No Effects of Transcranial Direct Current Stimulation on Visual Evoked Potential and Peak Gamma Frequency

Abstract

Evidence suggests that the visual evoked potential (VEP) and gamma oscillations elicited by visual stimuli reflect the balance of excitatory and inhibitory (E-I) cortical processes. As tDCS has been shown to modulate E–I balance, the current study investigated whether amplitudes of VEP components (N1 and P2) and peak gamma frequency are modulated by transcranial direct current stimulation (tDCS). Healthy adults underwent two electroencephalography (EEG) recordings while viewing stimuli designed to elicit a robust visual response. Between the two recordings, participants were randomly assigned to three tDCS conditions (anodal-, cathodal-, and sham-tDCS) or received no-tDCS. tDCS electrodes were placed over the occipital cortex (Oz) and the left cheek with an intensity of 2 mA for 10 min. Data of 39 participants were analysed for VEP amplitudes and peak gamma frequency using mixed-model ANOVAs. The results showed no main effects of tDCS in any metric. Possible explanations for the absence of tDCS effects are discussed.

Keywords Excitation-Inhibition Balance, Neuromodulation, tDCS, EEG, Visual Evoked Potential, Peak Gamma Frequency

Introduction

Cortical Excitation–inhibition (E–I) balance plays a crucial role in cognition and behaviour (Edden et al., 2012; Yizhar et al., 2011). Disruptions in cortical E–I balance are suggested to underlie neurological disorders such as autism, schizophrenia, and migraine (Baroncelli et al., 2011; Bertone et al., 2005; Coghlan et al., 2012; Dickinson, Jones, et al., 2016; Nguyen et al., 2016; Rubenstein & Merzenich, 2003). Such disruptions in cortical E–I balance can be indirectly inferred from visual psychophysical task performance, including Binocular Rivalry and visual Orientation Discrimination Tasks (ODT) (Dickinson,

Bruyns-Haylett, et al., 2016; Freyberg et al., 2015; Nguyen et al., 2016; Robertson et al., 2013; Robertson et al., 2016; Sysoeva et al., 2016). Inferences about E–I balance from these tasks are made because they are associated with the resting-state gamma-aminobutyric acid (GABA) concentration levels in the primary visual cortex (V1) measured by magnetic resonance spectroscopy (MRS) (Edden et al., 2009; Kurcyus et al., 2018; van Loon et al., 2013). For instance, participants completing binocular rivalry tasks are simultaneously presented with two visual images in a monocular manner (one image for each eye) leading to an alternating perception of these two images. Studies of binocular rivalry task performance have shown an association between higher GABA concentration level in the visual cortex and slower perceptual dynamics, as indicated by slower perceptual switches and longer percept duration (van Loon et al., 2013). In the ODT, as another example, participants are visually presented with pairs of gratings in a sequence and are instructed to judge whether the second grating had been tilted clockwise or anti-clockwise compared to the first grating. Similar to the binocular rivalry task, a higher resting-state GABA concentration level in the primary visual cortex was associated with enhanced orientation discriminability, as indicated by lower orientation discrimination thresholds on ODT (Edden et al., 2009). However, our recent study investigating the causal relationship between E–I balance and ODT performance revealed that only placebo effects of occipital tDCS could be observed (Bin Dawood et al., 2020), despite tDCS being a non-invasive neuromodulation technique shown to modulate the main excitatory and inhibitory transmitters (Krause et al., 2013; Stagg et al., 2009). The failure to observe any genuine behavioural effects of tDCS on ODT performance did not rule out the possibility that tDCS might induce changes in cortical E–I balance that are not reflected in task performance. As such, the current study aimed to investigate this possibility by evaluating the effects of occipital tDCS with identical tDCS protocols and montages to that of the previous study (Bin Dawood et al., 2020) on 2 basic neurophysiological markers of E–I balance in visual cortex: VEP amplitudes (N1 and P2) and visually induced peak gamma frequency. The links between E–I balance and these neurophysiological measures have been repeatedly reported (Kujala et al., 2015; Muthukumaraswamy et al., 2009; Purpura, 1959; Zemon et al., 1980).

Indeed, VEP activity is thought to reflect the summation of excitatory and inhibitory postsynaptic potentials (EPSP, IPSP, respectively) (Purpura, 1959; Zemon et al., 1980). Accordingly, animal and human studies have used the amplitude of the VEP response as indicators of E–I balance (Aloisi et al., 1997; Andrade et al., 2016; Ding et al., 2016; Gawel et al., 1983; Kennard et al., 1978; Moon & Lim, 2009; Moskowitz & Sokol, 1985; Nguyen et al., 2016). For instance, abnormally high VEP amplitudes have been suggested to indicate cortical hyperexcitability (Aloisi et al., 1997; Nguyen et al., 2016), while reduced VEP amplitudes indicate increased cortical inhibition (Ding et al., 2016; Moon & Lim, 2009). Additionally,

pharmacological manipulations of GABA activity in animal and human models modulate VEP amplitudes (Daniels & Pettigrew, 1975; Hudnell & Boyes, 1991; Kraut et al., 1990; Schafer et al., 1984; Zemon et al., 1980; Zemon, Kaplan, et al., 1986; Zemon, Victor, et al., 1986; Zeneroli et al., 1981). For instance, administration of GABA agonist aminooxyactic acid in rats has been shown to reduce the amplitude of VEP-N1 but increase the amplitude of VEP-P2 (Zeneroli et al., 1981). In contrast, administering GABA antagonist bicuculline has been shown to increase the amplitude of VEP-N1 and decrease the amplitude of VEP-P2 (Zemon et al., 1980). These findings support the suggestion of a relationship between E–I balance and the VEP components (Aloisi et al., 1997; Nguyen et al., 2016; Zemon et al., 1980; Zeneroli et al., 1981).

Similarly, the peak frequency of oscillations in the gamma range (30–90 Hz) has been used to indirectly assay E–I balance (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015), and evidence suggests that interactions between pyramidal excitatory cells and inhibitory GABAergic interneurons generate neural oscillatory activity in the gamma band (Brunel & Wang, 2003; Börgers & Kopell, 2003). In line with this evidence, several studies have found that peak gamma frequency positively correlates with increased resting-state GABA concentration level in V1 (Edden et al., 2009; Kujala et al., 2015; Muthukumaraswamy et al., 2009), (however see (Cousijn et al., 2014)). In addition, peak gamma frequency was shown to inversely be associated with blood-oxygenation-level dependent (BOLD) response measured by functional MRI (Muthukumaraswamy et al., 2009). Such an association possibly reflects E–I balance, given the findings of a negative correlational relationship between functional MRI BOLD response and GABA concentration (Donahue et al., 2010; Kurcyus et al., 2018; Muthukumaraswamy et al., 2010). Additionally, pharmacological manipulation of GABA receptors influences peak gamma frequency. For instance, the application of indirect GABA agonists such as alcohol and tiagabine led to a reduction in peak gamma frequency (Campbell et al., 2014; Magazzini et al., 2016). However, these findings are unexpected based on findings of a positive correlation between GABA and peak gamma frequency (Edden et al., 2009; Kujala et al., 2015; Muthukumaraswamy et al., 2009), suggesting that the relationship between cortical inhibition and peak gamma frequency requires further investigation. In addition, peak gamma frequency has been linked to performance on psychophysical tasks such as binocular rivalry and the ODT, which are associated with resting-state GABA concentration level (Edden et al., 2009; van Loon et al., 2013). For instance, higher gamma frequency has been linked to slower perceptual dynamics (Fesi & Mendola, 2015) and enhanced orientation discrimination performance (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015). Accordingly, increased peak gamma frequency has been suggested to indicate increased cortical inhibition (Dickinson et al., 2015; Fesi & Mendola, 2015).

Thus, using identical tDCS protocols and montages to those used previously (Bin Dawood et al., 2020), the current study investigated the effects of occipital tDCS on E-I processes by examining electrophysiological signatures of E-I balance, namely, VEP components (N1 and P2) and peak gamma frequency measured by electroencephalogram (EEG). As VEP activity and gamma frequency are sensitive to the features of visual task (e.g., stimulus size, contrast, and frequency) (Bach & Ullrich, 1997; Busch et al., 2004; Korth & Nguyen, 1997; Schadow et al., 2007) and are unlikely to be clearly elicited by behavioural tasks such as ODT, we used an EEG task that has been shown to elicit a robust VEP response and clear peak gamma frequency (Milne et al., 2018; Milne et al., 2019). It was hypothesised that anodal-tDCS would increase the amplitude of VEP-N1 and decrease the amplitude of VEP-P2, whereas cathodal-tDCS would lead to the opposite effects (decrease VEP-N1 and increase VEP-P2), in accordance with the findings and suggestions of animal and human studies (Antal et al., 2004; Zemon et al., 1980; Zeneroli et al., 1981). Additionally, it was expected that anodal-tDCS would decrease peak gamma frequency, while cathodal-tDCS would increase it, based on the suggested links between GABA and tDCS (Krause et al., 2013; Stagg et al., 2009) and between GABA and peak gamma frequency (Edden et al., 2009; Kujala et al., 2015; Muthukumaraswamy et al., 2009).

Method

Participants

Forty-nine healthy adult volunteers from the University of Sheffield participated in the study. All had normal or corrected-to-normal vision with no history of neurological disorders (e.g., epilepsy and migraine) and received a £10–12 gift voucher for participation. Participants gave written informed consent at the beginning of the experimental session. The study received full ethical approval from the Department of Psychology University of Sheffield ethics committee and was conducted in accordance with the Helsinki declaration.

Electroencephalogram task

Apparatus

EEG data were collected using 64 electrodes BioSemi ActiveTwo system (Biosemi Instrumentation BV, Amsterdam, The Netherlands). The electrodes were placed in accordance with the international 10/10 system (Jasper, 1958; Klem et al., 1999). EEG data were filtered online with a bandpass of 0.01–140 Hz and digitized by BioSemi ActiView software. The EEG data were recorded in an electrically shielded, dimly lit room. All electrodes impedance was kept within the range of +/−25 kΩ. A linearised Viglen LCD monitor with a spatial resolution of 1280 × 1024 pixels and a temporal resolution of 60 Hz was used to display the stimuli.

Transcranial direct current stimulation (tDCS)

Identical to the previous study (Bin Dawood et al., 2020), direct current was delivered to the scalp using a battery-driven device (TCT research, Hong Kong) connected to two saline-solution-soaked sponge electrodes. A target electrode (5 × 5 cm) was placed over the primary visual (occipital) cortex that corresponds to the site of Oz according to the international 10–10 electrode placement system (Jasper, 1958; Klem et al., 1999), (Fig 1A). The efficacy of tDCS over the occipital cortex has been reported previously ((Antal et al., 2003a, 2003b; Antal et al., 2001, 2006; Ding et al., 2016); see (Antal & Paulus, 2008), for review). To avoid any confounding effects that might be caused by stimulating an additional brain region (Im et al., 2012; Tseng et al., 2018), a reference electrode (5 × 7 cm) was placed over the participant's left cheek. This location is commonly used in tDCS studies with different montages (Aytemür et al., 2017; Berryhill et al., 2010; Hsu et al., 2011; Nasseri et al., 2015; Reinhart et al., 2017).

