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The effect of transcranial Direct Current Stimulation on gamma activity and working memory in schizophrenia

Kate E. Hoy *, Neil W. Bailey, Sara L. Arnold, Paul B. Fitzgerald

Monash Alfred Psychiatry Research Centre, The Alfred and Monash University, Central Clinical School, Victoria, Australia

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ABSTRACT

Working memory impairments in schizophrenia have been strongly associated with abnormalities in gamma oscillations within the dorsolateral prefrontal cortex (DLFPC). We recently published the first ever study showing that anodal transcranial Direct Current Stimulation (tDCS) to the left DLPFC was able to significantly improve working memory performance in schizophrenia. In the current paper we present a secondary analysis from this study, specifically looking at the effect of tDCS on gamma activity and its relationship to working memory. In a repeated measures design we assessed the impact of anodal tDCS (1mA, 2mA, sham) on gamma activity in the left DLPFC at three time-points post-stimulation (0 min, 20 min, 40 min). EEG data was available for 16 participants in the 2mA condition, 13 in the 1mA condition and 12 in the sham condition. Following 2mA stimulation we found a significant increase in gamma event-related synchronisation in the left DLPFC, this was in the context of a significantly improved working memory performance. There was also a significant decrease in gamma event-related synchronisation, with no changes in working memory, following sham stimulation. The current study provides preliminary evidence that tDCS may enhance working memory in schizophrenia by restoring normal gamma oscillatory function.

1. Introduction

Cognitive impairments are a core feature of schizophrenia. They are highly prevalent, result in considerable functional disability, and are not effectively treated by current approaches (Insel, 2010). Pharmacotherapy, despite its effectiveness for the positive symptoms of schizophrenia, has shown little to no effect on the cognitive impairments (Kreyenbuhl et al., 2010). Cognitive remediation has generally resulted in only modest improvements in cognition following many hours of therapy (Vinogradov et al., 2012).

Working memory refers to the process of keeping information 'in mind' for short periods of time. It is an essential component of higher level cognitive functions (for example language, learning, problem solving), and indeed improvements in working memory have been shown to enhance more complex thought and action (Jaušovec and Jaušovec, 2012). In non-clinical populations working memory functioning has been consistently associated with activity in the dorsolateral prefrontal cortex (DLPFC) (For review see Curtis and D'Esposito (2003)). While working memory is subserved by a number of brain regions, it has been shown that the DLPFC is a central node for the systems responsible for the manipulation of information (Barbey et al., 2013). Indeed, impairments in working memory in schizophrenia have been reliably associated with impaired functioning DLPFC; more specifically it is abnormalities in neural synchrony within this brain region that are believed to underlie the working memory deficits (Chen et al., 2014; Haenschel et al., 2009; Lett et al., 2013). Neural synchrony, referring to large populations of neurons firing simultaneously at specific frequencies, has been shown to be essential for successful cognitive functioning (Uhlhaas and Singer, 2006). Working memory in particular is associated with synchronous activity at the gamma frequency ($>$ 40 Hz), with increased cognitive effort associated with increased gamma synchrony in healthy populations (Basar-Eroglu et al., 2007; Howard et al., 2003). Dysfunctional gamma activity in schizophrenia has been repeatedly reported in the literature, believed to be related to the well-established GABA impairments seen in the illness (Chen et al., 2014; Lett et al., 2013;). GABA is the brains' primary inhibitory neurotransmitter and, amongst other functions, has a central role in both generating and modulating synchronous gamma activity (Chen et al., 2014). The literature is somewhat mixed with respect to the nature of the gamma abnormalities in schizophrenia, namely whether gamma is excessive or impaired (Basar-Eroglu et al., 2007; Chen et al., 2014; Gonzalez-Burgos et al.,

* Correspondence to: Monash Alfred Psychiatry Research Centre, Level 4 607 St Kilda Road, Melbourne, 3004. Tel.: +61 3 9076 5034; fax: +61 3 9076 6588.
E-mail address: Kate.Hoy@monash.edu (K.E. Hoy).

