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ORIGINAL RESEARCH

Investigating the Effects of tDCS on Visual Orientation Discrimination Task Performance: "the Possible Influence of Placebo"

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Abstract

The non-invasive neuromodulation technique tDCS offers the promise of a low-cost tool for both research and clinical applications in psychology, psychiatry, and neuroscience. However, findings regarding its efficacy are often equivocal. A key issue is that the clinical and cognitive applications studied are often complex and thus effects of tDCS are difficult to predict given its known effects on the basic underlying neurophysiology, namely alterations in cortical inhibition-excitation balance. As such, it may be beneficial to assess the effects of tDCS in tasks whose performance has a clear link to cortical inhibition-excitation balance such as the visual orientation discrimination task (ODT). In prior studies in our laboratory, no practice effects were found during 2 consecutive runs of the ODT, thus in the current investigation, to examine the effects of tDCS, subjects received 10 min of 2 mA occipital tDCS (sham, anode, cathode) between a first and second run of ODT. Surprisingly, subjects' performance significantly improved in the second run of ODT compared to the first one regardless of the tDCS stimulation type they received (anodal, cathodal, or sham-tDCS). Possible causes for such an improvement could have been due to either a generic "placebo" effect of tDCS (as all subjects received some form of tDCS) or an increased delay period between the two runs of ODT of the current study compared to our previous work (10-min duration required to administer tDCS as opposed to ~ 2 min in previous studies as a "break"). As such, we tested these two possibilities with a subsequent experiment in which subjects received 2-min or 10-min delay between the 2 runs (with no tDCS) or 10 min of sham-tDCS. Only sham-tDCS resulted in improved performance thus these data add to a growing literature suggesting that tDCS has powerful placebo effect that may occur even in the absence of active cortical modulation.

Keywords Neuromodulation · tDCS · Visual Orientation Discrimination Task · Placebo

Introduction

Transcranial direct current stimulation (tDCS), a non-invasive neuromodulation technique, offers the promise of a low-cost tool for both research and clinical applications in psychology, psychiatry, and neuroscience (Brunoni et al. 2011a; Kuo et al. 2014; Mondino et al. 2014; Mondino et al. 2015a; Tanaka and Watanabe 2009). Indeed, tDCS has been shown to alter performance and enhance training effects in a wide range of psychological paradigms (Ditye et al. 2012; Martin et al. 2014; Ruf et al. 2017; Saunders et al. 2015; Segrave et al. 2014). In the case of clinical applications, tDCS has been shown to ameliorate the symptoms of a range of conditions from tinnitus to depression (Antal et al. 2011; Boggio et al. 2012; Faber et al. 2012; Loo et al. 2012; Loo et al. 2010; Mondino et al. 2015b; Vanneste and De Ridder 2011). However, findings regarding tDCS are often equivocal and difficult to replicate with a number of recent meta-analyses suggest that tDCS may have small effects if any (Berlim et al. 2013; Horvath et al. 2015; Medina and Cason 2017; Santos et al. 2018). Furthermore, a recent special issue of frontiers of neuroscience provided 56 papers detailing null effects of neuromodulation

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interventions, the majority related to tDCS. A number of factors have been raised such sample size (Medina and Cason 2017; Minarik et al. 2016) and experimental design (Chew et al. 2015; Jantz et al. 2016; Martin et al. 2014). However, a more fundamental problem is that clinical and cognitive applications studied are complex and thus effects of tDCS are difficult to predict given its known effects on the basic underlying neurophysiology (Das et al. 2016; Giordano et al. 2017; Stagg et al. 2018).

tDCS principally modulates cortical excitation-inhibition (E-I) balance and this has been demonstrated in both human subjects (Krause et al. 2013; Nitsche and Paulus 2001) and animal models (Bindman et al. 1962; Márquez-Ruiz et al. 2012). Although HD-tDCS uses complex arrays of multiple electrodes (e.g., Cole et al. 2018), conventional tDCS delivers a low intensity (2 mA or less) of direct current to targeted cortical areas via two electrodes of opposite current polarities (Hogeveen et al. 2016; Nikolin et al. 2015; Villamar et al. 2013), one is placed on the scalp overlying the cortical region of interest while the other is placed in a "reference" location, which can be either cephalic (i.e., prefrontal cortex) or extracephalic location (i.e., left cheek) (Berryhill et al. 2010; Im et al. 2012; Tseng et al. 2018). Anodal-tDCS, in which the active electrode is positively charged increases neural excitability (Nitsche and Paulus 2000), while cathodal-tDCS in which the active electrode is negatively charged, decreases neural excitability of the "stimulated" area (Nitsche et al. 2003b). The typically used control condition "sham-tDCS" consists of active stimulation (anodal or cathodal) for a few seconds mimicking the stimulation experienced with active stimulation in order to blind participants to the stimulation condition (Gandiga et al. 2006; Palm et al. 2013). It has been suggested that the short active stimulation of sham-tDCS does not change cortical excitability (Nitsche et al. 2008; Siebner et al. 2004) and is widely used as a "placebo" control protocol (Filmer et al. 2014; Greinacher et al. 2018).

Active tDCS has been shown to modulate the concentration levels of the main excitatory and inhibitory neurotransmitters (glutamate, gamma-aminobutyric acid (GABA), respectively) (Antonenko et al. 2017; Clark et al. 2011; Kim et al. 2014; Stagg et al. 2009). For instance, a magnetic resonance spectroscopy (MRS) study found a reduction of GABA concentration level following anodal-tDCS stimulation compared to sham-tDCS and a reduction of the level of glutamate concentration level following cathodal-tDCS stimulation compared to sham-tDCS (Stagg et al. 2009). Given these known effects of tDCS, it may be easier to assess, observe, and interpret the effects of tDCS on performance in psychological tasks that have clear links to cortical E-I balance such as Binocular Rivalry (Blake 1989; van Loon et al. 2013) and Orientation Discrimination Task (ODT) (Edden et al. 2009; Katzner et al. 2011; Li et al. 2008; Sillito 1975; Sillito et al. 1980). Such perceptual judgments often depend on inhibition between primary sensory representations in cortex and thus tasks of this nature, maybe more easily be altered by tDCS than those requiring higher cognitive regions where the link between E-I balance and performance is less easy to intuit. Indeed, tDCS has been shown to alter somatosensory discrimination (Fujimoto et al. 2016; Labbé et al. 2016) and auditory pitch discrimination (Mathys et al. 2010). Surprisingly, as far as we are aware, no authors have investigated whether tDCS can alter performance on a visual ODT, a task with clear links to E-I balance in cortex. During the ODT, participants are visually presented with pairs of gratings in a sequence and are instructed to judge whether the second grating has been rotated clockwise or anti-clockwise compared to the first grating (Edden et al. 2009). The ODT is a task that should be susceptible to manipulation by tDCS as performance in the task has been linked to E-I balance of the primary sensory representations of orientation. Individual neural receptive fields are strongly tuned to a particular visual stimulus orientation providing a neurophysiology basis for the ability to discriminate the orientation of visual stimuli (Hubel and Wiesel 1962). It has long been thought that inhibition and excitation between these neurons play a key role in shaping orientation selectivity (Hubel and Wiesel 1962). For instance, topical application of GABA agonists in primary visual cortex (V1) in animal models increases the orientation tuning of visual cortical neurons (Li et al. 2008; Xia et al. 2013), whereas GABA antagonists decrease orientation tuning (Katzner et al. 2011; Sillito 1975, 1979; Sillito et al. 1980; Xia et al. 2013). As such, E-I balance in V1 should relate to orientation discrimination performance. Indeed, in human subjects, MRS measurements of GABA concentration in V1 negatively correlates with actual ODT thresholds (greater GABA concentration corresponds to increase performance) (Edden et al. 2009). As glutamate has opposing effects on cortical excitability to GABA it should also relate to ODT performance. Indeed, although inter-individual differences in glutamate concentration did not correlate with individual differences ODT performance in one study (Kurcyus et al. 2018), manipulations of glutamate have been shown to alter orientation turning of visual cortical neurons (Liang et al. 2007). As such given the links of ODT to cortical E-I balance, the purpose of the present investigation is to explore whether tDCS can alter performance on the ODT.

