The use of transcranial direct current stimulation to investigate the link between excitation–inhibition balance in visual cortex and psychophysical and neurophysiological measures

Abdullah Bin Dawood

A thesis submitted for the degree of Doctor of Philosophy (PhD)

The University of Sheffield

Faculty of Science

Department of Psychology

August 2019

Contents

List of Figures

List of Tables

List of Abbreviations

2AFC	Two alternative-force choice
ANOVA	Analysis of variance
ASC	Autism spectrum conditions
BOLD	Blood-oxygen-level-dependent
E-I	Excitation-inhibition
EEG	Electroencephalogram
EPSP	Excitatory postsynaptic potentials
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
IC	Independent components
ICA	Independent component analysis
IPSP	Inhibitory postsynaptic potentials
ISI	Inter-stimulus interval
K layer	Koniocellular layer
KSU	King Saud University
M layer	Magnocellular layer
MEG	Magnetoencephalography
MEP	Motor evoked potentials
MRS	Magnetic resonance spectroscopy
NMDA	N-methyl-d-aspartic acid
ODT	Orientation discrimination task
OSSS	Orientation-specific surround suppression

P layer	Parvocellular layer
PET	Positron emission tomography
rTMS	Repetitive transcranial magnetic stimulation
SEP	Somatosensory evoked potential
SNR	Signal-to-noise ratio
tDCS	Transcranial direct current stimulation
TES	transcutaneous electrical stimulation
TMS	Transcranial magnetic stimulation
V1	Primary visual cortex
VAT	Vernier acuity task
VEP	Visual evoked potential

Publications and presentations arising from this thesis`

Dawood, A. B., Dickinson A., Aytemur, A., Howarth, C., Milne, E. & Jones, M. (2018. March). *The effects of tDCS on orientation discrimination task performance.* Poster session presented at the 25th annual meeting of Cognitive Neuroscience Society, Boston, MA.

Dawood, A. B., Dickinson, A., Aytemur, A., Howarth, C., Milne, E., & Jones, M. (2019). Investigating the Effects of tDCS on Visual Orientation Discrimination Task Performance:"the Possible Influence of Placebo". Journal of Cognitive Enhancement, 1-15.

Acknowledgments

To my mother, Jawaher, who has been calling me every day asking, When I will come back home?

To my wife, Maha, who has— without showing any boredom—been listening with care to my boring, lengthy descriptions of each step I take.

To my brother, Abdulmohsen, whom I have been consulting in every matter of importance.

To my children, Aljoharah, Rayan, and Nawaf, who learned to walk and talk far away from Najd-KSA, the heart of the Arabian Peninsula.

To my Alhanouf, who delightfully came to our world at the end of my PhD journey.

To my brother, Mohammed, whose life guidance is priceless.

To Dr Humood, a humble and thoughtful person whose upcoming companionship at King Saud University (KSU) motivates me to speed my work on this thesis.

To Faisal, who put an enormous effort to help me recruit participants for my experiments in KSU.

To Mohammed, Kamal, and Sultan, who played a major role in recruiting participants for my first experiment.

To Saad, an old friend who asked me when I would come home, but prematurely left our world before I could tell him I am on my way…

To Azzam and Kalifah, who were so generous in sharing their time and experience with me.

To my psychology department and my KSU, who gave me the great opportunity to study abroad.

To the participants of this thesis, whose participation will never be forgotten.

To the people who have contributed to the success of this project but whose names my memory has failed.

To Dr Adam Prus, whose supportive words have been of great impact on me, personally and professionally.

To Dr Abigail, whose scientific trail was worth following.

To Dr Clare, who made me realize that some problems are the best gifts.

To Dr Elizabeth, whose work and achievements inspire me.

To Ali, who made this journey more joyful and fruitful.

To my supervisor, Dr Myles, whose endless and unconditional support, interesting and useful clarifications, and humorous and inspiring guidance were more than I could wish for.

To all of you,

My gratitude is as big as the sky,
my thankfulness is as deep as the sea,
and my appreciation is as wide as the earth!

Abstract

The thesis investigates the link between cortical excitation–inhibition (E–I) balance in the visual cortex, on the one hand, and psychophysical and neurophysiological measures, on the other, using transcranial direct current stimulation (tDCS). The existing literature suggests that performance in the visual orientation discrimination task (ODT), peak gamma frequency, and the amplitudes of visual evoked potential (VEP) components (N1 and P2) can be indirect indicators of cortical E–I balance (Edden, Muthukumaraswamy, Freeman, & Singh, 2009; Siper et al., 2016), but some aspects of these relationships remain uncertain. As such, since tDCS has been suggested to modulate cortical E–I balance (Krause, Márquez-Ruiz, & Cohen Kadosh, 2013), it was used to attempt to manipulate these variables. The research presented in the thesis investigates, through a series of experiments, whether manipulating E–I balance of the visual cortex using a 10-min tDCS with an intensity of 2 mA could modulate the outcomes of the psychophysical (ODT performance) and neurophysiological (EEG) measures (peak gamma frequency, VEP amplitudes of N1 and P2). Additionally, it confirmed and extended the findings of previous studies investigating the relationship between ODT performance and peak gamma frequency by including the amplitudes of VEP components (N1 and P2) (Dickinson, Bruyns-Haylett, Smith, Jones, & Milne, 2016). The results provide no evidence of tDCS modulating the outcomes of the psychophysical and neurophysiological measures other than a noticeable placebo effect of tDCS on ODT performance. Furthermore, the result successfully replicated and extended previous studies' findings of an association between performance in the oblique condition of ODT and peak gamma frequency as both high peak gamma frequency and/or lower VEP-N1 amplitude are associated with enhanced oblique ODT performance. The findings of the null effects of tDCS on the outcomes of the psychophysical and neurophysiological measures with a clear link to E–I balance add to the growing literature questioning the efficacy of tDCS on cognition (Medina & Cason, 2017). In addition, the finding of a strong relationship between ODT performance and both peak gamma frequency and the VEP-N1 amplitude in the same direction—as expected

based on their association with gamma-aminobutyric acid (GABA) concentration and activity (as shown previously (Edden et al., 2009; Zemon, Kaplan, & Ratliff, 1980; Zeneroli, Penne, Parrinello, Cremonini, & Ventura, 1981)—supports the suggestion that these measures may be useful indirect indicators of E–I balance.

Chapter 1 : General Introduction

Overview

Excitation–inhibition (E–I) balance plays important role in cognitive processes such as attention and perception (Adesnik, 2017; Koelewijn, Rich, Muthukumaraswamy, & Singh, 2013; Kondo, Pressnitzer, Shimada, Kochiyama, & Kashino, 2018; Magazzini & Singh, 2018; Sokolov, Pavlova, Lutzenberger, & Birbaumer, 2004; van Loon et al., 2013). Furthermore, disruption in E–I balance has been suggested to explain atypical cognitive processes associated with conditions such as autism (Dickinson, Bruyns-Haylett, et al., 2016; Freyberg, Robertson, & Baron-Cohen, 2015; Sysoeva, Davletshina, Orekhova, Galuta, & Stroganova, 2016), schizophrenia (Rokem et al., 2011; Shaw et al., 2019; Yoon et al., 2010; Yoon et al., 2009), and migraine (Shepherd, 2000; Tibber, Guedes, & Shepherd, 2006; Wilkinson, Karanovic, & Wilson, 2008). However, such suggested disruptions in E–I balance have often been indirectly inferred from visual psychophysical (i.e., orientation discrimination task [ODT]) and neurophysiological measurements (i.e., peak gamma frequency, visual evoked potential [VEP]) rather than direct measurement of excitatory and inhibitory neurotransmitters.

During the ODT, participants are presented pairs of consecutive vertical or oblique gratings and are asked to indicate whether the secondly presented grating has been rotated clockwise or anticlockwise compared to the first presented grating (Edden et al., 2009). The degree of rotation is varied (staircase) until a threshold is calculated for which the participant can correctly assess the direction of the grating's rotation. As seminal work in animal models suggest that topical application of gamma-aminobutyric acid (GABA) antagonists decreases the tuning sensitivity of orientation neurons in the primary visual cortex (V1) (Sillito, 1975), performance in the ODT is often thought to indicate cortical E–I balance. This notion is further supported by data from actual human subjects in which performance in components of the ODT correlates with magnetic resonance spectroscopy (MRS) measures of resting GABA concentration (Edden et al., 2009). As such, ODT

performance has been used to infer cortical E–I balance in conditions such as autism and schizophrenia (Dickinson, Bruyns-Haylett, et al., 2016; Shaw et al., 2019). Other indirect markers of E–I balance are neuronal oscillations and evoked potentials measured with electroencephalogram (EEG) and magnetoencephalography (MEG). The peak frequency of gamma oscillations also correlates with MRS measures and with performance on the ODT (Edden et al., 2009; Muthukumaraswamy, Edden, Jones, Swettenham, & Singh, 2009). Like ODT performance, peak gamma frequency has also been used to make inferences about E–I balance in both autism and schizophrenia (Dickinson, Bruyns-Haylett, et al., 2016; Shaw et al., 2019). However, inferring E–I balance from the ODT and EEG or MEG metrics may not be as straightforward as is often implied. The majority of the studies relate the ODT and the EEG or MEG metrics to cortical E–I balance are correlational without a manipulation to allow actual inference of causality (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson, Bruyns-Haylett, Jones, & Milne, 2015; Dickinson, Jones, & Milne, 2014; Shaw et al., 2019). In studies that do contain direct pharmacological manipulations of GABA in human subjects often produce changes in, for instance, peak gamma frequency in the opposite direction than would be hypothesized by the MRS work (Campbell, Sumner, Singh, & Muthukumaraswamy, 2014; Magazzini et al., 2016).

Evoked potentials are also thought to be indicative of E–I balance (Siper et al., 2016; Zemon et al., 1980), but no one has checked whether they correlate with the ODT. Furthermore, when ODT and peak gamma frequency have been used to assess E–I balance in clinical populations with autism spectrum conditions (ASC) (Dickinson, Bruyns-Haylett, et al., 2016), the change in these metrics has been in the opposite direction than would be expected in E–I balance theories (Hussman, 2001; Rubenstein & Merzenich, 2003). As such, the relationship between E–I balance, ODT, and EEG metrics requires further investigation. One way to investigate these issues is a low cost non-invasive neuromodulation tool, transcranial direct current stimulation (tDCS), which is known to modulate cortical E–I balance in human subjects (Krause et al., 2013; Stagg et al., 2009). As such, this thesis will investigate whether tDCS alters performance on the ODT (Chapter 2); whether tDCS alters EEG metrics (visually elicited gamma, and VEP amplitudes); (Chapter 3) and further investigate the relationships between visually induced peak

gamma, VEP amplitudes, and ODT. A further rationale for the studies involving tDCS in this thesis is that tDCS is often used in complex clinical conditions and cognitive paradigms and produces equivocal results (Berlim, Van den Eynde, & Daskalakis, 2013; Kuo, Paulus, & Nitsche, 2014; Mancuso, Ilieva, Hamilton, & Farah, 2016; Medina & Cason, 2017). This equivocation occurs in because the link between cortical E–I balance, on the one hand, and clinical outcomes or cognitive performance, on the other, is uncertain. Further investigations using tDCS in tasks that are clearly related to E–I balance, in some forms, can assist in confirming or refuting its efficacy.