A 10-minute duration of offline tDCS was used in this study, given previous studies' findings that 9–13 min offline tDCS has an aftereffect lasting up to 90 minutes after stimulation is terminated (Kuo et al., 2013; Nitsche, Nitsche, et al., 2003; Nitsche & Paulus, 2001). Similarly, ten minutes of tDCS with an intensity of 2 mA over the visual cortex was shown to produce polarity-dependent, long-lasting effects on behavioural and neurophysiological outcomes (Ding et al., 2016). Such an aftereffect of tDCS covers

the duration of resetting the EEG equipment (3–7 min) and the EEG task (12-15 min duration, including a self-directed break period). The tDCS duration started with a 30-s ramp up until the current intensity reached 2 mA to minimize any possible adverse effect (Nitsche, Liebetanz, et al., 2003). In the active mode of tDCS (anodal-, cathodal- tDCS), the current was delivered for 10 min, the whole stimulation duration. However, in the sham mode of tDCS, the current was delivered for only 30 s out of the 10 min stimulation time, mimicking the sensation of the active mode in order to blind participants to the type of stimulation they were receiving (Gandiga et al., 2006; Palm et al., 2013). Such a brief duration of stimulation has been suggested to produce no observable changes in cortical excitability (Nitsche et al., 2008; Siebner et al., 2004). The current density distributions generated by the tDCS protocols and montage of the current study were simulated using computation of electric field due to transcranial current stimulation (COMETS), a MATLAB toolbox for simulating local electric fields generated by tDCS (Jung et al., 2013), (Fig 1B).

Fig 1

Fig 1. A) Illustration of the positions of tDCS electrodes as the target tDCS electrode (5 × 5 cm) was placed over the occipital cortex (Oz) and the reference tDCS electrode (5 × 7 cm) was placed over the left cheek via a head model of COMETS. B) Illustration of the simulation of the current density distributions generated by the tDCS protocols and montage of the current study via COMETS.

Procedures

After setting up the EEG equipment, participants were asked to complete two runs of an EEG task before and after 10 min of occipital tDCS. The EEG task has been used previously (Milne et al., 2018; Milne et al., 2019). The task was generated using Psychtoolbox-MATLAB (Brainard & Vision, 1997) and presented on a 20-inch LCD monitor. The task consisted of a static, high contrast black and white checkerboard that subtended 13.5 × 11.5 degrees of visual angle. Each checkerboard subtended .4 degrees of visual angle.

Participants were seated comfortably on a chair 57 cm from the monitor during the EEG recording and asked to keep movement to a minimum. A static black and white checkerboard stimulus repeatedly appeared on the centre of the monitor for an average of 2000ms (1500-2500ms) with an inter-stimulus interval (ISI) of 1500–2500 ms (mean=2000 ms). Participants were instructed to fixate on a red dot appearing on the centre of the monitor throughout the recording and press the spacebar when the checkerboard disappeared to maintain attention. Each EEG recording consisted of two blocks of 100 trials, with a self-timed break (1–3 min) between the two blocks. Participants were asked to respond in the first block using their right hand and their left hand in the second block. Each run lasted 12–15 min, depending on the duration of participants' break of optional duration between the run's two blocks (Fig 2).

Fig 2

Fig 2. Schematic diagram of the electroencephalogram (EEG) task. This Fig is reprinted with permission from (Milne et al., 2018).

Between the two runs of the EEG task, participants were randomly assigned to one of four tDCS type groups (anodal-tDCS, cathodal-tDCS, sham-tDCS, and 10-min delay with no-tDCS). During the stimulation, participants were asked to notify the experimenter about any uncomfortable sensation related to the experimental setting so that the experimental session would be immediately terminated.

Although sham-tDCS has been widely suggested as a placebo control condition (Dinn et al., 2017; Gandiga et al., 2006; Palm et al., 2013), the findings of recent studies imply that sham-tDCS may not be very effective in blinding participants to the stimulation mode (active vs. sham), based on participants' stimulation experiences (Kessler et al., 2012; Turi et al., 2019). Therefore, in order to ensure that participants' experience of active-tDCS (anodal and cathodal) would not differ from that of sham-tDCS, participants were asked to complete questionnaires assessing tDCS adverse effects (Brunoni et al., 2011) and post-stimulation ratings of pain, attention, and fatigue (Galea et al., 2009) at the end of the experimental session.

Transcranial direct current stimulation electroencephalogram setting

After the end of the first run of the EEG task, the EEG amplifier was switched off, and the electrodes were disconnected from the EEG amplifier. For the groups receiving anodal-, cathodal-, sham-tDCS, the strap of the EEG chin was undone, and five EEG electrodes (POz, Oz, O1, O2, Iz) over the occipital cortex were removed from the cap. The target tDCS electrode (5 × 5 cm) was then gently inserted in-between the EEG cap and the scalp until it was centrally aligned to the Oz electrode site. The reference tDCS electrode (5 × 7 cm) was placed over the left cheek. Afterwards, tDCS was switched on for 10 min, starting in a ramp-up like fashion over the first 30 s until it reached 2 mA. During the stimulation duration, participants were asked to relax and notify the experimenter if discomfort occurred so that the session could be discontinued. At the end of the stimulation duration and after the removal of tDCS electrodes, the strap of the EEG chin was comfortably closed. The gel was injected on the electrodes on the cap (which were previously removed), and then these five electrodes were plugged in on the EEG cap again. After that, the EEG electrode wires were connected to the EEG amplifier, which was then switched on. The second run of the EEG task was then started after checking the electrode stability and impedance (within the range of +/−25 kΩ.). For the group receiving no-tDCS, the same steps were followed except that no-tDCS electrodes were placed between the two runs of the EEG task. An approximate duration of 5 minutes (3–7 min) elapsed between the end of the first run of the EEG task and the beginning of the tDCS as well as between the end of the tDCS and the beginning of the second run of the EEG task. Given that aftereffect of 10-minute tDCS lasts up to 90 minutes (Kuo et al., 2013; Nitsche, Nitsche, et al., 2003; Nitsche & Paulus, 2001), it covers the duration of the entire second (post-tDCS) run of EEG task, including the resetting the EEG equipment (3–7 min) and the EEG task (12-15 min duration, including a self-directed break period).

Electroencephalogram analysis

Similar to previous studies (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015), continuous EEG data were sampled online at 2048 Hz using BioSemi ActiView software, and then were down-sampled offline at 512 Hz using BioSemi DBF Decimator software (Biosemi Instrumentation BV). Then,

the EEG data were analysed offline using EEGLAB and in-house MATLAB scripts. Using EEGLAB, EEG data was referenced to the vertex electrode (Cz) and 1 Hz high pass filter was used to remove the low frequencies. Then, visual inspection of the EEG data was conducted to remove any artifactual segments and channels contaminating the neural activity of interest (Luck, 2014; Tatum et al., 2011; Teplan, 2002). The number of channels that remained in the pre-tDCS run after removing the 'artifactual' channels did not significantly differ from that of post-tDCS run for each of the tDCS type groups, $p > .05$ (Table 1).

Table 1

Table 1. Removed electroencephalogram (EEG) channels of pre- and post- transcranial direct current stimulation (tDCS) runs for each of the tDCS type groups (Anodal-, Cathodal-, Sham-, no-tDCS). Although 49 participants took part in the study, only 44 participants completed the two runs of the EEG task (pre- and post-tDCS) and were randomly assigned to one of the four tDCS type groups. Each group consisted of 11 participants. *"M"* stands for "mean", "Min." stands for "minimum", "Max." stands for "maximum", and "*SD*" stands for "standard deviation." There was no significant difference in numbers of removed EEG channels between the pre- and post-tDCS run for each of the tDCS type groups (*ps* > .05).

Then, continuous EEG data were segmented into epochs from 200 ms prior to the stimulus onset to 1,500. The number of epochs that remained in the pre-tDCS run after removing the 'artifactual' channels did not significantly differ from that of the post-tDCS run for each tDCS type group, $p > .05$ (Table 2).

Table 2

Table 2. The remaining epochs of pre- and post-transcranial direct current stimulation (tDCS) runs for each of the tDCS type groups. Each group consisted of 11 participants. "*M*" stands for "mean", "Min." stands for "minimum", "Max." stands for "maximum", and "*SD*" stands for "standard deviation". There was no significant difference in the number of epochs between pre- and post-tDCS run for each of the tDCS groups (*ps* > .05).

Visual evoked potentials of the occipital cortex (Oz)

As the target tDCS electrode was placed over this occipital cortex (Oz), we analysed VEP of Oz channel given that tDCS effects on cortical excitability have been observed within the stimulated brain region

(Siniatchkin et al., 2011; Stagg et al., 2009). After cleaning and epoching EEG data (200 ms pre-stimulus to 1,500 ms post-stimulus), peak amplitudes of N1 (the absolute value of the maximum negative amplitude between 80–155 ms post-stimulus onset) and P2 (the maximum positive amplitude between 175–250 ms post-stimulus onset) components were calculated using an in-house MATLAB script. The time windows of VEP were selected based on visual inspection of the grand-averaged VEP waveforms pre- and post-tDCS for each of the tDCS-type groups (Fig 3. This method of selecting time windows for evoked potential events is commonly used (Hanslmayr et al., 2005; Kissler et al., 2009; Milne et al., 2018).

Fig 3

Fig 3. Grand-averaged visual evoked potential (VEP) waveforms in response to the checkerboard stimulus for all tDCS-type groups (anodal-, cathodal-, sham-, and 10-min delay with no-tDCS).

Independent component analysis for the time-frequency analysis

A signal-blind source separation technique known as independent component analysis (ICA) (Makeig et al., 1997) was used to isolate the occipital neural responses to the visual stimulus from other activities (Jung et al., 2000). ICA decomposed EEG signals into maximally temporally independent components, and a single component representing the best neural response (e.g., distinct event-related dynamics) to the visual checkerboard stimulus for each participant in each run was chosen to be included in the analysis.

Although combining the two 'runs' (pre and post tDCS) for each participant into a single time series for Independent Components Analysis (ICA) eliminates the possibility of choosing two different independent components (ICs) pre and post tDCS, it was decided to run two separate ICAs for each subject. Performing two separate ICAs for each participant's pre- and post-tDCS EEG datasets had the advantage of ensuring that the placement and removal of tDCS electrodes had not artefactually altered the EEG recordings, and the components pre and post tDCS could be compared. As such, running two separate ICAs seemed a good option to ensure not violating one of the assumptions underlying the use

of ICA that a signal source of data is spatially stationary (Luck, 2014; Ullsperger & Debener, 2010). Furthermore, it has been shown previously that analysis of two separate ICAs by selecting the best matched ICs from two data sets was not statistically different from that of the one ICA combining the two datasets (Arbabshirani et al., 2013).