A further possible confound for tDCS studies is practice or training effects following repeated attempts at a task which could mask, interfere, or interact with tDCS (Eddy et al. 2017; Furuya et al. 2014; Hsu et al. 2015; Peters et al. 2013; Thair et al. 2017; Wong et al. 2018). Fortunately, the ODT is quite resilient to repeated attempts as no robust performance improvement could be observed without extensive training (Song et al. 2010; Vogels and Orban 1985). Participants show no overall difference in performance in an initial or second run of the ODT task both in our laboratory (Dickinson et al. 2014,

2015, 2016) and in the data of the group who devised the task (Edden et al. 2009). As no practice effects had been observed during 2 runs of ODT, in this study participants were asked to complete 2 runs of the ODT and received 10 min of 2 mA occipital-tDCS (sham, anode, cathode) between the first and second run. Given the findings of Edden and colleagues that greater inhibition (increased GABA concentration) correlated with better performance on the ODT task (Edden et al. 2009), we hypothesized that anodal-tDCS would impair performance whereas cathodal-tDCS would improve it.

In addition to investigating the efficacy of tDCS in a well-defined perceptual task, the study is also of clinical interest as differences in ODT performance have been used to infer the E-I balance in clinical groups such as those with autistic spectrum conditions (Dickinson et al. 2014, 2015, 2016; Shafai et al. 2015; Sysoeva et al. 2016). As such, data regarding the effects of tDCS on the ODT would further allow the correct interpretation of differences in performance in clinical groups in terms of cortical E-I balance.

Therefore, the current study aimed to investigate whether manipulating E-I of the primary visual cortex (V1) using tDCS could affect performance of ODT. An identical ODT was used to the previous studies that found difference in performance in ASC (Dickinson et al. 2016) and correlations between GABA concentration in V1 and ODT performance (Edden et al. 2009). The ODT consisted of both cardinal and oblique conditions. We hypothesized that anodal-tDCS would impair performance in ODT, whereas cathodal-tDCS would improve performance in ODT based on previous studies suggesting a positive correlation between increased inhibition in visual cortex and ODT performance (Dickinson et al. 2015, 2016; Edden et al. 2009). Improvements in performance between groups of subjects have been easier to observe in paradigms with oblique stimuli (Dickinson et al. 2014, 2016) rather than cardinal stimuli (Brock et al. 2011). This is thought to be due to the "easier to judge" cardinal stimuli resulting in a ceiling effect. As such, we suspected that hypothesized enhancements in performance following cathodal tDCS stimulation would be easier to observe for the oblique condition compared to cardinal (vertical) and decrements in performance would be easier to observe in the cardinal condition.

Experiment 1 (Examination of the Effect of tDCS on ODT Performance)

Experiment 1 was conducted to investigate the effects of tDCS on ODT performance. Healthy human participants were invited to attend a single session consisting of 2 runs of ODT with tDCS applied between the ODT runs. This experimental design was anticipated to allow the effects of tDCS to be observed due to limited performance improvements between 2 ODT runs within one session.

Method

Orientation Discrimination Task

Orientation discrimination thresholds were measured using a two-alternative forced choice adaptive staircase procedure task based on the work of (Edden et al. 2009) which has been previously used by (Dickinson et al. 2014, 2016). The task was programmed in MatLab (The MathWorks Inc., Natick, MA, 2000) with PsychToolbox (Brainard and Vision 1997), Fig. 1 illustrates the task design. In each trial, a circular reference and a targeting grating (diameter 4°; spatial frequency three cycles/degree; contrast 99%; mean luminance 83 cd/m^2) were sequentially presented for 350 ms with a 500 ms fixation between them. The task consisted of two orientation conditions based on the reference grating orientation (vertical = 0°, oblique = 45°). In each condition, there were two staircases based on the stimulus' rotation direction (clockwise, anti-clockwise). The staircases used the method of one-up three-down procedures converging on 79% accuracy (Leek 2001). On the first trial of each staircase, the target grating was presented 5° away from the reference grating with an initial step size of 1° decreasing 75% after each reversal.

Participants were asked to sit comfortably on a chair with a distance of 57 cm between their heads and the monitor. A black circular aperture was placed over the monitor to eliminate any external cues of orientation provided by the monitor edges. As the studies of ourselves and other investigators measuring orientation discrimination thresholds (Dickinson et al. 2014, 2016; Edden et al. 2009) did not use a chin rest, a chin rest was not used in this experiment. Participants were instructed to judge whether the target grating had been rotated clockwise or anti-clockwise compared to the reference grating using right and left arrow keys. In a practice run, participants completed 10 trials for each of the 4 staircases. In the experimental runs, however, participants completed 140 trials for each staircase, if they did not converge after 8 reversals the run would terminate. Depending on the experiment, the last 6 or 4 reversals of each staircase were used to calculate discrimination thresholds after discarding the first two reversals, which were considered practice trials. Thresholds of vertical and oblique conditions were calculated separately by averaging the left and right staircases of each condition.

Main Exclusion Criteria

Three exclusion criteria were applied for this experiment. One was regarding the unsuccessful completion of the 6 reversals for each condition in any ODT session's run. Therefore, participants who failed to reach 6 reversals in each staircase were excluded from analysis. Inspection of the previous data (Dickinson et al. 2014, 2015, 2016) suggests that 6 reversals are sufficient to calculate a reliable threshold. The second

