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Brain Stimulation

Stimulating cognition in schizophrenia: A controlled pilot study of the effects of prefrontal transcranial direct current stimulation upon memory and learning

Natasza D. Orlov [a, *], Derek K. Tracy [a, b], Daniel Joyce [a, c], Shinal Patel [a], Joanna Rodzinka-Pasko [a], Hayley Dolan [a], John Hodsoll [a], Tracy Collier [a], John Rothwell [d], Sukhwinder S. Shergill [a, c]

[a] Institute of Psychiatry, Psychology and Neuroscience, King's College London, United Kingdom
[b] Oxleas National Health Service (NHS) Trust, London, United Kingdom
[c] South London and Maudsley NHS Trust, London, United Kingdom
[d] Institute of Neurology, University College London, United Kingdom

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ABSTRACT

Background: Schizophrenia is characterized by prominent cognitive deficits, impacting on memory and learning; these are strongly associated with the prefrontal cortex.
Objective/hypothesis: To combine two interventions, transcranial direct current stimulation (tDCS) over the prefrontal cortex and cognitive training, to examine change in cognitive performance in patients with schizophrenia.
Methods: A double blind, sham-controlled pilot study of 49 patients with schizophrenia, randomized into real or sham tDCS stimulation groups. Subjects participated in 4 days of cognitive training (days 1, 2, 14, 56) with tDCS applied at day-1 and day-14. The primary outcome measure was change in accuracy on working memory and implicit learning tasks from baseline. The secondary outcome measure was the generalization of learning to non-trained task, indexed by the CogState neuropsychological battery. Data analysis was conducted using multilevel modelling and multiple regressions.
Results: 24 participants were randomized to real tDCS and 25 to sham. The working memory task demonstrated a significant mean difference in performance in the tDCS treatment group: at day-2 (b = 0.68, CI 0.14–1.21; p = 0.044) and at day-56 (b = 0.71, 0.16–1.26; p = 0.044). There were no significant effects of tDCS on implicit learning. Trend evidence of generalization onto untrained tasks of attention and vigilance task (b = 0.40, 0.43–0.77; p = 0.058) was found.
Conclusions: This is the first study to show a significant longer-term effect of tDCS on working memory in schizophrenia. Given the current lack of effective therapies for cognitive deficits, tDCS may offer an important novel approach to modulating brain networks to ameliorate cognitive deficits in schizophrenia.

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1. Introduction

There has been an increasing awareness of the importance of cognitive deficits in schizophrenia. They have a greater role, relative to positive symptoms such as hallucinations and delusions, in predicting 'real world' functioning such as employment and relationships [1], sufficient that there have been calls to reconceptualize psychosis as a primarily cognitive disorder [2]. Increasing evidence has accumulated that cognitive deficits are largely unresponsive to conventional antipsychotic treatment [3,4].

Cognitive deficits span a wide range of domains and while individual cognitive profiles can vary considerably, there are typically impairments in memory, attention, and executive function, relating to reasoning and problem solving [5]. Such deficits are associated with aberrant, predominantly hypoactive, prefrontal cortical activation, compared with healthy participants [6]. Dysfunctional activation specifically of the dorsolateral prefrontal cortex (DLPFC) - conventionally associated with executive functioning and working

memory - is a common finding in the neuroimaging literature. Neuroimaging data have also shown prefrontal activation deficits to be associated with impaired performance during memory tasks [6]. Meta-analyses have reported reduced activation in the DLPFC of patients with schizophrenia, during encoding and retrieval of episodic memory, suggesting that the aberrant activation in the DLPFC may be a contributing factor in the deficits observed in other cognitive domains. Such aberrant activation can predate the onset of psychotic disorders and is not secondary to treatment with antipsychotic medication [7].