Selection of components for independent component analysis for the time-frequency analysis

As in previous studies (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015), an extended (runica) ICA was performed separately on continuous EEG data for pre- and post-tDCS EEG task run for each participant using EEGLAB. This was done after the application of procedures stated earlier in the *"electroencephalogram analysis"* section, including referencing EEG data to the vertex electrode (Cz), high-pass filtering (>1Hz), and cleaning. Following ICA, continuous EEG data were then epoched (-200 ms pre-stimulus to 1500 ms post-stimulus) with no additional filtering. A visual inspection was performed for the scalp topography of all IC components. Any ICs with focal activity in the occipital cortex were selected, leading to up to four (M = 2.89, SD = .72) ICs being selected for each participant in the pre-tDCS run and up to five ICs in the post-tDCS run (M = 2.80, SD = .85), irrespective of tDCS groups (anodal-, cathodal-, sham-, 10-min delay with no-tDCS). The selected ICs from both pre-tDCS and post-tDCS run for each subject were then analysed using time-frequency analysis (wavelet transforms) (Cohen, 2014; Daubechies, 1990; Hazarika et al., 1997). The time-frequency analysis was performed via an in-house MATLAB script that was developed by (Torrence & Compo, 1998), identical to that used previously (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015). Any ICs with no- or unclear event-related dynamics were excluded.

From the remaining ICs of the pre- and post- tDCS run, the best matching pairs of ICs from the pre- and post-tDCS sharing similar distinct event-related dynamics for each participant were selected. Finally, a single IC pair was selected for each participant based on the clarity of the sustained visually induced activity in the gamma frequency band. In cases where there were two or more IC pairs for a participant, a single IC pair was selected based on visual inspection of the clarity of the sustained visually induced

changes in gamma band power. It can be seen without further analyses that the ICA before and after tDCS produced identical topographies and time series (Fig 4).

Fig 4

Fig 4. Illustrations of ICA components selections for one participant pre- and post-tDCS. A, C, and E illustrate scalp map, event-related dynamics, and induced gamma activity of IC components pre-tDCS for one participant. B, D, and F illustrate scalp map, event-related dynamics, and induced gamma activity of IC components pre-tDCS for one participant. Based on the visual inspection of scalp tomography of all components for the participant, three components pre-tDCS (IC 4,6, and 7) and post-tDCS (IC 3, 6, and 8) were initially selected. The best matching pair from pre- and post-tDCS IC components sharing distinct event-related dynamics and the clearest induced gamma activity (i.e., Pre-tDCS IC 4 and Post-tDCS IC 3) were included in the analysis to investigate tDCS effects on peak gamma frequency.

After selecting a single IC pair from pre- and post-tDCS run for each participant based on their similarity of the associated time series and induced gamma activity, mixed-model analyses of variance (ANOVAs) were performed to examine tDCS effects on induced gamma frequency calculated as below.

Time-frequency analysis

The time-frequency analysis used here has been used previously (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Milne et al., 2018). Each of the selected ICs from each participant was analysed using wavelet transforms in the time-frequency domain (Cohen, 2014; Daubechies, 1990; Hazarika et al., 1997). The advantage of using wavelet methods over windowed Fourier methods is that it is not affected by edge effects, as each of the wavelets is specific to both domains of time and frequency. Furthermore,

the advantage of using wavelet methods over multi-taper methods is having greater spectral and temporal resolution due to less effective smoothing in domains of time and frequency (Cohen, 2014).

The selection of the complex Morlet wavelet as the function ψ_0 was made for its good balance between the localization of time and frequency for purposes of extracting features (Grinsted et al., 2004; Müller et al., 2004). The complex Morlet wavelet consists of a complex exponential modulated by a Gaussian, $\omega_0 = 6$; where ω_0 is a nondimensional frequency and is described as follows:

$$\boldsymbol{\psi_0(\eta) = \pi^{-1/4} e^{i\omega_0 \eta} e^{-\eta^2/2}}$$

As in (Dickinson et al., 2015), "The wavelet transform $\boldsymbol{W^x(n, s)}$ is a complex quantity whose modulus expresses the amount of power in $\boldsymbol{x}$ and whose angle represents the local phase localised in time and frequency (scale). Scale determines the temporal resolution of the analysis. The continuous wavelet transform of a time series $\boldsymbol{x_n}$ of $\boldsymbol{N}$ subsampled data points at equal time increments of $\boldsymbol{\delta t}$ (Kaiser, 1994), is defined as the convolution of $\boldsymbol{x_n}$ with a scaled and translated version of $\boldsymbol{\psi_0}$:

$$\boldsymbol{W^x(n, s) = \sqrt{\frac{\delta t}{s}} \sum_{n'-1}^{N} x_{n'} \; \psi_0^* \left[\frac{(n' - n)\delta t}{s} \right]}$$

where $\boldsymbol{\psi_0^*}$ is the complex conjugate of $\boldsymbol{\psi_0}$, $\boldsymbol{n}$ is the time index and $\boldsymbol{s}$ denotes the wavelet scale." The number of octaves for each wavelet scale was set at 1/60, providing an optimally "smooth" picture of wavelet power with a sufficient spectral resolution in the gamma band range for the purpose of the present investigation (<1 Hz). Similar to previous studies (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Milne et al., 2018), the time series of all the selected (pre- and post-tDCS) components for each subject were analysed using the wavelet method to examine visually-induced peak gamma frequency (via an in-house MATLAB script). Induced gamma frequency is non-phase locked to the stimulus' onset, but is related to it (Lee & Jones, 2013; Pantev, 1995; Tallon-Baudry & Bertrand, 1999). Induced gamma frequency consists of oscillatory bursts that vary between trials on their onset latency. Thus, trials averaging before performing time-frequency analyses highly unlikely will result in observable induced gamma activity, as this type of oscillatory activity is non-phase locked. To infer

induced gamma activity, time-frequency analyses are needed to be performed for each trial, and then the power changes at gamma frequency can be averaged (Fig 5B). However, such analysis contains, in addition to induced gamma activity, the power changes of evoked gamma responses (Fig 5B). As such, the problem arises of how to ensure induced peak gamma activity is selected. Notwithstanding, this can simply be done by comparing the wavelet spectrogram conducted on each trial and averaged (Fig 5B) with the wavelet spectrogram of the data trial averaged prior to wavelet analysis (evoked response, Fig 5A).

Evoked responses are phase-locked to the stimulus onset, which usually occur around 100 ms following the stimulus onset (Pantev, 1995). To detect evoked activity, the time series of single-trial responses can be averaged and then submitted to time-frequency analysis (i.e., the wavelet transform). The power's mean values for each scale during the period before the stimulus onset are considered baseline and are subtracted from the wavelet transform. The maxima of the subsequent matrix provide the maximum increase in evoked power in gamma frequency band (30-90 Hz) following stimulus presentation (Fig 5A). Thus, to obtain a better estimate of induced gamma activity, the power changes of evoked responses at gamma frequency band is compared to from the induced gamma activity (Fig 5B) and the selection of the peak response is set to time points after cessation of the initial evoked response. A Gaussian non-linear least squares curve was then fitted to the frequency spectra at the time point that was associated with the gamma power maximum increase following the presentation of the stimulus. The frequency that is associated with fitted curve' maximum point was considered as the metric for each subject's peak gamma frequency, (Fig 5C).

Fig 5

Fig 5. Illustrations of evoked gamma frequency, induced gamma frequency, and power changed at gamma frequency band of an independent component of a single participant. (A) Time-frequency decomposition of evoked gamma frequency for an independent component of one participant. (B) Time-frequency decomposition of induced and evoked gamma frequency for an independent component of one participant. Note the contribution of evoked gamma power can clearly be seen by eye to occur immediately following stimulus onset and then subside leaving the prolonged sustained induced response. (C) The total power change at each frequency (solid line) at the maximum induced gamma response and the curve-fitted total power change at gamma frequency (dashed line) for an independent component of one participant.

To summarise, the initial step was to check the scalp topography of all components and then select the components with a focal activity in the visual cortex. Then, the time-frequency analysis was run for all the selected components of pre- and post-tDCS EEG data sets for each participant. Any IC components with unclear event-related dynamics were excluded for two reasons. The first reason is that it is quite difficult to match IC with no clear event-related dynamics with IC of the other EEG data set for the same participant. The second reason is that ICs with unclear event-related dynamics have unclear induced gamma frequency. After that IC of pre- and post-tDCS EEG data set sharing similar distinct event-related dynamics with the clearest induced gamma frequency were selected. Out of the selected ICs from the pre- and post-tDCS sharing similar distinct event-related dynamics, a single IC component pair from the pre- and post-tDCS EEG data sharing the best matched distinct event-related dynamics and clearest induced gamma frequency of each participant was included in the final analysis to investigate effects of tDCS on gamma frequency activity.

Results

Out of the 49 participants, three participants were ineligible to participate in the experiment due to headwear (e.g. hair extensions) (N = 2) or being on medication (N = 1), and they were, therefore, excluded from the analysis. Also, two participants were excluded from the analysis due technical issues related to tDCS connection (N=1), and uncomfortable tingling sensation of tDCS (N=1). Out of the remaining 44 participants who successfully completed the two runs of the EEG task (pre- and post-tDCS runs), five participants were also excluded due to having peak amplitudes of VEP components (N1, P2) deviating from the mean by more than 3 standard deviations (N=1) or/and excessive noise in their EEG signals with no clear induced gamma activity (N=4). Thus, the analysis was performed on data from 39 participants, randomly assigned to one of four groups (anodal-tDCS, cathodal-tDCS, sham-tDCS, or 10-min delay with no-tDCS). The group of anodal-tDCS consisted of 10 participants (female = 3, right-handed = 9; age, M = 27.30, SD = 4.74); the group of cathodal-tDCS consisted of 10 participants (female = 3, right-handed = 8; age, M = 28.30, SD = 6.99); the group of sham-tDCS consisted of 11 participants (female = 4, right-handed = 9; age, M = 27.27, SD = 11.09); and the group of 10-min delay with no-tDCS consisted of 8 participants (female = 4, right-handed = 8; age, M = 29.38, SD = 7.50).

During the stimulation period, one participant notified the experimenter about discomfort feeling (tingling in the stimulated area) caused by tDCS, so the experimental session was immediately

terminated. No other participants reported any severe adverse effects of tDCS during the stimulation period or at the end of the experimental session. Although 33 participants received tDCS (either active-tDCS: anodal and cathodal (N=22) or sham-tDCS (N=11)) between the two runs of EEG task, only 27 participants successfully completed the post stimulation-rating questionnaire (9 participants from the anodal-tDCS group, 11 participants from the cathodal-tDCS group, and 8 participants from the sham-tDCS group). In this questionnaire, participants were asked to rate the level of pain, attention, and fatigue from 1 (minimum) to 7 (maximum) as well as to report their thoughts of whether they had received active- or sham (placebo)-tDCS. We investigated whether the stimulation experience would differ based on stimulation type (either active- vs. sham-tDCS) by comparing the post-stimulation rating questionnaire responses of active-tDCS groups (anodal- and cathodal-tDCS) with that of sham-tDCS group. The results revealed no significant differences in the stimulation experience between active-tDCS and sham-tDCS in terms of level of pain (active-tDCS (M = 1.50, SE = .20) and sham-tDCS (M = 1.25, SE = .25), (t (26) = .708, p = .485)), level of attention (active-tDCS (M = 4.65, SE = .37) and sham-tDCS (M = 3.88, SE = .69), (t (26) = 1.060, p = .299)), and level of fatigue (active-tDCS (M = 2.80, SE = .34) and sham-tDCS (M = 2.88, SE = .67), (t (26) = -1.09, p = .914)). Furthermore, more than 70% of participants receiving sham-tDCS thought that they had received real (active-tDCS) stimulation, consistent with a large body of research suggesting that sham-tDCS is an effective tool in blinding participants about stimulation condition (active vs. sham) (Dinn et al., 2017; Gandiga et al., 2006; Palm et al., 2013).