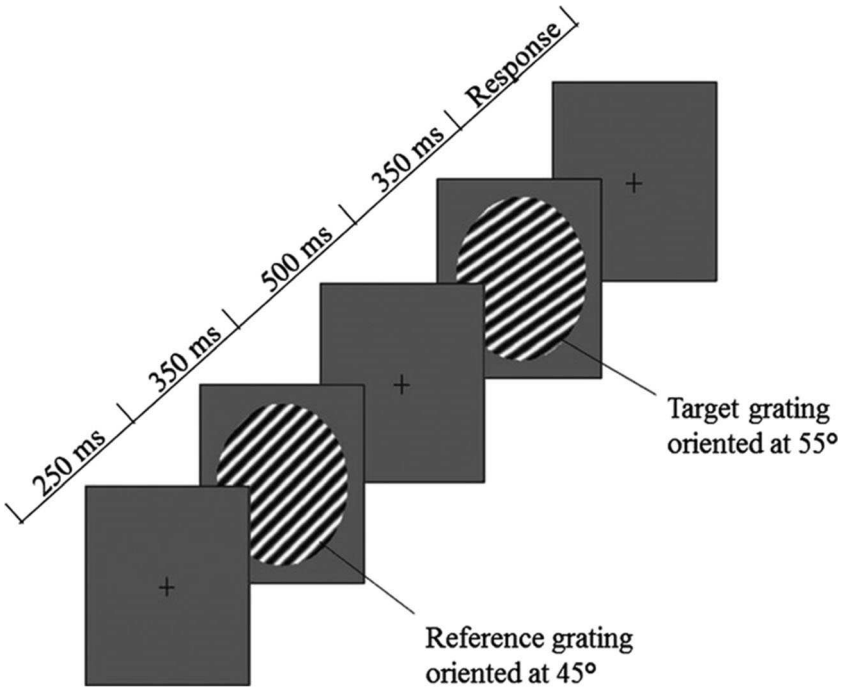

Fig. 1 Schematic diagram of the orientation discrimination task. The task consisted of vertical and oblique conditions, depending on the orientation of the reference grating. The reference grating was oriented at 0° in the vertical condition and was orientated at 45° in the oblique condition. The reference grating was always followed by the target grating. Participants were instructed to indicate whether the target grating was rotated clockwise or anti-clockwise compared to the reference grating using the left and right arrow keys of the keyboard

criterion for exclusion was based on the condition of thresholds being +/− 2 standard deviations from mean threshold of the group. Finally, participants who did not receive tDCS (i.e., due to headwear) or did not complete the complete duration of tDCS stimulation for any reason (i.e., due to any uncomfortable sensations during tDCS) were also excluded from analysis.

Transcranial Direct Current Stimulation

A battery-driven constant generator (TCT research, Hong Kong) was used to generate direct current via two saline-solution-soaked sponge electrodes. One electrode (5 × 5 cm) was placed over the primary visual occipital cortex (V1) corresponding to Oz according to the international 10–20 Electrode Placement System (Klem et al. 1999). To locate Oz, the distance from the nasion to inion was measured, and then 10% of this total distance from the inion was used or Oz location. The other electrode (5 × 7 cm) was placed over the left cheek (extracephalic) to avoid confounding effects that might be generated by stimulating an additional brain region (Berryhill et al. 2010; Im et al. 2012; Tseng et al. 2018).

Previous studies have confirmed the efficacy of transcranial direct current stimulation (tDCS) for visual cortex stimulation at this locus (Antal et al. 2003a, b; Antal et al. 2006; Ding et al. 2016); see Antal and Paulus (2008) for review. The stimulation intensity gradually increased over 30 s until it reached 2 mA to minimize the possibility of adverse sensations (Nitsche et al. 2003a), and lasted for 10 min. Durations of 9–13 min offline tDCS have been shown to produce after-effects lasting up to 60 min (Nitsche et al. 2003b; Nitsche and Paulus 2001), which easily covers the duration of the entire ODT including self-directed break periods (~ 25 min total maximum duration). Although tDCS can be delivered during the task (online-tDCS) or before the task (offline-tDCS) (Thair et al. 2017), we used an offline-tDCS design. This was to avoid any possible changes in expected tDCS polarity effects induced by increased stimulation duration for some participants who might spend longer time to complete the ODT than others, given putative non-linear relationships between the tDCS effects and stimulation duration. For instance, it has been found that typically excitatory anodal-tDCS can induce an inhibitory effect on cortex if stimulation durations longer than are typically used (e.g., 26 min rather than 10–20 min (Monte-Silva et al. 2013).

Although 1 mA has been shown sufficient to produce functionally relevant changes in inhibition and excitation in the visual system (Antal et al. 2004) see Antal et al. (2006) for review). In some brain regions, such as the frontal lobe, 2 mA is required to elicit an effect in cognitive tasks (Iyer et al. 2005). As such, 2 mA was chosen to ensure that the chances of observing the effects of tDCS were maximized (Marshall et al. 2016). Furthermore, the stimulation intensity of 2 mA has also been found effective in inducing changes in the cortical excitability of occipital cortex in a polarity manner indicated by changes in performance in various visual perception tasks (Ding et al. 2016; Mancini et al. 2012; Reinhart et al. 2016).

Participants

Eighty-nine healthy volunteers from the University of Sheffield with normal or corrected to normal vision participated in this one-tDCS session study. None of the participants

had history of neurological disorders (e.g., epilepsy, head injuries, and migraine). Twenty-seven of the participants were first-year Psychology students and received credits for participation. The rest were recruited from the students and staff-volunteering list of the University of Sheffield and received a £7 gift voucher for participation in the study. Participants provided a written consent form at the beginning of the session. The study received full ethical approval from the Department of Psychology University of Sheffield ethics committee.

Procedures

At the beginning of the experimental session, participants provided a written consent form to take part in the study after reading the information sheet (detailing information about the purpose and procedures of the study, brief information about tDCS and its potential risks, participants rights, and confidentiality conditions - see supplementary material). The information sheet stated that the purpose of the study was to examine the relationship between tDCS and orientation discrimination performance and received the following information regarding tDCS "What is transcranial direct-current stimulation (tDCS)? Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation modulating the cortical excitability. It is shown that Anodal-tDCS increases the cortical excitability whereas Cathodal-tDCS decreases it. The measurable effects of tDCS are small and last about an hour. Participating in this study should not prevent you from continuing your normal activities such as driving home." If participants asked the experimenter about the potential/expected effects of tDCS on ODT performance, participants were told that there were no specific expectations as to whether tDCS might improve, impair, or not affect the ODT performance.

Participants performed a practice run of ODT followed by the first run. Participants were then randomly assigned to one of three in between-run conditions, in which they received anodal-, cathodal-, or sham-tDCS. Subjects were blind to the condition they received but the experimenter was not (single-blinded). Participants were asked to relax during the period of tDCS stimulation duration. Also, participants were asked to notify the experimenter if they experienced any discomfort related to the stimulation so that stimulation would cease immediately. Although sham-tDCS has been shown to produce no effects on cortical excitability (Nitsche et al. 2008; Siebner et al. 2004), we counterbalanced the polarity of sham-tDCS to balance any potential neurobiological effects of the 30-s stimulation (Fonteneau et al. 2019) however slight. Thus, half of the sham-tDCS group received sham-tDCS with a 30 s of anodal-tDCS whereas the other half received sham-tDCS with a 30 s of cathodal-tDCS.

After 10-min tDCS (2 mA) stimulation, participants performed a second run of ODT. During the session, participants were repeatedly asked to notify the experimenter whenever they were uncomfortable so that the experimental session could be terminated. At the end of the session, participants were requested to complete an adverse effect questionnaire (Brunoni et al. 2011b) and the post-stimulation rating form (including pain, attention, and fatigue (Galea et al. 2009, Table 1). This was to examine whether there were any differences based on stimulation experience between active- and sham-tDCS.

