Transcranial Direct Current Stimulation to Enhance Cognition and Functioning in Schizophrenia

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Abstract

Schizophrenia is a heterogeneous disorder with characteristic symptoms, including cognitive impairments that are associated with the illness and its outcome. Cognitive impairments include deficits in processing speed and working memory, inattention, and impaired problem-solving ability. These cognitive insufficiencies are considered to reflect the core of the disorder and to worsen as the disorder progresses, further impairing functioning. Novel approaches to treat cognitive impairments are greatly needed and transcranial Direct Current Stimulation (tDCS) is a promising modality that may address these cognitive impairments. TDCS is a noninvasive, non-pharmacological neuromodulation technique that has demonstrated efficacy in improving attention processing in normal controls and in persons with diverse pathologies. By modulating cortical excitability, anodal (excitatory) tDCS to the Prefrontal Cortex (PFC) may facilitate access to existing PFC neural reserves in people with schizophrenia, potentially improving attention. However, this possibility has been only minimally investigated to date. Because cognitive deficits are the strongest determinant of poor functional outcomes in schizophrenia, the development of novel treatments and the combination of innovative neuromodulation and medication strategies to improve cognition and functional capacity are needed. In addition to reviewing cognitive impairments in schizophrenia, this article discusses the potential of tDCS targeting the PFC in patients. It also describes the use of measurement tools as proposed by the National Institute of Mental Health (NIMH) initiative "Measurement and Treatment Research to Improve Cognition in Schizophrenia" (MATRICS), to improve attention processing and to isolate distinct cognitive disruptions in patients with schizophrenia. Recommendations are made for future research approaches.

Keywords: Schizophrenia; Stimulation; Neuroplasticity

Introduction

Schizophrenia is a heterogeneous neurobiological disorder that affects 24 million people worldwide. It is associated with a multitude of symptoms including hallucinations, delusions, affective dysregulation, motivational decline, motor abnormalities, and social withdrawal. Cognitive impairments that are related to the disorder as well as to side effects of some pharmacological agents are evident in a substantial portion of cases, although others demonstrate relative cognitive preservation. Our studies indicate that the heterogeneity of schizophrenia illness manifests in distinct pathophysiologies with respect to disease course and effective treatments [1], with response to both pharmacological and psychosocial treatment quite varied.

Notably, cognitive impairment is the strongest determinant of poor functional outcomes [2]. Cognitive deficits are evident at the time of the first psychotic episode; they persist and may worsen in midlife and late life [3]. Conventional psychopharmacology has only minimally improved cognition [4]. This has led the National Institute of Mental Health to organize a government/academic/industry cooperative initiative ("Measurement and Treatment Research to Improve Cognition in Schizophrenia [MATRICS]") to isolate distinct cognitive disruptions, identify putative molecular targets active in modulating cognition, find drug candidates for those targets, and promote development of novel treatments for schizophrenia such as transcranial Direct Current Stimulation (tDCS).

Neurobiological Function and Cognitive Impairments in Schizophrenia

As we describe in more detail below, mounting evidence of structural abnormalities as well as neuroplastic, neurochemical and circuitry impairments suggest potential etiologies for understanding the altered neurological functions underlying cognitive deficits in schizophrenia [5]. These deficits are also manifest in intentionality, or Theory of Mind (ToM). Additionally, genetic vulnerability related to schizophrenia and cognition is an increasing focus of study.

Structural abnormalities

Because of the heterogeneity of schizophrenia, a variety of structural abnormalities have been documented in schizophrenia, differing based on the subsyndromes of the illness [6]. Visual imaging of the cortex has consistently identified deficits in both gray and white matter as well as changes in amygdala, hippocampus, thalamus, and basal ganglia. General cortical volume changes have been demonstrated in frontal, prefrontal, orbitofrontal, and temporal cortices as well as in the cerebellum. Additional structural changes are found in the ventricular system and the superior temporal gyrus.

Neuroplastic and neurochemical changes

Neuroplasticity refers to the ability of neurons to adapt and change in response to environmental conditions [7]. Disturbances in neuroplasticity have been associated with the cognitive deficits expressed in schizophrenia and reduced Brain Derived Neurotropic

Factor (BDNF). BDNF promotes neuron development and survival [8] and its diminution in the Pre-Frontal Cortex (PFC) is associated with impaired cognitive functioning and learning seen in schizophrenia [9]. Notably, animal studies suggest that transcranial Direct Current Stimulation (tDCS) induces BDNF dependent long term plasticity [9] suggesting the need for further research concerning potential clinical applications.