Visual evoked potential analysis

Two separate mixed-model ANOVA analyses were performed to investigate the effect of tDCS on the peak amplitude of VEP components (N1, P2) where tDCS-type groups (anodal-, cathode-, sham-, and 10-min delay with no-tDCS) were between-subjects variables and session time of EEG task (pre-tDCS vs. post-tDCS) was within-subjects variable. All statistical analyses were performed using SPSS version 24 for Mac (IBMSPSS, Armonk, New York).

There was a significant main effect of session time of EEG task on the peak amplitude of VEP-N1, (F(1, 35) = 6.485, p = .015), indicating that the amplitude of VEP-N1 was significantly lower in the second (post-tDCS) run (M = 5.27 Hz, SE = .73) compared to the first (pre-tDCS) run ((M = 6.24 Hz, SE = .81), (Fig 6A). However, no significant interaction between session time of EEG task and tDCS-type groups was

found, (F(3, 35) = 1.363, p = .27), nor main effect of tDCS- type groups (F(3, 35) = .125, p = .95), (Fig 7A and 8).

There was no significant main effect of session time of EEG task on the peak amplitude of VEP-P2, (F(1, 35) = 2.190, p = .15), (Fig 6B). Additionally, no significant interaction between the session time of EEG task and tDCS-type groups was found, (F(3, 35) = .246, p = .86), nor main effect of tDCS- type groups (F(3, 35) = .313, p = .816), (Fig 7B and 8).

Fig 6

Fig 6 A and B. Box plots demonstrating the means and standard error of the amplitudes of visual evoked potential (VEP)-N1 and P2 pre- and post-transcranial direct current stimulation (tDCS) for all tDCS-type groups (anodal-, cathodal-, sham-, and 10-min delay with no-tDCS). A) Box plots demonstrating VEP-N1 pre- and post-tDCS for all the tDCS type groups. B) Box plots demonstrating VEP-P2 pre- and post-tDCS for all the tDCS type groups. * p = .015.

Fig 7

Fig 7 A and B. Bar charts demonstrating the mean and standard error of the amplitudes of visual evoked potential (VEP)-N1 and P2 pre-transcranial direct current stimulation (tDCS) (blue line) and post-tDCS (red line) for each of the tDCS-type groups (anodal-, cathodal-, sham-, and 10-min delay with no-tDCS). Bar chart demonstrating the mean and standard error of the VEP components (N1 and P2) pre-tDCS (blue line) and post-tDCS (red line) for all tDCS-type groups (anodal-, cathodal-, sham-, and 10-min delay with no-tDCS). The VEP-N1 is the negative signal between 80 and 155 ms post-stimulus onset. The VEP-P2 is the positive signal between 175 and 250 ms post-stimulus onset. A) VEP-N1 pre-tDCS (blue line) and post-tDCS (red line) for each of the tDCS-type groups (anodal-, cathodal-, sham-, and 10-min delay with no-tDCS). B) VEP-P2 pre-tDCS (blue line) and post-tDCS (red line) for each of the tDCS-type groups (anodal-, cathodal-, sham-, and 10-min delay with no-tDCS). VEP waves pre- and post-tDCS for each of the tDCS type groups. The N1 is the negative signal between 80 and 155 ms post-stimulus onset. The P2 is the positive signal between 175 ms and 250 ms post-stimulus onset.

Fig 8

Fig 8. Grand-averaged visual evoked potential (VEP) waveforms in response to the checkerboard stimulus for each of the transcranial direct current stimulation (tDCS) type groups pre-tDCS (blue line) and post-tDCS (red line). A) VEP waveforms for anodal-tDCS pre-tDCS (blue line) and post-tDCS (red line). B) VEP waveforms for cathodal-tDCS pre-tDCS (blue line) and post-tDCS (red line). C) VEP waveforms for sham-tDCS pre-tDCS (blue line) and post-tDCS (red line). D) VEP waveforms for 10-min delay with no-tDCS pre-tDCS (blue line) and post-tDCS (red line). The VEP-N1 is the negative signal between 80 and 155 ms post-stimulus onset. The VEP-P2 is the positive signal between 175 ms and 250 ms post-stimulus onset.

Peak gamma frequency analysis

Similar to the VEP analysis, two separate mixed-model ANOVA analyses were performed to investigate the effect of tDCS on the induced gamma frequency activity (peak gamma frequency, gamma frequency power) where tDCS-type groups (anodal-, cathode-, sham-, and 10-min delay with no-tDCS) were between-subjects variables and session time of EEG task (pre-tDCS vs. post-tDCS) was within-subjects variable.

There was a significant main effect of session time of EEG task on peak gamma frequency, (F(1, 35) = 7.927, p = .008), indicating that peak gamma frequency was significantly higher in the second (post-tDCS) run (M = 50.17 Hz, SE = 2.20) compared to the first (pre-tDCS) run ((M = 48.28 Hz, SE = 2.07), (Fig 9A). However, no significant interaction between session time of EEG task and tDCS-type groups was found, (F(3, 35) = .746, p = .53), nor main effect of tDCS- type groups (F(3, 35) = .711, p = .55), (Fig 10A and 11).

There was also no significant main effect of session time of EEG task on gamma power (F(1, 35) = .757, p = .390), (Fig 9B). Additionally, there was no significant interaction between session time of EEG task and tDCS- type groups, (F(3, 35) = .982, p = .41), and no significant main effect of tDCS- type groups (F(3, 35) = .464, p = .71), (Fig 10 B and 11).

Fig 9

Fig 9 A and B. Box plots demonstrating the mean and standard error of the neurophysiological measures pre- and post-transcranial direct current stimulation (tDCS) for all the tDCS type groups. A) Box plots demonstrating peak gamma frequency pre- and post-tDCS for all the tDCS type groups. B) Box plots demonstrating gamma power frequency pre- and post-tDCS for all the tDCS type groups. * p = .008.

Fig 10

Fig 10 A and B. Bar charts demonstrating the mean and standard error of induced gamma frequency oscillations (peak and power) pre-transcranial direct current stimulation (tDCS) (blue line) and post-tDCS (blue line) for each of the tDCS-type groups (anodal-, cathode-, sham-, and 10-min delay with no-tDCS). A) Bar chart demonstrating peak gamma frequency pre- and post-tDCS for each of the tDCS-type groups (anodal-, cathodal sham-, and 10-min delay with no-tDCS). B) Bar chart demonstrating gamma power frequency pre- and post-tDCS for each of the tDCS-type groups (anodal-, cathodal-, sham-, and 10-min delay with no-tDCS).

Fig 11

Fig 11. Illustrations of the scalp map, event-related dynamics, and decomposition of time-frequency of the selected independent components (IC) pre- and post-transcranial direct current stimulation (tDCS) of one participant from every tDCS type group (anodal-, cathodal-, sham-, and 10-min delay with no-tDCS, respectively). A) and B) The scalp map of the selected independent components (IC) pre- and post-tDCS of one participant from every tDCS type group (anodal-, cathodal-, sham-, and 10-min delay with no-tDCS, respectively). C) and D) The event-related dynamics of the selected IC pre- and post-tDCS of one participant from every tDCS type group (anodal-, cathodal- sham-, and 10-min delay with no-tDCS, respectively). E) and F) The decomposition of time-frequency of the selected independent components (IC) pre- and post-tDCS of one participant from every tDCS type group (anodal-, cathodal- sham-, and 10-min delay with no-tDCS, respectively).

Discussion

This study investigated the effects of offline tDCS on oscillatory gamma activity (peak gamma frequency and gamma frequency power), and the amplitudes of VEP components (N1 and P2). Participants completed two runs of an EEG task in which they were instructed to fixate on a red dot appearing on the centre of a monitor while a black and white checkerboard stimulus was repeatedly presented. Between the two runs of the EEG task, there was an interval where participants randomly received 10 minutes anodal-tDCS, cathodal-tDCS, sham-tDCS, or had 10-min delay with no-tDCS (tDCS-type groups). The statistical analyses of all chosen metrics of VEP amplitude and gamma oscillations revealed no actual main effects of tDCS type in modulating either induced gamma frequency, power or the amplitude of VEP components (N1 and P2). As such, no actual effects of tDCS per se were observed. Possible explanations for the observation of no effects of tDCS in the amplitude of VEP components (N1 and P2) and induced gamma frequency are discussed below.

As the association between cortical E–I balance and the amplitude of VEP components has been suggested in animal and human studies (Ding et al., 2016; Kennard et al., 1978; Nguyen et al., 2016; Zemon et al., 1980; Zemon, Kaplan, et al., 1986; Zeneroli et al., 1981), the current study investigated whether VEP could be modulated using tDCS (a non-invasive brain stimulation technique that is suggested to modulate the main excitatory and inhibitory transmitters). Although several studies have investigated whether tDCS could modulate the amplitude of VEP (Accornero et al., 2007; Antal et al., 2004; Ding et al., 2016; Viganò et al., 2013), inconsistent results have been reported. For instance, Ding et al. (2016) showed that anodal-tDCS increased the VEP amplitude (N75–P100), whereas cathodal-tDCS decreased it. Inconsistently, Accornero et al. (2007) found that anodal-tDCS reduced VEP-P100 amplitude whereas cathodal-tDCS increased it. Nevertheless, Antal et al. (2004) found that anodal-tDCS did not affect the amplitude of VEP-P100, whereas cathodal-tDCS increased it. Furthermore, Viganò et al. (2013) did not find any effect of tDCS in modulating the amplitudes of VEP (N1 and P1). Consistent with this null finding of tDCS effects on the amplitudes of VEP, the current study found no significant tDCS effects in modulating the amplitude of VEP components (N1 and P2).

As cortical E–I balance (indicated by GABA concentration in V1) has been shown to be associated with peak gamma frequency (Edden et al., 2009; Kujala et al., 2015; Muthukumaraswamy et al., 2009), a time-frequency analysis was performed to investigate whether peak gamma frequency would be modulated by tDCS, given the findings that tDCS modulates the main excitatory and inhibitory transmitters (glutamate and GABA, respectively) (Krause et al., 2013; Stagg et al., 2009). While several MEG studies have investigated the effects of occipital tDCS in modulating the power and basal neural oscillatory activity in the gamma frequency band (Hanley et al., 2016; Wiesman et al., 2018; Wilson et al., 2017), only one study, to date, has evaluated the effects of tDCS on peak gamma frequency (Wilson et al., 2017). Wilson et al. (2017) found no visual peak gamma frequency changes following 20-min anodal-tDCS with an intensity of 2 mA compared to sham-tDCS. Additionally, the findings of the other MEG studies regarding the effects of tDCS on gamma frequency oscillations are inconsistent. For instance, compared to sham-tDCS, anodal-tDCS was found to both reduce the gamma frequency power (Hanley et al., 2016) and increase the local 'amplitudes' (power) of gamma frequency compared to sham-tDCS (Wilson et al., 2017) depending on the study (Luck, 2014; Tatum et al., 2011). While cathodal-tDCS has been found to decrease the power of spontaneous gamma frequency compared to anodal- and sham-tDCS (Wiesman et al., 2018). Inconsistent with these, other studies found no tDCS effects on gamma frequency band activity (Marshall et al., 2016; Medina & Cason, 2017). Similarly, our findings are consistent with

previous studies that report no effects of tDCS for any type of stimulation (anode or cathode) in modulating peak gamma frequency (Wilson et al., 2017).

