M1 excitability following bilateral tDCS. • In subjects with schizophrenia, no plasticity was induced with either stimulation paradigm

tDCS, transcranial direct current stimulation; DLPFC, dorsolateral prefrontal cortex; TPC, temporoparietal cortex; EEG, electroencephalography.

patients with schizophrenia through tDCS based experiments (Table 3).[33-38] They have shown that both long term potentiation (LTP) and long term depression (LTD) like neuroplasticity is deficient in patients with schizophrenia.[39] This finding has further been extended to unaffected first degree relatives, suggesting a possible endophenotype for the disorder. In these studies, single session of tDCS has been used to induce real time, instantaneous plasticity changes which have been validated by alteration in the motor evoked potentials (MEPs), as studied by TMS. This line of research is quite exciting as it demonstrates, in a very direct and consistent manner, that tDCS causes real, measurable changes in the way neuronal circuits behave. Even more exciting, perhaps, is the finding that these changes are transferred across hemispheres, at least in healthy controls.[35,36] This line of work has been taken a step further in a recent case report,[37] where adaptive changes in this altered state of neuroplasticity were seen after a therapeutic trial of tDCS, and this improvement was in parallel with clinical improvement. This deserves further systematic exploration as an altered neuroplastic state has the potential to become both an endophenotype *and* a biomarker of clinical status in schizophrenia.

tDCS in Schizophrenia: Mechanism of Action

A good summary of the putative mechanisms of action by which tDCS causes benefits has been provided in a recent review.[9] A lot remains unknown with many of the hypothesized mechanisms of action yet to be proven, and understanding these is an area of active research. What is

clear; however, is that the effects of tDCS are highly polarity specific, at least at the neuronal level, and probably, by extension, at the circuit level. Anodal stimulation has been shown to enhance neuronal excitability while the reverse happens if cathode is used.[40] This change in excitability is likely due to shift of the resting membrane potential and is understood to be the primary mechanism underlying the short term effects of tDCS.[11,40] The longer term effects of tDCS are proposed to be due a combination of changes in the synaptic microenvironment—specifically—by NMDA and GABA receptor activity alterations,[9,41] which can then lead to changes along the lines of LTP or LTD. tDCS can result in adaptive modulation of neuroplasticity through brain derived neurotrophic factor (BDNF) dependent mechanism,[42,43] since BDNF abnormalities are linked with the pathogenesis of positive symptoms in schizophrenia including auditory hallucinations,[44] it is possible this might have mechanistic relevance. A cascading butterfly effect of the resulting changes in local neuronal circuitry over longer range neuron networks by means of alteration in the intracellular and extracellular molecular and structural profile is plausible, and may underlie the long term effects of tDCS. Interestingly, it has been found that the effects of tDCS do not appear to be limited to the site of stimulation or to the local networks, even in the short term; in this context it is interesting to note that tDCS of the prefrontal cortex was demonstrated to activate the midbrain and this might have potential mechanistic basis in treating schizophrenia patients.[45] Changes in the MEP parameters have been noted in the opposite hemisphere shortly after a single session of tDCS.[35] Together, all these might be linked with the proposed mechanism of tDCS in altering cortical excitation/inhibition balance,[46] since such cortical dis-inhibitory states have been proposed to underlie the genesis of auditory hallucinations in schizophrenia.[47]

In the context of schizophrenia, the reduction in auditory hallucinations could be understood as hyper polarization in the region of Heschl's gyrus, or activation of an underperforming fronto-temporal circuitry or a combination of both.[20] That the response is sometimes, almost immediate suggests that electrophysiological alterations are primarily at play.[40] The persistence of the effect, as is reported in many studies, is likely to be due to longer lasting structural changes at the synaptic and network level.[41]

FUTURE DIRECTIONS

The most immediate issue that needs to be addressed is perhaps, establishing further support for the effectiveness of tDCS for positive symptoms through further large scale systematic studies; in addition, the impact of tDCS on other symptom dimensions needs to be evaluated. Equally important are long-term studies to establish the safety of tDCS in schizophrenia. Contextually, understanding the predictors of clinical response, the specific symptoms that respond best to the intervention, and those that do not are very important and relevant clinical questions. Given the potential utility of tDCS to enhance cognition in neuropsychiatric disorders, the impact of tDCS monotherapy/combining tDCS with cognitive training to improve cognitive deficits in schizophrenia is another critical area for further research.[48,49] Given the safety of tDCS, this might be considered as an important avenue to explore in ultra-high risk subjects with attenuated psychosis symptoms. Apart from tDCS, parallel techniques with variations in the stimulation parameter like transcranial random noise stimulation (tRNS) and similar others need to be examined systematically. In this context, it is interesting to note that tRNS has recently been reported to improve negative symptoms in schizophrenia.[50] Further refinements in the technique of application of tDCS, like use of more focused application by means of high definition tDCS,[51] or array based applications[52] and their impact on clinical efficacy is another area which needs systematic enquiry. On a larger timeframe, one needs to understand the mechanism of action of tDCS in the context of schizophrenia. The size of the effect and the immediacy and persistence of response suggest that tDCS is altering a fundamental pathology in the diseased brain. Concurrent application of investigative tDCS to characterize the neurobiological aberrations in subjects with genetic risk for schizophrenia is another critical area for future research. Understanding this would be crucial from the pathophysiological point of view since it can provide important leads towards identifying a reliable biomarker for schizophrenia—something that has eluded the research community for several years. This will have far reaching impact on the diagnosis and treatment of this chronic and often difficult to manage disease.

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