Reductions in cortical inhibition and dysfunctional long term potentiation-like plasticity [10] in schizophrenia are linked to a dysfunctional neurochemical system, in particular, the glutamate system. Impairment in cortical activity and glutamatergic activity induce neuroplastic changes [11] and thus, developing target sites and stimulation parameters in the regions and circuits associated with cognitive impairment may help regulate underlying molecular activity. By enhancing neuroplasticity in targeted regions, tDCS may help elucidate mechanisms of cognitive compromise in schizophrenia [12]. McClintock et al. [13] point out that brain stimulation-related endophenotypes for distinct neuropsychiatric disorders may provide valuable biomarkers of disease. Using neuro-investigation tools such as tDCS, mechanisms of plasticity that underscore differing trajectories of cognitive disruption may be elucidated and point us toward targets for novel treatments.

Abnormal prefrontal cortex activity and neurociruitry

Research on the neurocircuitry of schizophrenia shows abnormal prefrontal cortex activation demonstrated in neuroimaging studies [14-17]. The most replicated finding has been one of relatively less dorsolateral prefrontal cortex function (hypofrontality), but several functional Magnetic Resonance Imaging (fMRI) studies of patients with schizophrenia have either failed to find hypofrontality or found greater dorsolateral prefrontal cortex activation (hyperfrontality) [14]. Both hypo-and hyperfrontality are hypothesized to be valid and informative reflections of prefrontal cortex dysfunction in schizophrenia. Hypofrontal activity is associated with characteristic symptom expressions of apathy and lack of spontaneity. Hyperfrontal activity is correlated with symptoms such as distractibility, impulsivity and disinhibition. The main cognitive manifestations that suggest prefrontal dysfunction are deficits in response initiation and suppression, focused attention, rule deduction and problem solving as well as difficulties in planning, information generation, maintaining a response pattern and changing a response pattern to another [18].

Executive Functioning (EF) is impaired in schizophrenia [19-21]. EFs describe a range of higher level thinking skills which include, but are not limited to, divided and sustained attention, working memory, abstract thought, flexibility, planning/organizing, inhibition, the regulation of goal-directed behavior and self-monitoring [22-26]. Deficits in EF significantly predict long term outcome and are mostly associated with the dorsolateral Prefrontal Cortex (PFC) [26-27]. Besides EF, the PFC is involved in self regulation of behaviors as well as the capacity to infer one's own and other persons' mental states (Theory of Mind-ToM). Lee et al. [28] demonstrated reduced neural activation in the medial prefrontal cortex for subjects (compared with healthy controls) with schizophrenia during a false belief condition testing ToM.

Theory of Mind (ToM)

ToM is the ability to explain and predict behavior by making attributions about the intentions and mental states of others [29-31]. It is hypothesized to be one of several social cognitive mechanisms that have driven brain size evolution. Although the brain activity associated with attribution processing has been studied extensively, the neuroanatomical correlates of these abilities (e.g. whether subjects who perform better have greater volume of associated brain regions) have yet to be investigated. Because social abilities of this type appear to have evolved relatively recently, and because the prefrontal cortex was the last brain region to develop both phylogenetically and ontogenetically, we anticipate that the PFC may be a target region for tapping into ToM circuitry. Impaired PFC has been associated with impairments in attention, language and memory [5] and neuroimaging of persons with schizophrenia reveals decreased activation of the PFC [31]. We also anticipate that the orbitofrontal cortex may be associated with cognitive deficits in schizophrenia and with ToM in particular [32]. Recent literature has suggested that any deficit within the PFC could cause various levels of cognitive impairments [5]. When electrical stimulation has been applied to the PFC, cognitive functioning and neuroplasticity is improved in patients with schizophrenia [33].

Genetic vulnerability

Genetic vulnerability of schizophrenia has long been researched and supported through various twin and adoption studies [34]. These studies suggest that heritability may be as high as 85 percent [35]. Research has found that siblings of patients suffering from schizophrenia have an increased rate of neuropsychological impairments in executive function, attention, sequencing ability, visual scanning, and verbal reasoning and comprehension [36]. These data have recently pointed to the possible global impairments in cognition that occur across families with a shared genetic pool, making impaired cognition a possible endophenotype for schizophrenia. The most robust findings on deficits among relatives is of impaired verbal fluency, cognitive flexibility and inhibition and working memory [37].

Despite the plethora of data yielding promising results of a genetic basis, the evidence for any specific susceptibility gene for schizophrenia (and its subtypes) is limited [37]. It appears more likely to be a "collective" genetic risk involving multiple genes [35]. Recent evidence has supported an association with specific genome and copy number variations related to schizophrenia [35]. The major histocompability complex region on chromosome 6p21.3-22.1 is thought to be related to the immune response implicating genetic risk of schizophrenia. The neurogranin gene on 11q24.2 and the intron four of the transcription factor 4 on 18q21.2 may be associated with the cognitive deficits found in schizophrenia [38].

