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DOI:
10.1016/j.pnpbp.2017.04.002

Document Version
Peer reviewed version

Citation for published version (Harvard):
Eddy, C, Shapiro, K, Clouter, A, Hansen, P & Rickards, H 2017, 'Transcranial direct current stimulation can enhance working memory in Huntington's disease', *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 77, pp. 75-82. https://doi.org/10.1016/j.pnpbp.2017.04.002

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

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Running title: TDCS for working memory in Huntington's

Word count: abstract=250; main text=5190 + 2 tables + 2 figures + 1 supplementary table. Running head=39 characters including spaces. Title=90 characters including spaces.

Presentations: The 9th EHDN Plenary Meeting, The Hague, The Netherlands, 16-18 September 2016. Meeting abstract: Eddy et al (2016) Transcranial direct current stimulation and cognitive training for working memory in Huntington's disease. *J Neurol Neurosurg Psychiatry 2016;**87**:Suppl 1 A104 doi:10.1136/jnnp-2016-314597.293*

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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 1.5mA 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 minutes 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

Key words: cognition; dorsolateral prefrontal cortex; Huntington's disease; movement disorder; tDCS; working memory

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 frequently 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,* 20014) 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 (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 2mA (but not 1mA) enhanced WM in Parkinson's disease. The behavioral effects of 20-30 minutes 1mA anodal tDCS over left DLPFC can still be

observed 30 minutes 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 &

Vanderhasselt, 2014). In contrast, another review of tDCS studies (Horvath *et al*, 2015) 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.) which 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 & Slagter, 2015). Task difficulty is an important methodological consideration. One study of tDCS effects on visual WM in healthy participants (Jones & 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. Bognadov & 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 used 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 there 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 1-4 (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 Reilman 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).

Table 1. Patient clinical characteristics and baseline assessment scores

Patient	Age	Disease burden	UHDRS motor score	Medication	Baseline WAIS forward	Baseline WAIS backward	Baseline verbal fluency	Baseline semantic fluency	HADS depression	HADS anxiety
1[a]	54	513	62	MTZ	5	3.5	45	36	5	5
2	65	422.5	59	TBZ	5.5	3	12	24	4	4
3	50	425	49	CMZ	5.5	3	18	25	2	3
4	50	225	42	AMY/MTZ	3.5	2.5	16	33	11	8
5[a]	62	279	58	FLX	5.5	1.5	19	25	21	14
6	65	422.5	58	FLX	6.5	4	26	24	5	7
7	56	364	12	N	6.5	4	65	52	5	0
8	62	527	56	N	5	3	22	25	7	0
9	50	275	19	N	8	3	53	51	11	13
10[a]	58	377	21	N	6.5	5.5	42	46	8	8
11	48	120	20	SRT	6	6	35	28	5	10
12[a]	61	457.5	73	RSP/SRT	6.5	3	13	15	6	12
13	43	279.5	16	AMY/CTL	8	8	57	53	13	16
14	50	375	30	N	4.5	2.5	11	20	5	11
15	68	374	42	CTL	5	3	19	33	7	9
16	72	396	62	N	5.5	4	27	35	5	13
17	46		55	OLZ/VFX	7	3	20	28	2	4
18	48	216	13	N	7	3.5	50	56	2	1
19	58	319	23	N	6	4.5	38	41	2	7
20[a]	45	202.5	5	N	6.5	7	39	44	5	4

AMY: amitriptyline; CMZ: carbamazepine; FLX: fluoxetine; HADS: Hospital Anxiety and Depression Scale; MTZ: mirtazapine; OLZ: olanzapine; RSP: risperidone; SRT: sertraline; TBZ: tetrabenazine; VFX: venlafaxine; WAIS:

Wechsler Adult Intelligence Scale. [a]stimulation procedure aborted and restarted during one session (due to skin resistance).

2.2 Study design

The study received local and regional ethical approvals and all participants gave written informed consent. Participants attended the study centre (National Centre for Mental Health, and University of Birmingham, Birmingham, UK) on two occasions to receive anodal tDCS and sham stimulation. This within-participants design was double-blind: both patient and assessor (CME) were blinded to condition order (determined at random by AC) during data collection. The stimulation protocol was piloted on three healthy volunteers.