Although we observed no effects of tDCS on VEP amplitude or peak gamma frequency, several factors related to the task (e.g., properties of visual stimulus) and tDCS configurations (e.g., montage and parameter) have been suggested to play an important role in the efficacy of tDCS (Medina & Cason, 2017; Thair et al., 2017). Notwithstanding, such factors are unlikely to account for the absence of tDCS effects in modulating neural activity (peak gamma frequency, amplitudes of VEP N1 and P2 components) in the current study as effects of tDCS on the occipital cortex have been observed with similar stimulus properties and tDCS parameters: high contrast visual stimulus (Wiesman et al., 2018), monopolar montage (e.g., occipital cortex-cheek) (Reinhart et al., 2016), over 30 minutes after the application of 10-min tDCS with an intensity of 2 mA (Ding et al., 2016). Another possible factor for the absence effects of tDCS on both and peak gamma frequency and VEP amplitude could be related to the experimental design involving task repetition (pre- and post-tDCS), reflecting the well-known phenomenon of habituation where behavioural and neural responses to repeated stimulus reduced over time (Rankin et al., 2009; Thompson & Spencer, 1966). However, this seems unlikely given previous studies findings' of observable effects of tDCS in neural activity in pre- post- experimental design (Ding et al., 2016; Hoy et al., 2015; Vecchio et al., 2016). For example, compared to baseline, significant changes in visual stimulation-induced VEP amplitudes have been observed following 10 minutes tDCS of 2mA over the occipital cortex (Ding et al., 2016). Thus, our findings of no effects of tDCS on neural activity (VEP amplitudes and peak gamma frequency) are unlikely to be due to the visual task, tDCS configurations, or the experimental design used in this study. Also, our findings of no effects of tDCS on neural activity are consistent with a growing number of studies observing no effects of tDCS on cognition (Galli et al., 2019; Harris et al., 2019; Horvath et al., 2015b; Vannorsdall et al., 2016; Westwood & Romani, 2017). It is also possible that our null findings of tDCS effects on neural activity may be due to the relatively small sample size of the current study (Medina & Cason, 2017; Minarik et al., 2016). Each tDCS group in this study consisted of 8–11 participants possibly underpowering the analysis to detect any potential effects of tDCS (Horvath et al., 2015b; Medina & Cason, 2017). However, such a limitation is not uncommon in tDCS studies (Medina & Cason, 2017; Minarik et al., 2016), and effects of tDCS have been detected in studies with small sample sizes (Accornero et al., 2007; Antal et al., 2004; Ding et al., 2016; Kraft et al., 2010; Spiegel et al., 2012). For example, effects of occipital-tDCS with a small sample-sized group of healthy human participants (N=10-12) have been observed on behavioral (i.e., contrast sensitivity and surround suppression) (Ding et al., 2016; Kraft et al., 2010; Spiegel et al., 2012) and neurophysiological (i.e., VEP amplitudes) measures (Accornero et al., 2007; Antal et al., 2004; Ding et al., 2016). In spite of that, the

relatively small sample size of tDCS studies has been suggested to explain the inconsistent findings of tDCS effects on cognition because findings of small sample sized studies may lead to under- or overestimation of tDCS efficacy (Medina & Cason, 2017; Minarik et al., 2016). As the small sample size of this study might prevent the detectability of tDCS effects on amplitudes of VEP components and peak gamma frequency activity, future studies with a larger sample size may render significant effects of tDCS on such neural activity.

While we found no effects of tDCS per se, our analyses did reveal main effects of EEG task session time (pre- vs. post- all forms of tDCS combined anode, cathode, sham, and no tDCS) on both the amplitude of VEP-N1 component and peak gamma frequency. For example, the amplitude of VEP-N1 component statistically significantly decreased in the second (post-tDCS) run compared to the first (pre-tDCS) run of the EEG task. Similarly, but in the opposite direction, peak gamma frequency statistically significantly increased in the second run (post-tDCS) compared to the first (pre-tDCS) run of the EEG task. These changes in both VEP amplitudes and induced gamma frequency related to the EEG task repetition are inconsistent with previous studies finding no observable difference in neural activity (i.e., peak gamma frequency and VEP amplitude) between three recordings in a single session (Ding et al., 2016; Magazzini et al., 2016; Muthukumaraswamy et al., 2013). A reduction in VEP-N1 and an increase in peak gamma frequency are commensurate with a change (increase) cortical inhibition, given the findings of animal and human studies suggesting a negative relationship between GABA concentration level and VEP-N1 amplitude (Gawel et al., 1983; Kennard et al., 1978; Zemon et al., 1980; Zeneroli et al., 1981), but a positive correlation between GABA concentration and peak gamma frequency (Edden et al., 2009; Kujala et al., 2015; Muthukumaraswamy et al., 2009). Notwithstanding, despite concomitant changes in VEP-N1 (0.97 μV ↓) and peak gamma frequency (1.89 Hz ↑) the differences pre- and post- all forms of tDCS are small (<1 μV for VEP-N1, <2 Hz for peak gamma frequency). Observation of Fig 4 of Edden et al. (2009) suggests that 1.89 Hz change would correspond to a change in GABA concentration of <5% (Edden et al., 2009).

Unlike the previous finding of the tDCS-induced placebo effect on ODT performance (Bin Dawood et al., 2020), in this current study, we observed no such placebo effect of tDCS on amplitudes of VEP components nor on the activity of induced gamma frequency. An explanation for the failure of observing a placebo effect of tDCS on the current neurophysiological measures might be due to the nature of the ODT versus the EEG 'task' used here. During the EEG task, participants were asked to fixate on the repeatedly presented stimulus and to indicate the disappearance of the stimulus to maintain their attention on the task. In ODT, however, participants were asked to judge whether the sequentially

presented pairs of gratings had the same orientation or not (Bin Dawood et al., 2020). Thus the ODT could involve additional neural and cognitive processes that may be susceptible to placebo. Although the metrics (VEP amplitude, Gamma frequency and orientation discrimination) associated with both tasks are exquisitely related to inhibition-excitation balance in the primary visual cortex (bottom-up processing), the ODT also involves a perceptual decision that could require and be sensitive to additional mechanisms (possibly commensurate with a 'top-down' effect). This explanation is in line with previous studies indicating that placebo responses are mediated by "top-down" cognitive processes such as anticipation and expectation (Diederich & Goetz, 2008; Schambra et al., 2014; Skyt et al., 2018). Additionally, placebo effects have been shown to be most evident in conditions that involve mainly top-down processing such as depression and pain syndromes (Diederich & Goetz, 2008). For instance, levels of depression and pain perception were reduced following the application of Sham-tDCS (Aslaksen et al., 2014; Egorova et al., 2015; Loo et al., 2018; Schambra et al., 2014). Accordingly, conditions with solely bottom-up processing may be less susceptible to placebo effects (Diederich & Goetz, 2008), possibly explaining the lack of observable effects of tDCS on visual stimulus-driven neurophysiological responses of the current study.

While the lack of effect of tDCS on both VEPs and peak gamma frequency activity may be due to the small sample size of the tDCS groups (Minarik et al., 2016; Thair et al., 2017), effects of tDCS on neural activity have been previously observed with relatively small sample sizes (Accornero et al., 2007; Bolognini et al., 2011; Nitsche et al., 2004; Stagg et al., 2009; Sung & Gordon, 2018). For instance, in groups of 7-11 participants, tDCS polarity-dependent changes in cortical neurotransmitters were observed. Specifically, anodal-tDCS led to a significant reduction in GABA concentration whereas cathodal-tDCS led to a significant reduction in glutamate (Stagg et al., 2009). Similarly, significant tDCS polarity-dependent changes in the amplitude of VEP-P100 have been observed in a group of 10 participants as anodal-tDCS led to a significant reduction in the VEP-P100 amplitude while cathodal-tDCS led to the opposite pattern (Accornero et al., 2007). Such observed effects of tDCS may be limited to the tDCS parameters and experimental designs used (Nitsche et al., 2008; Thair et al., 2017), and thus may not be extended or generalized to other experimental sets. Accordingly, the current null tDCS effects on neural activity are consistent with the previous findings of null tDCS effects on the performance of the orientation discrimination task (ODT) where the same tDCS parameters and protocol were used (Bin Dawood et al., 2020). Although the ODT per se would most likely elicit different patterns of neural activity than the passive checkerboard viewing used here, inter-individual differences in gamma frequency and VEP elicited by similar visual stimuli have previously been shown to correlate with GABA concentration and

ODT performance measured separately in the same subject (see Edden et al., 2009). As such, the effects of tDCS (which allegedly modulates E-I balance) in the two tasks should be comparable.

Furthermore, it is worth considering that the efficacy of tDCS has been a controversial topic given the growing body of inconsistent and null findings related to its efficacy in neurological and cognitive domains (Blacker et al., 2020; Brückner & Kammer, 2016; Friehs et al., 2021; Galli et al., 2019; Harris et al., 2019; Horvath et al., 2015a, 2015b; Jonker et al., 2021; Klaus & Hartwigsen, 2020; Marshall et al., 2016; Medina & Cason, 2017). Even though the efficacy of tDCS has been suggested to be region-dependent as it is more observable in the motor cortex compared to the visual cortex (Jacobson et al., 2012), recent studies have failed to observe any significant effects of tDCS on cortical excitability in motor and visual cortex (Brückner & Kammer, 2016; Horvath et al., 2015a; Jonker et al., 2021). Additionally, systematic reviews of tDCS effects on cognition of healthy adults failed to support the suggestion that tDCS induces reliable effects on cognition and its neural bases (Galli et al., 2019; Horvath et al., 2015b). Bearing in mind the inconsistency of tDCS findings, it is largely admitted that tDCS studies suffer from the limited sample size (Minarik et al., 2016; Thair et al., 2017), which may negatively influence the detectability and reproducibility of tDCS effects (Button et al., 2013; Li et al., 2015; Minarik et al., 2016). As such, further investigations of larger sample sizes are needed to confirm the current null finding of tDCS effects on both VEPs and peak gamma frequency.