Research has also identified specific subtypes of schizophrenia that further point to a genetic (and possibly to an epigenetic) etiology. Fathers older than 45 to 55 years are approximately three times as likely to have offspring with schizophrenia [39]. Persons with Paternal Age Related Schizophrenia (PARS) have a distinct presentation from patients with other etiologies. PARS subjects have been found to present differently in several domains, including increased symptom severity and increased responsiveness to treatment [40], suggesting that the PARS subtype may exhibit increased cognitive impairment, but may potentially be more responsive to interventions such as tDCS.

Cognitive Impairments in Schizophrenia

Research suggests that those with schizophrenia will have cognitive decline that will pervasively impact overall functioning resulting in decreased social and community functioning [41]. One cognitive domain commonly affected in schizophrenia includes selective attention. Selective attention is the ability to maintain concentration on an intended stimulus and to inhibit non-relevant information. A deficit in selective attention can be indexed by increased distractibility

[42], impairing social skills, problem solving and functionality [2]. Working memory, also commonly affected by schizophrenia, is the ability to retain, recall, manipulate and associate information. Other disturbances observed in schizophrenia include impaired skill learning and task acquisition and the ability to retrieve and relate information, thereby reducing language function, sensory function, and processing speed [5].

Long-term risks related to impaired cognition

There are multiple long term risks related to impaired cognition in schizophrenia. When evaluating longitudinal studies, cognitive impairments that affect vocabulary are evident in childhood. Whereas normal controls increase vocabulary, a decline in vocabulary (verbal memory) is evident from childhood in persons with schizophrenia [43]. One study demonstrated that on average, subjects with schizophrenia were one standard deviation below that of the controls when comparing cognitive performance and had decreased IQ and global cognition abilities [3]. Further evidence supports the presence of cognitive impairment at the time of the first psychotic episode, with an IQ decline during prodrome and the first episode of psychosis [44].

Strong evidence exists for deteriorating cognition in aging subjects with schizophrenia. According to Friedman et al. [45], geriatric schizophrenic patients have an increase in cognitive decline comparable to subjects with Alzheimer's disease and cognitive decline accelerates after age 65. One study of hospitalized psychiatric geriatric patients showed a decline in cognition and adaptive functioning at 2.5 years after hospitalization, thereby underscoring the bi-directional relationship between functioning and cognitive capacity [42]. A meta-analysis examining functional outcomes in the community suggested that functioning was significantly influenced by social cognition [46]. Verbal fluency, verbal learning, memory, and processing speed were most associated with community functioning outcomes, and verbal learning and memory were highly associated with social behavior.

Treatments for Enhancing Cognition

There are few effective treatments for enhancing cognition. The lack of treatment options has been addressed by the National Institute of Mental Health through an initiative entitled "MATRICS," Measurement and Treatment Research to Improve Cognition in Schizophrenia [47]. MATRICS was developed to address the barriers that prevent the development of new pharmacological treatments for cognitive deficits in schizophrenia. The barriers include: the lack of effective measurement tools to assess cognitive deficits, the incapability of neurocognitive test scores to serve as the primary measure for outcomes and the need for additional outcome measures. The lack of an effective design for clinical trials and the lack of collaboration with other governmental agencies and academic institutions are additionally identified as barriers [48].

Recommendations were made by MATRICS to address the cognitive deficits that affect nearly every individual with schizophrenia and are closely tied to functional impairments that result in poor community adaptation. The MATRICS called for reliable and valid assessment of cognition at the level of all individual major cognitive domains including speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition [48]. The MATRICS consensus group emphasized the importance of test-retest reliability, utility of the test for repeated measures (i.e., tests that did not have substantial practice effects), inclusion of functional outcome measures, tolerability and practicality of cognitive batteries [47].

In 2011, the MATRICS consensus cognition battery was utilized in a study to assess the cognitive domains, symptoms and functional outcomes in persons with schizophrenia. It was found that a subject's educational and occupation status was predicted by the working memory and severity of negative symptoms. The ability to live independently was related to verbal memory scores. Lastly, social functioning was predicted by social cognition, attention and negative symptoms [48]. Since functional outcomes are so closely tied to cognitive functioning, it is important to advance knowledge and understanding of schizophrenia pathology and treatment by applying neuroplasticity concepts as a framework to theories of the illness [49,50]. Several of the barriers addressed are relevant to clinical research of tDCS in this population.