Visit one commenced with consent and demographic interview, followed by baseline clinical and cognitive assessments (see below). A trained rater assessed motor symptoms. Participants next completed pre-stimulation tests on the primary outcome measures: computerised 1-back test; Digit Ordering Test-Adapted (DOT-A); computerised 2-back test; Stroop test (control task). They then received (blinded) anodal or sham stimulation, while completing further blocks of n-back. Immediately after the stimulation, participants completed post-stimulation tests on the above four outcome measures in the same order. Finally, participants were interviewed about side-effects. Visit two was identical except that participants received the other stimulation condition, and were debriefed at the end. Nineteen of the twenty participants attended visit two after the planned one week washout period. One participant was unable to attend until approximately one month later.

2.2.1 Baseline assessments

Unified Huntington's Disease Rating Scale: Motor Subscale (Huntington Study Group, 1996)

Each participant was examined for motor signs using standard tests (e.g. finger tapping, tongue protrusion, tandem walking). Scores were summed to generate a total motor score (possible range 0–124). Higher scores indicate more severe symptoms.

Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983)

This brief measure contains seven items to assess depression, and seven to measure anxiety. Scores were summed for each subscale. A clinically relevant cut-off of ≥8 has been proposed (e.g. Olssøn *et al*, 2005).

Verbal Fluency Tasks (Lezak, 1995)

To assess phonological fluency, participants were asked to say as many words as they could beginning with a given letter in one minute. The letters F, A and S were used in turn. People's names and repeats were not counted. Semantic fluency was assessed using the prompts fruit, animals and vegetables. Scores reflect the total number of items generated over the three letters/categories. Verbal fluency is likely to involve a combination of verbal control and executive ability (Shao et al., 2014). These tasks were included as a baseline measure as they are frequently impaired in HD, even at an early stage (e.g. Eddy and Rickards, 2015b), and use of a semantic fluency task as part of clinical assessment may offer insight into functional capacity (Eddy & Rickards, 2015a).

WAIS forward and backward digit span tasks (Wechsler, 1997)

Participants listened to a series of numbers and repeated them back immediately after presentation, with strings ranging from 2-9 digits in length. For the backward span task, participants began with the last number they heard and finished with the first (strings ranged from 2-8 digits). Pairs of trials were presented at each length. When a participant answered both trials of one length incorrectly testing ended. Half a point was deducted from the total span where only one trial from a pair was answered correctly.

2.2.2 Outcome measures (pre and post-tests)

Digit Ordering Test-Adapted (Werheid *et al,* 2002; Cooper *et al,* 1991)

Participants listened to mixed strings of digits spoken by the experimenter (e.g. 3-8-4-7) and then immediately recalled these digits in ascending order. String length ranged from 3-8 digits, with two of each length. When a participant responded incorrectly to both strings of one length testing was terminated. Half a point was deducted from the maximum span when only one string of that length was answered correctly. Two sets of stimuli were used to reduce any practice effects.

1-back and 2-back tests

This task was a modified version of the n-back task in PEBL version 0.14 (http://pebl.sf.net.). Blocks were 151 seconds long and contained 50 'randomly' generated stimuli, including 10 targets. Participants pressed the space key to initiate the block, and watched a series of white uppercase letters (from the set "C","H","K","N","R","W","X","Y") randomly appearing one-by-one on a black background with an inter-stimulus interval of 3.0s. Visual presentation was coincident with an audioclip of the letter being sounded out by the program. For 1-back, the instructions were to respond using the spacebar key whenever the current letter matched the immediately preceding letter (e.g. K,K). For the 2-back task, participants responded for a match to two stimuli previous (e.g. K,N,K). The header "1-back" or "2-back" was shown at the top of the screen throughout the block. At the start of each block, standardised instructions were shown onscreen. Example series of letters were provided and participants watched the experimenter complete short demonstration blocks before they completed three practice blocks. After practice and a short break, participants completed three blocks (pre-stimulation test). During the stimulation procedure, participants completed 2 blocks of 1-back, followed by 2 blocks of 2-back with a 2 minute break between tasks. Post-stimulation tests consisted of 3 additional blocks of each n-back task. Hit rates (out of 30) were

calculated as percentages for each n-back for pre- and post-test. Reaction times for correct responses and total errors for three blocks (misses plus false alarms) were also recorded.

Stroop test (Stroop, 1935)

The Stroop task is considered to measure response inhibition. It requires participants to name the ink color in which stimuli are printed, along rows from left to right. We used the incongruent condition in the current study: stimuli were color names that were inconsistent with the color of the ink in which they were presented (e.g., the word 'red' printed in green ink). Errors and the time taken to complete the task were recorded.