What is Excitation-Inhibition Balance?

The term cortical Excitation-inhibition balance can be defined from different levels (He & Cline, 2019; Sohal & Rubenstein, 2019). For instance, it can be defined as the co-tuning of excitatory and inhibitory synaptic activities from the neuronal level. It also can be defined as the ratio of the excitatory and inhibitory activity within particular neural circuits at the global level. The ratio of excitation and inhibition for neuronal levels is highly regulated to maintain normal neural activity (Isaacson & Scanziani, 2011; Wu, Tao, & Zhang, 2011). For example, on individual excitatory neurons, the number of excitatory and inhibitory synapses is constantly regulated, maintaining a relatively invariant ratio of excitatory and inhibitory synapses throughout dendritic segments. The excitatory and inhibitory synaptic activities are highly coupled as the increase in the excitatory synaptic activity in response to; for example, a simple visual stimulation is coupled with an increase in the inhibitory synaptic activity (Isaacson & Scanziani, 2011; Wilent & Contreras, 2005). Such coupling between the excitatory and inhibitory activity also occurs even in the absence of explicit task (i.e., sensory and motor outputs) (Atallah & Scanziani, 2009; Hasenstaub et al., 2005). The main feature of the relationship between excitation and inhibition is that inhibition is balanced with excitation resulting in a relatively constant ratio of excitation and inhibition. Balanced inhibition plays important roles as it restricts the activity from spreading spatially and temporally, preventing excitotoxicity and epileptiform discharges (Tao, Li, & Zhang, 2014). Also, balanced inhibition plays a part in sharpening sensory neurons' tuning to

particular features of stimuli (i.e., orientation) (Anderson, Carandini, & Ferster, 2000; Monier, Chavane, Baudot, Graham, & Frégnac, 2003). Neural selectivity of simple and complex cortical cells to particular orientation is affected by the concentration of inhibitory transmitters. For instance, neural selectivity of simple and complex cortical cells to particular orientation increased following the application of GABA agonist (Leventhal, Wang, Pu, Zhou, & Ma, 2003; Li, Yang, Liang, Xia, & Zhou, 2008) and decreased following the application of GABA antagonist (Katzner, Busse, & Carandini, 2011; Sillito, 1975)

Similarly, the ratio of excitation inhibition is also highly regulated to maintain normal activity at the levels of neural circuits (He & Cline, 2019), which refers to a spatial scale of brain functional/anatomical organization consisting of a population of neurons that are highly interconnected with each others in comparison to their connections with neighboring circuits (Cohen, 2017). For instance, if the amount of excitation is greater than that of inhibition, there likely will be an increase in the activity until the neural circuit' maximum ability to generate activity is reached or until the neural activity's marginal increases start recruiting more inhibition relative to excitation which in turns results in a state of balance (Sohal & Rubenstein, 2019). Contrarily, if the amount of inhibition is greater than that of excitation, there likely will be a decrease in the activity until the neural circuit becomes quiescent or until the neural activity's marginal decrease in activity which in turns results in drops in inhibition that is greater than that of excitation, leading to the state of balanced ratio of excitation and inhibition (Sohal & Rubenstein, 2019).

Neural inhibition is generated by neurons releasing γ-aminobutyric acid (GABA), the main inhibitory transmitter (Isaacson & Scanziani, 2011). These neurons are approximately 20 percent of the population of the cortical neurons(Meinecke & Peters, 1987), and are known as local circuit interneurons because their influence is generally within a limited and local cortical region (Isaacson & Scanziani, 2011). In contrary to these inhibitory GABAergic interneurons, the excitatory cells form long range-projections. These cells release glutamate, the main excitatory transmitter. They are the most cells of the population of the cortical neurons. The most popular member of those excitatory cells is a pyramidal cell, which comprises about 60 percent of cortical cells' population (Abeles, 1991; Meinecke & Peters, 1987). The interaction between the excitatory glutamatergic

cells and inhibitory GABAergic interneurons are reciprocal as excitatory cells excite inhibitory interneuron and are inhibited by them (Isaacson & Scanziani, 2011).

Neural circuits with imbalanced ratio of excitation and inhibition (i.e., too noisy or too quiet neural circuits from very high level of excitation or very low-level of inhibition) could be detrimental (Sohal & Rubenstein, 2019), causing neurodevelopmental and neurological disorders such as autism spectrum conditions and schizophrenia (Rubenstein & Merzenich, 2003; Yizhar et al., 2011). An example of the neural circuits is the orientation-tuned columns in visual cortex of primates (Cohen, 2017), whose cells respond best to particular orientations (Hubel & Wiesel, 1968, 1974). The activity of neural circuits produces large-scale fluctuations of electrical brain activities measured by, for instance, EEG via electrodes placed over the scalp (Cohen, 2017). The most prominent feature of EEG is neural oscillations (i.e., gamma frequency oscillations) (Cohen, 2017). Neural oscillations at gamma frequency band (>30 Hz) have been suggested to result from the interactions between the excitatory postsynaptic potentials (EPSP) and inhibitory postsynaptic potentials (IPSP) of large populations of cortical neurons (Brunel & Wang, 2003; Börgers & Kopell, 2003). Such interactions between the EPSP and IPSP of cortical neurons have also been thought to produce visual evoked potentials (VEPs) (Purpura, 1959; Zemon, Kaplan, & Ratliff, 1980). Empirical studies implying and suggesting that neurological disorders may be linked to or resulted from disrupted E-I balance have used indirect indicators to infer E-I balance such as performance in perceptual tasks (i.e., orientation discrimination task [ODT]) (Dickinson, Bruyns-Haylett, et al., 2016; Shaw et al., 2019), and neurophysiological measures (i.e., induced peak gamma frequency) (Dickinson, Bruyns-Haylett, et al., 2016; Shaw et al., 2019). As such, this thesis investigated the links between cortical E-I balance and visual psychophysical and neurophysiological measures using transcranial direct current stimulation (tDCS).

Inferring Excitation–Inhibition from Visual Psychophysical and Neurophysiological Measures

The visual system

Visual psychophysical and neurophysiological measures have been shown to be associated with GABA concentrations in V1 (Edden et al., 2009; Hudnell & Boyes, 1991; Muthukumaraswamy et al., 2009; van Loon et al., 2013), the first cortical region responsible for visual information processing (Li & Gilbert, 2017). Visual information is transmitted to V1 from the retinas through the left and right lateral geniculate of the thalamus, through the optic nerve (Hubel, 1995). Each lateral geniculate nucleus has six layers, the inner two of which are known as magnocellular (M) layers, while the remaining outer four layers are known as parvocellular (P) layers. Between these principle layers are very thin layers known as koniocellular (K) layers (Hubel, 1995). Because of their thinness, K layers had been ignored until recently, as they were thought to have no substantial contribution to any cortical module (Martinovic, 2014). Cells in the M and P layers differ anatomically and physiologically (Liu et al., 2006). For instance, cells in the M layers are large, while cells in the P layers are small. Additionally, cells in the M layers are sensitive to stimuli with high contrast, low spatial frequencies, and high temporal frequencies, but are insensitive to colour in conditions with balanced luminance. On the other hand, cells in the P layers are sensitive to visual stimuli with colours, high spatial frequencies, and low temporal frequencies (Liu et al., 2006). Such relatively distinct functions of these layers led to the suggestion of the existence of specialized neural pathways (Breitmeyer & Ganz, 1976; Livingstone & Hubel, 1988).

The first pathway is the dorsal stream pathway, whose input is predominantly provided by M cells; this pathway leads to dorsolateral occipital and posterior parietal cortical regions (Culham, He, Dukelow, & Verstraten, 2001; Goodale & Westwood, 2004). The dorsal stream pathway is very responsive to motion and rapidly alternating stimuli. The second pathway is the ventral stream pathway, whose input is predominantly provided by the P

cells; this second pathway leads to occipito-temporal cortical regions. The ventral stream pathway is very responsive to attributes of stimulus such as colour, shape (Culham et al., 2001; Goodale & Westwood, 2004). The ventral pathway is also known as the "what" visual pathway, responsible for objects' perceptual identification and recognition. By contrast, the dorsal stream pathway is also known as the "where" visual pathway, responsible for processing visual information for action guidance (Goodale & Milner, 1992). The distinct division between the lateral geniculate pathways is also maintained in V1, which also has six layers (Martinovic, 2014; Wandell, 1995). Inputs from M cells are transmitted to a layer containing cells that are highly tuned to motion, while inputs from P cells are transmitted to layers containing cells that are highly tuned to colour and contrast information and spatial patterns (i.e., orientation) (Armstrong & Cubbidge, 2014; Hubel & Livingstone, 1990). For instance, simple and complex cells of the visual cortex are organized in functional columns based on their preferred orientations (Hubel & Wiesel, 1968, 1974). Cortical cells in each of the orientation columns respond best to visual stimuli with particular orientations. The orientation preference of such cells has been shown to be mediated by inhibitory mechanisms. For instance, pharmacological manipulations of GABA, the major inhibitory transmitter in the brain, have been shown to lead to robust changes in orientation selectivity, as application of GABA agonist increases neural selectivity of a particular orientation (Leventhal et al., 2003; Li et al., 2008; Xia et al., 2013) while application of GABA antagonist decreases it (Katzner et al., 2011; Sillito, 1975; Xia et al., 2013). In addition to orientation columns, there are ocular columns where cells in the visual cortex respond best to visual inputs from a particular eye (Hubel & Wiesel, 1968, 1974). The orientation and ocular columns are known as hypercolumns (Figure 1.1).

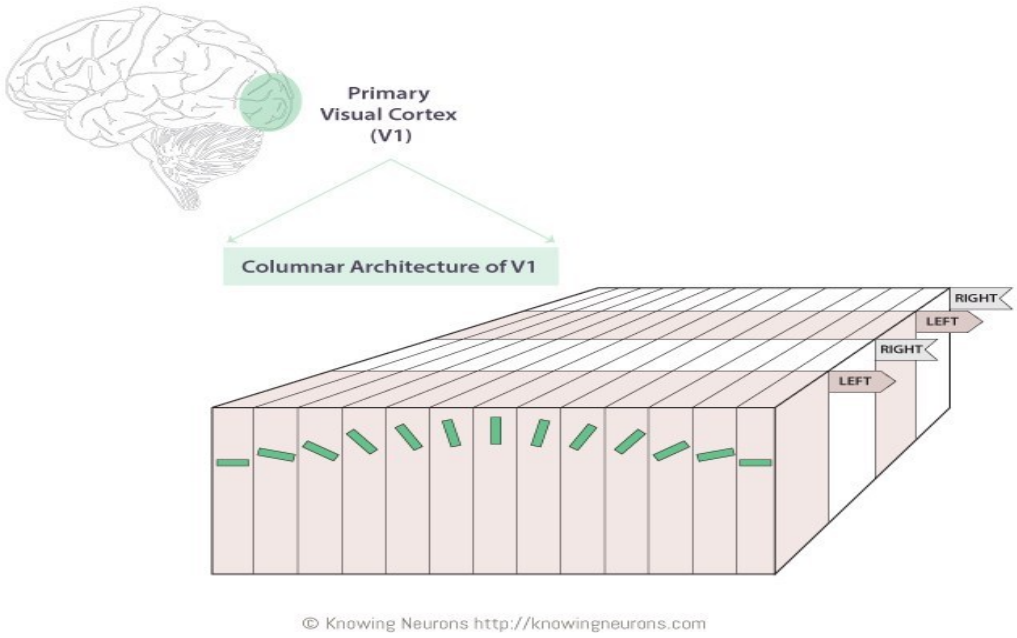


Figure 1.1. Illustration of the orientation and ocular columns in the primary visual cortex (V1). This figures is reprinted with permission from Fehlhaber (2014).