Results

During the stimulation duration, 4 participants notified the experimenter about uncomfortable sensations (scale pain) caused by the tDCS, as such the experimental session was immediately terminated and these subjects were excluded from analysis. Data from 13 participants were excluded from analysis because their thresholds in any condition of ODT were 2 standard deviations above their tDCS type group mean. An additional participant was excluded because they did not receive tDCS stimulation due to headwear (e.g., hair extensions). Data from 71 participants (anodal-tDCS (N = 24, male = 10, age: M = 24, SD = 7.2), cathodal-tDCS (N = 24, male = 10, age: M = 22.2, SD = 4.9), and sham-tDCS (N = 23, male = 9, age: M = 23.4, SD = 6.1)) were used in the analysis (Table 1).

Although 71 participants completed the two runs of ODT, only 66 participants successfully completed the post stimulation-rating questionnaire (22 participants from the anodal-tDCS group, 24 from the cathodal-tDCS group, and 20 from the sham-tDCS group), in which participants were asked to rate the level of pain, fatigue, and fatigue from 1 (minimum) to 7 (maximum) in addition to report their thoughts of whether they had received active- or sham (placebo)-tDCS.

To investigate whether the stimulation experience would differ based on stimulation type as either active- or sham-tDCS, responses of active-tDCS groups (anodal- and cathodal-tDCS) to the post-stimulation rating questionnaire were compared to that of sham-tDCS group using independent sample t test. The results showed no significant differences in the stimulation experience between active-tDCS and sham-tDCS in terms of level of pain (active-tDCS (M = 1.43, SE = .09) and sham-tDCS (M = 1.45, SE = .15), (t (64) = − .89, p = .930)), level of attention (active-tDCS (M = 4.80, SE = .22) and sham-tDCS (M = 4.00, SE = .37), (t (64) = 1.841, p = .070)), and level of fatigue (active-tDCS (M = 3.04, SE = .21) and sham-tDCS (M = 3.55, SE = .37), (t (64) = 1.266, p = .210)).

Data were analyzed using repeated-measures ANOVA. Condition (vertical, oblique) and run (first, second) were the within-subject variables while the tDCS type (anodal-tDCS, cathodal-tDCS, sham-tDCS) was the between-subject variable.

Table 1 In experiment 1, participants received anodal-, cathodal, or sham-tDCS between the two ODT runs. During the experimental session, 4 participants notified the experimenter about uncomfortable sensations (scalp pain) caused by the tDCS during the stimulation time, as such the experimental session was immediately terminated and these subjects were excluded from analysis and were not included in the table. The stimulation experience of participants in experiments 1 did not significantly differ for active- or sham-tDCS in terms of pain, attention, and fatigue based on the post-stimulation ratings, (ps > 0.05). In experiment 2, participants had either no-tDCS with 2-min delay between the two runs (2-min delay), no-tDCS with 10-min delay between the two runs (10-min delay), or received 10-minsham-tDCS between the two runs. Based on the analysis of the post-stimulation questionnaire, more than 70% of the participants received sham-tDCS in experiment 2 thought that they had received a real (active) stimulation

Experiment	tDCS Type	Participants (male/female)	Age (M, SD)	tDCS side effects
Experiment 1	Anode-tDCS	(10/14)	(M = 24, SD = 7.2)	Skin redness (N = 2), sleepiness (N = 1)
	Cathode-tDCS	10/14)	(M = 22.2, SD = 4.9)	None
	Sham-tDCS	(9/14)	(M = 23.4, SD = 6.1)	Scalp pain (N = 1)
Experiment 2	2 mins-delay	(14/0)	(M = 20.6, SD = 0.7)	N.A
	10 mins-delay	(13/0)	(M = 20.9, SD = 1.5)	N.A
	Sham-tDCS	(14/0)	(M = 20.8, SD = 1.5)	Itching (N = 1), fatigue (N = 1)

There was a main effect of condition (F (1, 68) = 639.67, p < .0001, ηp2 = .90). As expected, thresholds were significantly lower for the vertical condition (M = 1.63, SE = 0.11) compared to the oblique condition (M = 6.81, SE = 0.25). Surprisingly, there was also a main effect of run (F (1, 68) = 51.92, p < .0001, ηp2 = .43). Thresholds were significantly lower (indicating increased performance) in the second run (M = 3.80, SE = 0.16) compared to the first run (M = 4.64, SE = 0.18).

Additionally, a significant interaction was found between condition and run (F (1, 68) = 35.76, p < 0.0001, ηp2 = .34). Pairwise comparisons showed that only the thresholds for the oblique condition were significantly reduced in the second run (p < 0.0001, d = 0.92), and not those of the vertical condition (p = 0.066, d = 0.22). However, the result showed no main effect of tDCS type, (F (2, 68) = 0.79, p = 0.457, ηp2 = .02). Additionally, no significant interactions were found between run and tDCS type (F (2, 68) = 0.37, p = 0.694, ηp2 = .01), nor between condition, run, and tDCS type (F (2, 68) = 1.20, p = 0.308, ηp2 = .034). Despite the non-significant interactions, further pairwise comparisons were conducted to check whether the statistically significant performance improvement in oblique condition (p < 0.0001) and the trend towards performance improvement in the vertical condition (p = 0.066) occurred for all tDCS type (anodal-, cathodal-, sham-tDCS). The results indicated a significant performance improvement in oblique condition for all tDCS type, (ps < 0.0001), (anodal-tDCS: d = 1.07, cathodal-tDCS: d = 0.843, sham-tDCS: d = 0.816). Additionally, the result showed that only the vertical thresholds of cathodal-tDCS were significantly reduced (better performance) in the second run (compared to the first run (p = 0.009, d = 0.55). However, no such vertical ODT performance improvement at the second run was found for anodal-tDCS (p = 0.98, d = 0.005) or sham-tDCS (p = 0.60, d = 0.15), (Fig. 2).

Experiment 2 (Examining the Possible Causes of Improved ODT Performance: Placebo Effect or Temporal Duration Between Runs)

Experiment 1 examining tDCS effects on ODT revealed an unexpected and robust performance improvement occurred in the second run of ODT compared to the first run irrespective of tDCS type being given (anodal-, cathodal-, sham-tDCS). One possibility of such improvement could be due to a generic placebo effect of tDCS (Aslaksen et al. 2014; Turi et al. 2018). Another possibility could be related to increasing delay time between the 2 runs. Unlike our previously published studies (Dickinson et al. 2014, 2015, 2016) that found no difference in performance in 2 runs of ODT, experiment 1 of the current study increased the delay time between the 2 runs (10 min to deliver tDCS rather than the ~ 2 min given in the previous studies as a self-directed break), raising the possibility that this increase temporal duration between runs could have also resulted in improvement in performance. The increase in temporal duration between the 2 runs is a plausible explanation for the improvement in ODT performance as a number of studies have suggested a crucial role of resting time following practice in perceptual learning (Bönstrup et al. 2019; Dewar et al. 2014; Schoups et al. 1995). Although, Schoups et al. (1995) demonstrated that improvements in perceptual learning occur following a rest period (a day) far greater than in study 1 of the current investigation, several reports have demonstrated that a passive consolidation of periods of 15 (Dewar et al. 2014) or even 12 min (Bönstrup et al. 2019) can improve performance. These timescales are extremely similar to those observed in experiment 1 suggesting that such an increase of temporal duration between runs (from 2 to 10 min) is a possible explanation for improvement. Therefore, experiment 2 was conducted to investigate these two possible causes of the unexpected performance improvement that occurred in the