Tolerability interview

Participants were asked if they thought stimulation had led to any change in concentration, memory or mood. They were also asked about the following side-effects: Headache; neck pain; itching; sleepiness; trouble concentrating; acute mood change; fatigue; nausea; muscle twitches in face or neck (not motor symptoms); tingling sensation on head/scalp; burning sensation on head/scalp; seizure; light flashes; or other uncomfortable feeling.

2.2.3 Stimulation protocol

Stimulation was provided by a NeuroElectrics device. After the stimulation procedure was explained, participants were fitted with the appropriate sized cap, to which the electrodes and battery-driven stimulator were attached. Saline solution was used to soak the electrode pads (anodal 25mm, return 35mm). The anode was placed over F3 to stimulate left DLPFC (based on the 10-20 EEG system), and the cathode was placed over the contralateral orbital area (FP2). When the patient was ready, the current ramped up over 60 seconds, during which participants were asked to relax and report any sensations. When the current reached 1.5mA, participants were asked to begin the n-back tasks.

TDCS Stimulation and sham sessions were managed by Neuroelectrics Instrument Controller software (neuroelectrics.com). For the tDCS session, 1.5mA tDCS was sustained for 15 minutes, followed by a 60-second ramp down. For the sham session, after the 60 second ramp up, stimulation was programmed to ramp down again (this was obscured to the patient and assessing experimenter). The initial ramp-up causes the same sensations in both conditions. After completion of the 17 minute procedure, the equipment was removed, and post-stimulation tests were initiated.

For five participants, stimulation aborted early due to skin resistance. On these occasions, assistance was given by a second un-blinded experimenter (AC). Additional saline was applied, and on some occasions the cap was removed in order to do this. This second experimenter then restarted the NeuroElectrics software to ramp up and sustain 1.5mA stimulation (or re-run sham template) for the remaining time. This experimenter observed a satisfactory maintenance of conduction during ramp up into the first minute of sustained stimulation, before leaving the blinded experimenter to continue the protocol. The total amount of stimulation time was maintained at approximately 15 minutes (plus ramp up/down) across all participants. All participants completed at least four 'online' n-back blocks. To ensure that concealment of condition order was maintained, the stimulation software was pre-programmed (by AC) so that on a few occasions it would abort during a sham session.

2.2.4 Data analysis

To test for differences in the means for pre- and post-intervention sessions for the two intervention conditions, 2 (session: pre-intervention, post-intervention) x 2 (intervention: tDCS, sham stimulation) ANOVAs were calculated for the primary outcome measures (DOT-A span; 1- and 2-back mean reaction times and percentage correct; and Stroop interference for completion times and errors). Given the exploratory nature of the study, follow-up paired t-tests were conducted (Table 2).

To aid interpretation of any significant t-test results (p<.05), three further stages of analysis were carried out. First, in order to check for pre-intervention differences in baseline task performance, we compared pre-intervention scores for tDCS versus sham. As a verification step, we compared post-intervention scores for tDCS versus sham. Finally, to check for order effects, we investigated differences between participants undergoing tDCS on visit one (and sham on visit two) versus those receiving the opposite order using 2 (session: pre, post) x 2 (intervention: tdcs, sham) x 2 (testing order; tdcs-sham, sham-tdcs) ANOVA.

To determine whether baseline clinical measures predicted treatment efficacy, we calculated correlations between task scores (i.e. difference before and after stimulation) and the baseline measures: phonological and semantic fluency scores, WAIS forward and backward span, UHDRS motor symptom scores, HADS anxiety and depression scores, and disease burden (using the formula of Penney *et al,* 1997). Post-hoc tests were conducted based on significant correlations. As this study is the first of its kind, we discuss all values at p<.05 with a view to informing further research.

3. RESULTS

All 20 recruited participants completed both tDCS and sham stimulation. The 2 x 2 anovas (interaction results) and paired t-tests are shown in Table 2 (for individual results see Supplementary Table 1). Significant t-tests were apparent for three measures: DOT-A scores, 2-back scores and Stroop times.