Inferring excitation–inhibition balance from psychophysical measures

Given the important role of inhibitory mechanisms in neural selectivity of stimulus features (i.e., colour, contrast, and orientation), performance in visual psychophysical tasks (i.e., binocular rivalry, surround suppression, and ODTs) that manipulate such stimulus features has been thought to be mediated by inhibitory mechanisms, which are suggested to indicate excitation–inhibition (E–I) balance (Blake, 1989; Edden et al., 2009; van Loon et al., 2013; Yoon et al., 2010; Yoon et al., 2009). Indeed, performance in these psychophysical tasks has been shown to be associated with the concentration level of GABA in the visual cortex of humans, as measured by MRS (Edden et al., 2009; van Loon et al., 2013; Yoon et al., 2010). For instance, a higher GABA concentration level in the visual cortex has been shown to be associated with slower perceptual dynamics, as indicated by perceptual switches and percept duration, which were measured by binocular rivalry task (van Loon et al., 2013). During the task, participants presented two visual

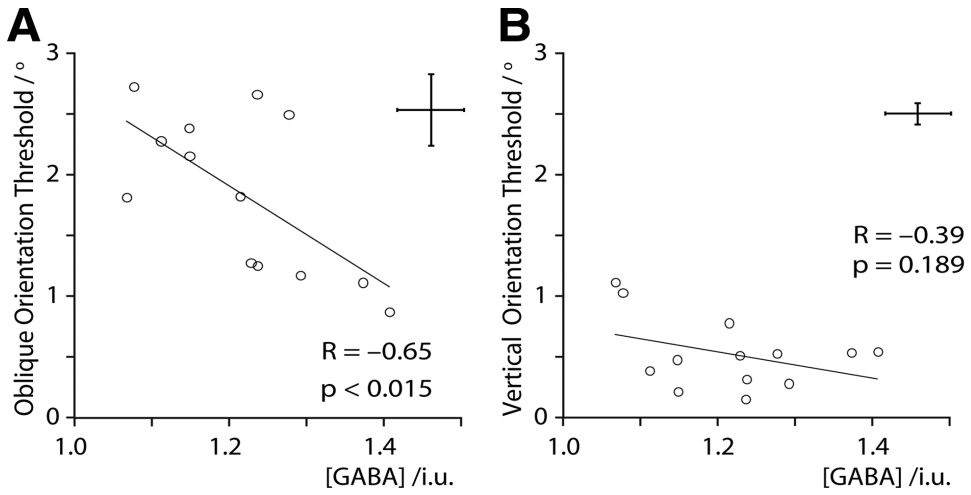
images simultaneously in a monocular manner (one image for each eye), leading to an alternating perception of these two images. The higher GABA concentration associated with slower perceptual dynamics as indicated by slower perceptual switches and longer percept duration. Similarly Yoon et al. (2010) found that GABA concentration level associated with orientation-specific surround suppression (OSSS). Surround suppression can be defined as a reduction in response to a visual stimulus driven by its surrounding stimulus. Such surround suppression is greater when the target and the surrounding stimuli share similar features, such as orientation. During the OSSS task, participants presented a target grating in a larger surrounding grating with the same or different orientation and asked participants to indicate whether there was a contrast difference between the target and the surrounding grating. Higher GABA concentration was found to be associated with greater OSSS (Yoon et al., 2010).

Orientation discrimination task

Performance in binocular rivalry and suppression tasks has been suggested to relate to cortical E–I balance; however, a task probably more strongly linked to cortical E–I balance is the visual orientation discrimination task (ODT) (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Dickinson et al., 2014; Edden et al., 2009; Shaw et al., 2019; Sysoeva et al., 2016). During the ODT, participants are visually presented with pairs of gratings in a sequence, and are instructed to judge whether the second grating has been rotated clockwise or anti-clockwise, compared to the first grating (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009). The ODT can have different orientation conditions based on the first grating orientation (cardinal = 0° or 90°, oblique = 45° or 135°). A series of "staircases" are used to estimate the lowest threshold in degrees that the individuals can reliably detect (Treutwein, 1995). The strong link between

ODT and E–I balance comes from studies using animal models and human subjects to investigate the role of GABA in neural selectivity of objects' orientations and orientation discriminability (Katzner et al., 2011; Kurcyus et al., 2018; Leventhal et al., 2003; Li et al., 2008; Sillito, 1975; Song, Sandberg, Andersen, Blicher, & Rees, 2017). Animal studies, for instance, have shown that neural selectivity of specific orientations depends on GABA concentration, as administering GABA agonist increases neural selectivity of specific orientations (Leventhal et al., 2003; Li et al., 2008), whereas administering GABA antagonist decreases it (Katzner et al., 2011; Sillito, 1975).

Consistent with the findings of animal studies, human studies have found an association between performance in the ODT and GABA concentration level in the primary visual cortex (Edden et al., 2009). The results show that a negative correlation between performance in vertical and oblique condition and the resting-state GABA concentration level in the primary visual cortex. However, the correlation with GABA concentration was only statistically significant for the oblique condition of the ODT. A higher GABA concentration level is significantly associated with better performance in the oblique condition of the ODT, as indicated by lower thresholds (in degrees) (Figure 1.2). A possible explanation for the lack of a significant association between GABA concentration level and performance in vertical condition of the ODT has been suggested to result from a ceiling effect (i.e., that is, the vertical condition is too easy, so that most study participants had very low thresholds limiting the detectability of any relationship between GABA concentration level and the performance in the vertical condition) (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2014; Edden et al., 2009).



Figures 1.2 A and B. Illustrations of the relationship between orientation thresholds in vertical and oblique conditions and a resting-state gamma-aminobutyric acid (GABA) concentration level in visual cortex. These figures are reprinted with permission from (Edden et al., 2009).

Indeed, it has long been known that performance on ODTs comprising cardinal (i.e., horizontal or vertical) stimuli is far easier than those with obliquely orientated stimuli (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2014; Tibber et al., 2006; Vogels & Orban, 1985). Orientation discrimination task thresholds are about fivefold lower for the vertical condition, as compared to the oblique condition (Dickinson et al., 2015; Dickinson et al., 2014; Edden et al., 2009). The robust ODT performance difference in vertical and oblique conditions reflects the oblique effect (Appelle, 1972). A likely explanation of this phenomenon is that more cortical cells in the visual cortex are tuned to cardinally oriented objects, as compared to obliquely oriented objects (Li, Peterson, & Freeman, 2003; Mansfield, 1974; Rose & Blakemore, 1974; Yu & Shou, 2000). Additionally, cardinally oriented objects also have been suggested to exhibit narrow neural tuning width compared to obliquely oriented objects (Li, et al., 2003; Nelson, Kato, & Bishop, 1977; Orban & Kennedy, 1981). The preference and selectivity of neurons for particular orientations have been shown to be associated with inhibition (Katzner et al.,

2011; Leventhal et al., 2003; Li et al., 2008; Sillito, 1975, 1979; Sillito, Kemp, Milson, & Berardi, 1980). Taken together, the findings from animal (Katzner et al., 2011; Li et al., 2008; Sillito, 1975) and human research (Edden et al., 2009; Kurcyus et al., 2018) suggests a strong link between level of inhibition (as indicated by GABA concentration level) and performance in the ODT.

Inferring excitation–inhibition balance from neurophysiological measures

Peak induced gamma frequency

Excitation–inhibition (E–I) balance in the cortex has also been thought to be associated with specific attributes of neural oscillations (Brunel & Wang, 2003; Mann & Paulsen, 2007). Neural oscillations are repetitive and rhythmic fluctuations in the neuroelectrical activity within the brain, resulting from the reciprocal interactions between excitatory and inhibitory neurons (Avella Gonzalez, 2014; Brunel, 2000; Brunel & Hakim, 1999; Whittington, Traub, Kopell, Ermentrout, & Buhl, 2000). These neural oscillations can be measured non-invasively by MEG and EEG (Uhlhaas, Roux, Rodriguez, Rotarska-Jagiela, & Singer, 2010; Ward, 2003). Neural oscillations are classified, based on their frequency, into five frequency bands: delta band (0.5–3.5 Hz), theta band (4–7 Hz), alpha band (8–12 Hz), beta band (13–30 Hz), and gamma band (>30 Hz) (Engel & Fries, 2010). Neural oscillations from different frequency bands reflect different generators and contribute to cognition in different ways (Başar, Başar-Eroglu, Karakaş, & Schürmann, 2001; Herrmann, Fründ, & Lenz, 2010; Joliot, Ribary, & Llinas, 1994; Neustadter, Mathiak, & Turetsky, 2016).

Arguably, neural oscillations in the gamma frequency are highly associated with cognitive processes such as attention, memory, and perception (Jensen, Kaiser, & Lachaux, 2007;

Magazzini & Singh, 2018; Tallon-Baudry, Bertrand, Peronnet, & Pernier, 1998). The generation of gamma frequency oscillations has been suggested to result from the interactions between the excitatory pyramidal and inhibitory GABAbergic neural population (Brunel, 2003; Börgers & Kopell, 2003), as increased inhibition leads to higher and faster gamma frequency oscillations (Brunel & Wang, 2003). In relation to the existence of an external stimulus, gamma frequency oscillations have been classified into three categories: evoked, induced, and spontaneous oscillations. Evoked gamma frequency oscillations are phase-locked to the onset of the stimulus while induced gamma frequency oscillations are non-phase-locked to the onset of the stimulus, but are related to the stimulus (Lee & Jones, 2013; Pantev, 1995; Tallon-Baudry & Bertrand, 1999). However, spontaneous gamma frequency oscillations occur in the absence of any external stimulation (Galambos, 1992; S Karakaş, Başar-Eroğlu, Özesmi, Kafadar, & Erzengin, 2001).