In conclusion, the current study investigated tDCS effects in modulating brain activity by recording EEG data before and after 10 min of occipital tDCS with an intensity of 2 mA (anodal-, cathodal-, sham-, 10-min delay with no-tDCS). The result showed statistically significant amplitude reduction in VEP-N1 and increase in peak gamma in the second (post-tDCS) session of EEG task compared to the first (tDCS-pre) session, irrespective of the tDCS type groups. However, no effects of tDCS were found in modulating the amplitudes of VEP components (N1 and P2) and peak gamma frequency in V1. This is the first study to examine the effects of offline tDCS on EEG correlates of E-I balance (VEP amplitudes and peak gamma frequency). Methodologically, our results demonstrate the usefulness of isolating the VEP to ICA components to compare VEP responses pre- and post-tDCS. While we find some evidence of tDCS affecting certain EEG measures, these effects are small and highlight the need for future larger studies that investigate if there are other task/stimulus-related EEG changes that are more sensitive to tDCS modulation and could serve as non-invasive assays of E-I balance.

Declaration of interest

The authors declare no conflict of interest.

Ethical approval

The study received full ethical approval from the Department of Psychology University of Sheffield ethics committee (reference number: 016126) and was conducted in accordance with the Helsinki declaration.

Informed Consent

Written informed consent was obtained from all participants at the beginning of the experimental session.

Consent for Publication

Permission was obtained from all participants to use their anonymised data for publication purposes.

Reference

Accornero, N., Voti, P. L., La Riccia, M., & Gregori, B. (2007). Visual evoked potentials modulation during direct current cortical polarization. *Experimental Brain Research*, *178*(2), 261-266.

Aloisi, P., Marrelli, A., Porto, C., Tozzi, E., & Cerone, G. (1997). Visual evoked potentials and serum magnesium levels in juvenile migraine patients. *Headache: The Journal of Head and Face Pain*, *37*(6), 383-385.

Andrade, G., Butler, J., Peters, G., Molholm, S., & Foxe, J. J. (2016). Atypical visual and somatosensory adaptation in schizophrenia-spectrum disorders. *Translational psychiatry*, *6*(5), e804.

Antal, A., Kincses, T. Z., Nitsche, M. A., Bartfai, O., Paulus, W. J. I. o., & science, v. (2004). Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: direct electrophysiological evidence. *45*(2), 702-707.

Antal, A., Kincses, T. Z., Nitsche, M. A., & Paulus, W. (2003a). Manipulation of phosphene thresholds by transcranial direct current stimulation in man. *Experimental brain research*, *150*(3), 375-378.

Antal, A., Kincses, T. Z., Nitsche, M. A., & Paulus, W. (2003b). Modulation of moving phosphene thresholds by transcranial direct current stimulation of V1 in human. *Neuropsychologia*, *41*(13), 1802-1807.

Antal, A., Nitsche, M. A., & Paulus, W. (2001). External modulation of visual perception in humans. *Neuroreport*, *12*(16), 3553-3555.

Antal, A., Nitsche, M. A., & Paulus, W. (2006). Transcranial direct current stimulation and the visual cortex. *Brain research bulletin*, *68*(6), 459-463.

Antal, A., & Paulus, W. (2008). Transcranial direct current stimulation and visual perception. *Perception*, *37*(3), 367-374.

Arbabshirani, M. R., Havlicek, M., Kiehl, K. A., Pearlson, G. D., & Calhoun, V. D. (2013). Functional network connectivity during rest and task conditions: a comparative study. *Human brain mapping*, *34*(11), 2959-2971.

Aslaksen, P. M., Vasylenko, O., & Fagerlund, A. J. (2014). The effect of transcranial direct current stimulation on experimentally induced heat pain. *Experimental brain research*, *232*(6), 1865-1873.

Aytemür, A., Almeida, N., & Lee, K.-H. (2017). Differential sensory cortical involvement in auditory and visual sensorimotor temporal recalibration: Evidence from transcranial direct current stimulation (tDCS). *Neuropsychologia*, *96*, 122-128.

Bach, M., & Ullrich, D. (1997). Contrast dependency of motion-onset and pattern-reversal VEPs: interaction of stimulus type, recording site and response component. *Vision Research*, *37*(13), 1845-1849.

Baroncelli, L., Braschi, C., Spolidoro, M., Begenisic, T., Maffei, L., & Sale, A. (2011). Brain plasticity and disease: a matter of inhibition. *Neural plasticity*, *2011*.

Berryhill, M. E., Wencil, E. B., Coslett, H. B., & Olson, I. R. J. N. l. (2010). A selective working memory impairment after transcranial direct current stimulation to the right parietal lobe. *479*(3), 312-316.

Bertone, A., Mottron, L., Jelenic, P., & Faubert, J. (2005). Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain*, *128*(10), 2430-2441.

Bin Dawood, A., Dickinson, A., Aytemur, A., Howarth, C., Milne, E., & Jones, M. (2020). Investigating the Effects of tDCS on Visual Orientation Discrimination Task Performance: "the Possible Influence of Placebo". *Journal of Cognitive Enhancement*, *4*(3), 235-249. https://doi.org/10.1007/s41465-019-00154-3

Blacker, K. J., Peltier, C., McKinley, R. A., & Biggs, A. T. (2020). What Versus How in Visual Search: Effects of Object Recognition Training, Strategy Training, and Non-invasive Brain Stimulation on Satellite Image Search. *Journal of Cognitive Enhancement*, *4*(2), 131-144.

Bolognini, N., Rossetti, A., Casati, C., Mancini, F., & Vallar, G. (2011). Neuromodulation of multisensory perception: a tDCS study of the sound-induced flash illusion. *Neuropsychologia*, *49*(2), 231-237.

Brainard, D. H., & Vision, S. (1997). The psychophysics toolbox. *Spatial vision*, *10*, 433-436.

Brunel, N., & Wang, X.-J. (2003). What determines the frequency of fast network oscillations with irregular neural discharges? I. Synaptic dynamics and excitation-inhibition balance. *Journal of neurophysiology*, *90*(1), 415-430.

Brunoni, A. R., Amadera, J., Berbel, B., Volz, M. S., Rizzerio, B. G., & Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *International Journal of Neuropsychopharmacology*, *14*(8), 1133-1145.

Brückner, S., & Kammer, T. (2016). No modulation of visual cortex excitability by transcranial direct current stimulation. *PloS one*, *11*(12), e0167697.

Busch, N. A., Debener, S., Kranczioch, C., Engel, A. K., & Herrmann, C. S. (2004). Size matters: effects of stimulus size, duration and eccentricity on the visual gamma-band response. *Clinical Neurophysiology*, *115*(8), 1810-1820.

Button, K. S., Ioannidis, J. P., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S., & Munafò, M. R. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nature reviews neuroscience*, *14*(5), 365-376.

Börgers, C., & Kopell, N. (2003). Synchronization in networks of excitatory and inhibitory neurons with sparse, random connectivity. *Neural computation*, *15*(3), 509-538.

Campbell, A. E., Sumner, P., Singh, K. D., & Muthukumaraswamy, S. D. (2014). Acute effects of alcohol on stimulus-induced gamma oscillations in human primary visual and motor cortices. *Neuropsychopharmacology*, *39*(9), 2104.

Coghlan, S., Horder, J., Inkster, B., Mendez, M. A., Murphy, D. G., & Nutt, D. J. (2012). GABA system dysfunction in autism and related disorders: from synapse to symptoms. *Neuroscience & Biobehavioral Reviews*, *36*(9), 2044-2055.

Cohen, M. X. (2014). *Analyzing neural time series data: theory and practice*. MIT press.

Cousijn, H., Haegens, S., Wallis, G., Near, J., Stokes, M. G., Harrison, P. J., & Nobre, A. C. (2014). Resting GABA and glutamate concentrations do not predict visual gamma frequency or amplitude. *Proceedings of the National Academy of Sciences*, *111*(25), 9301-9306.

Daniels, J., & Pettigrew, J. (1975). A study of inhibitory antagonism in cat visual cortex. *Brain research*, *93*(1), 41-62.

Daubechies, I. (1990). The wavelet transform, time-frequency localization and signal analysis. *IEEE transactions on information theory*, *36*(5), 961-1005.

Dickinson, A., Bruyns-Haylett, M., Smith, R., Jones, M., & Milne, E. (2016). Superior orientation discrimination and increased peak gamma frequency in autism spectrum conditions. *Journal of abnormal psychology*, *125*(3), 412.

Dickinson, A., Bruynssychology M., Smith, R., Jones, M., & Milne, E. (2016). Superior orientation discrimination and increr levels of autistic traits. *European Journal of Neuroscience*, *41*(8), 1095-1101.

Dickinson, A., Jones, M., & Milne, E. (2016). Measuring neural excitation and inhibition in autism: Different approaches, different findings and different interpretations. *Brain research*, *1648*, 277-289.

Diederich, N. J., & Goetz, C. G. (2008). The placebo treatments in neurosciences: new insights from clinical and neuroimaging studies. *Neurology*, *71*(9), 677-684.

Ding, Z., Li, J., Spiegel, D. P., Chen, Z., Chan, L., Luo, G., Yuan, J., Deng, D., Yu, M., & Thompson, B. (2016). The effect of transcranial direct current stimulation on contrast sensitivity and visual evoked potential amplitude in adults with amblyopia. *Scientific reports*, *6*, 19280.

Dinn, W., Göral, F., Adigüzel, S., Karamürsel, S., Fregni, F., & Aycicegi-Dinn, A. (2017). Effectiveness of tDCS blinding protocol in a sham-controlled study. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *10*(2), 401.

Donahue, M. J., Near, J., Blicher, J. U., & Jezzard, P. (2010). Baseline GABA concentration and fMRI response. *Neuroimage*, *53*(2), 392-398.

Edden, R. A., Crocetti, D., Zhu, H., Gilbert, D. L., & Mostofsky, S. H. (2012). Reduced GABA concentration in attention-deficit/hyperactivity disorder. *Archives of general psychiatry*, *69*(7), 750-753.

Edden, R. A., Muthukumaraswamy, S. D., Freeman, T. C., & Singh, K. D. (2009). Orientation discrimination performance is predicted by GABA concentration and gamma oscillation frequency in human primary visual cortex. *Journal of Neuroscience*, *29*(50), 15721-15726.

Egorova, N., Yu, R., Kaur, N., Vangel, M., Gollub, R. L., Dougherty, D. D., Kong, J., & Camprodon, J. A. (2015). Neuromodulation of conditioned placebo/nocebo in heat pain: anodal vs. cathodal transcranial direct current stimulation to the right dorsolateral prefrontal cortex. *Pain*, *156*(7), 1342.

Fesi, J. D., & Mendola, J. D. (2015). Individual peak gamma frequency predicts switch rate in perceptual rivalry. *Human brain mapping*, *36*(2), 566-576.

Freyberg, J., Robertson, C., & Baron-Cohen, S. J. J. o. v. (2015). Atypical Binocular Rivalry Dynamics of Simple and Complex Stimuli in Autism. *15*(12), 643-643.

Friehs, M. A., Brauner, L., & Frings, C. (2021). Dual-tDCS over the right prefrontal cortex does not modulate stop-signal task performance. *Experimental Brain Research*, 1-10.

Galea, J. M., Jayaram, G., Ajagbe, L., & Celnik, P. (2009). Modulation of cerebellar excitability by polarity-specific noninvasive direct current stimulation. *Journal of Neuroscience*, *29*(28), 9115-9122.

