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Assessment of anodal and cathodal transcranial direct current stimulation (tDCS) on MMN-indexed auditory sensory processing

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ABSTRACT

Transcranial direct current stimulation (tDCS) is a non-invasive form of brain stimulation which uses a very weak constant current to temporarily excite (anodal stimulation) or inhibit (cathodal stimulation) activity in the brain area of interest via small electrodes placed on the scalp. Currently, tDCS of the frontal cortex is being used as a tool to investigate cognition in healthy controls and to improve symptoms in neurological and psychiatric patients. tDCS has been found to facilitate cognitive performance on measures of attention, memory, and frontal–executive functions. Recently, a short session of anodal tDCS over the temporal lobe has been shown to increase auditory sensory processing as indexed by the Mismatch Negativity (MMN) event-related potential (ERP). This preliminary pilot study examined the separate and interacting effects of both anodal and cathodal tDCS on MMN-indexed auditory pitch discrimination. In a randomized, double blind design, the MMN was assessed before (baseline) and after tDCS (2 mA, 20 min) in 2 separate sessions, one involving 'sham' stimulation (the device is turned off), followed by anodal stimulation (to temporarily excite cortical activity locally), and one involving cathodal stimulation (to temporarily decrease cortical activity locally), followed by anodal stimulation. Results demonstrated that anodal tDCS over the temporal cortex increased MMN-indexed auditory detection of pitch deviance, and while cathodal tDCS decreased auditory discrimination in baseline–stratified groups, subsequent anodal stimulation did not significantly alter MMN amplitudes. These findings strengthen the position that tDCS effects on cognition extend to the neural processing of sensory input and raise the possibility that this neuromodulatory technique may be useful for investigating sensory processing deficits in clinical populations.

1. Introduction

Brain stimulation is a current research tool for elucidating the neurobiological mechanisms underlying cognitive processes and a possible treatment for cognitive dysfunction, including deficits in memory and executive function. Transcranial direct current stimulation (tDCS) is a non-invasive and cost-effective method to temporarily increase or decrease cortical excitability in targeted, localized brain regions. Stimulation is administrated by applying a weak (~1–2 mA), constant current to the scalp via two electrodes: the anode and the cathode. The electrodes can be used as the active or reference electrode depending on the bipolar placement and size of the electrodes, which are typically superimposed on saline-soaked sponges to increase the conductivity of the current and to reduce any skin irritation that may be experienced during stimulation (Nitsche et al., 2005, 2008). The low constant current, flowing from the active to the reference electrode, with peak current densities over the targeted region (Neuling, Wagner, Wolters, Zaehle, & Herrmann, 2012), is typically applied for 10–30 min, and the effects of a single stimulation can persist for up to one hour post-stimulation (Nitsche & Paulus, 2001). In clinical research studies with tDCS, repeated stimulations are needed to produce long lasting effects (lasting weeks; Brunelin et al., 2012). The moderating factors affecting the effects of tDCS include current strength and polarity, electrode size, stimulation duration, and position of the electrodes on the scalp (McKinley, Bridges, Walters, & Nelson, 2012; Nitsche et al., 2008). These factors mediate the relationship between the induced intracerebral flow of current from the electrodes and alterations of local neuronal activity, which allows for the investigation of the relationships between the modulated neural activity and cognitive

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processes or behaviour. As the relationship between tDCS and auditory sensory functioning is not well established, the current study will investigate the effects of 20 min of both active anodal and cathodal tDCS over scalp sites overlapping the primary auditory cortex, using a constant current of 2 mA, compared to 'sham' stimulation (where the electrodes are set up on the scalp, but no current is applied).

The majority of tDCS studies have focused on motor cortex function, the first target for tDCS investigation (Nitsche & Paulus, 2000, 2001). These tDCS studies established that tDCS-induced prolonged effects are not only polarity-specific, with anodal stimulation typically having an excitatory effect by depolarizing neuronal membrane potentials in the region beneath the anodal electrode, and cathodal stimulation generally having the opposite effect through a process of hyperpolarization beneath the cathode electrode (Nitsche et al., 2007), but the strength and endurance of the after-effects depend on current intensity, duration and electrode placement (Nitsche & Paulus, 2000; Nitsche et al., 2008). A simple relation between polarity and behavioural modification has been recently challenged as evidence has shown tDCS can both depolarize and hyperpolarize within the same gyrus and different types of neurons are differently affected depending on their structural features and orientation (Radman, Ramos, Brumberg, & Bikson, 2009; Reato et al., 2013). However, pharmacological studies have elucidated some of the mechanisms of action underlying tDCS effects. The immediate and long-term 'after-effects' of anodal stimulation are no longer present with sodium and calcium channel blockers, while blocking glutamate receptors via N-methyl-D-aspartate receptor (NMDAR) antagonists reduces the after-effects, regardless of current polarity (Nitsche, Fricke, et al., 2003; Nitsche, Liebetanz, et al., 2003). Specifically, NMDAR antagonists have been found to prevent functional 'after-effects' while NMDA agonists can prolong motor potential after-effects over several hours (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche, Fricke, et al., 2003). Although tDCS modulations are dependent on the NMDAR system, which is implicated in synaptic plasticity and memory function, GABAergic interneurons also play a role, as well as dopaminergic, serotonergic and cholinergic activity (Medeiros et al., 2012; Stagg & Nitsche, 2011).