Table 2. Effect of tDCS and sham on outcome measures

Measure	Condition	Pre	Post	Change	Paired t-test	Anova
		Mean (SD)	Mean (SD)	Mean (SD)	T(19), p	F(1, 19), p
DOT-A span	tDCS	4.6 (1.12)	5.05 (1.00)	+0.45 (0.78)	2.592, 0.018	2.979, 0.101
	Sham	4.65 (0.92)	4.73 (1.07)	+0.08 (0.69)	0.513, 0.614	
1-back RT	tDCS	1247	1170	-77	-1.419, 0.172	1.999, 0.174

		(489.84)	(376.86)	(242.71)		
	Sham	1241 (379.67)	1263 (357.45)	+21.7 (197.07)	0.492, 0.628	
1-back % correct	tDCS	93.67 (12.98)	95.34 (7.13)	+1.67 (11.37)	0.655, 0.521	1.085, 0.311
	Sham	96.34 (5.50)	95.34 (7.67)	-1 (6.95)	-0.644, 0.527	
2-back RT	tDCS	1379 (441.84)	1343 (341.25)	-36.1 (227.35)	-0.710, 0.486	0.072, 0.792
	Sham	1323 (315.27)	1307 (390.30)	-15.95 (194.71)	-0.366, 0.718	
2-back % correct	tDCS	66.50 (23.05)	74.84 (20.71)	+8.35 (16.90)	2.208, 0.040	3.662, 0.072
	Sham	72.34 (20.76)	70.67 (24.02)	-1.68 (15.70)	0.477, 0.639	
Stroop CT	tDCS	-48.79 (31.36)	-34.44 (23.31)	-14.43 (23.40)	2.742, 0.012	0.011, 0.917
	Sham	-46.42 (25.51)	-32.75 (16.17)	-13.66 (16.80)	3.63, 0.002	
Stroop Errors	tDCS	-3.35 (3.95)	-2.40 (2.50)	-0.95 (3.31)	1.281, 0.216	0.217, 0.647
	Sham	-2.80 (3.17)	-2.25 (2.55)	-0.55 (2.19)	1.124, 0.274	

KEY: CT: completion time; DOT-A: Digit Ordering Test-Adapted; RT: reaction time; %: percentage correct hits. ANOVA column shows only interaction between session (pre;post) and intervention (tdcs;sham)

3.1 DOT-A intervention and session effects

For DOT-A scores (i.e. the main outcome measure), the 2 (session: pre, post) x 2 (intervention: tDCS, sham) ANOVA revealed a main effect of session ($F(1,19)=4.93$, $p=.039$). Scores were higher at post-intervention testing than in the pre-intervention session. However, the intervention x session interaction only approached a trend towards significance (Table 2). Follow-up t-tests revealed a significant improvement from pre- to post-intervention for tDCS (Cohen's $d=0.424$, nearing medium effect size) but not for sham (Table 2). While there was no difference in DOT-A score between tDCS and sham on the first day of intervention (i.e., no initial baseline performance differences: $t(19)=-0.3258$, $p=.748$), the DOT-A score after tDCS was significantly higher than after sham on the second intervention day ($t(19)=2.096$, $p=.0497$). Importantly, this suggests that the improvement for tDCS (but not sham) is unlikely to simply reflect lower baseline scores for the tDCS condition. On average, WM span as measured by the DOT-A task increased by half a point from pre- to post-intervention for the tDCS condition (Fig 1; Supplementary Table 1).