The DLPFC offers as a promising target for improving cognition in schizophrenia (6). Cognitive training, or cognitive remediation (as it is known when applied to clinical deficits), is a behavioral intervention (e.g. drill and practice, strategy teaching) targeted at improving the cognitive domains of attention, memory, executive functioning and social cognition [8]. While improvement on the specific trained task is considered a prerequisite of such training, the goal is to induce generalization to other non-trained tasks within the same cognitive domain and ideally improvement in global functioning. A recent meta-analysis of cognitive training in schizophrenia suggested that improvements can generalize to global cognition [8]; however such effects were modest, and generally more effective when added to interventions enhancing psychosocial rehabilitation. This has prompted an interest in the potential of combined approaches with both cognitive remediation and adjunct pharmacological treatments [9]. Individual pharmacological studies investigating a range of agents impacting different neurotransmitter systems - including the glutamatergic and acetylcholinergic nicotinic receptors [4,9] - have not yielded significant clinical benefits. This has led to a renewed interest in the benefit of more mechanistic interventions focused on modulating regional brain function, particularly transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) [10]. While rTMS has been demonstrated to be beneficial for treatment of auditory hallucinations, there has been limited direct application to cognitive deficits in schizophrenia [11]. This has been primarily due to the practical difficulties of applying this technique during the performance of more complex cognitive tasks, with tolerability and utility also adversely affected by noise and some participant discomfort. Logistically tDCS has advantages over rTMS in that it is portable, low cost and with, arguably, better patient tolerability. Further, from an experimental design perspective it permits the effective blinding of subject through a simple sham condition and can be applied directly during the online performance of a cognitive task [12]. The technique produces a weak electrical field that, when applied transcranially, renders neuronal populations more or less likely to fire in response to additional incoming action potential inputs. tDCS effectively alters neuronal excitability, with neural effects demonstrated to outlast the active stimulation for up to 90 min [13]; such changes are thought to be mediated through N-methyl-D-aspartate (NMDA) receptors and share the characteristics of synaptic long-term potentiation [14].

A recent meta-analysis of thirty three experiments, investigating the effects of a single application of non-invasive brain stimulation (tDCS and rTMS) on working memory in healthy volunteers and clinical populations, found improvement in both accuracy and reaction times on the n-back task, following the real stimulation condition [15]. Furthermore, the available longitudinal data suggests that enhanced learning after tDCS, motor and numerical skills acquisition, can be maintained for between 6 weeks and 3 months in healthy volunteers [16,17].

To date there have been three studies that have examined the effects of tDCS on task performance in patients with schizophrenia, all utilizing single application protocols [18–20]. Hoy et al. [19,20] found that higher (2 mA) but not lower (1 mA) tDCS facilitated performance on a working memory task (n-back) compared with the sham condition. However, interestingly, Vercammen et al. [18], in a cross-over design, found that only a sub-group of patients demonstrated enhanced learning rates after tDCS, as measured on an implicit learning task (weather prediction).Patients who showed an initial capacity for learning during baseline trials benefitted from subsequent stimulation, whereas those that did not show such learning at baseline did not show any significant benefits from the stimulation.

Here, we examined the feasibility, effectiveness, generalizability, and longer-term effects of tDCS on cognitive functioning in schizophrenia, in a pilot study. We hypothesized that acute administration of real tDCS would significantly facilitate performance on the cognitive training tasks, and that participants treated with real tDCS would demonstrate improved retention of performance evident on next-day and the longer-term follow-up. Furthermore, the effects of cognitive training and real tDCS would generalize onto significant performance improvements on related cognitive domains of executive function, and attention and vigilance as measured by the CogState neuropsychological assessment battery [21].

2. Material and methods

2.1. Participants and protocol

49 right-handed medicated participants with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder [22], on stable antipsychotic doses for the previous three months, were enrolled from three clinical sites in south London. Participants were recruited by the study investigators and were offered incentives for their travel expenses and time (£25/visit). Participants who were taking benzodiazepines or other hypnotics, met criteria for alcohol or substance dependence in the previous six months, or had a history of any neurological disorder or head injury accompanied with loss of consciousness and/or required hospitalization were excluded. This study was approved by the Stanmore National Research Ethics Committee (REC number 11/LO/0248); all study procedures have been conducted in accordance with the Declaration of Helsinki.

Participants attended for study visits on five separate days (Fig. 1): a baseline assessment and four cognitive training days (day 1, day 2, day 14 and day 56). Clinical and neuropsychological assessments were completed at the baseline visit using the Positive and Negative Syndrome Scale (PANSS) [23]; neuropsychological functioning was measured with the CogState battery [21]; participants' intelligence quotient was assessed using II subsets (Matrix reasoning, and vocabulary) of the Wechsler Abbreviated Scale of Intelligence [24].

Eight training sessions occurred, two on each day separated by a 45 min gap (Fig. 1), to maintain the study design across all visits. During sessions 2 and 6 participants received concomitant real or sham tDCS; half of participants — both real and sham tDCS - also underwent fMRI scanning during session 6; the neuroimaging data are not reported in this current work. The CogState battery was repeated on all participants 45 min after session 6. The stimulation was applied during the second session of the training on each day, in order to ensure that this was modulating performance when the task was familiar to the patients, reducing any novelty effect and thus reducing any initial attentional variability in task performance. The use of paired testing with stimulation applied only during the second session on each day permitted the assessment of retention effects after a short overnight period and across longer periods, independent of the stimulation session itself.