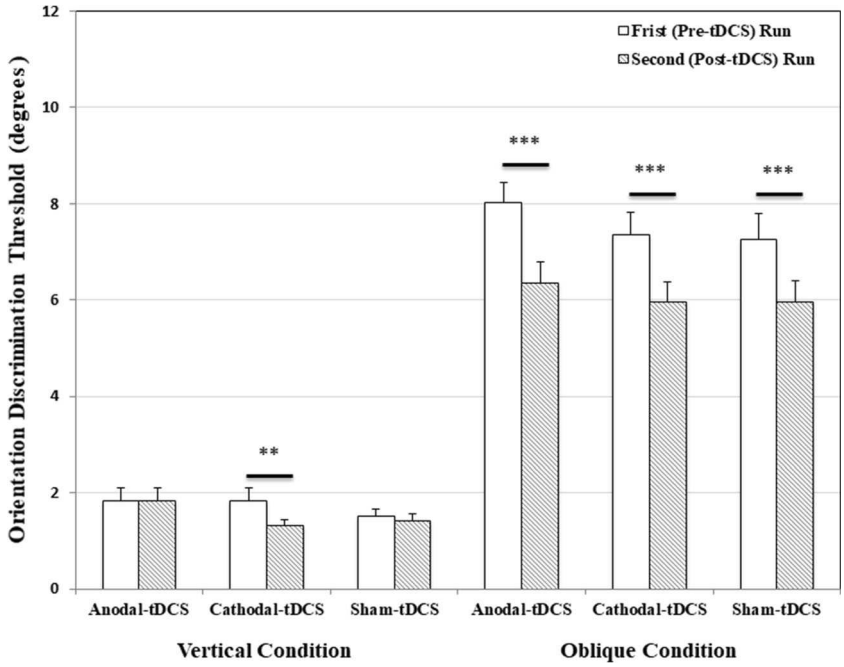

Fig. 2 Mean oblique orientation discrimination threshold (degrees, decreased threshold is associated with increased performance) before and following 10-min tDCS simulation. Participants received tDCS stimulation between 2 runs of ODT. Anodal-tDCS consisted of 24 participants, cathodal-tDCS consisted of 24 participants, and sham-tDCS consisted of 24 participants. Error bars represent standard error. $^{**}p < 0.01$, $^{***}p < 0.0001$

second run of ODT by comparing duration (2min, 10min no tDCS) between the 2 runs and 10-min sham tDCS.

Participants

Forty-seven male undergraduate students at the Psychology Department of King Saud University participated in this one experimental session study. Participants had normal or corrected to normal vision, and had no history of neurological disorders (e.g., epilepsy, head injuries, and migraine). Participants received course credits for participation in the study. The study received full ethical approval from the Department of Psychology University of Sheffield ethics committee, as well as written permission from the Psychology Department of King Saud University, to conduct the study at their department.

Procedures

The task, procedures, and exclusion criteria and information sheet were identical to experiment 1. As the experiment was conducted in Saudi Arabia, information sheet, consent form, and the instruction were in Arabic. After providing a written consent form to take part in the study, participants performed a practice run of ODT followed by the first run. Participants were then randomly assigned to one of three between-run conditions: having either no-tDCS with 2 min (2-min delay) or 10-min delay between runs (10-min delay) or receiving 10-min sham-tDCS between the two runs. For the sham-tDCS group, half of the participants received sham-tDCS with 30 s of anodal-tDCS, whereas the other half received sham-tDCS with 30 s of cathodal-tDCS to balance any possible neurophysiological effects of the 30-s stimulation (Fonteneau et al. 2019) however unlikely. As participants received an identical information sheet to experiment 1, participants in the sham-tDCS condition did not know they received sham-tDCS (the information sheet suggested they may receive active tDCS). Participants were asked to relax during the period between the two runs of ODT regardless of their assigned condition (2-min delay, 10-min delay, or sham-tDCS). Subjects who were assigned to the 2 min and 10-min delay conditions did not have tDCS electrodes placed.

At the end of the experiment, participants received sham-tDCS were requested to complete the adverse effect and post-stimulation rating questionnaires (Brunoni et al. 2011b, Table 1.)

Results

One participant in the middle of the first run notified the experimenter that they were feeling fatigued so the experimental session was immediately terminated. Data of 6 participants were excluded: 4 due to unsuccessful completion of 6–8 reversals, one due to their thresholds being 2 standard deviations above their group's mean and one participant who did not complete the task due to feeling unwell, Table 1. Thus, data from 41 participants (2-min delay ($N = 14$, age: $M = 20.6$, SD = 0.7), 10-min delay ($N = 13$, age: $M = 20.9$, SD = 1.5), sham-tDCS ($N = 14$, age: $M = 20.8$, SD = 1.5)) were used in the analysis (Table 1). Based on the analysis of the post-stimulation questionnaire, more than 70% of the participants

who received sham-tDCS thought that they had received a real (active) stimulation.

Data were analyzed using repeated-measures ANOVA analysis. Condition (vertical, oblique) and run (first, second) were treated as within-subject variables while delay condition group (sham-tDCS, 10-min delay, 2-min delay) was treated as a between-subjects variable.

There were main effects of both condition (F (1, 38) = 287.793, $p < 0.0001$, ηp2 = .91) and run (F (1, 38) = 6.186, $p = 0.017$, ηp2 = .14). As expected, thresholds were significantly lower for the vertical condition compared to the oblique condition, as well as for the second run compared to first run. Additionally, significant interactions between run and delay condition group (F (2, 38) = 3.910, $p = 0.029$, ηp2 = 0.17), and between ODT condition (oblique, vertical) and run (F (1, 38) = 7.665, $p = 0.009$, ηp2 = 0.17) were found. Pairwise comparisons analysis showed that only sham-tDCS thresholds were significantly lower in the second run compared to the first run, ($p = 0.001$, $d = 0.76$), (Fig. 3a). Another pairwise comparison analysis showed that only thresholds of oblique condition were significantly lower at the second run compared to the first run ($p = 0.005$, $d = 0.44$). However, there was no main effect of delay condition group (F (2, 38) = .363, $p = 0.698$, ηp2 = 0.019) nor a significant interaction between condition, run, and delay condition group (F (2, 38) = 2.111, $p = 0.135$, ηp2 = 0.10). Yet, a further pairwise comparison was conducted to check whether ODT performance improvement of sham-tDCS occurred in both vertical and oblique condition. The result showed that only oblique performance of sham-tDCS was statistically significantly improved in the second run ($M = 7.02$, SE = 0.66) compared to first run ($M = 8.90$, SE = .62), ($p < 0.0001$, $d = 0.84$) (Fig. 3b. However, no such performance improvement of sham-tDCS was found in vertical condition at the second run ($M = 1.95$, SE = 0.28) compared to the first run (($M = 2.47$, SE = 0.25), $p = 0.073$, $d = 0.428$).