Gamma frequency oscillations have been shown to be associated with GABA concentration levels (Edden et al., 2009; Kujala et al., 2015; Muthukumaraswamy et al., 2009), functional magnetic resonance imaging (fMRI) blood-oxygen-level-dependent (BOLD) responses (Edden et al., 2009; Magri, Schridde, Murayama, Panzeri, & Logothetis, 2012; Muthukumaraswamy et al., 2009; Uji, Wilson, Francis, Mullinger, & Mayhew, 2018), and visual psychophysical task performance (Edden et al., 2009; Fesi & Mendola, 2015; Kurcyus et al., 2018). For example, an associational relationship between induced gamma frequency oscillations and the resting-state GABA concentration in the visual cortex has been shown in MRS studies (Edden et al., 2009; Kujala et al., 2015; Muthukumaraswamy et al., 2009), as peak gamma frequency is positively associated with higher GABA concentration level. However, such an association could not be replicated in the work of Cousijn et al. (2014), possibly be due to technical differences in methods of measuring GABA (i.e., type of MRS sequence) and differences in sample size (Cousijn et al., 2014; Kujala et al., 2015) (Figure 1.3, A and B). As such, the relationship between peak gamma frequency and GABA concentration requires further investigation. Furthermore, this relationship is correlational, having no option to allow inference of causality. Although peak gamma frequency has also been shown to be modulated by pharmacological manipulations of excitatory and inhibitory receptors (Campbell et al.,

2014; Lozano-Soldevilla, ter Huurne, Cools, & Jensen, 2014; Magazzini et al., 2016), the changes produced are in the opposite direction that would be expected from the MRS studies (Kujala et al., 2015; Muthukumaraswamy et al., 2009). For instance, administration tiagabine, a selective reuptake inhibitor of GABA, resulted in a reduction rather that an increase of peak gamma frequency (Magazzini et al., 2016). A similar pattern of the result was seen following the administration of alcohol (Campbell et al., 2014; Magazzini et al., 2016), which is thought to block excitatory N-methyl-d-aspartic acid (NMDA) receptor and enhance inhibitory GABA type A receptor (Grant & Lovinger, 1995; Valenzuela, 1997). Similarly, administration of Lorazepan (GABA agonist) was found to increase occipital gamma power and decrease visually induced gamma frequency (Lozano-Soldevilla et al., 2014). As such, more investigations are required to evaluate the casual relationships between these variable.

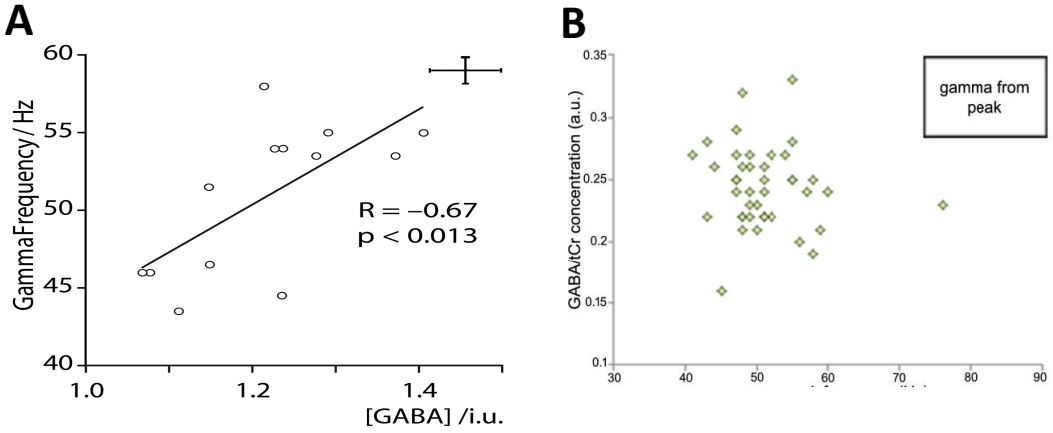


Figure 1.3 A and B. Illustrations of the inconsistent findings regarding the relationship between gamma-aminobutyric acid (GABA) and peak gamma frequency. A) The figure illustrates the correlational relationship between GABA and peak gamma frequency, ($p < .05$). This figure is reprinted with permission from (Edden et al., 2009). B). The figure illustrates the correlational relationship between GABA and peak gamma frequency, ($p > .05$). This figure is reprinted with permission from (Cousijn et al., 2014).

In addition, further indirect evidence has linked peak gamma frequency to GABA concentration. For instance, peak gamma frequency has been shown to negatively correlate with BOLD responses to a simple visual stimulus measured by fMRI in the visual cortex (Muthukumaraswamy et al., 2009), which is inversely associated with GABA concentration (Donahue, Near, Blicher, & Jezzard, 2010; Muthukumaraswamy et al., 2009). Additionally, peak gamma frequency has been shown to relate to ODT performance, as higher peak gamma frequency correlates with enhanced ODT performance (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009). The association between peak gamma frequency oscillations and ODT performance is condition specific. Similar to the correlation to GABA concentration, only increased performance in the oblique condition of the ODT highly correlates with higher peak gamma frequency (Figure 1.4 A and B). The insignificant correlation between performance in the vertical condition and peak induced gamma oscillations was due to a "ceiling effect," caused by the low difficulty of the vertical condition task, reflected in lower thresholds (in degrees) in majority of subjects (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009). Thus, although peak gamma frequency may be a useful indirect indicator of cortical E–I balance (Dickinson, Jones, & Milne, 2016), some of the supporting evidence is equivocal, particularly as to whether increasing peak gamma frequency reflects increased or decreased inhibition. Thus, further investigation is required.

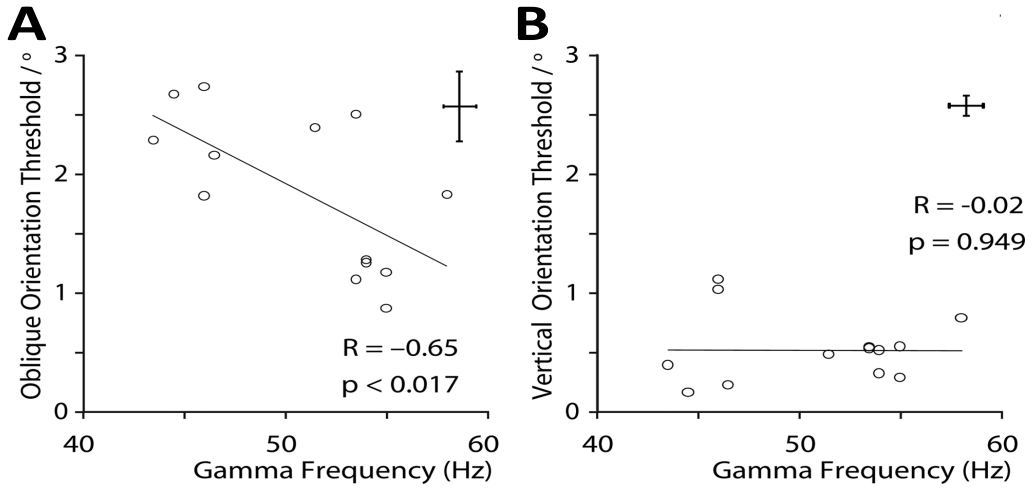


Figure 1.4 A and B. illustration of the relationship between orientation thresholds in vertical and oblique condition and peak gamma frequency. The figure is reprinted with permission from (Edden et al., 2009).

Visual evoked potential

The amplitude and phase of EEG oscillations are altered by stimulus presentation and can be observed by analysing data in the time frequency domain. However, simply averaging the time series of EEG data results in characteristic responses for evoked potentials. Visual evoked potentials (VEPs) are electrical brain activities in response to a visual stimulus. They can be non-invasively recorded at the scalp over the occipital cortex by EEG (Creel, 2016). Visual evoked potential comprises waveforms of negative and positive polarity. The negative waveform is denoted as N, while the wave positive form is donated as P. Each waveform is followed by an approximate latency in milliseconds (Pal, 2001). Similar to gamma frequency oscillations, VEPs have been suggested to reflect the summation of the excitatory postsynaptic potentials (EPSP) and inhibitory postsynaptic potentials (IPSP) of cortical cells (Purpura, 1959; Zemon et al., 1980). Additionally, VEPs have been used to indicate the E–I balance of the cortex (Ding et al., 2016; Nguyen, McKendrick, & Vingrys, 2016; Siper et al., 2016; Zemon et al., 1980; Zeneroli et al., 1981). For instance, atypically higher or smaller amplitudes of VEP have been suggested to reflect disrupted E–I balance (Declerck, Oei, Arnoldussen, & te Dorsthorst, 1985; Ding et al., 2016; Nguyen et al., 2016).

Early components of VEP (i.e., N1, P1, P2) have been shown to relate to GABA concentration in animal models and human subjects (Daniels & Pettigrew, 1975; Declerck et al., 1985; Kennard, Gawel, Rudolph, & Rose, 1978; Kraut, Arezzo, & Vaughan Jr, 1990; Kulikowski, McGlone, Kranda, & Ott, 1984; Pappas, Ferenci, Schafer, & Jones, 1984; Rockstroh, Elbert, Lutzenberger, & Altenmüller, 1991; Schafer, Pappas, Brody, Jacobs, & Jones, 1984; Zemon et al., 1980; Zemon, Kaplan, & Ratliff, 1986; Zemon, Victor, &

Ratliff, 1986; Zeneroli et al., 1981). For instance, application of GABA agonist has been found to decrease amplitudes of N1 and P1 and to increase P2 amplitude in rats (Zeneroli et al., 1981), while application of GABA antagonist has been found to increase the amplitude of N1, reduce the amplitude of P2, and not change the amplitude of P1 in cats (Zemon et al., 1980). Additionally, administration of GABA agonist increased the amplitude of P1 compared to placebo treatment for healthy humans (Rockstroh et al., 1991). Although these findings support the suggested link between E–I balance and VEP amplitude (Gawel, Connolly, & Rose, 1983; Kennard et al., 1978). Hammond and Wilder (1985) observed no robust changes in the VEP of human subjects related to the pharmacological administration of GABA agonist. Given the inconsistent findings regarding the relationship between GABA activity and VEP amplitudes, further investigation is required to assess the causal relationship between these variables.

Transcranial Direct Current Stimulation

What is transcranial direct current stimulation?