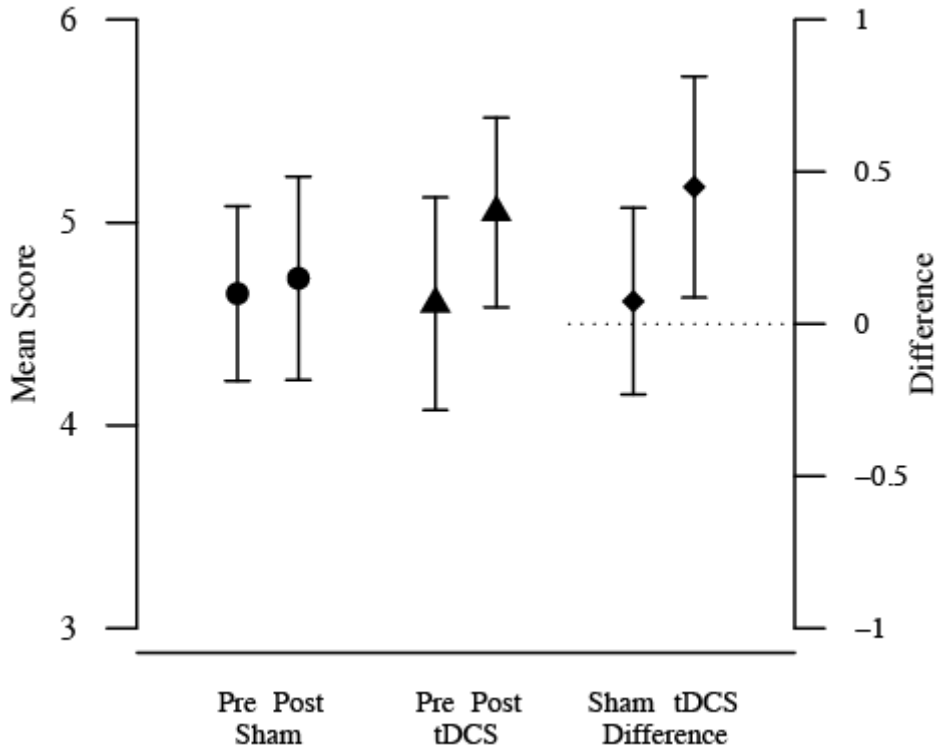

Figure 1. Performance on the Digit Ordering Test-Adapted

Left axis: Mean score, pre-intervention (Pre) and post-intervention (Post) in the sham-stimulation (Sham) and real stimulation (tDCS) conditions. Right axis: The difference between the pre and post-intervention mean scores for the sham and tDCS conditions. Error bars represent 95% confidence intervals.

3.2 DOT-A order effects

In checking for possible effects of the order in which the intervention conditions were given, the 2 (session: pre, post) x 2 (intervention: tDCS, sham) x 2 (testing order: sham-tDCS, tDCS-sham) ANOVA also revealed a main effect of session ($F(1,18)=4.74$, $p=.042$): scores were higher in the post-intervention session than at pre-intervention testing. However, we noted that testing order interacted with intervention ($F(1,18)=7.79$, $p=.012$). Examining this interaction revealed that among the participants who received sham stimulation on visit one and tDCS on visit two, performance was significantly improved on the tDCS day (main effect of intervention: $F(1,9)=18.58$, $p=.001$). However, if tDCS was applied on visit one and sham stimulation on visit two, scores were not different

between the interventions (F(1,9)=0.58, p=.46). This could suggest that sufficient familiarity with or practice on the administered tasks was necessary prior to treatment with tDCS, and that practice alone is not responsible for the observed improvement in DOT-A scores.

3.3 DOT-A correlations and subgroup effects

The change in DOT-A WM span was positively related to baseline motor symptom score (Pr=.573, p=.008), and negatively related to both semantic (Pr=-.541, p=.014) and phonological (Pr=-.485, p=.030) fluency scores. Patients with motor scores above 30 showed most improvement in WM after tDCS (Fig 2; Supplementary Table 1).

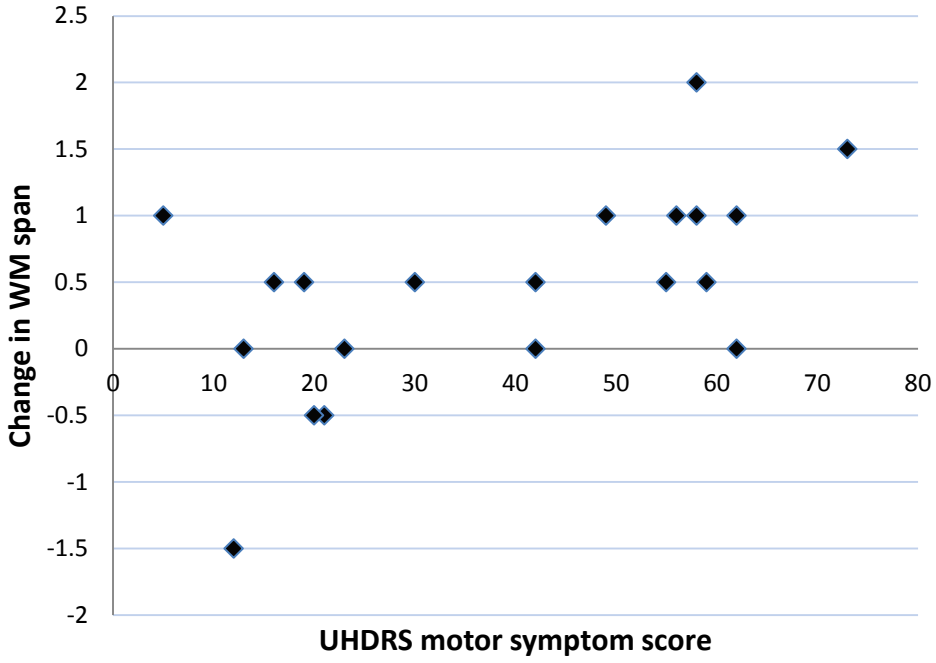

Figure 2. Correlation between change in working memory span on the DOT-A pre to post-test and UHDRS motor score at baseline