Transcranial Direct Current Stimulation (tDCS) for Cognitive Impairment

Transcranial Direct Current Stimulation (tDCS) is a promising treatment for cognitive impairment in schizophrenia and otherwise. TDCS is a neuromodulation technique that delivers electrical current stimulation to the cerebral cortex [51]. The primary mechanism of action is to induce a polarity shift of the resting potential [52]. Anodal stimulation increases cortical excitability whereas cathodal stimulation decreases cortical excitability [51,52]. By altering neuronal activity, long term potentiation and depression are affected [51]. Because decreased cortical activity, specifically in the prefrontal cortex, has been found in persons with schizophrenia and is associated with cognitive impairments, stimulation of this region has been found to enhance a variety of cognitive functions [53]. TDCS has been studied in persons with Parkinson's disease, Major Depressive Disorder (MDD), stroke, Alzheimer's disease, and among healthy subjects. Findings suggest that tDCS has great potential as a non-invasive therapeutic strategy for depression, cognitive impairment and facilitating learning [54].

tDCS is delivered through a battery operated device that serves as a distributor of weak electrical current stimulation [55]. The device is connected to a pair of electrodes, one of which is anodal and the other of which is cathodal [56]. The electrodes are covered in saline soaked sponges that are placed on the scalp with surface areas ranging from 25 to 35 cm2. Depending on the therapeutic target, stimulation may be unipolar, with only one electrode on the scalp, and the other below the neck, or bipolar, with both electrodes on the scalp [56]. Placement is determined according to the EEG 10-20 System, with the cortex as the primary target for improving cognition [56]. The intensity of the current ranges from 0.5 to 2 mA and duration of treatment varies from 5 to 35 minutes [57]. The safety of tDCS has been established through various studies, with the most common side effects being mild tingling or itching, fatigue or headache [56].

The Effect of tDCS on Cognition in Neurodegenerative Disorders other than Schizophrenia

Ferrucci et al. [58] demonstrated that anodal tDCS to the temporoparietal region in patients with Alzheimer's disease improved recognition memory, whereas cathodal stimulation decreased recognition memory performance. Boggio et al. [59] found that both anodal and cathodal stimulation to the left temporal cortex improved cognition compared with sham tDCS.

The impairments in cognitive functioning in Major Depressive Disorder (MDD) have been documented [60]. In 26 patients with MDD, anodal tDCS was applied to the Dorsolateral Prefrontal Cortex (DLPFC) or the occipital cortex as compared with sham control

[61]. Results showed that subjects who received one session of tDCS stimulation to the left DLPFC had improvements in task performance and positive emotional processing [61].

Cerebral vascular accidents directly impede blood flow resulting in neuronal death. Patients who suffer from a stroke often experience cognitive dysfunction. Anodal tDCS has been applied to the left DLPFC in a single blind sham controlled study. The results showed improvements in working memory, one of the primary areas affected after a stroke [62]. Attention has been improved in this population with similar tDCS parameters [63]. The effects of cathodal tDCS have been tested in subacute stroke patients to Wernicke's area. Improvements in auditory verbal comprehension were demonstrated for anodal vs. sham tDCS [64].

Parkinson's disease is a neurodegenerative disease that also has a wide range of cognitive deficits. Anodal tDCS has been applied to the left frontal cortex and the motor cortex at varying degrees of electrical intensity in subjects with Parkinson's disease [65]. Improvements in working memory were only seen with increased stimulation to the left PFC demonstrating the importance of identifying both optimal site and dose parameters for distinct clinical populations [65].

The Effect of tDCS on Cognition in Healthy Subjects

A large body of research points to efficacy of tDCS in improving memory in healthy subjects. Fregni et al. [66] conducted a study of 14 subjects comparing anodal stimulation to the left DLPFC, cathodal stimulation to the left DLPFC and anodal stimulation to the motor cortex. They found that healthy adults receiving 10 minutes of 1 milliampere anodal stimulation to the DLPFC had improved working memory. These results were replicated in a study that evaluated oscillatory power relative to outcomes in working memory. Here, healthy adults received 20 minutes of 1 milliampere anodal tDCS stimulation to the left DLPFC and likewise experienced increased working memory [67], tDCS over DLPFC has been found to induce changes in current densities of delta band [68] and in theta and alpha bands [67] which are thought to increase working memory. Notably, cathodal stimulation not only decreased oscillatory power but also decreased working memory. Research supports an increase in verbal and visual memory following anodal tDCS to the left DLPFC [65-68].

tDCS can also effectively augment planning ability. Dockery et al. [69] used cathodal stimulation during the early stage of learning and alternated anodal stimulation during the later stage of learning to the left DLPFC. They demonstrated enhanced planning ability that endured at 6 and 12 month intervals [69] Set shifting is considered a complex cognitive skill and applying anodal tDCS to the PFC and to the primary motor cortex improved performance on cognitive tasks. Importantly, tDCS improved the speed of set shifting, but did not decrease the errors or accuracy in relation to the task [70]. Complex verbal associative learning assessed via the remote associates showed that tDCS to the left PFC improved test scores [71].