As the aim of this thesis was to investigate the links between between E-I balance and psychophysical and neurophysiological measures, a method for modulating E-I balance was required. As such transcranial electrical stimulation (tES) techniques such as transcranial alternating current stimulation (tACS) and transcranial direct current stimulation (tDCS) could be good tools to examine such relationships. For instance, tACS has been shown to modulate cognitive processes (i.e., attention and perception) (Laczó, Antal, Niebergall, Treue, & Paulus, 2012; Schuhmann et al., 2019) and neural activity (i.e., oscillatory activity in gamma band (Herring, Esterer, Marshall, Jensen, & Bergmann, 2019; Khatoun, Asamoah, & Mc Laughlin, 2017), possibly via modulating cortical

excitability (Chaieb, Antal, & Paulus, 2011; Fresnoza et al., 2018). Similarly, tDCS has also been shown to modulate cognitive process (Antal, Nitsche, et al., 2004; Antal, Nitsche, & Paulus, 2001; Reinhart, Xiao, McClenahan, & Woodman, 2016) and neural activity (Antal et al., 2004; Antal, Varga, Kincses, Nitsche, & Paulus, 2004; Nitsche & Paulus, 2001; Wilson, McDermott, Mills, Coolidge, & Heinrichs-Graham, 2017), possibility via inducing changes in the activity of excitatory and inhibitory neurotransmitters (Krause et al., 2013; Stagg et al., 2009). As empirical evidence linking effects of transcranial electrical stimulation (tES) to cortical excitability modulations seems larger in tDCS literature compared to tACS literature (Antal et al., 2004; Antal, Varga, et al., 2004; Bachtiar et al., 2018; Krause et al., 2013; Nitsche et al., 2004; Nitsche, Nitsche, et al., 2003; Nitsche & Paulus, 2000; Stagg et al., 2009), tDCS seemed an ideal to tool to fulfil the thesis's aim of investigating the links between between E-I balance and psychophysical and neurophysiological measures. tDCS is a non-invasive, tolerable, safe, and low-cost. It passes constant current to the scalp via a pair of electrodes resulting in modulation the cortical excitability of the stimulated brain region (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016; Nitsche, Liebetanz, et al., 2003). Anodal-tDCS increases cortical excitability (Nitsche & Paulus, 2000) while cathodal-tDCS increases cortical inhibition (Nitsche, Nitsche, et al., 2003). tDCS has been shown to be a safe technique for brain stimulation when applied over the human scalp up to 20 minutes with an intensity up to 2 mA (Iyer et al., 2005; Nitsche et al., 2008; Nitsche, Liebetanz, et al., 2003). Although no indications of severe side effects of tDCS have been reported (Arul-Anandam, Loo, & Sachdev, 2009), possible side effects of tDCS (i.e., itching sensation, headache, fatigue, nausea, and redness under the tDCS electrodes) have been reported (Brunoni et al., 2011; Matsumoto & Ugawa, 2017; Poreisz, Boros, Antal, & Paulus, 2007)

Transcranial direct current stimulation has two modes: active and sham mode. In the active mode of tDCS, the current is delivered for the duration of the stimulation. However, in the sham mode, current is delivered only for a short period (i.e., 30 s) at the beginning of the stimulation duration (i.e., 10 min), mimicking the sensation of the active mode in order to blind participants to the type of stimulation they receive (Gandiga, Hummel, & Cohen, 2006; Palm et al., 2013). Sham-tDCS has been shown to induce no changes in cortical

excitability (Nitsche et al., 2008; Siebner et al., 2004) and is used to control for stimulation and possible placebo effects (Filmer, Dux, & Mattingley, 2014; Greinacher, Buhôt, Möller, & Learmonth, 2018). Although sham- tDCS has proven a successful tool for blinding participants about the type of stimulation (i.e., active or sham) they received (Dinn et al., 2017; Gandiga et al., 2006; Palm et al., 2013; Russo, Wallace, Fitzgerald, & Cooper, 2013), it is useful to check the blinding effectiveness of sham-tDCS on participants' perceptions of stimulation to better understand the outcomes of the stimulation, given the findings of recent studies suggesting that sham-tDCS may not be a sufficient method to blind participants about the stimulation type (Kessler, Turkeltaub, Benson, & Hamilton, 2012; Turi et al., 2019). Thus, to evaluate the extent to which participants' experiences or perceptions of sham-tDCS would differ from that of active-tDCS, participants of all the tDCS experiments in this thesis were requested to complete questionnaires to record post-stimulation ratings (Galea, Jayaram, Ajagbe, & Celnik, 2009) and tDCS adverse effects (Brunoni et al., 2011) at the end of each tDCS session (Chapters 2 and 3).

Effects of transcranial direct current stimulation on neurophysiology

Spontaneous neural activity

Although transcranial direct current stimulation (tDCS) does not produce action potentials in the stimulated cortical regions, per se, as current intensity of or below 2 mA/cm has been suggested to be well below the cortical neurons' action potential thresholds (Tehovnik, 1996; Wagner et al., 2007), tDCS has been suggested to modulate spontaneous neural activity, based on findings of animal and human studies (Bindman, Lippold, & Redfearn, 1964; Callan, Falcone, Wada, & Parasuraman, 2016; McDermott et al., 2019; Pellegrino et al., 2018; Purpura & McMurtry, 1965; Saiote, Turi, Paulus, & Antal, 2013; Wiesman et al., 2018). For instance, animal studies using intercellular recordings showed

that the firing rate of spontaneous neural activity increased following the application of positive (anodal) stimulation and decreased following the application of negative (cathodal) stimulation (Bindman et al., 1964; Purpura & McMurtry, 1965). Additionally, stimulation-induced changes in spontaneous neural activity have been found to last up to five hours following 5–10 min of stimulation (Bindman et al., 1964). Similarly, human studies using different neuroimaging techniques, such as fMRI and MEG, have found that tDCS modulates spontaneous neural activity during and following tDCS (Callan et al., 2016; Pellegrino et al., 2018; Wiesman et al., 2018).

Non-synaptic mechanism

The effects of tDCS have been suggested to depend on changes in the membrane excitability of neurons (Nitsche & Paulus, 2000). Evidence to support this conclusion comes from findings in animal and human research (Bikson et al., 2004; Chan, Hounsgaard, & Nicholson, 1988; Creutzfeldt, Fromm, & Kapp, 1962; Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche et al., 2003). For instance, animal studies showed that anodal stimulation caused membrane depolarisation while cathodal stimulation with similar intensity and duration caused the opposite effects (membrane hyperpolarisation) (Purpura & McMurtry, 1965). Similarly, human research found a dependency of tDCS effects on the membrane potentials of pre- and post-synaptic neurons (Liebetanz et al., 2002; Nitsche et al., 2003; Nitsche & Paulus, 2000). For instance, pharmacological manipulations of sodium and calcium channels led to the elimination of enhanced excitability induced on motor cortex during and after anodal-tDCS (Nitsche et al., 2003). However, this effect seems to be polarity-dependent, as no effect of such pharmacological manipulations was observed on cortical excitability changes during and following cathodal-tDCS (Nitsche et al., 2003). Additionally, the elimination of the anodal-tDCS

effect, possibly due to the lack of membrane depolarization following the application of sodium-channel blocker (carbamazepine), supports the dependency of tDCS effects on the resting membrane potentials (Liebetanz et al., 2002; Nitsche et al., 2005).

Additional support for the non-synaptic mechanism of tDCS comes from the work of Nitsche & Paulus (2000), who found that application of tDCS over the motor cortex induced tDCS polarity-dependent effects on the size of transcranial magnetic stimulation (TMS)-elicited motor evoked potentials (MEP), which was recorded from human participants' peripheral muscles. Anodal-tDCS increased the size of MEP, whereas cathodal-tDCS decreased it (Nitsche & Paulus, 2000). Although this finding suggests a non-synaptic mechanism of tDCS, it could not rule out the possibility that the synaptic mechanism could contribute to the tDCS effects, as TMS could stimulate both cortico-cortical and corticospinal circuits. However, the findings of (Ardolino, Bossi, Barbieri, & Priori, 2005) using transcutaneous electrical stimulation (TES) showed that cathodal stimulation over the ulnar nerve at the wrist induced significant changes in axonal excitability, supporting the contribution of the non-synaptic mechanism of tDCS to the observed effects of tDCS.

Synaptic mechanisms

Although there is evidence for non-synaptic mechanisms, one of the main ways in which tDCS is thought to exert its effects on cognition is by modulating concentrations of intracortical neurotransmitters (Krause et al., 2013; Nitsche et al., 2003; Roche, Geiger, & Bussel, 2015; Stagg et al., 2009). For instance, Stagg et al. (2009) investigated the modulation of intracortical neurotransmitter concentrations following 10 min unilateral tDCS with an intensity of 1 mA using MRS, which allows quantification of the levels of transmitters non-invasively. The result revealed a polarity-dependent effect of tDCS in

modulating the neurotransmitter concentrations. Anodal-tDCS resulted in a robust reduction in GABA concentration compared to sham-DCS, with no significant changes in the concentration level of glutamate. In contrast, cathodal-tDCS resulted in robust reduction in concentrations of both GABA and glutamate, compared to sham-tDCS. These findings led to the suggestion that the excitatory effect of anodal-tDCS might be partially mediated by the inhibitory transmitter GABA, while the inhibitory effect of cathodal-tDCS might be partially mediated by the excitatory transmitter glutamate. Consistently, using similar tDCS montage and parameters (unilateral tDCS over M1 for 10 min with an intensity of 1 mA), Bachtiar et al. (2018) found that anodal-tDCS led to a reduction in GABA concentration levels in both the stimulated and unstimulated M1, while cathodal-tDCS led to a reduction in GABA levels only in the unstimulated M1. However, using higher intensity (1.5 mA) with longer duration (15 min), Kim, Stephenson, Morris, and Jackson (2014) replicated the previous findings of a reduced GABA concentration levels in the motor cortex following anodal-tDCS (Stagg et al., 2009), but with no robust changes following cathodal-tDCS. Such a discrepancy has been suggested to stem from differences in tDCS parameters (i.e., duration and intensity), given the non-linear relationship between effects of tDCS and its parameters, as increasing the duration or the current intensity of the stimulation may lead to inverse effects of tDCS (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013; Monte-Silva et al., 2013).

Additionally, concentration levels of intracortical neurotransmitters have also been suggested to play a crucial role in the efficacy of tDCS. For instance, the application of the GABA agonist lorazepam modulates tDCS-induced cortical excitability changes (Nitsche et al., 2004). Typically enhanced excitability of the motor cortex following anodal-tDCS was delayed after the application of GABA agonist. However, no such effect of pharmacological manipulation of GABA was observed on the aftereffects of cathodal-tDCS (Nitsche et al., 2004). Additionally, administration of NMDA antagonist was shown to suppress the aftereffects of both anodal and cathodal-tDCS, reflecting the important role of the activity of the excitatory NMDA receptor in tDCS-induced aftereffects (Liebetanz et al., 2002; Nitsche et al., 2003). Thus, despite equivocal findings regarding the relationship between tDCS effects and the activity of the excitatory and inhibitory receptors, there is a

general consensus in the literature that anodal-tDCS is excitatory while cathodal-tDCS is inhibitory (Nitsche & Paulus, 2000), and the aftereffect of tDCS depends on glutamate and GABA, the major excitatory and inhibitory transmitters (Stagg & Nitsche, 2011).