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2011; Haenschel et al., 2009). In reviewing this literature Sun et al. (2011) concluded that gamma activity is in fact not optimally regulated in patients with schizophrenia wherein patients are not able to increase gamma when the level of cognitive effort requires it and that below a certain level of cognitive demand, (when gamma suppression is thought to be adaptive), they instead show an increase. Indeed, research has indicated that patients with schizophrenia are not able to modulate gamma activity in response to cognitive task demands (Basar-Eroglu et al., 2007; Chen et al., 2014; Gonzalez-Burgos et al., 2011; Haenschel et al., 2009; Moran and Hong, 2011; Sun et al., 2011). Treatment approaches which target such processes would have considerable potential for significantly improving working memory function in schizophrenia.

Transcranial Direct Current Stimulation (tDCS) is a non-invasive form of brain stimulation which has shown considerable promise for the enhancement of cognition (Utz et al., 2010; Jacobson et al., 2012). tDCS involves the application of a very weak electrical current applied using two surface electrodes (anode and cathode) applied to the scalp. This current alters the excitability of brain cells by shifting their membrane potentials in a de- or hyperpolarising direction; thus making them more or less likely to fire (Nitsche and Fregni, 2007). Stimulation of brain cells under the anode appears to increase brain activity whereas stimulation under the cathode generally has the opposite effect (Jacobson et al., 2012). tDCS is a non-polarising form of brain stimulation, unlike Transcranial Magnetic Stimulation (TMS), and therefore is not associated with a risk of seizure induction (Nitsche and Fregni, 2007). Indeed tDCS, when provided within defined safety limits, has been shown to be a safe and well tolerated technique being associated with only minor adverse effects such as tingling or itching at the stimulation site (Poreisz et al., 2007).

There is evidence from Magnetic Resonance Spectroscopy (MRS) investigations that anodal tDCS has its excitatory effects via the direct modulation of GABA-ergic activity (Stagg et al., 2011, 2009), with a growing number of studies also showing enhanced neural synchrony following anodal tDCS (Hoy et al., 2013; Zaehle et al., 2011), including in the gamma frequency range (Antal et al., 2004). In light of the converging evidence connecting the dysfunctional processes thought to underlie working memory deficits in schizophrenia and the proposed mechanisms of action of tDCS, we recently undertook a proof of concept study to investigate whether tDCS was able to enhance working memory in schizophrenia (Hoy et al., 2014). We revealed a significant improvement in working memory performance over time following a single 20 min stimulation session of 2mA anodal tDCS to the left DLFPC, while 1mA and sham stimulation had no effect on performance. While we have shown tDCS to have considerable promise with respect to enhancing behavioural performance in schizophrenia, we have yet to examine the effect of tDCS on the abnormal gamma thought to underlie working memory impairments.

The aim of the current study was to investigate whether our previously reported improvements in working memory following 2mA anodal tDCS (Hoy et al., 2014) were reflected by changes in gamma activity in the left DLPFC. In Hoy et al. (2014) significant improvements in working memory performance were seen over time following 2mA tDCS as compared to no changes in performance over time post 1mA or sham stimulation. Therefore, in the current analyses we investigated the effect of 2mA, 1mA and sham stimulation on change in gamma event-related synchronization (ERS) during performance of a working memory task across the three time-points post-stimulation (i.e. 0 min, 20 min and 40 min). We hypothesised that 2mA anodal tDCS would result in increased gamma activity over time, in line with the improvements seen in working memory performance. We also hypothesised that neither 1mA nor sham stimulation would result in significant changes in gamma, consistent with the lack of behavioural improvement in these conditions.

Table 1
Patient demographics and clinical data.