The Role of Perception of tDCS on the Placebo-Related Improvement in ODT Performance

Experiment 2 examined whether a generic placebo effect of tDCS or temporal duration between runs required for delivering tDCS caused the unexpected performance improvement in ODT found in experiment 1. Experiment 2 found that ODT performance was significantly improved in sham-tDCS alone and not improved in subject assigned to conditions with no tDCS (2-min delay, 10-min delay). This robust performance improvement following sham-tDCS suggests a placebo effect of tDCS on ODT. As placebo effects have been linked to the belief and expectations about the efficacy of the treatment/interventions (Mayberg et al. 2002; Schambra et al. 2014; Wager 2005; Wager et al. 2004), we investigated whether ODT performance improvement depended on participants' perception of the stimulation's type they had received as either active- or sham-tDCS using the experiment 1 data. Participants at the end of each session were asked to indicate whether they thought they had received real/active- or sham-tDCS in the post-stimulation questionnaire (Galea et al. 2009). Based on their belief of the stimulation type they had received regardless of the actual stimulation they had received, participants were categorized into a "perceived active tDCS" group ($N = 54$) and "perceived sham-tDCS" group ($N = 12$). Given the more susceptibility of oblique ODT thresholds to improve compared to that of vertical one, two paired-sample t test analyses were conducted to evaluate oblique ODT performance improvement pre- and post-tDCS for each group separately. For participants who thought that they had received active-tDCS (active perceived stimulation) regardless of the actual stimulation, the result showed a robust performance improvement in oblique condition of ODT at the second (post-tDCS) run ($M = 6.80°$, SE = .39°) compared to the first (pre-tDCS) run ($M = 8.53°$, SE = .40°), ($d = 1.05$, $p < .0001$). For participants who thought that they had received sham-tDCS (sham perceived stimulation) regardless of the actual stimulation, the result almost reached statistical significant ($d = 0.63$, $p = .052$) as performance in the oblique condition of ODT at the second (post-tDCS) run ($M = 6.30$, SE = .56) was better compared to the first (pre-tDCS) run ($M = 7.35$, SE = .62), (Fig. 4). The statistical insignificance may possibly be due to the small sample size. Although the results are consistent with findings of previous studies showing an association between perception of treatment/intervention and the expected behavioral outcomes, the results cannot rule out the possibility that placebo effects of tDCS could occur even in the absence of a belief that the subject had received active-tDCS.

Discussion

We investigated the effect of tDCS on orientation discrimination task performance in 2 experiments. As expected from previous studies, thresholds for the vertical condition were significantly lower (indicating increased performance) than for the oblique condition in all of the studies. Consequently, compared to vertical thresholds, oblique thresholds were much more susceptible to change in all of the experimental paradigms. In experiment 1, participants were asked to complete 2 runs of ODT and received one type of tDCS (anodal-, cathodal-, or sham-tDCS) between the 2 runs. The data found no effect of tDCS type (anodal-, cathodal-, or sham-tDCS) on ODT performance. However, unexpectedly, a strong performance improvement occurred in the second run irrespective of stimulation type. This improvement could have been due to either a generic placebo effect of tDCS on ODT performance

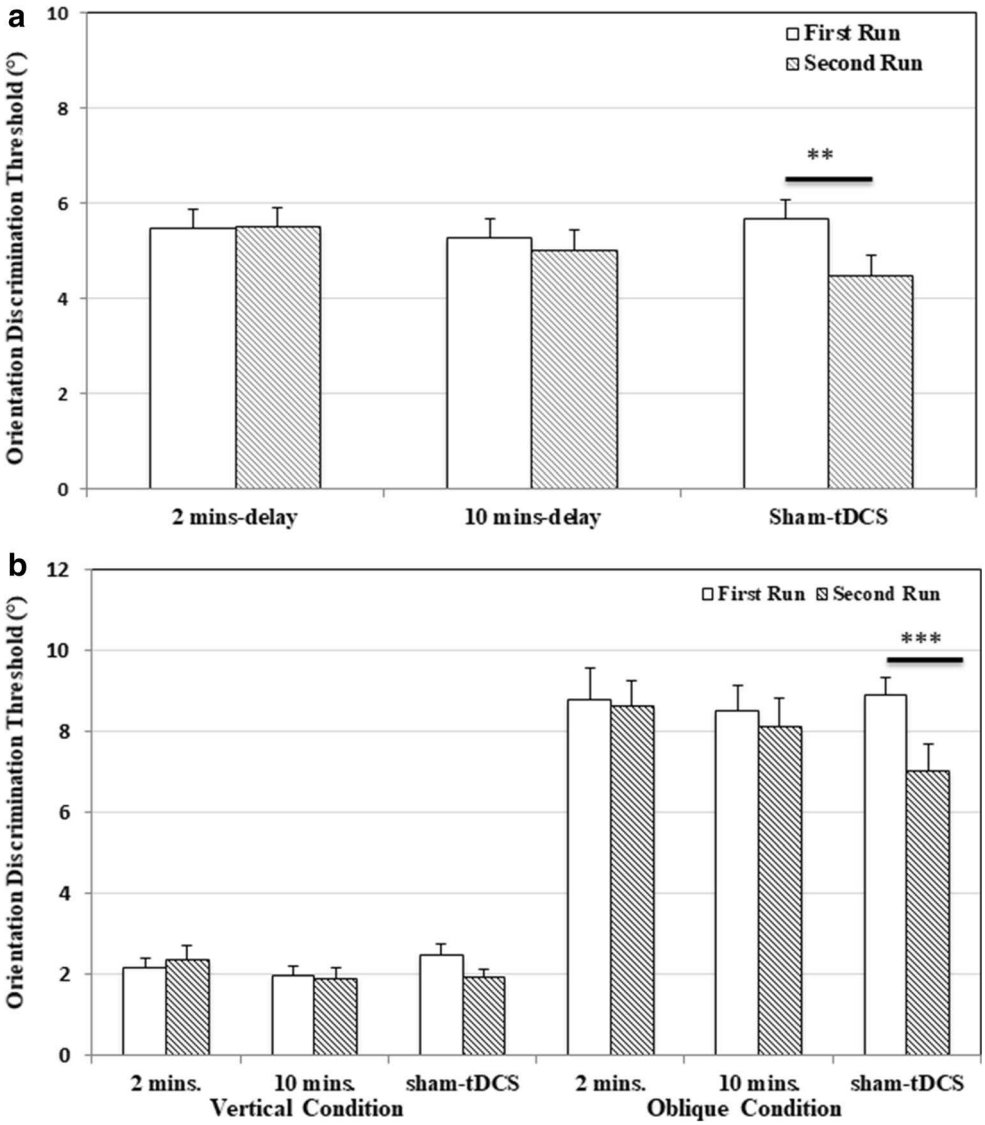

Fig. 3 **a** Mean orientation discrimination thresholds (degrees, a decreased threshold is associated with increased performance) in both vertical and oblique conditions of the visual orientation discrimination tasks before and following a 2-min delay, 10-min delay, and 10-min sham-tDCS (sham-tDCS). **b** Mean orientation discrimination thresholds (degrees, a decreased threshold is associated with increased performance) in vertical and oblique condition of the visual orientation discrimination tasks before and following 2-min delay, 10-min delay, and 10-minsham-tDCS (sham-tDCS). Fourteen participants had a 2-min delay between the two ODT runs, 13 participants had a 10-min delay between the two ODT runs, and 14 participants received 10-min Sham-tDCS between the two ODT runs. Error bars represent standard error. $^{**}p = 0.001$, $^{***}p < 0.0001$