Galli, G., Vadillo, M. A., Sirota, M., Feurra, M., & Medvedeva, A. (2019). A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) on episodic memory. *Brain stimulation*, *12*(2), 231-241.

Gandiga, P. C., Hummel, F. C., & Cohen, L. G. (2006). Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical neurophysiology*, *117*(4), 845-850.

Gawel, M., Connolly, J., & Rose, F. C. (1983). Migraine patients exhibit abnormalities in the visual evoked potential. *Headache: The Journal of Head and Face Pain*, *23*(2), 49-52.

Grinsted, A., Moore, J. C., & Jevrejeva, S. (2004). Application of the cross wavelet transform and wavelet coherence to geophysical time series. *Nonlinear processes in geophysics*, *11*(5/6), 561-566.

Hanley, C. J., Singh, K. D., & McGonigle, D. J. (2016). Transcranial modulation of brain oscillatory responses: A concurrent tDCS–MEG investigation. *NeuroImage*, *140*, 20-32.

Hanslmayr, S., Klimesch, W., Sauseng, P., Gruber, W., Doppelmayr, M., Freunberger, R., & Pecherstorfer, T. (2005). Visual discrimination performance is related to decreased alpha amplitude but increased phase locking. *Neuroscience letters*, *375*(1), 64-68.

Harris, D. J., Wilson, M. R., Buckingham, G., & Vine, S. J. (2019). No effect of transcranial direct current stimulation of frontal, motor or visual cortex on performance of a self-paced visuomotor skill. *Psychology of Sport and Exercise*, *43*, 368-373.

Hazarika, N., Chen, J. Z., Tsoi, A. C., & Sergejew, A. (1997). Classification of EEG signals using the wavelet transform. *Signal processing*, *59*(1), 61-72.

Horvath, J. C., Forte, J. D., & Carter, O. (2015a). Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: a systematic review. *Neuropsychologia*, *66*, 213-236.

Horvath, J. C., Forte, J. D., & Carter, O. (2015b). Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). *Brain stimulation*, *8*(3), 535-550.

Hoy, K. E., Bailey, N. W., Arnold, S. L., & Fitzgerald, P. B. (2015). The effect of transcranial direct current stimulation on gamma activity and working memory in schizophrenia. *Psychiatry research*, *228*(2), 191-196.

Hsu, T.-Y., Tseng, L.-Y., Yu, J.-X., Kuo, W.-J., Hung, D. L., Tzeng, O. J., Walsh, V., Muggleton, N. G., & Juan, C.-H. (2011). Modulating inhibitory control with direct current stimulation of the superior medial frontal cortex. *Neuroimage*, *56*(4), 2249-2257.

Hudnell, H., & Boyes, W. (1991). The comparability of rat and human visual-evoked potentials. *Neuroscience & Biobehavioral Reviews*, *15*(1), 159-164.

Im, C.-H., Park, J.-H., Shim, M., Chang, W. H., Kim, Y.-H. J. P. i. M., & Biology. (2012). Evaluation of local electric fields generated by transcranial direct current stimulation with an extracephalic reference electrode based on realistic 3D body modeling. *57*(8), 2137.

Jacobson, L., Koslowsky, M., & Lavidor, M. (2012). tDCS polarity effects in motor and cognitive domains: a meta-analytical review. *Experimental brain research*, *216*(1), 1-10.

Jasper, H. H. (1958). The ten-twenty electrode system of the International Federation. *Electroencephalogr. Clin. Neurophysiol.*, *10*, 370-375.

Jonker, Z. D., Gaiser, C., Tulen, J. H., Ribbers, G. M., Frens, M. A., & Selles, R. W. (2021). No effect of anodal tDCS on motor cortical excitability and no evidence for responders in a large double-blind placebo-controlled trial. *Brain Stimulation*, *14*(1), 100-109.

Jung, T.-P., Makeig, S., Humphries, C., Lee, T.-W., Mckeown, M. J., Iragui, V., & Sejnowski, T. J. (2000). Removing electroencephalographic artifacts by blind source separation. *Psychophysiology*, *37*(2), 163-178.

Jung, Y.-J., Kim, J.-H., & Im, C.-H. (2013). COMETS: A MATLAB toolbox for simulating local electric fields generated by transcranial direct current stimulation (tDCS). *Biomedical engineering letters*, *3*(1), 39-46.

Kaiser, G. (1994). A Friendly Guide to Wavelets, Birkhauser, Boston. In: MA.

Kennard, C., Gawel, M., Rudolph, M. N., & Rose, F. C. (1978). Visual evoked potentials in migraine subjects. *Research and clinical studies in headache*, *6*, 73-80.

Kessler, S. K., Turkeltaub, P. E., Benson, J. G., & Hamilton, R. H. (2012). Differences in the experience of active and sham transcranial direct current stimulation. *Brain stimulation*, *5*(2), 155-162.

Kissler, J., Herbert, C., Winkler, I., & Junghofer, M. (2009). Emotion and attention in visual word processing—An ERP study. *Biological psychology*, *80*(1), 75-83.

Klaus, J., & Hartwigsen, G. (2020). Failure to improve verbal fluency with transcranial direct current stimulation. *Neuroscience*, *449*, 123-133.

Klem, G. H., LuÈders, H. O., Jasper, H., & Elger, C. (1999). The ten-twenty electrode system of the International Federation. *Electroencephalogr Clin Neurophysiol*, *52*(3), 3-6.

Korth, M., & Nguyen, N. X. (1997). The effect of stimulus size on human cortical potentials evoked by chromatic patterns. *Vision research*, *37*(5), 649-657.

Kraft, A., Roehmel, J., Olma, M. C., Schmidt, S., Irlbacher, K., & Brandt, S. A. (2010). Transcranial direct current stimulation affects visual perception measured by threshold perimetry. *Experimental Brain Research*, *207*(3-4), 283-290.

Krause, B., Márquez-Ruiz, J., & Cohen Kadosh, R. (2013). The effect of transcranial direct current stimulation: a role for cortical excitation/inhibition balance? *Frontiers in human neuroscience*, *7*, 602.

Kraut, M. A., Arezzo, J. C., & Vaughan Jr, H. G. (1990). Inhibitory processes in the flash evoked potential of the monkey. *Electroencephalography and clinical neurophysiology*, *76*(5), 440-452.

Kujala, J., Jung, J., Bouvard, S., Lecaignard, F., Lothe, A., Bouet, R., Ciumas, C., Ryvlin, P., & Jerbi, K. (2015). Gamma oscillations in V1 are correlated with GABA A receptor density: A multi-modal MEG and Flumazenil-PET study. *Scientific reports*, *5*, 16347.

Kuo, H.-I., Bikson, M., Datta, A., Minhas, P., Paulus, W., Kuo, M.-F., & Nitsche, M. A. (2013). Comparing cortical plasticity induced by conventional and high-definition 4× 1 ring tDCS: a neurophysiological study. *Brain stimulation*, *6*(4), 644-648.

Kurcyus, K., Annac, E., Hanning, N. M., Harris, A. D., Oeltzschner, G., Edden, R., & Riedl, V. (2018). Opposite dynamics of GABA and glutamate levels in the occipital cortex during visual processing. *Journal of Neuroscience*, *38*(46), 9967-9976.

Lee, S., & Jones, S. R. (2013). Distinguishing mechanisms of gamma frequency oscillations in human current source signals using a computational model of a laminar neocortical network. *Frontiers in human neuroscience*, *7*, 869.

Li, L. M., Uehara, K., & Hanakawa, T. (2015). The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. *Frontiers in cellular neuroscience*, *9*, 181.

Loo, C. K., Husain, M. M., McDonald, W. M., Aaronson, S., O'Reardon, J. P., Alonzo, A., Weickert, C. S., Martin, D. M., McClintock, S. M., & Mohan, A. (2018). International randomized-controlled trial of transcranial Direct Current Stimulation in depression. *Brain stimulation*, *11*(1), 125-133.

Luck, S. J. (2014). *An introduction to the event-related potential technique*. MIT press.

Magazzini, L., Muthukumaraswamy, S. D., Campbell, A. E., Hamandi, K., Lingfordonzo, A., Weickert, C. S., Mart, D. J., Sumner, P., Wilson, S. J., & Singh, K. D. (2016). Significant reductions in human visual gamma frequency by the gaba reuptake inhibitor tiagabine revealed by robust peak frequency estimation. *Human brain mapping*, *37*(11), 3882-3896.

Makeig, S., Jung, T.-P., Bell, A. J., Ghahremani, D., & Sejnowski, T. J. (1997). Blind separation of auditory event-related brain responses into independent components. *Proceedings of the National Academy of Sciences*, *94*(20), 10979-10984.

Marshall, T. R., Esterer, S., Herring, J. D., Bergmann, T. O., & Jensen, O. (2016). On the relationship between cortical excitability and visual oscillatory responses—A concurrent tDCS–MEG study. *Neuroimage*, *140*, 41-49.

Medina, J., & Cason, S. (2017). No evidential value in samples of transcranial direct current stimulation (tDCS) studies of cognition and working memory in healthy populations. *Cortex*, *94*, 131-141.

Milne, E., Dunn, S., Zhao, C., & Jones, M. (2018). Altered neural dynamics in people who report spontaneous out of body experiences. *Cortex*.

Milne, E., Gomez, R., Giannadou, A., & Jones, M. (2019). Atypical EEG in autism spectrum disorder: Comparing a dimensional and a categorical approach. *Journal of abnormal psychology*.

Minarik, T., Berger, B., Althaus, L., Bader, V., Biebl, B., Brotzeller, F., Fusban, T., Hegemann, J., Jesteadt, L., & Kalweit, L. (2016). The importance of sample size for reproducibility of tDCS effects. *Frontiers in human neuroscience*, *10*, 453.

Moon, S.-K., & Lim, K. (2009). Patten Visual Evoked Potential (P-VEP) in Adult Monocular Amblyopia. *Investigative Ophthalmology & Visual Science*, *50*(13), 4708-4708.

Moskowitz, A., & Sokol, S. (1985). Effect of stimulus orientation on the latency and amplitude of the VEP. *Investigative ophthalmology & visual science*, *26*(2), 246-248.

Muthukumaraswamy, S. D., Edden, R. A., Jones, D. K., Swettenham, J. B., & Singh, K. D. (2009). Resting GABA concentration predicts peak gamma frequency and fMRI amplitude in response to visual stimulation in humans. *Proceedings of the National Academy of Sciences*, *106*(20), 8356-8361.

Muthukumaraswamy, S. D., Myers, J. F., Wilson, S. J., Nutt, D. J., Hamandi, K., Lingford-Hughes, A., & Singh, K. D. (2013). Elevating endogenous GABA levels with GAT-1 blockade modulates evoked but not induced responses in human visual cortex. *Neuropsychopharmacology*, *38*(6), 1105.

Muthukumaraswamy, S. D., Singh, K. D., Swettenham, J. B., & Jones, D. K. (2010). Visual gamma oscillations and evoked responses: variability, repeatability and structural MRI correlates. *Neuroimage*, *49*(4), 3349-3357.