	2mA ($n=16$)	1mA ($n=13$)	Sham ($n=12$)
Gender (*f*/*m*)	6/10	5/8	4/8
Handedness (*r*/*l*)	16/0	13/0	12/0
Age	41.31 ± 10.25	40.62 ± 8.81	40.42 ± 10.65
Years of education	13.88 ± 1.78	13.92 ± 1.98	13.25 ± 1.60
Years since diagnosis	15.45 ± 8.57	15.22 ± 8.30	15.00 ± 7.18
PANSS positive	17.69 ± 7.64	17.92 ± 6.86	18.75 ± 7.92
PANSS negative	15.50 ± 3.95	15.85 ± 4.20	15.83 ± 4.22
PANSS general	36.06 ± 8.87	35.92 ± 8.49	37.92 ± 8.21
PANSS total	69.25 ± 17.15	69.69 ± 15.99	72.50 ± 16.98

2. Method

2.1. Participants

Eighteen participants with schizophrenia were recruited into the repeated measures within subjects study; our previous manuscript reported the behavioural findings only from all 18 participants (Hoy et al., 2014). The current paper reports a secondary analysis from this study which examined neurophysiological changes. Due to the presence of excessive noise, the EEG data from a number of participants across the conditions was not able to be used. Analysable EEG data for the current analysis was available for 16 participants in the 2mA condition, 13 in the 1mA condition and 12 in the sham condition. (See Table 1 for demographic and clinical data by stimulation condition).

Diagnosis was confirmed using the Mini-International Neuropsychiatric Interview (MINI), administered by research staff experienced in its use (KH/SA) (Sheehan et al., 1998). All recruited participants were regularly taking atypical antipsychotics (i.e. 3 Risperidone; 3 Aripiprazole; 2 Olanzapine; 2 Amisulpride;1 Clozapine; 1 Paliperidone; 1 Olanzapine+Paliperidone; 1 Olanzapine+Aripiprazole; 1 Aripiprazole+Quetiapine; 1 Quetiapine+Ziprasidone; 1 Pericyazine+Asenapine and 1 Quetiapine+Asenapine), nine were additionally taking antidepressant medication (i.e. 2 SNRI; 4 SSRI; 1 TCA and 1 SNRI+TCA). There are a number of known, as well as many potential unknown, interaction effects between medication and tDCS (Brunoni et al., 2010). Therefore, in addition to excluding participants on medication that has been shown to influence the effects of tDCS (see Brunoni et al. (2010)), we also required participants to remain on their current dose and type of medication throughout the study. Exclusion criteria consisted of the presence of any neurological or serious medical conditions, or current pregnancy. Written consent was obtained from participants prior to commencement of the study. Ethical approval was granted by Monash University and the Alfred Hospital ethics committees.

2.2. Procedure

This was a randomised repeated-measures double-blind study design. Participants attended for three sessions which were held at least 72 h apart (See Fig. 1 for study design). Sessions were randomised and counterbalanced, and each involved the provision of 20 min of 1mA, 2mA or sham tDCS followed by working memory assessment with concurrent EEG recordings. An electrode array which allowed recording of frontal activity was applied, namely F3, FZ, and F4; facial electrodes were used for measurement of eye movements (positioned adjacent to the left and right outer canthus of each eye and above and below the left orbit) and left and right mastoids were employed for referencing. The limited EEG array was used to ensure we were able to quickly replace the required electrodes to allow for immediate recording following stimulation. The EEG array was set up and impedances of less than 5 kΩ were achieved before tDCS was applied. Immediately prior to stimulation, the F3 EEG electrode was removed and the anodal tDCS electrode was positioned over the F3 position and the cathode over the right supraorbital region. While montages can vary, particularly with respect to position of the reference electrode, the montage used in the current study is widely accepted as a standard for anodal stimulation of the left DLPFC stimulation (Nitsche et al., 2008). Immediately following stimulation the F3 EEG electrode was replaced and impedances were re-checked, this was achieved within 60 s of the end of stimulation for all participants. Participants undertook the 2-back working memory task immediately following stimulation and at 20 and 40 min post-stimulation. EEG was sampled at 1000 Hz (band pass 0.1–100 Hz) using a SynAmps 2 amplifier (Compumedics, Melbourne Australia). Impedances were maintained at less than 5 kΩ. Electrodes were single Ag/AgCl electrodes.

2.3. Transcranial Direct Current Stimulation

tDCS was applied using an Eldith Stimulator Plus (neuroConn GBH) delivering direct current through two surface electrodes (35 cm² saline soaked sponges). Saline solution was 0.9% saline. Anodal stimulation was applied at the left DLPFC for 20 min (ramp up of 120 s and ramp down of 15 s) across three conditions: 1 mA,