Effects of transcranial direct current stimulation in modulating perceptual outcomes

Performance in perceptual tasks has been shown to be modulated by motor transcranial direct current stimulation (tDCS) (Kang & Paik, 2011; Molero-Chamizo et al., 2018; Nitsche & Paulus, 2000), auditory tDCS (Ladeira et al., 2011; Mathys, Loui, Zheng, & Schlaug, 2010; Mori et al., 2016; Tang & Hammond, 2013), and somatosensory tDCS (Fujimoto et al., 2016; Fujimoto, Yamaguchi, Otaka, Kondo, & Tanaka, 2014; Ragert, Vandermeeren, Camus, & Cohen, 2008). For instance, tDCS over the motor cortex has been found to modulate the reaction time of a go/no-go simple task, as anodal-tDCS robustly reduced performance reaction time compared to sham-tDCS (Molero-Chamizo et al., 2018). Additionally, Kang and Paik (2011) found that anodal-tDCS over the motor cortex robustly improves implicit motor learning sequence. Also, anodal-tDCS over the auditory cortex has been found to reduce frequency discrimination compared to sham-tDCS (Tang & Hammond, 2013), while cathodal-tDCS over the primary auditory cortex (HG) enhanced performance in pitch discrimination compared to sham-tDCS (Mathys et al., 2010). Furthermore, anodal-tDCS over the auditory cortex enhances the detectability of temporal gaps between pairs of tones, whereas cathodal-tDCS reduced it compared to baseline performance (Ladeira et al., 2011). Similarly, somatosensory tDCS has been found to modulate tactile perception, as performance in tactile grating orientation discrimination increased following anodal-tDCS in the absence of such performance improvement for sham-tDCS (Ragert et al., 2008). Similarly, performance in tactile spatial

discrimination has been found to be significantly enhanced following somatosensory anodal-tDCS (Fujimoto et al., 2014)

Effects of occipital transcranial direct current stimulation on perceptual outcomes

In addition to motor, auditory, and somatosensory cortex, the effects of tDCS over the occipital cortex on perceptual outcomes have been investigated (Behrens et al., 2017; Costa et al., 2015; Ding et al., 2016; Kraft et al., 2010; Spiegel, Hansen, Byblow, & Thompson, 2012; Yoon et al., 2010), with inconsistent results. For instance, contrast sensitivity was found to increase following occipital anodal-tDCS and decrease following occipital cathodal-tDCS (Behrens et al., 2017; Ding et al., 2016). Moreover, a robust decrease in dynamic and static contrast sensitivity has been found during and directly following 7 min of occipital cathodal-tDCS. However, no effects of occipital tDCS on both static and dynamic conditions of the contrast sensitivity were observed during and directly following anodal-tDCS (Antal et al., 2001). Additionally, Peters, Thompson, Merabet, Wu, and Shams (2013) found no significant modulation of contrast sensitivity during the application of anodal- and cathodal-tDCS over the occipital cortex of healthy subjects. The discrepancy between findings of previous studies regarding effects of occipital tDCS on contrast sensitivity performance might stem from methodological differences (i.e., current intensity) that could lead to reversed polarity effects (Batsikadze et al., 2013). For instance, while Ding et al. (2016) used 2 mA tDCS for 20 min, Peters et al. (2013) used 1 mA tDCS over the same duration.

Additionally, occipital tDCS was shown to modulate the psychophysically measured surround suppression in a polarity-dependent manner (Spiegel et al., 2012). Anodal-tDCS induced observed changes in surround suppression (i.e., reduction in the surround suppression), whereas cathodal-tDCS had no robust effect (Spiegel et al., 2012). The

reduction in surround suppression following anodal-tDCS has been suggested to indicate a decrease in the concentration levels of GABA in the visual cortex, given the positive correlation between the surround suppression and GABA concentration levels (Yoon et al., 2010). Additionally, tDCS over the visual cortex has been found to influence the sensitivity of human participants to the orientations of line stimuli. During that experiment, participants were presented with consecutive pairs of lines and were asked to judge whether the second line had been tilted clockwise or counter-clockwise, as compared to the first one, which had a fixed orientation (45° or 135°). The angular differences between the first and second line were also fixed (±1.10°, 1.21°, 1.33°, and 1.46°), and auditory feedback was provided following each response. The result showed that better task performance was observed for participants who received offline anodal-tDCS (in which stimulation was applied before the task) compared to the performance of those who received either online anodal-tDCS (in which stimulation is applied during the task) or sham-tDCS. Similarly, tDCS was also reported to modulate performance in a vernier acuity task (VAT) (Reinhart et al., 2016). During the task, participants were instructed to attend to a fixation presented on the centre of a monitor while pairs of line segments were peripherally presented. The accuracy of the line position judgments was higher for participants who received anodal-tDCS compared to that of participants who received sham-tDCS. Additionally, an opposite effect was found for cathodal-tDCS, as the accuracy of the line position judgments was lower for participants who received cathodal-tDCS compared to that of participants who received sham-tDCS (Reinhart et al., 2016). However, despite the findings of tDCS effects on the performance of visual perception tasks, investigating tDCS effects on the performance of a simple task with a clear link to cortical E–I balance has not been investigated. Thus, one aim of the thesis is to investigate whether tDCS effects could lead to observable manipulations to performance in the ODT, which has been shown to be associated with resting-state GABA concentrations level in the visual cortex (Edden et al., 2009).

Effects of transcranial direct current stimulation in modulating neurophysiological outcomes

Effects of transcranial direct current stimulation on visual gamma frequency oscillations

In light of the suggested links between E–I balance and neural oscillations, several MEG studies have causally investigated such links using transcranial direct current stimulation (tDCS) (Hanley, Singh, & McGonigle, 2016; Marshall, Esterer, Herring, Bergmann, & Jensen, 2016; Wiesman et al., 2018; Wilson et al., 2017). For instance, Wilson et al. (2017) found that occipital anodal-tDCS, compared to sham-tDCS, led to a robust increase in the amplitude of visually elicited gamma frequency responses and the baseline of alpha frequency oscillations, with no significant changes in peak gamma frequency. Additionally Wiesman et al. (2018) showed that occipital tDCS could modulate spontaneously induced neural oscillations in alpha and gamma bands as anodal increased spontaneous alpha frequency activity, whereas cathodal-tDCS decreased spontaneous gamma frequency activity with no such effects of tDCS on visually induced alpha and gamma responses. However, Marshall et al. (2016) found no robust effects of occipital tDCS in modulating visually induced neural oscillations in alpha and gamma bands. Additionally, (Hanley et al., 2016) found no significant modulations of occipital tDCS on visual gamma frequency. The inconsistent findings of these studies investigating tDCS effects on neural oscillations could stem from methodological differences (i.e., tDCS protocol and montage). For instance, both Wilson et al. (2017) and Wiesman et al. (2018) investigated the effects of offline tDCS effect on neural frequency activity, whereas Hanley et al. (2016) investigated the effects of online tDCS on neural frequency activity. Additionally, Wilson et al. (2017) and Wiesman et al. (2018) used tDCS with an intensity of 2 mA for 20 min, whereas Hanley et al. (2016) used tDCS with an intensity of 1 mA for 10 min. Furthermore, while Wilson et al. (2017) and Wiesman et al. (2018) used a monopolar tDCS montage (Oz, right frontal cortex), Hanley et al. (2016) used a bipolar montage (Oz, Cz). Such differences may explain the inconsistent findings regarding tDCS effects on neural activity (Nitsche et al., 2008; Thair, Holloway, Newport, & Smith, 2017; Wilson et al., 2017). Indeed, most of

the MRS studies finding effects of tDCS on the excitatory and inhibitory transmitters used a monopolar montage with a varying intensity (1–2 mA) and duration (10–20 min). Given the inconsistent findings of tDCS studies regarding the causal relationship between E–I balance and neural oscillation, further studies are needed, especially to investigate the causal link between modulations of GABA concentration and visual peak gamma frequency. Despite several investigations of the effects of tDCS on neural oscillations, only one MEG study, as far as I am aware, has investigated whether tDCS could modulate peak gamma frequency, and this study did not include cathodal-tDCS as a target electrode (Wilson et al., 2017). As such, one aim of the current thesis was to investigate the effects of anodal and cathodal-tDCS effects on visually induced peak gamma frequency.

Effects of transcranial direct current stimulation on visual evoked potential amplitudes

Previous studies have shown that transcranial direct current stimulation (tDCS) could modulate evoked neural activity in different brain regions such as motor (Bastani & Jaberzadeh, 2012; Nitsche, Nitsche, et al., 2003; Nitsche & Paulus, 2000, 2001; Nitsche et al., 2005) and somatosensory (Dieckhöfer et al., 2006; Kirimoto et al., 2011; Matsunaga, Nitsche, Tsuji, & Rothwell, 2004; Tokimura et al., 2000). For instance, Nitsche & Paulus (2000) examined the effects of tDCS on the TMS elected MEPs. Nitsche & Paulus (2000) found that MEP amplitudes increased following anodal-tDCS and decreased following cathodal-tDCS. Similarly, anodal-tDCS over the somatosensory cortex was found to increase components of somatosensory evoked potentials (SEPs) (i.e., P25/N33) (Matsunaga et al., 2004), while cathodal-tDCS decreased the amplitudes of SEP components (i.e., N20) (Dieckhöfer et al., 2006).

Effects similar to those of tDCS on the motor and somatosensory cortex have also been observed on occipital cortex, indexed by changes in VEP activity (Accornero, Voti, La

Riccia, & Gregori, 2007; Antal et al., 2004; Ding et al., 2016; Reinhart et al., 2016). For instance, administration of anodal-tDCS over occipital cortex increases VEP amplitude whereas administration of cathodal-DCS over occipital cortex decreases it (Ding et al., 2016). Similarly, occipital tDCS was reported to modulate the amplitude of TMS elicited VEP-N70 component in a polarity demented manner, as anodal-DCS increased the amplitude of VEP-N70 component while cathodal-tDCS decreased it (Antal et al., 2004). However, no such polarity-dependent effect of tDCS was observed on the VEP-P100 component. Only robust changes in the amplitude of VEP-P100 were observed following cathodal-tDCS reflected in a significant increase of the VEP-P100 amplitude (Antal et al., 2004). Inconsistent with this, Reinhart et al. (2016) found that anodal-tDCS increased the amplitudes of N1 and P1, whereas cathodal-tDCS only reduced the amplitude of N1, with no observed effects on P1 amplitudes. Moreover, Accornero et al. (2007) found a polarity-dependent effect of tDCS on VEP-P100, elicited by low- and high-contrast checkerboard stimuli, as the amplitude of P100 decreased during anodal-tDCS but increased during cathodal-tDCS. The discrepancy between the findings of previous studies investigating occipital tDCS's effect on VEP amplitudes might result from differences in tDCS protocols or experimental paradigms (Antal, Varga, et al., 2004; Batsikadze et al., 2013; Thair et al., 2017). For instance, while Antal et al. (2004) used bipolar tDCS montages, Accornero et al. (2007) used a monopolar tDCS montage. Additionally, Antal et al. (2004) used striped pattern visual stimuli, whereas Accornero et al. (2007) used standard pattern-reversal checkerboard stimuli. Despite the equivocal and inconsistent results of tDCS studies on VEP activity, the effects of tDCS on VEP components (i.e. P2) with putative links to E–I balance have remained uninvestigated. Thus, one of the main aims of the current thesis is to investigate the effects of tDCS on VEP components associated with E–I balance (i.e., N1 and P2) in order to further the understanding of the relationship between E–I balance and the evoked neurophysiological activity.

Transcranial direct current stimulation protocol and montage

As inconsistent results of tDCS effects have often been attributed to differences in tDCS protocol and montage, the efficacy of tDCS has been suggested to depend on tDCS protocol and montage (Nitsche et al., 2008; Woods et al., 2016). Indeed, using different tDCS protocols (i.e., electrode size, stimulation intensity) and montages (i.e., electrodes placement) has been found to lead to different results (Antal et al., 2004; Bastani & Jaberzadeh, 2013; Batsikadze et al., 2013; Ho et al., 2016; Leite et al., 2018), possibly undermining the reproducibility of tDCS studies' findings (Bikson et al., 2018; Nitsche et al., 2008). The important roles of tDCS protocols (i.e., electrode size, duration and current intensity of tDCS) and montages (electrodes' positions and placement) are considered in the following sections.

