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Transcranial direct current stimulation can enhance working memory in Huntington's disease☆

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ABSTRACT

Transcranial direct current stimulation (tDCS) combined with a cognitive task can enhance targeted aspects of cognitive functioning in clinical populations. The movement disorder Huntington's disease (HD) is associated with progressive cognitive impairment. Deficits in working memory (WM) can be apparent early in the disease and impact functional capacity. We investigated whether tDCS combined with cognitive training could improve WM in patients with HD, and if baseline clinical or cognitive measures may predict efficacy. Twenty participants with HD completed this crossover trial, undergoing 1.5 mA anodal tDCS over left dorsolateral prefrontal cortex and sham stimulation on separate visits. Participants and assessor were blinded to condition order, which was randomised across participants. All participants completed baseline clinical and cognitive assessments. Pre- and post-stimulation tasks included digit reordering, computerised n-back tests and a Stroop task. During 15 min of tDCS/sham stimulation, participants practiced 1- and 2-back WM tasks. Participants exhibited an increase in WM span on the digit re-ordering span task from pre- to post-stimulation after tDCS, but not after sham stimulation. Gains in WM were positively related to motor symptom ratings and negatively associated with verbal fluency scores. Patients with more severe motor symptoms showed greatest improvement, suggesting that motor symptom ratings may help identify patients who are most likely to benefit from tDCS. Conclusions: Dorsolateral prefrontal tDCS appears well tolerated in HD and enhances WM span compared to sham stimulation. Our findings strongly encourage further investigation of the extent to which tDCS combined with cognitive training could enhance everyday function in HD.

ClinicalTrials.gov; NCT02216474 Brain stimulation in Movement Disorders; https://clinicaltrials.gov/ct2/show/NCT02216474

1. Introduction

The inherited neurodegenerative movement disorder Huntington's disease (HD) frequently features cognitive impairment from around middle age (Ho et al., 2003). One aspect of cognition often impaired in HD (Papp et al., 2011) is working memory (WM), which is used to maintain, manipulate and update information (Baddeley, 1992). Everyday skills such as comprehension (Daneman and Carpenter, 1980) and reasoning (Kane et al., 2004) rely on WM. In HD, WM deficits can precede motor symptom onset (You et al., 2014) and are correlated with reduced functional capacity (Eddy and Rickards, 2015a). We therefore conducted a double-blind, sham-controlled, randomised cross-over trial of electrical brain stimulation for WM in HD.

Transcranial direct current stimulation (tDCS) passes a mild electrical current between two electrodes on the surface of the skull. This can enhance cortical excitability for a short period after stimulation, increasing neuronal firing rates, and influencing processes such as long term potentiation (Pelletier and Cicchetti, 2014). Anodal stimulation over the cortical area that underpins a targeted cognitive skill can enhance that skill in both healthy and clinical populations (Coffman et al., 2014; Tortella et al., 2015). For example, tDCS can improve executive functions in stroke (You et al., 2011), Alzheimer's disease (Hsu et al., 2015) and Parkinson's disease (Doruk et al., 2014). TDCS is very safe, with a low incidence of reported side-effects (Tortella et al., 2015; Brunoni et al., 2012; Poreisz et al., 2007).

Neuroimaging studies implicate dorsolateral prefrontal cortex

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(DLPFC) in WM (Courtney, 2004), and previous studies have enhanced WM through anodal stimulation over left DLPFC (Fregni et al., 2005; Zaehle et al., 2011). Indeed, anodal tDCS over this area (but not sham stimulation) improves WM in stroke (Jo et al., 2009) and major depression (Oliveira et al., 2013). The effectiveness of tDCS may be influenced by stimulation intensity and duration. For example, Boggio et al. (2006) reported that continuous tDCS for 20 min at 2 mA (but not 1 mA) enhanced WM in Parkinson's disease. The behavioral effects of 20–30 min 1 mA anodal tDCS over left DLPFC can still be observed 30 min after stimulation ends (Ohn et al., 2008), although repeated administration may lead to stronger and longer lasting effects (Richmond et al., 2014). The likelihood that tDCS may influence WM via modulation of brain activity is supported by studies that indicate anodal tDCS increases task-related activation of the DLPFC (e.g. Stagg et al., 2013). However, individual anatomical differences could affect efficacy (e.g. Kim et al., 2014).

The effects of tDCS appear greatest when applied during an 'online' task involving the targeted cognitive function (Mancuso et al., 2016). Andrews et al. (2011) showed that anodal DLPFC tDCS paired with one WM task (n-back task) resulted in improved performance on a different WM task (digit span), but no improvement was apparent without a concurrent online task. These authors suggest that their findings demonstrate how an adjunctive task can enhance the effect of tDCS, and that this could involve the mechanism of long-term potentiation i.e. when a brief period of strong synaptic activation results in longer-term strengthening of synaptic transmission. Pairing tDCS with tasks may result in selective alterations in brain activity, and this is likely to depend on the extent to which the adjunctive tasks engage the targeted cognitive skill and related brain networks (Gill et al., 2015). Some studies have found that stimulation is not effective without concurrent cognitive training (e.g. Filmer et al., 2016) and that tDCS induced brain plasticity is task dependent (e.g. Bortoletto et al., 2015). Other studies have indicated that tDCS in conjunction with WM training appeared to augment learning beyond the training paradigm leading to a more generalised effect on cognition (Richmond et al., 2014). Enhancing WM could therefore have the potential to benefit cognition more generally.