Changes in neuronal activity with tDCS have implications not only for motor behaviours, but also for cognition. Anodal stimulation applied to the prefrontal cortex has improved performance on a variety of cognitive tasks, when compared to 'sham' stimulation (Fregni et al., 2005; Hecht, Walsh, & Lavidor, 2010; Zaehle, Sandmann, Thorne, Jäncke, & Herrmann, 2011). The most robust effects are seen with working memory (WM) tasks (as measured through n-back tasks and the Sternberg task), where anodal stimulation has increased performance and reaction times (Andrews, Hoy, Enticott, Daskalakis, & Fitzgerald, 2011; Gladwin, den Uyl, Fregni, & Wiers, 2012; Teo, Hoy, Daskalakis, & Fitzgerald, 2011). Fregni et al. (2005) found that anodal tDCS (1 mA) enhanced accuracy in a 3-back letter task and Ohn et al. (2008) found an increase in correct responses based on the same paradigm starting 20 min after the beginning of active stimulation. In clinical populations, beneficial effects of anodal stimulation applied over the left DLPFC have been reported for working memory, attentional performances, and information processing in patients with depression (Fregni et al., 2006; Oliveira et al., 2013; Wolkenstein & Plewnia, 2013), probabilistic association learning in a subset of schizophrenic patients (Vercammen et al., 2011), visual recognition memory performance in Alzheimer's disease (Boggio et al., 2009), amelioration of memory deficits in Parkinson's disease (Boggio et al., 2006), and improved response accuracy in a Go/NoGo task and verbal 2-back WM task in patients with post-stroke cognitive decline (Jo et al., 2009; Kang, Baek, Kim, & Paik, 2009). Unlike motor performance, cathodal stimulation has failed to show consistent significant modulation in cognitive tasks, either decreasing or having little impact on performance on similar tasks (Fregni et al., 2005; Hecht et al., 2010). However, cathodal tDCS over the primary and secondary auditory cortex has been found to negatively modulate pitch discrimination and pitch memory performance (Mathys, Loui, Zheng, & Schlaug, 2010; Vines, Schnider, & Schlaug, 2006). Very few tDCS studies have focused on information processing in the auditory cortex and only two investigators to date have assessed the effect of anodal tDCS on auditory discriminability (Chen, Hämmerer, D'Ostilio, et al., 2014; Chen, Hämmerer, Strigaro, et al., 2014; Impey & Knott, 2015), which motivates the current investigation.

Event-related potentials (ERPs) provide an objective, non-invasive neural measure of information processing and ERP components are frequently used to investigate early pre-attentive auditory processes, including sensory gating (indexed by the P50), sensory discrimination (indexed by the mismatch negativity [MMN]) and novelty detection (measured by P3a), as well as higher order processes such as attentional allocation and processing speed (measured by P3b) in healthy volunteers and clinical populations (for review see Braff & Light, 2004). The MMN, an early (~120–250 ms) frontal-maximum negative-going ERP component, is a measure of pre-attentive auditory discrimination mediated by a comparison process within sensory memory (Näätänen, Jacobsen, & Winkler, 2005; Näätänen, Paavilainen, Rinne, & Alho, 2007). MMN is usually elicited when a sequence of repetitive, 'standard' stimuli are interrupted with a rare, deviant 'oddball' stimulus. MMN is elicited automatically when an acoustic feature is detected in brief 'echoic' memory, which deviates from feature memory traces comprising the standard stimulus (Näätänen et al., 2005). Typically, MMN amplitudes increase and latencies shorten with larger deviance and shorter stimulus onset asynchrony (SOA). The MMN is generated primarily in the temporal (auditory) cortex, which is a marker of automatic auditory change, but it also receives contributions from frontal brain regions, which reflect mechanisms involved in involuntary attention switching in response to the change in stimuli (Näätänen et al., 2007; Opitz, Rinne, Mecklinger, Von Cramon, & Schröger, 2002; Shalgi & Deouell, 2007). MMN amplitude is associated with higher-order cognitive and psychosocial functioning in healthy adults, as indexed by performance on a standardized memory task, and overall ratings of psychosocial functioning (Light & Braff, 2005), and has been found to be a biomarker of deficient sensory processing in populations with cognitive dysfunction, such as in schizophrenia (Turetsky et al., 2007; Umbricht & Krljes, 2005). Similar to tDCS, NMDAR activity has also been found to play a key role in MMN generation as antagonists have been found to block MMN generation in animal studies (Javitt, Steinschneider, Schroeder, & Arezzo, 1996) and diminish MMN amplitudes in humans (Umbricht et al., 2000). As MMN amplitude is a direct brain measure of auditory sensory discrimination, which correlates with more complex cognitive functioning, investigations into tDCS effects on MMN alteration are warranted and results can be used to determine the utility of the MMN as a quick and reliable biomarker (Butler et al., 2012; Green et al., 2009) of tDCS treatment effects on auditory cognition.

Although there is an increasing interest in the cognitive modulating actions of tDCS, there have been very few studies assessing tDCS effects on early, pre-attentive auditory processing. Zaehle, Beretta, Jancke, Herrmann, and Sandmann (2001) found that anodal tDCS increased amplitudes of the auditory P50 (an early positivity at ~50 ms) ERP, while cathodal tDCS induced larger N1 (an early negativity at ~100 ms) amplitudes, indicating increases in early sensory registration. However, in a study by Chen, Hämmerer, D'Ostilio, et al. (2014), which assessed tDCS over the right frontal cortex, MMN to pitch deviants were reduced with