The Effect of tDCS on Cognition in Schizophrenia

There is some evidence for the direct effect that tDCS treatment may have on cognition in schizophrenia. Enhancing probabilistic association learning with tDCS has been investigated with 20 subjects with schizophrenia/schizoaffective disorder in a single blind sham controlled crossover design [34]. Anodal stimulation to the PFC significantly improved learning as compared with controls. Subjects with higher baseline cognitive functioning were found to be more responsive to tDCS [34].

Neuromodulation stimulation of the PFC stimulation has also been shown to improve working memory. In a 4-week randomized double-blind sham-controlled pilot study design, Barr et al. [72], tested verbal working memory n-back task before and after stimulation to the left and right dorsolateral PFC in persons with schizophrenia. The results were promising. The rTMS significantly improved 3-back accuracy for targets compared with placebo sham (Cohen's d=.92). These pilot data suggest that PFC stimulation may be an efficacious, and safe treatment for working memory deficits in patients with schizophrenia. This suggests that other neuromodualtion approaches such as tDCS targeting the PFC may improve working memory.

To evaluate the effects on Long Term Potentiation (LTP) plasticity, Hasan et al. [73] delivered anodal tDCS to subjects with single and multiple episode psychosis. Notably, these subjects (compared with single-episode and healthy subjects) had significant reductions in LTP plasticity with altered signal to noise ratios, likely contributing to dysfunctional filtering and cognitive deficits. Both groups of patients with psychotic episodes showed diminished cortical inhibition as compared to healthy subjects. Deficits in cortical inhibition have been attributed to lack of inhibition of gamma oscillations in the Dorsolateral Prefrontal Cortex (DLPFC) [73,74]. Notably, there is evidence to suggest that anodal tDCS at a frequency of 2 milliamperes in patients with schizophrenia may increase oscillatory power. The induction of action potentials using tDCS causes a slight change in the resting potential of the stimulated cells that may improve information processing by increasing oscillatory activity and bringing neurons closer to neuronal depolarization thresholds [66-67].

Challenges in the use of transcranial direct current stimulation as an effective treatment in schizophrenia

There are specific challenges related to the conduct of tDCS trials. First, any proposed intervention that is outside of conventional practice can adversely affect recruitment. Encouraging subjects to come to the lab for a single to multiple treatments can also be a concern. Inclusion criteria should address the severity and baseline functioning of the person with schizophrenia [34]. Maintaining necessary blinding can be compromised by the localized redness seen at the site versus the lack of redness with sham subjects. Typical study designs include (1) active tDCS versus sham tDCS, (2) tDCS versus another therapy, (3) tDCS plus another therapy versus sham tDCS and another therapy, or (4) a combination of the above [56]. The amount of stimulation applied must be chosen correctly [66]. Lastly, the outcome measures used should include valid and reliable tests, as described by MATRICS that are not compromised by learning effects [47]. Additionally, measures may include EEG, PET, functional MRI, and measures of symptom severity. They may also include biomarkers such as BDNF or genetic testing to identify subtypes of schizophrenia with more optimal responses to tDCS, including durability of effect [56].

Conclusion

The literature supports the use of tDCS for improving cognition, not only in the general population and chronically ill subjects with neurodegenerative diseases, but also for those with schizophrenia [33]. Evidence clearly supports the need for further study of tDCS as a therapeutic treatment modality for improving cognition and improving functioning, thereby decreasing the burden of this illness to the individual and to society. The findings described suggest that tDCS may emerge as a non-invasive therapeutic modality in the future, particularly for select cognitive domains in schizophrenia. However, there is a need for additional clinical trials with sham controls and clarification of the subgroups of patients most likely to benefit. Further research using appropriate cognitive batteries, neuroimaging, symptom measurement and genetic testing is needed to evaluate the potential therapeutic benefits of tDCS alone and in combination with evidence-

based pharmacological strategies. With a stronger evidence base, tDCS may present an attractive addition or alternative to available treatments for improving neurocognitive impairments in schizophrenia, particularly given its mild side-effect profile, low cost and potential compatibility with pharmacological and psychotherapeutic strategies.

Acknowledgment

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