Change in working memory span is in number of digits on the Digit Ordering Test-Adapted; motor symptom severity is as measured using the Unified Huntington's Disease Rating Scale.

As change in WM span correlated with baseline motor symptom score, we conducted post-hoc testing on DOT-A scores after splitting the patient sample into two groups based on UHDRS motor score (>30 n=11; ≤ 30 n=9). A repeated measures 2 (motor score: high, low) x 2 (intervention: tDCS, sham) x 2 (session: pre, post) ANOVA revealed two significant main effects and two significant interactions. The higher motor symptom group exhibited lower WM spans than the lower motor symptom group (main effect of motor score: $F(1,18)=10.968$, $p=.004$); and WM spans post-intervention were higher than pre-intervention (main effect of session: $F(1,18)=4.740$, $p=.043$). Moreover, the session x intervention interaction was significant ($F(1,18)=6.035$, $p=.013$): scores were higher at post-intervention testing than at pre-intervention for tDCS, but not for sham. There was also a three way interaction ($F(1,18)=20.488$, $p=.043$). While post-intervention scores were higher than pre-intervention in the tDCS condition (and not sham) for the higher motor symptom group, they were not for the lower motor symptom group. This could imply a greater placebo effect in this latter group who exhibited higher scores for post-test in the sham condition.

3.4 N-back tasks

Analysis of scores on the 1-back task revealed no significant effect of session, intervention, or interaction, which is unsurprising given that performance was near ceiling for all session-intervention combinations (ranging from 93.67% to 96.34%). For 2-back scores, the session x intervention interaction neared significance ($F(1,19)=3.453$, $p=.079$). Follow-up paired t-tests showed a significant improvement from pre- to post-intervention (Cohen's $d=0.381$, approaching medium effect size) for tDCS, but not for sham (Table 2). The order of stimulation had no significant effect ($t(18)=1.160$, $p=.261$), and changes in 2-back scores were not significantly correlated with any baseline variables.

3.5 Stroop task

Analysis of Stroop times revealed a significant main effect of session ($F(1,19)=19.220$, $p<.001$), but no interaction with the intervention. Both tDCS and sham conditions were associated with faster post-intervention performance compared to pre-intervention test. There were no significant effects in the analysis of Stroop errors.

3.6 Tolerability

There were no drop-outs and no evidence that side-effects were more common with tDCS than sham (no reported effects: anodal tDCS n=7; sham n=7). The most commonly reported effects were mild, and included tingling (anodal tDCS n=6; sham n=6), itching (anodal tDCS n=5; sham n=3), or feelings of increased/decreased alertness and concentration (anodal tDCS n=5; sham n=5). Questioning of participants suggested that they were no better than chance at identifying which session involved real stimulation.

4. DISCUSSION

The current study was a double-blind, randomised, within-participants, sham-controlled trial of tDCS plus cognitive training for WM in HD. A single session of anodal tDCS over left DLPFC combined with training on the n-back task improved patients' performance on a digit reordering task. This effect was not seen for sham, and pre-stimulation scores were no different for the two conditions. An average increase of half a point in digit reordering span is an encouraging finding, and suggests that future interventions combining tDCS and cognitive training could have significant effects on cognition. While the scope of the current study did not accommodate investigation of either carry-

over to other tasks, or effects on everyday function, it has previously been found that DOT-A scores are significantly related to patients' functional capacity (Eddy and Rickards, 2015a).

There was some evidence that tDCS also led to small improvements in the online WM measures (i.e. 2-back scores). However, given that the n-back test was used as a training measure, and used adjunctive to stimulation, we place less emphasis on these findings than on those for the transfer task (DOT-A). Both 1-back and 2-back tests were included because participants were expected to demonstrate a range of ability. However, near-ceiling baseline performance on the 1-back task probably prevented detection of any improvement. Importantly, the study design, plus the observed combination of selective improvements on the WM tasks, coupled with no significant improvements in the sham condition, suggests that observed effects were not due to practice, but rather a result of tDCS.