as some form of tDCS was always administered between the 2 runs (anodal-, cathodal-, or sham-tDCS) or an increased temporal delay (10 min compared to about 1–3 min in previous studies where no improvement occurred) between the two runs (during which tDCS stimulation was administered). Experiment 2 investigated these two possible causes of performance improvement. In this experiment of two runs of ODT, participants were randomly assigned to one of three between-run conditions, which were 2-min delay between the two runs (2-min delay), 10-min delay between the two runs (10-min delay), or 10 min of sham-tDCS. The result of experiment 2 confirmed that the unexpected performance improvement in the second ODT run resulted from a placebo tDCS effect rather than the extended delay period. Only the ODT performance of the sham-tDCS group was significantly improved in the second run whereas no such improvements were found in the groups of participants receiving no-tDCS. Taken together, the current study did not observe any reliable evidence for an effect of active-tDCS on ODT performance, but instead found a strong placebo effect of tDCS that lead to increased ODT performance.

ODT performance of participants in the two experiments varied based on condition (oblique versus horizontal). In line with previous studies (Dickinson et al. 2016; Edden et al. 2009; Shafai et al. 2015), ODT performance is better on vertical ODT compared to that on oblique condition. This condition effect is known as an oblique effect (Appelle 1972) and is attributed to a higher sensitivity of neurons in visual cortex to vertical and horizontal visual stimuli (cardinal) compared to oblique ones (Furmanski and Engel 2000; Vogels and Orban 1985).

When examining effects of tDCS on ODT, experiment 1 observed no specific effect of tDCS on ODT performance (active compared to sham). Although the null finding of tDCS effects on ODT performance could be related to the tDCS protocol, this is unlikely. Notwithstanding, tDCS effects

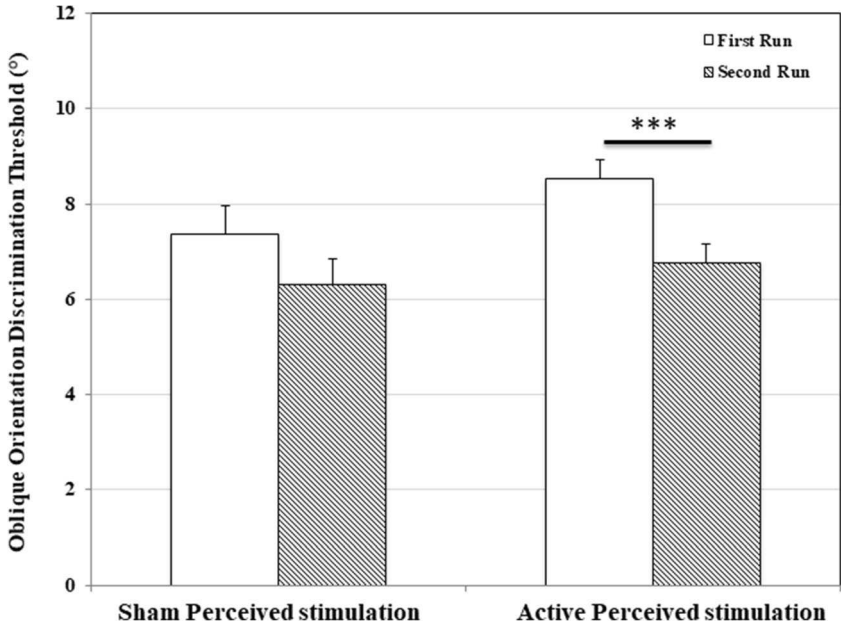

Fig. 4 Mean of oblique orientation discrimination thresholds (degrees, a decreased threshold is associated with increased performance) before and following active- and sham-tDCS. The active-perceived stimulation group consists of 54 participants who thought they had received active-tDCS regardless of the actual stimulation was received (either active- or sham-tDCS). The sham-perceived stimulation group consists of 12 participants who thought they had received sham-tDCS regardless of the actual stimulation was received (either active- or sham-tDCS). Error bars represent standard error. ***$p = 0.0001$

can vary based on many factors such as location of electrode, time, intensity, and duration of stimulation (Nitsche et al. 2008). For instance extended tDCS stimulation (20 min) may lead to effects on neural excitability in the opposite direction of that expected. Indeed, 20 min of cathodal-tDCS can actually increase neural excitability (Batsikadze et al. 2013) compared to the expected decreases that occur with shorter durations (e.g., 9 min (Batsikadze et al. 2013; Nitsche et al. 2003b)). However, the 10 min used here is a common duration (Antal et al. 2001, 2003b, 2004), and is known to produce the expected changes in cortical excitability in primary visual cortex depending on whether stimulations is cathodal or anodal. The 10-min duration chosen here has been shown to produce up to 60 minutes of after effects, which is a temporal duration that is far longer the runs of the ODT completed post-tDCS (Nitsche et al. 2003b; Nitsche and Paulus 2001; see Antal et al. (2006) for review). Also, whereas it is common to obtain anodal-excitation and cathodal-inhibition effects in studies of motor cortex, it is not as common to find neural inhibition effects of cathodal-tDCS as compared to neural excitation effects of anodal-tDCS in some cognitive domains (Jacobson et al. 2012) possibly due to difference in the cortices' structures (Antal et al. 2006). Notwithstanding, the expected direction of excitability changes elicited by tDCS has been reported in association cortices associated with higher cognitive functions such as the frontal lobe (Iyer et al. 2005). Furthermore, in the case of the visual system, V1 has been shown to respond to tDCS in a similar fashion to M1 (Antal et al. 2001, 2003b, 2004); see Antal et al. (2006) for review. In the case of current intensity, although 1 mA has been shown to be sufficient to produce functionally relevant changes in inhibition and excitation in the visual system (Antal et al. 2004); see Antal et al. (2006) for review, in some brain regions such as the frontal lobe, 2 mA is required to elicit an effect in cognitive tasks (Iyer et al. 2005). As such, in the current study, 2 mA was chosen to ensure that the chances of observing the effects of tDCS were maximized (Marshall et al. 2016). To summarize, the duration, intensity, and location of tDCS were chosen to maximize the effects of tDCS and thus these parameters were unlikely to have resulted in the null finding observed.

