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Short Communication

Transcranial direct current stimulation of prefrontal cortex: An auditory event-related potential study in schizophrenia

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ABSTRACT

Cognitive impairment is one of the most significant factors determining the long-term rehabilitation prospects of schizophrenia patients. Cognitive training has been shown to be beneficial; however, effect sizes of cognitive remediation remain relatively low. Anodal transcranial direct current stimulation (tDCS) increases cortical excitability along with larger N1 auditory event-related potentials (ERPs), thus providing a non-invasive physiological mechanism that is potentially capable of facilitating cognitive training of schizophrenia patients. The current study investigated the effects of left-prefrontal anodal tDCS on auditory discrimination performance and N1, Mismatch Negativity (MMN), and P3b ERPs, which have been linked to cognitive and global function deficits in schizophrenia. We compared 20 min of 2 mA tDCS versus sham stimulation in 14 schizophrenia patients by employing a randomised crossover design. Patients performed equally well in a go/no-go auditory discrimination task when compared to healthy subjects but presented with significantly smaller N1, MMN and P3b amplitudes, which did not change with tDCS. Auditory discrimination performance and reaction times also remained unaffected by tDCS. Our findings suggest that a single application of tDCS has no acute effects on ERPs and associated auditory information processing in schizophrenia patients.

1. Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique which is affecting regional neuronal excitability[1] through the application of a weak electrical current (e.g. 2 mA for 20 min) without directly evoking action potentials.[2] Preclinical studies suggest that tDCS shifts resting membrane potentials of both pre- and postsynaptic neurons, thereby resulting in *hyper*-excitability with anodal or *hypo*-excitability with cathodal stimulation.[1,3]

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When applied in clinical populations, the procedure is proven to be safe and well tolerated.[4,5] Clinical studies to date have provided some evidence for beneficial effects when treating depression symptoms while there are also promising effects reported suggesting better cerebral stroke recovery as well as improved pain treatment and cognitive remediation outcomes with tDCS in neurodegenerative and neurodevelopmental conditions (reviewed in Ref. 5).

Improving the efficacy of cognitive remediation in conditions like schizophrenia would be particularly important since cognitive symptoms are one of the most significant factors determining the long-term rehabilitation prospects of patients suffering from this condition. Little is known, however, how tDCS affects neural processing in schizophrenia. Hence, the current study investigated the effects of prefrontal tDCS on auditory event-related potentials (ERPs), which are known to be reduced in schizophrenia patients and have also been described to be linked to cognitive deficits of the disorder.[6–9]

We hypothesised that anodal prefrontal tDCS increases cortical excitability along with increased ``negativity'' in ``pre-attentive'' ERPs such as N1[10,11,20] and Mismatch Negativity (MMN;[12–16]). We further hypothesised that increased cortical excitability facilitates subsequent ``attentive'' information processing (i.e. improving hit rates and increasing errors of commission whilst performing an auditory discrimination task) along with associated ERPs, such as P3b amplitudes.[17,18]

2. Methods

The study was approved by the University of Newcastle Human Research Ethics Committee (Reference H-2011-0075, H-2011-0367) and took place at the University of Newcastle's Priority Centre for Translational Neuroscience & Mental Health Research in 2013.

2.1. Subjects

Nine male and five female schizophrenia patients (12 right and 2 left-handed) with a mean age of 46.7 (SD 6.4) were recruited from the local community by advertisement. All patients met DSM-IV criteria for schizophrenia.[19] Symptoms were rated on the Scale for the Assessment of Positive Symptoms (SAPS[21]) and the Scale for the Assessment of Negative Symptoms (SANS[22]). Study participation exclusion criteria were a history of epilepsy and/or alcohol/illicit drug abuse/dependence, a previous head injury with unconsciousness, or a hearing impairment. Findings were compared to published data of healthy subjects who underwent an identical psychophysiological research protocol.[20]

2.2. tDCS procedure and study design

tDCS was applied via 35 cm^2 saline-soaked sponge electrodes (Transcranial Direct Current Stimulator PLUS, Magstim). The anodal electrode was placed left-prefrontal at F3 (International 10-20 System) and the cathodal electrode in the right supraorbital region.

Brain stimulation effects were tested single blind by employing a randomised and counterbalanced repeated measurement crossover design comparing ``active'' versus ``sham'' stimulation. In the ``active'' condition, the current was gradually increased over 30 s to 2 mA and maintained for 20 min while in the ``sham'' condition no stimulation was applied after the initial 30-s stimulation (i.e. 10 s of gradually increasing to 2 mA, followed by maintaining 2 mA for 10 s before gradually decreasing the current over 10 s from 2 mA to 0 mA.). The ``active'' condition also ended with gradually reducing the current from 2 mA to 0 mA over 10 s. ``Sham'' and ``active'' tDCS took place one hour apart.

2.3. EEG recording and analyses

EEG recordings commenced 10 min after ``sham'' or ``active'' tDCS while subjects were presented with acoustic stimuli via calibrated headphones (Sennheiser HD 280). A randomised tone sequence with a stimulus-onset asynchrony (SOA) of 600 ms with three types of pure tones were generated (Presentation Software, Neurobehavioral Systems Inc.): a frequent ($p = 0.9$) 1 kHz-tone of 100 ms duration together with a rare ($p = 0.1$) duration-deviant tone of 1 kHz and 50 ms duration or, alternatively, with a rare ($p = 0.1$) pitch-deviant tone of 1.2 kHz and 100 ms duration in two separate recording sessions of 700 stimulus presentation of 630 frequent standard stimuli and 70 rare deviant or oddball stimuli, respectively. Two deviant tones were never presented consecutively. Duration and pitch deviant sessions were alternated between the repeat sessions of ``sham'' or ``active'' tDCS. During EEG recordings, subjects were asked to watch a silent movie and to ignore the tones.

This passive listening task was followed by an active auditory ``go/no-go'' discrimination task. Subjects were presented with a random sequence of frequent ($p = 0.9$) 1 kHz tone with 100 ms duration and rare ($p = 0.1$) digitally composed complex sound with a high frequency cut-off at 11 kHz at 1000 ms SOA (Presentation Software, Neurobehavioral Systems Inc.). Individual sound stimuli were never presented consecutively. The sound stimuli served as the target stimuli in the ``go/no-go'' discrimination task and required a simultaneous button-press response with both thumbs.

Continuous EEG was recorded (NuAmps, Neuroscan Ltd.) against nose reference with tin electrodes (Quick-cap, Compumedics Ltd.) with a 500 Hz sampling rate (high pass 0.1 Hz, low pass 30 Hz, and 50 Hz notch filter) from FZ, CZ, PZ, F3, C3, P3, F4, C4, and P4 (International 10-20 System) and from left and right mastoid. Potential eye movement artefacts were recorded via vertical and horizontal EOG. Impedance was kept below 5 kΩ.

Raw data were corrected for eye-blink artefacts[23] and high pass-filtered (0.2 Hz/12 dB). Epochs were created for −422 ms to 600 ms intervals relative to stimulus onset and rejected for EEGs exceeding ±100 μV. Epochs were then low-pass filtered at 20 Hz and ERPs calculated and averaged relative to a 200 ms pre-stimulus onset baseline.

Mismatch negativity (MMN) was extracted in the passive listening task by subtracting ERPs in response to the frequent standard stimuli from ERPs in response to the rare deviant stimuli (duration and pitch oddballs, respectively). Post-stimulus onset intervals for mean ERP amplitude measures were calculated at Fz for N1 between 100 and 140 ms, 140–240 ms for MMN in response to pitch deviance, 150–250 ms for