Electrode size

The size of tDCS electrodes has been suggested to play an important role in the focality of tDCS (Bastani & Jaberzadeh, 2013; Ho et al., 2016; Kirimoto et al., 2011; Nitsche et al., 2007). For instance, reducing the electrode size has been shown to increase stimulation focality and efficacy, while increasing the electrode size led to the opposite effects (Bastani & Jaberzadeh, 2013; Nitsche et al., 2007). The electrode size effect was reflected on changes in cortical excitability as well as corticospinal excitability. For instance, stimulating motor cortex with a small-sized electrode was shown to result in spatially more restricted tDCS-related effects compared to the effects of a larger-sized electrode (Nitsche et al., 2007). Kirimoto et al. (2011) have shown that a 16 cm^2-sized tDCS electrode produces robust changes on components of MEP and SEP, while a 9-cm^2 sized tDCS

electrode produces no observable effects on the components of either MEP or SEP, possibly because of stimulation of a small portion of the cortical region of interest. Furthermore, increasing the electrode size could result in inefficient cortical changes related to the stimulation. As such, a larger reference electrode could be used to avoid or reduce the effects of stimulating another region (Nitsche et al., 2007). For instance, increasing the electrode size from 35 cm^2 to 100 cm^2 resulted in the disappearance of the stimulation effect. Electrode size can also affect current flow, as small-sized electrodes (i.e., 1 × 1 cm) have been shown to be associated with the so-called shunting effect (Wagner et al., 2007), which refers to reduction in the concentration of current that reaches the targeted brain regions due to current's dissipation across the scalp (Thair et al., 2017). Thus, in this thesis, the sizes of the active (5 × 5 cm) and reference electrodes (5 × 7 cm) were chosen in accordance with the conventional electrode size for tDCS (Nitsche et al., 2008; Thair et al., 2017), which has been used previously (Aytemür, Almeida, & Lee, 2017; Molero-Chamizo et al., 2018).

Electrode montage

The efficacy of tDCS has been suggested to depend on the correct placement and position of the electrodes (Antal et al., 2004; Leite et al., 2018; Nitsche & Paulus, 2000; Woods et al., 2016). Studies investigating the effects of tDCS on the motor and visual cortex have shown the importance of tDCS montage for achieving the desired effect of tDCS (Antal et al., 2004; Nitsche & Paulus, 2000). For instance, comparing to the effects of several occipital tDCS montages (i.e., Oz–Cz, LO1–RO2, Oz–LM montages) in modulating cortical excitability in the visual cortex, Antal et al. (2004) found that a montage of Oz–Cz was effective to significantly modulate the cortical excitability in the visual cortex. This finding supports the suggested dependency of tDCS efficacy on the direction of the current flow, as previously observed in the motor cortex (Nitsche & Paulus, 2000). However,

although placing the target and reference electrodes over the scalp has been recommended as an effective type of tDCS montage for modulating cortical excitability in motor and visual cortex, such montages could cause unwanted effects due to stimulating additional cortical regions by the reference electrode (Hsu et al., 2011; Reinhart & Woodman, 2014). Indeed, a previous study found an effect of the reference electrode in addition to the effect of the target electrode (Nitsche et al., 2007). While the target electrode, placed over the motor cortex, induced changes in cortical excitability, the reference electrode induced changes in performance of implicit learning task when placed over the frontal cortex—depending on the electrode size of the reference, as this reference that induced changes in performance was observed with a 35-cm^2 electrode rather than a 100-cm^2-electrode, which did not differ from sham stimulation (Nitsche et al., 2007). Thus, to avoid any potential effects of modulating additional brain regions, monopolar montages have been increasingly used (Aytemür et al., 2017; Hsu et al., 2011; Reinhart, Cosman, Fukuda, & Woodman, 2017; Reinhart & Woodman, 2014; Reinhart et al., 2016). In the monopolar montage, the target electrode is placed over the cortical region of interest, while the reference electrode is placed on an extracephalic area (i.e., cheek, shoulder, or leg) (Nasseri, Nitsche, & Ekhtiari, 2015). The monopolar montage of tDCS has been shown to manipulate the concentrations of excitatory and inhibitory transmitters in the stimulated areas (Krause et al., 2013; Stagg et al., 2009).

Additionally, the distance between the target and the reference electrode has been suggested to play an important role in the efficacy of tDCS (Moliadze, Antal, & Paulus, 2010). For instance, increasing the distance between the electrodes could result in greater cortical modulation as the current passes through the cortex, while reducing the distance between tDCS electrodes could lead to the shunting effect (Bikson, Datta, Rahman, & Scaturro, 2010; Miranda, Lomarev, & Hallett, 2006). To avoid this effect, electrodes should be placed at least 4 cm apart (Moliadze et al., 2010; Rush & Driscoll, 1968). As such, a monopolar electrode montage (Oz, left cheek) was used in this thesis. This montage satisfies the recommended distance between the electrodes (at least 4 cm) to avoid

shunting effects, and it is ideal to prevent any potential effects from stimulating additional cortical regions. Such a montage has been shown effective to modulate the activity of motor, auditory, and visual cortices (Aytemür et al., 2017; Hsu et al., 2011; Reinhart et al., 2016).

Stimulation duration

The duration of tDCS plays a crucial role in tDCS-induced aftereffects (Furubayashi et al., 2008; Nitsche, Nitsche, et al., 2003; Nitsche & Paulus, 2000, 2001). Transcranial direct current stimulation-induced aftereffects have been shown to be related to the duration of the stimulation (Nitsche, Nitsche, et al., 2003; Nitsche & Paulus, 2000). For instance, inducing an aftereffect of tDCS with a current of 1 mA been suggested to require at least 3 min of stimulation (Nitsche & Paulus, 2000). Such a short-lived effects that nevertheless last after the stimulation's termination are called intra-tDCS effects (Nitsche et al., 2005). The effects of stimulation duration the tDCS aftereffect can be seen in the work of Nitsche, Nitsche et al. (2003), who investigated the effect of stimulation duration over the motor cortex on the length of aftereffect duration. They found that the duration of the aftereffect depends on the stimulation duration, as 5–7 min of tDCS induced an aftereffect of no longer than 5 min, while increasing the duration of tDCS to 9–13 min increased the duration of the aftereffect up to 90 min. A similar stimulation duration-related tDCS aftereffect was also observed in the visual cortex (Antal et al., 2004; Antal et al., 2001). Indeed, 10 min of occipital tDCS produced a polarity-dependent aftereffect on the amplitudes of VEP, which was observed 10, 20, and 30 min after the stimulation termination, with no further recording of VEP after the 30 min post-stimulation was reported (Ding et al., 2016). Although the stimulation duration is crucial for the aftereffect length, a non-linear relationship holds between the effects of tDCS and its duration. For

instance, it has been found that excitatory anodal-tDCS induces an inhibitory effect on cortical excitability after 26 min of stimulation (Monte-Silva et al., 2013). As such, in the experiments detailed in this thesis, the temporal duration of 10-min offline tDCS was carefully chosen to ensure that the effects of tDCS would be expected to last well beyond the duration of the psychophysical paradigm (12–25 min), and the EEG task was employed (up to 20 min) without any changes in its polarity-dependent effects.

Stimulation intensity

In addition to temporal duration, stimulation intensity (current selected) has been shown to play an important role on the effects of tDCS (Batsikadze et al., 2013; Murray et al., 2015; Priori, Berardelli, Rona, Accornero, & Manfredi, 1998). For instance, anodal stimulation over the motor cortex with an intensity of 0.3 mA has been shown to reduce the size of MEP, while using a higher intensity (i.e., 1 mA) enlarged MEP size (Priori et al., 1998). Moreover, a different intensity of the same polarity could lead to different behavioural and neurophysiological outcomes. For instance, Batsikadze et al. (2013) investigated the effects of stimulation intensity on perceptual task performance and cortical activity in the visual cortex. Batsikadze et al. (2013) found that anodal-tDCS induced robust effects on task performance as well as on cortical activity only with a higher stimulation intensity of 2 mA compared to intensities of 1 and 1.5 mA. Such intensity-dependent effects of tDCS were also found to modulate corticospinal excitability, as only anodal-tDCS with 2 mA led to a robust increase in corticospinal excitability, as compared to lower intensity (i.e., 1 mA) (Murray et al., 2015). This finding is consistent with the suggestion that higher current intensity of tDCS results in larger effects (Iyer et al., 2005; Nitsche & Paulus, 2000), and enough current intensity is necessary in order to produce detectable effects

(Boggio et al., 2006; Iyer et al., 2005; Nitsche & Paulus, 2000; Nitsche et al., 2005). Indeed, using different current intensities (1, 1.5, and 2 mA) to stimulate visual cortex using tDCS, Reinhart et al. (2016) found that occipital tDCS with 2 mA robustly affected behavioural and neurophysiological outcomes compared to that with lower intensity (1 and 1.5 mA). Similar effects of occipital tDCS with an intensity of 2 mA were also reported in the work of Ding et al. (2016). Accordingly, tDCS with a 2-mA current intensity was used in all the tDCS experiments of this thesis.

The selected transcranial direct current stimulation protocols and montage

As mentioned, tDCS protocol (i.e., intensity and duration) and montage (electrode placement positions) play an important role on the stimulation efficacy (Antal, Varga, et al., 2004; Bikson et al., 2010; Nitsche et al., 2008; Woods et al., 2016). Therefore, a tDCS protocol and montage from previous studies reporting robust changes in behavioural or neurophysiological outcomes following the cessation of the stimulation was adapted (Ding et al., 2016; Reinhart et al., 2016), as recommended (Thair et al., 2017). In all experiments of the thesis that used tDCS (Chapters 2 and 3), tDCS was delivered for 10 min with an intensity of 2 mA via two saline-soaked surface electrodes. The target electrode (5 × 5 cm) was placed over V1 (Oz 10:20 EEG position (Jasper, 1958; Klem, LuÈders, Jasper, & Elger, 1999)) while the reference (5 × 7 cm) electrode was placed over the participant's left cheek to avoid any potential effects resulting from stimulating additional brain regions of no interest (Nasseri et al., 2015; Reinhart et al., 2017). The stimulation intensity was increased gradually over the first 30 s in a ramp-up like fashion until reaching 2 mA, in order to minimize any possible discomfort and adverse effects (Nitsche, Liebetanz, et al., 2003). Given the suggestion that 9–13-min tDCS produces aftereffects on cortical excitability lasting 60–90 min (Kuo et al., 2013; Nitsche, Nitsche, et al., 2003; Nitsche &

Paulus, 2001), the duration of the post-tDCS ODT runs (Chapter 2: 12–25 min) and EEG runs (Chapter 3: up to 20 min) would be easily covered by the expected temporal duration of the aftereffects produced by 10 min of tDCS.