One review with a focus on tDCS and WM found that consistent data suggestive of robust effect combined anodal stimulation of left DLPFC with n-back tasks across both healthy and clinical populations (Berryhill et al., 2014). TDCS related improvement was concluded to be constant across a range of populations, simulation intensities and durations. In addition, a meta-analysis showed reliable evidence for an improvement in n-back reaction time for active tDCS over the DLPFC in healthy participants, with more evidence for increases in accuracy in clinical samples (Brunoni and Vanderhasselt, 2014). In contrast, another review of tDCS studies (Horvath et al., 2016) concluded that there were no reliable effects on cognitive functions including WM. However, use of pooled data (in relation to e.g. electrode placement, task etc.) could weaken results where there are heterogeneous effects reported across studies relating to other factors.

Evaluating the efficacy of TDCS can be complex, as there may be contrasting effects within an inhomogeneous population (Berryhill et al., 2014). For example, the impact of left DLPFC tDCS may depend on baseline performance on the task in question (e.g. Hsu et al., 2016; Kim et al., 2014; London and Slagter, 2015). Task difficulty is an important methodological consideration. One study of tDCS effects on visual WM in healthy participants (Jones and Berryhill, 2012), showed that when including tasks of varying difficulty, effects may only be found on the more difficult task. In addition, it has been shown that anodal right DLPFC tDCS may help with WM by helping prevent stress induced deficits, in comparison to cathodal or sham stimulation (e.g. Bogdanov and Schwabe, 2016). This raises the potential mediating effects of stress or anxiety on performance and could help to explain some of the variability in response across subjects with perhaps greatest relevance to clinical samples.

In summary, previous studies indicate individual differences may be related to the efficacy of tDCS when applied to improve cognitive functions such as WM (e.g. Talsma et al., 2016), and emphasise the importance of using multiple tasks to test outcome and careful consideration of the potential influence of factors such as baseline test performance. Additional insights into the efficacy of tDCS will be gained through well controlled studies in clinical populations containing individuals with a range of ability. The current study investigated tDCS for WM in HD, using an n-back task (which involves attending to a stream of letters and indicating when the current letter matches the letter presented 'n' letters earlier) before, during and after tDCS and sham stimulation. This measure has been linked to more robust evidence of improvement with anodal tDCS based on previous reviews (e.g. Berryhill et al., 2014). Both reaction time and accuracy were assessed. The offline measure of WM was a digit reordering task (Werheid et al., 2002; Cooper et al., 1991) already shown to be sensitive to impairment in HD (Eddy et al., 2012; Eddy and Rickards, 2015b) and associated with functional capacity (Eddy and Rickards, 2015a). We investigated whether tDCS, as opposed to sham stimulation, improved performance on these measures of WM, and the Stroop task as a non-WM control. We included two training tasks of varying difficulty (1-back and 2-back), and because factors such as baseline ability (Kim et al., 2014) may be related to outcome, we collected a range of data to characterise our sample and considered the relationships between tDCS efficacy and these variables in our analyses. As this may be the first trial of tDCS in HD, we explored the tolerability and efficacy of one 15-minute session of 1.5 mA anodal tDCS over left DLPFC. All participants underwent both tDCS and sham conditions with patient and assessor blinded to condition order. Given the findings of previous studies involving healthy participants and patients with Parkinson's disease (e.g. Andrews et al., 2011; Boggio et al., 2006), we anticipated that WM measures would reveal improvement after tDCS but not after sham stimulation. More specifically, we anticipated an overall group improvement in performance on the offline measure (DOT-A) after tDCS but not after the sham session. In addition, we also expected to see improved performance on the more difficult training task (2-back) after tDCS but not after sham. Furthermore, we expected to identify relationships between efficacy and baseline characteristics, such that improved digit reordering span would be more likely to reach significance in patients who exhibited more severe WM deficits at baseline.

2. Method

2.1. Patient population

Twenty volunteers diagnosed with HD, which was confirmed via positive genetic test, took part. Exclusion criteria included severe motor and cognitive problems; history of seizure or migraine; and current involvement in any drug trial (screened by HER, enrolled by CME February–December 2015). DCL ranged from 1 to 4 (1 = 1; 2 = 7; 3 = 8; 4 = 4; where 1 suggests no clear clinical signs or symptoms; 2 indicates subtle motor and/or cognitive signs; 3 and 4 indicate more significant motor and cognitive signs that impact functioning. See Reilmann et al., 2014). All participants exhibited some motor symptoms (Table 1) as assessed by the Unified Huntington's Disease Rating Scale (UHDRS: Huntington Study Group, 1996) which measures core motor signs of HD. Some patients also exhibited evidence of anxiety or depression as assessed using the Hospital Anxiety and Depression Scale (HADS: Zigmond and Snaith, 1983). Including patients at different disease stages allowed us to explore how baseline clinical characteristics may influence the effect of tDCS. Sample size was determined based on the novelty of the trial and lack of existing data on tDCS in this population (i.e. ethics), the rarity of the condition and the likelihood of sufficient power based on previous studies (e.g. Eddy and Rickards, 2015a).