We aimed to identify clinical and cognitive factors which may predict behavioral responses to tDCS. Disease burden and baseline mood ratings were not found to be related to outcomes. However, participants who showed most improvement in WM span exhibited lower scores on baseline tests of verbal fluency. Semantic fluency can be mildly impaired in premanifest HD (Eddy and Rickards, 2015b) and is linked to functional capacity in manifest patients (Eddy and Rickards, 2015a). Data for the verbal fluency measures suggested that patients unable to achieve around 40 words across each task (most of the sample) benefitted from tDCS. However, those patients scoring above this were less likely to show a significant improvement in DOT-A score after tDCS, with a few showing a slight decline in performance. Importantly, post-hoc testing indicated that patients with baseline motor symptom scores above 30 points on the UHDRS (Huntington Study Group, 1996) were more likely to show a statistically significant benefit of tDCS over sham. As motor symptom scores on the UHDRS can range from 0 to 120, a motor score of 30 is relatively low, and may still give an impression of manifest early stage HD. Therefore, motor symptoms and verbal fluency score are useful criteria for identifying patients who are most likely to benefit from tDCS.

A decline in cognitive function in premanifest HD patients (which tends to increase with proximity to motor symptom onset) is associated with reduced activation of left DLPFC (Paulsen *et al*, 2004). This may imply that tDCS could augment brain activity such that processes contributing to WM are more efficient. However, as motor symptoms become apparent, patients with manifest HD can show an increase in prefrontal activation which may in some cases allow them to achieve a same level of cognitive performance as controls (Gray *et al,* 2013). Therefore natural compensation effects may make the interpretation of the effects of tDCS more complex. It is possible that tDCS combined with cognitive training could augment these natural compensation effects in manifest patients, or reduce declining cognitive performance when applied at premanifest stage (see Andrews *et al*, 2015). Future studies combining tDCS with neuroimaging would offer valuable insight into the neural mechanisms underlying changes in WM performance after tDCS in HD.

Limitations of the current study include that we did not explore the effect of right DLPFC stimulation. However, the left side may be most appropriate to target when the WM task is verbal rather than spatial. Another possible limitation is the selection of the Stroop task as a control measure. Although the Stroop task used in the current study did not show a specific effect relating to active tDCS, while other (WM) measures did, recent studies have suggested that this task can activate the DLPFC (e.g. Xu et al., 2016). Our protocol was informed by previous research which reported a specific effect of anodal left DLPFC tDCS on WM in healthy participants (Andrews *et al,* 2011) and participants with Parkinson's disease (Boggio *et al,* 2006). To the authors' knowledge this is the first trial of tDCS in HD, therefore ethical and practical issues were taken into account when restricting the trial to one active stimulation session. TDCS was well tolerated, there were no drop-outs, and only mild side effects were reported which were as common for sham. Stimulation was interrupted on some occasions due to skin resistance or movement. Nevertheless, we believe the total dose of stimulation was successfully delivered in all participants, and software programming maintained blinding. Although t-tests indicated that WM improved with tDCS but not sham, the interaction between session and condition did not reach significance. We suggest that future studies

focused on patients most likely to benefit from stimulation (i.e. those with more severe motor symptoms) would be more likely to show a significant interaction. As participants received cognitive training with both anodal tDCS and sham, our results suggest that combining an online task with tDCS can have significantly more effect on WM. However, we cannot determine how much effect tDCS would have when given alone, or how long any effects would last. Furthermore, some participants were taking medications, which could have affected baseline cortical excitability.

A final limitation of the current study relates to the use of online and offline tasks. A recent review and meta-analysis (Hill *et al*, 2016) exploring the effects of anodal tDCS on WM revealed different effects in healthy and neuropsychiatric samples, such that only performance on offline tasks (tests used after stimulation) improved in healthy participants, whereas patient groups tended to show evidence of improvement on the online tasks (tasks used during stimulation). The current study tested performance on both the training task (used for online training) and the predetermined main outcome measure (DOT-A, only used offline), however we did not investigate potential improvements in performance on the training task during the stimulation period itself.