Although being deliberately designed to avoid practice effects, the result of experiment 1 revealed an unexpected and surprising robust improvement in the post-stimulation run regardless of whether active (anodal-, cathodal-tDCS) or sham-tDCS being administered. Given that there are several reports of anodal-tDCS actually blocking the occurrence of perceptual learning (Matsushita et al. 2015; Peters et al. 2013), this suggests that the performance improvement observed in this experiment is extremely robust. Such improvement in performance might hinder or mask the tDCS effects from being detected (Külzow et al. 2018), given that tDCS is characterized as relatively weak form of modulation (Horvath et al. 2015). However, rather than a practice effect per se, there were two possible explanations for such improvement. One was that the improvement might be a result of a placebo effect of tDCS since all conditions received some form of tDCS (anodal-, cathodal-, or sham-tDCS) given that placebo effects of tDCS have been suggested in clinical (Cortese et al. 2017; Schambra et al. 2014; Souto et al. 2014) and cognitive applications (Aslaksen et al. 2014; Turi et al. 2018). While many tDCS studies tend to use sham-tDCS as a placebo control condition, it can be difficult to distinguish the placebo effect from the stimulation effect (Fields and Levine 1984), and an inclusion of a no-treatment (i.e., no-tDCS) can be important to evaluate the size of a possible placebo effect (Aslaksen et al.

2014) since sham-tDCS alone is not sufficient for the estimation of placebo effect size (Benedetti et al. 2003). Another explanation for the observed improvement was related to the interval time between the runs. Whereas participants in our previous work conducted two runs of ODT with an average of 2-mininterval time between runs (Dickinson et al. 2014, 2015, 2016), participants in experiment 1 of the current study conducted the two runs of ODT with 10-min interval between the two runs (to provide the time required to administer the tDCS stimulation). Thus, the improvement might be a result of the resting time between the two runs. This is a reasonable possibility since time after practice has been suggested to be crucial for perceptual learning (Bönstrup et al. 2019; Dewar et al. 2014; Schoups et al. 1995). For instance, it is suggested that performance improvement on a simple visual task (i.e., Vernier Acuity Task "VAT") occurs within 60 min of the task performance. While performing another task within 60 min of performing VAT-disrupted VAT performance improvement, performing another task after 60 min did not disrupt VAT performance improvement (Seitz et al. 2005).

Experiment 2 examined both the putative placebo effect of tDCS and the possible effect of duration of interval between ODT runs on performance. Participants completed two runs of ODT and received 10-min sham-tDCS between the runs or had either 2 min or 10 min delay period between the runs with no tDCS. The result of experiment 2 confirmed that the improvement observed in the prior experiments was a result of a placebo effect of tDCS. Sham-tDCS group was the only group whose performance improved in the second run of ODT compared to those of no-tDCS. In spite of a large body of research investigating the effects of tDCS, little attention has been paid to the placebo effects of tDCS in modulating behavioral and neurophysiological outcomes. A small number of studies have suggested, reported placebo effects of tDCS in modulating clinical and/or cognitive outcomes (Aslaksen et al. 2014; Cortese et al. 2017; Egorova et al. 2015; Loo et al. 2018; Ray et al. 2019; Schambra et al. 2014; Turi et al. 2018). For instance, placebo effects of tDCS have been shown to reduce depression (Loo et al. 2018; Schambra et al. 2014), pain perception (Aslaksen et al. 2014; Egorova et al. 2015), and food craving and consumption (Ray et al. 2019). Such placebo effects may affect neurophysiological measures as investigating placebo effects of pharmacological (i.e., drug) and non-pharmacological interventions (i.e., lotion) on depression and pain perception were found to cause observable changes in neural activity (Mayberg et al. 2002; Wager 2005; Wager et al. 2004). For instance, a positron emission tomography (PET) study assessing effects of administering placebo drugs on depression showed that placebo effects produced robust brain changes in addition to clinical improvement in depression symptoms (Mayberg et al. 2002). Similarly, functional magnetic resonance imagining (fMRI) study showed that placebo effects of lotion application resulted in a reduction in neural activity in pain-related brain regions in addition to reducing pain perception (Wager et al. 2004). Such placebo-induced behavioral and neurophysiological changes possibly reflect high-level top-down cognitive processes (i.e., anticipation and expectation, Diederich and Goetz 2008; Schambra et al. 2014).

Placebo effects have been suggested to influence subjective self-reported measures but not objective ones (Schwarz and Büchel 2015; Stewart-Williams and Podd 2004). For instance, Schwarz and Büchel (2015) found dissociation between placebo effects based on the type of measures being used as either a subject or an objective measure. In their study, they manipulated participants' expectation about the effects of an intervention in modulating performance in a cognitive task. They found that inducing positive expectation about the effects of the intervention on a cognitive task performance enhanced the perceived effect of the intervention on task performance with no observable effects on the task performance (Schwarz and Büchel 2015). This finding suggests that placebo effects modulate outcomes of subjective but not that of objective measures. Inconsistent with this, several studies found that objectively measured outcomes could be modulated by placebo effects (Foroughi et al. 2016; Turi et al. 2018, 2017). For instance, expected and perceived performance in reward-based learning task improved (impaired) following a combination of sham-tDCS, conditioning, and a positive (negative) verbal instruction about the expected effect (Turi et al. 2017, 2018). Additionally, the efficacy of training in a working memory task (dual n-back task) was enhanced by instruction-induced placebo (Foroughi et al. 2016). Consistent with these findings of placebo effects manipulating performance in cognitive tasks, our results showed a robust placebo effect that enhanced performance in ODT. Unlike previous studies reporting placebo effects of tDCS on subjectively measured outcomes or including an explicitly suggestive positive/negative instruction about the expected effects of tDCS on performance (Foroughi et al. 2016; Schwarz and Büchel 2015; Turi et al. 2017, 2018), the current study found placebo effects on performance of an objectively measured low-level perceptual task (ODT) in the absence of an explicitly suggestive positive/negative instruction about the expected effects of tDCS on ODT performance. Thus, investigating the neurophysiological mechanisms underlying placebo effects of tDCS could increase our understanding about the actual effects of tDCS and may also have potential benefits for health and cognition. For instance, if active- and sham-tDCS have a similar effect on reducing pain perception and orientation discrimination thresholds, then sham-tDCS may become a useful tool, especially to those with neurological disorders (i.e., epilepsy) without the complexities of the direct effects of active-tDCS on neural activity.

In conclusion, our study with 2 experiments showed no effects of offline tDCS applied over the primary visual (occipital) cortex for 10 min with an intensity of 2 mA on the performance of orientation discrimination task. Experiment 1 of two runs of ODT unexpectedly found a

strong performance improvement that occurred in the second run of ODT regardless of tDCS type. This robust improvement was hypothesized to arise from either a placebo effect of tDCS or an increased temporal duration between the two run of ODT in comparison with our previous studies (10 min vs. ~ 2 min). Investigating these two possible causes of improvement in performance ODT by comparing performance of group receiving sham-tDCS with that of groups receiving no-tDCS, experiment 2 confirmed that the improvement in performance ODT was due to a placebo effect of tDCS. Thus, the current study demonstrates a novel positive placebo effect of tDCS on ODT performance. Furthermore, this study points to the importance of including a no-tDCS group in order to evaluate a possible placebo effect of tDCS independently of the stimulation effects. Given putative placebo effects, great care must be taken not to influence the participants' expectations of the effects of tDCS. Future studies should consider investigating the neurophysiological mechanisms of tDCS with the same protocols and task used in the current study to examine whether the expected anodal-excitation and cathodal-inhibition effects occur in such an experimental design.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethics Statement Participants provided a written consent form at the beginning of the session. The study received full ethical approval from the Department of Psychology University of Sheffield ethics committee.

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