Müller, K., Lohmann, G., Neumann, J., Grigutsch, M., Mildner, T., & von Cramon, D. Y. (2004). Investigating the wavelet coherence phase of the BOLD signal. *Journal of Magnetic Resonance Imaging: An Official Journal of the International Society for Magnetic Resonance in Medicine*, *20*(1), 145-152.

Nasseri, P., Nitsche, M. A., & Ekhtiari, H. (2015). A framework for categorizing electrode montages in transcranial direct current stimulation. *Frontiers in human neuroscience*, *9*, 54.

Nguyen, B. N., McKendrick, A. M., & Vingrys, A. J. (2016). Abnormal inhibition-excitation imbalance in migraine. *Cephalalgia*, *36*(1), 5-14.

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P. S., & Fregni, F. (2008). Transcranial direct current stimulation: state of the art 2008. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *1*(3), 206-223.

Nitsche, M. A., Liebetanz, D., Antal, A., Lang, N., Tergau, F., & Paulus, W. (2003). Modulation of cortical excitability by weak direct current stimulation–technical, safety and functional aspects. In *Supplements to Clinical neurophysiology* (Vol. 56, pp. 255-276). Elsevier.

Nitsche, M. A., Liebetanz, D., Schlitterlau, A., Henschke, U., Fricke, K., Frommann, K., Lang, N., Henning, S., Paulus, W., & Tergau, F. (2004). GABAergic modulation of DC stimulation ‐ induced motor cortex excitability shifts in humans. *European Journal of Neuroscience*, *19*(10), 2720-2726.

Nitsche, M. A., Nitsche, M. S., Klein, C. C., Tergau, F., Rothwell, J. C., & Paulus, W. (2003). Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. *Clinical Neurophysiology*, *114*(4), 600-604.

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*, *57*(10), 1899-1901.

Palm, U., Reisinger, E., Keeser, D., Kuo, M.-F., Pogarell, O., Leicht, G., Mulert, C., Nitsche, M. A., & Padberg, F. (2013). Evaluation of sham transcranial direct current stimulation for randomized, placebo-controlled clinical trials. *Brain stimulation*, *6*(4), 690-695.

Pantev, C. (1995). Evoked and induced gamma-band activity of the human cortex. *Brain topography*, *7*(4), 321-330.

Purpura, D. P. (1959). Nature of electrocortical potentials and synaptic organizations in cerebral and cerebellar cortex. In *International review of neurobiology* (Vol. 1, pp. 47-163). Elsevier.

Rankin, C. H., Abrams, T., Barry, R. J., Bhatnagar, S., Clayton, D. F., Colombo, J., Coppola, G., Geyer, M. A., Glanzman, D. L., & Marsland, S. (2009). Habituation revisited: an updated and revised description of the behavioral characteristics of habituation. *Neurobiology of learning and memory*, *92*(2), 135-138.

Reinhart, R. M., Cosman, J. D., Fukuda, K., & Woodman, G. F. (2017). Using transcranial direct-current stimulation (tDCS) to understand cognitive processing. *Attention, Perception, & Psychophysics*, *79*(1), 3-23.

Reinhart, R. M., Xiao, W., McClenahan, L. J., & Woodman, G. F. (2016). Electrical stimulation of visual cortex can immediately improve spatial vision. *Current Biology*, *26*(14), 1867-1872.

Robertson, C. E., Kravitz, D. J., Freyberg, J., Baron-Cohen, S., & Baker, C. I. (2013). Slower rate of binocular rivalry in autism. *Journal of Neuroscience*, *33*(43), 16983-16991.

Robertson, C. E., Ratai, E.-M., & Kanwisher, N. (2016). Reduced GABAergic action in the autistic brain. *Current Biology*, *26*(1), 80-85.

Rubenstein, J., & Merzenich, M. M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes, Brain and Behavior*, *2*(5), 255-267.

Schadow, J., Lenz, D., Thaerig, S., Busch, N. A., Fründ, I., Rieger, J. W., & Herrmann, C. S. (2007). Stimulus intensity affects early sensory processing: visual contrast modulates evoked gamma-band activity in human EEG. *International Journal of Psychophysiology*, *66*(1), 28-36.

Schafer, D., Pappas, S., Brody, L., Jacobs, R., & Jones, E. (1984). Visual evoked potentials in a rabbit model of hepatic encephalopathy: I. Sequential changes and comparisons with drug-induced comas. *Gastroenterology*, *86*(3), 540-545.

Schambra, H., Bikson, M., Wager, T., DosSantos, M., & DaSilva, A. (2014). It's all in your head: reinforcing the placebo response with tDCS. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *7*(4), 623-624.

Siebner, H. R., Lang, N., Rizzo, V., Nitsche, M. A., Paulus, W., Lemon, R. N., & Rothwell, J. C. (2004). Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex. *Journal of Neuroscience*, *24*(13), 3379-3385.

Siniatchkin, M., Sendacki, M., Moeller, F., Wolff, S., Jansen, O., Siebner, H., & Stephani, U. (2011). Abnormal changes of synaptic excitability in migraine with aura. *Cerebral cortex*, *22*(10), 2207-2216.

Skyt, I., Moslemi, K., Baastrup, C., Grosen, K., Svensson, P., Jensen, T., & Vase, L. (2018). Does conditioned pain modulation predict the magnitude of placebo effects in patients with neuropathic pain? *European Journal of Pain*, *22*(4), 784-792.

Spiegel, D. P., Hansen, B. C., Byblow, W. D., & Thompson, B. (2012). Anodal transcranial direct current stimulation reduces psychophysically measured surround suppression in the human visual cortex. *PLoS One*, *7*(5), e36220.

Stagg, C. J., Best, J. G., Stephenson, M. C., O'Shea, J., Wylezinska, M., Kincses, Z. T., Morris, P. G., Matthews, P. M., & Johansen-Berg, H. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *Journal of Neuroscience*, *29*(16), 5202-5206.

Sung, K., & Gordon, B. (2018). Transcranial direct current stimulation (tDCS) facilitates overall visual search response times but does not interact with visual search task factors. *PloS one*, *13*(3), e0194640.

Sysoeva, O. V., Davletshina, M. A., Orekhova, E. V., Galuta, I. A., & Stroganova, T. A. (2016). Reduced oblique effect in children with autism spectrum disorders (ASD). *Frontiers in neuroscience*, *9*, 512.

Tallon-Baudry, C., & Bertrand, O. (1999). Oscillatory gamma activity in humans and its role in object representation. *Trends in cognitive sciences*, *3*(4), 151-162.

Tatum, W. O., Dworetzky, B. A., & Schomer, D. L. (2011). Artifact and recording concepts in EEG. *Journal of clinical neurophysiology*, *28*(3), 252-263.

Teplan, M. (2002). Fundamentals of EEG measurement. *Measurement science review*, *2*(2), 1-11.

Thair, H., Holloway, A. L., Newport, R., & Smith, A. D. (2017). Transcranial direct current stimulation (tDCS): a beginner's guide for design and implementation. *Frontiers in neuroscience*, *11*, 641.

Thompson, R. F., & Spencer, W. A. (1966). Habituation: a model phenomenon for the study of neuronal substrates of behavior. *Psychological review*, *73*(1), 16.

Torrence, C., & Compo, G. P. (1998). A practical guide to wavelet analysis. *Bulletin of the American Meteorological society*, *79*(1), 61-78.

Tseng, P., Iu, K.-C., & Juan, C.-H. J. S. r. (2018). The critical role of phase difference in theta oscillation between bilateral parietal cortices for visuospatial working memory. *8*(1), 349.

Turi, Z., Csifcsák, G., Boayue, N. M., Aslaksen, P., Antal, A., Paulus, W., Groot, J., Hawkins, G. E., Forstmann, B., & Opitz, A. (2019). Blinding is compromised for transcranial direct current stimulation at 1 mA for 20 minutes in young healthy adults. *European Journal of Neuroscience*.

Ullsperger, M., & Debener, S. (2010). *Simultaneous EEG and fMRI: recording, analysis, and application*. Oxford University Press.

van Loon, A. M., Knapen, T., Scholte, H. S., John-Saaltink, E. S., Donner, T. H., & Lamme, V. A. (2013). GABA shapes the dynamics of bistable perception. *Current Biology*, *23*(9), 823-827.

Vannorsdall, T. D., Van Steenburgh, J. J., Schretlen, D. J., Jayatillake, R., Skolasky, R. L., & Gordon, B. (2016). Reproducibility of tDCS results in a randomized trial: failure to replicate findings of tDCS-induced enhancement of verbal fluency. *Cognitive and Behavioral Neurology*, *29*(1), 11-17.

Vecchio, F., Pellicciari, M. C., Miraglia, F., Brignani, D., Miniussi, C., & Rossini, P. M. (2016). Effects of transcranial direct current stimulation on the functional coupling of the sensorimotor cortical network. *Neuroimage*, *140*, 50-56.

Viganò, A., D'Elia, T. S., Sava, S. L., Auvé, M., De Pasqua, V., Colosimo, A., Di Piero, V., Schoenen, J., & Magis, D. (2013). Transcranial Direct Current Stimulation (tDCS) of the visual cortex: a proof-of-concept study based on interictal electrophysiological abnormalities in migraine. *The journal of headache and pain*, *14*(1), 23.

Westwood, S. J., & Romani, C. (2017). Transcranial direct current stimulation (tDCS) modulation of picture naming and word reading: A meta-analysis of single session tDCS applied to healthy participants. *Neuropsychologia*, *104*, 234-249.

Wiesman, A. I., Mills, M. S., McDermott, T. J., Spooner, R. K., Coolidge, N. M., & Wilson, T. W. (2018). Polarity-dependent modulation of multi-spectral neuronal activity by transcranial direct current stimulation. *Cortex*, *108*, 222-233.

Wilson, T. W., McDermott, T. J., Mills, M. S., Coolidge, N. M., & Heinrichs-Graham, E. (2017). tDCS modulates visual gamma oscillations and basal alpha activity in occipital cortices: evidence from MEG. *Cerebral Cortex*, *28*(5), 1597-1609.

Yizhar, O., Fenno, L. E., Prigge, M., Schneider, F., Davidson, T. J., O'Shea, D. J., Sohal, V. S., Goshen, I., Finkelstein, J., & Paz, J. T. (2011). Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature*, *477*(7363), 171.

Zemon, V., Kaplan, E., & Ratliff, F. (1980). Bicuculline enhances a negative component and diminishes a positive component of the visual evoked cortical potential in the cat. *Proceedings of the National Academy of Sciences*, *77*(12), 7476-7478.

Zemon, V., Kaplan, E., & Ratliff, F. (1986). The role of GABA-mediated intracortical inhibition in the generation of visual evoked potentials. *Frontiers of clinical neuroscience*, *3*, 287-295.

Zemon, V., Victor, J., & Ratliff, F. (1986). Functional subsystems in the visual pathways of humans characterized using evoked potentials. *Frontiers of clinical neuroscience*, *3*, 203-210.

Zeneroli, M., Penne, A., Parrinello, G., Cremonini, C., & Ventura, E. (1981). Comparative evaluation of visual evoked potentials in experimental hepatic encephalopathy and in pharmacologically induced coma-like states in rat. *Life sciences*, *28*(13), 1507-1515.