5. CONCLUSION

Our findings indicate that combining tDCS over the left DLPFC with n-back training can enhance performance on certain measures of WM span in HD. Larger longitudinal studies, involving repeated administration of tDCS will be necessary to determine whether this intervention could exert lasting effects which impact everyday cognitive function. In Parkinson's disease, a current strength of 2 mA may be needed to lead to more obvious effects on WM (Boggio *et al,* 2006). Therefore given that 1.5 mA was well tolerated by our sample, increasing to 2 mA in future studies could be more likely to yield significant results. More generally, tDCS may be beneficial for mood disorder (Poreisz *et al,*

2007) which is also frequent in HD. Our findings strongly encourage further evaluation of whether tDCS alone or in combination with tasks or therapy, could demonstrate a range of clinical benefits.

Author Contributions

CME: Study conception, project management, funding acquisition, design and methodology, investigation, formal analysis, interpretation, manuscript preparation; KS: Resources, design and methodology, interpretation, manuscript editing; AC: Design and methodology, formal analysis, manuscript editing; PCH: Design and methodology/computation, manuscript editing; HER: Resources, investigation, interpretation, manuscript editing.

Acknowledgements

We are grateful to Ellice Parkinson for assisting with recruitment, and to Ilja Sligte and Jess Kerlin for technical assistance during data collection.

Funding

This research was funded by the Jacques and Gloria Gossweiler Foundation. The funding source had no role in study design, execution, analyses, interpretation of the data, or decision to submit results for publication.

Conflicts of Interest/Disclosures

The authors have no conflicts of interest or financial disclosures to declare. All authors have approved the final version of the article.

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Supplementary Table 1. Individual change (pre – post) on outcome measures by patient

Patient	DOT-A	1-back %	1-back RT	2-back %	2-back RT	Stroop error	Stroop CT
1	+1	-13.3	-240	+6.7	-394	-6	-40
2	+0.5	+36.7	-521	+10	+56	-10	-17.17
3	+1	0	-138	+10	-348	+1	+3.75
4	0	-3.4	-161	+63.3	+133	-1	-19.6
5	+1	0	+44	0	-69	+3	-5.59
6	+2	0	-51	-3.3	-96	+2	+38.51
7	-1.5	0	+43	0	-92	-3	-13.92
8	+1	0	+76	+13.3	-385	0	-20.86
9	+0.5	0	+312	+6.7	+357	+1	-3.61
10	-0.5	-6.7	+81	+43.4	+338	-2	-63.87
11	-0.5	0	-48	0	+162	0	-23.65
12	+1.5	-3.4	-406	+3.3	+35	+3	+2.84
13	+0.5	0	+75	-3.3	-40	0	+10.11
14	+0.5	+30	-637	+3.3	-239	-4	-29.52
15	+0.5	-3.3	+248	+3.4	+232	-1	-1.38
16	0	0	-222	-6.6	+8	+1	-20.91
17	+0.5	-3.3	+5	-10	+12	-1	-29.71
18	0	0	+49	+13.3	-17	-2	-0.49
19	0	0	-190	+6.7	-397	-3	-26.04
20	+1	0	+141	+6.7	+22	-1	+1.89
				SHAM			
1	-0.5	-16.7	+15	-20	-2	-5	-13.86
2	0	+10	+274	-6.7	-102	+2	-24.29
3	0	0	-319	0	-9	-2	-137.3
4	0	-10	+371	+13.4	-77	-4	-21.77
5	-0.5	+3.4	-131	+13.4	+423	-3	-39.89
6	0	0	-203	-10	-60	+2	+23.36
7	-1	0	+280	+16.6	+53	0	-6.97
8	0	-16.7	-229	-36.7	+148	0	+11.41
9	+1	0	+56	+3.3	-333	+3	+0.94
10	0	0	+62	-23.4	+210	-1	-8.09
11	+0.5	+10	+36	+26.7	-203	-3	-39.85
12	+0.5	+3.4	-72	-13.3	+42	+1	-29.08
13	+0.5	0	-25	+10	-56	-1	-18.38
14	0	-6.7	-125	+6.6	-8	+2	+3.8
15	-1.5	0	-99	-16.7	-238	-2	-4.82
16	0	0	+165	-3.3	-93	-3	-26.72
17	+1	0	+277	-3.4	+399	0	-21.32
18	+0.5	0	-41	+6.7	-214	0	-9.95
19	+1.5	+3.3	-139	+13.3	-27	-2	-15.35
20	+0.5	0	+281	-10	-172	+2	-3.67

KEY: CT: completion time; DOT-A: Digit Ordering Test-Adapted; RT: reaction time; %: percentage correct hits.