Experimental designs for all transcranial direct current stimulation experiments

In all the transcranial direct current stimulation (tDCS) experiments of the current thesis, a repeated measures factorial design was used. Such a design involved both between- and within-subjects comparisons. This design overcomes or minimizes the limitations of the between-subjects design (Reinhart et al., 2017; Thair et al., 2017). For instance, the between-subjects design may mask individual differences in tasks performance and responsiveness to tDCS, and it requires a large number of participants (Chew, Ho, & Loo, 2015; Reinhart et al., 2017; Thair et al., 2017). However, the repeated measures factorial design has its own limitations, related mainly to session repetitions (i.e., practice effects and order effects) (Uehara, & Hanakawa, 2015; Thair et al., 2017). As such, the psychophysical and EEG tasks used in this thesis were anticipated to produce minimum perceptual changes related to task repetition based on the literature.

For instance, intensive training in the ODT led to robust improvement in the oblique condition of the ODT (Song, Peng, Li, et al., 2007; Song et al., 2010; Vogels & Orban, 1985), but not for the cardinal condition (Vogels & Orban, 1985; Westheimer & Lavian, 2013). The training effects on the oblique condition's performance were shown to occur in the absence of any feedback (Shiu & Pashler, 1992). Such performance improvement may be linked to GABA concentration levels, given that the behavioural outcomes of perceptual

training were shown to be predictable, based on the GABA concentration level at the baseline (Heba et al., 2015). Furthermore, the lack of training-related improvement in the cardinal condition has been suggested to result from a ceiling effect, as initial performance reaches maximum performance (Matthews & Welch, 1997; Song et al., 2010). Additionally, the performance improvement in the oblique condition did not occur between the two runs of the ODT in a single session without training (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Dickinson et al., 2014; Edden et al., 2009; Song et al., 2010). Similarly, (Rivest, Boutet, & Intriligator, 1997) observed no robust performance improvement in the ODT between two sessions when no training was provided. As the ODT has been shown to be resilient to practice and perceptual learning effects when training is not provided, the ODT seems to be resilient enough to practice effects to be used in a within-subject design of a single- and two-session experiment. Accordingly, experiments in Chapter 2 investigating the effects of tDCS on ODT performance use a repeated measures factorial design.

Similar to the ODT, peak gamma frequency and VEP measures have been shown to not be significantly affected by task repetition (Campbell et al., 2014; Ding et al., 2016; Magazzini et al., 2016; Muthukumaraswamy et al., 2013). For instance, it was shown that peak gamma frequency did not significantly differ across multiple measurements in a placebo condition (Magazzini et al., 2016; Muthukumaraswamy et al., 2013). A similar pattern of results was also observed with VEP activity, as no robust difference was observed across three measurement points within a single session (during 10 and 20 min of sham-tDCS, immediately after 10 and 20 min of sham-tDCS, and 30 min after 10 and 20 min of sham-tDCS) (Ding et al., 2016). Given the absence of robust effects of task repetitions on peak gamma frequency and VEP activity, a repeated measures factorial design was used to investigate the effects of tDCS on those neurophysiological measures (Chapter 3).

The selected visual orientation discrimination task

The orientation discrimination task (ODT) used in this thesis experiment is adapted from (Edden et al., 2009) and has been used by (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Dickinson et al., 2014). Performance in such task has been shown to be associated with E–I balance. For instance, Edden et al. (2009) have found an association between thresholds of the orientation conditions of this task and the resting-state GABA concentration level in the visual cortex; particularly, lower OD thresholds in the oblique ODT condition (increased or enhanced performance) was associated with higher levels of GABA. Similarly, lower OD thresholds in the oblique ODT condition have been shown to relate to higher peak gamma frequency elicited by high contrast black and white visual stimuli (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015). In accordance with these findings, this task is thought to indicate cortical E–I balance, so it seems a good task for evaluating the causal relationship between E–I balance and visual perceptual outcomes.

The selected visual electroencephalogram task

The visual electroencephalogram (EEG) task used in this thesis (Chapters 3 and 4) is identical to that of (Milne, Dunn, Zhao, & Jones, 2018; Milne, Gomez, Giannadou, & Jones, 2019), and it has been shown to elicit clear peak gamma frequency and VEP activity. The EEG task consists of a static high contrast black and white checkerboard stimulus appearing repeatedly in the centre of a monitor, during which a participant is instructed to press the space bar using one hand when the visual stimuli disappear from the screen. The selection of this task was made with consideration of a large body of research

showing that peak gamma frequency and VEP activity are sensitive to a stimulus's features. For instance, peak induced gamma frequency has been shown to be sensitive to stimulus features such as size (Gieselmann & Thiele, 2008; Jia, Xing, & Kohn, 2013), contrast (Hadjipapas, Lowet, Roberts, Peter, & De Weerd, 2015; Pantazis et al., 2018; van Pelt, Shumskaya, & Fries, 2018), velocity (Friedman-Hill, Maldonado, & Gray, 2000; Orekhova et al., 2015; Swettenham, Muthukumaraswamy, & Singh, 2009), eccentricity (Gregory, Fusca, Rees, Schwarzkopf, & Barnes, 2016; van Pelt & Fries, 2013), and orientation (Koelewijn, Dumont, Muthukumaraswamy, Rich, & Singh, 2011; Pantazis et al., 2018). Similarly, amplitudes of VEP have been suggested to be sensitive to stimulus features such as size (Busch, Debener, Kranczioch, Engel, & Herrmann, 2004; Mihaylova, Hristov, Racheva, Totev, & Mitov, 2015; Tobimatsu, Kurita-Tashima, Nakayama-Hiromatsu, Akazawa, & Kato, 1993), contrast (Kubová, Kuba, Spekreijse, & Blakemore, 1995; Tobimatsu et al., 1993), velocity (Kremláček, Kuba, Chlubnová, & Kubová, 2004; R. Müller, Göpfert, & Hartwig, 1985), eccentricity (Busch et al., 2004; Capilla et al., 2016; Meredith & Celesia, 1982; R. Müller, Göpfert, Schlykowa, & Anke, 1990), and stimulus orientation (Bonds, 1982; Yang et al., 2012). Thus, given the sensitivity of these neurophysiological measures (peak gamma frequency and VEP activity) to the visual stimulation's features, a visual EEG task shown previously to produce the neurophysiological activity of interest (peak gamma and VEP activity) is used in this thesis (see Chapters 3 and 4) (Milne et al., 2018; Milne et al., 2019).

Objectives

This thesis investigates the causal relationships between E–I balance and both behavioural and neurophysiological outcomes using tDCS. The second chapter of the thesis is devoted to investigating the causal relationship between E–I balance and ODT performance. It consists of four tDCS experiments with slight methodological differences regarding the number of the experimental sessions (i.e., one- vs two- experimental session) and the

timing of the tDCS (i.e., pre-ODT runs and between ODT runs). Each session in every experiment comprised two runs of the ODT during which participants presented pairs of gratings and were instructed to judge whether the second grating had been tilted clockwise or anticlockwise, as compared to the first grating. The ODT run lasted up to 12 min. The ODT has been used previously (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2014; Edden et al., 2009). The tDCS protocol and the montage were kept the same for all experiments. A target electrode (25 cm^2) was placed over the visual cortex (V1), while the reference electrode (35 cm^2) was placed over the left cheek, with an intensity of 2 mA for 10 min to avoid any potential effects from modulating another brain region (Nasseri et al., 2015; Reinhart & Woodman, 2014). Based on previous findings (Edden et al., 2009; Nitsche, Nitsche, et al., 2003; Nitsche & Paulus, 2000; Sillito, 1975), it was hypothesised that anodal-tDCS would impair ODT performance, while cathodal-tDCS would enhance it.

In the third chapter of this thesis, the causal relationships between E–I balance and neurophysiological measures (namely peak gamma frequency and VEP amplitudes) are investigated. In a one-session experiment, participants received tDCS between two runs of an EEG task known to elicit strong gamma oscillation responses and VEP activity (Milne et al., 2018). The tDCS protocol and montage of this tDCS-EEG experiment were similar to those used previously in behavioural experiments. Each run of the EEG task lasted up to 15 min, including a self-timed break. It was hypothesised that anodal-tDCS would reduce peak induced gamma frequency while cathodal-tDCS would increase it, based previous findings (Edden et al., 2009; Kujala et al., 2015; Muthukumaraswamy et al., 2009; Nitsche, Nitsche, et al., 2003; Nitsche & Paulus, 2000). Additionally, it was hypothesized that anodal-tDCS would increase the amplitude of the VEP-N1 component and decrease the amplitude of the VEP-P2 component, whereas cathodal-tDCS would have reverse effects, based on findings from animal and human studies (Antal et al., 2004; Zemon et al., 1980; Zeneroli et al., 1981).

The fourth chapter replicates and extends upon previous studies finding a correlational relationship between ODT performance and peak gamma frequency (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009) by investigating to what

extent ODT performance can be predicted by both peak gamma frequency and VEP amplitudes. Before conducting an EEG task, participants completed one run of the ODT following a practice run unless they had completed the ODT in previous experiments. The hypothesis was that enhanced performance in the ODT would be associated with both higher peak gamma frequency and reduced VEP-N1 and increased VEP-P2, based on previous findings (Antal et al., 2004; Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009; Zemon et al., 1980; Zeneroli et al., 1981).

Chapter 2 : Investigating the Effects of tDCS on Visual Orientation Discrimination Task Performance: "The Possible Influence of Placebo"

Abstract

Enhanced performance on visual orientation discrimination tasks (ODTs) has been suggested to be associated with increased cortical inhibition. Thus, to further investigate the role of cortical E–I balance in ODT performance, the current study investigates whether transcranial direct current stimulation (tDCS) of the occipital cortex could affect performance. Four experiments were conducted with a variety of experimental designs. Subjects received active (anodal and cathodal) and sham-tDCS and conducted the ODT. Although there was some initial evidence for cathodal (inhibition) tDCS being associated with enhanced performance, this finding was not replicated with counterbalanced randomised designs with a larger number of subjects. Unexpected improvements in ODT performance following repeating testing of subjects were found in some designs, despite trying to minimise them. A final experiment compared sham-tDCS to 'no-tDCS' (with an identical temporal delay) and suggested that the improvements in ODT performance observed in the first three experiments were, to some extent, caused by generic tDCS placebo effects in these paradigms. These data suggest that caution must be exercised in interpreting the effects of tDCS in certain experimental designs.

Introduction

Differences in cortical excitation-inhibition (E-I) balance play a crucial role in cognition and behaviour (Yizhar et al., 2011) as disrupted E-I balance has been associated with

neurological discarders such as autism spectrum condition (ASC), schizophrenia, and attention-deficit hyperactivity disorder (ADHD) (Edden, Crocetti, Zhu, Gilbert, & Mostofsky, 2012; Kehrer, Maziashvili, Dugladze, & Gloveli, 2008; Rubenstein & Merzenich, 2003). E-I balance may underlie psychophysical task performance in a variety of modalities (e.g., auditory pitch discrimination, visual contrast sensitivity, visual orientation discrimination, and somatosensory tactile discrimination) (Chowdhury & Rasmusson, 2003; Edden et al., 2009; Fuzessery & Hall, 1996; Hicks & Dykes, 1983; Houtgast, 1972; Hubel & Wiesel, 1968; Katzner et al., 2011; Mucke et al., 2010). One approach for investigating causal relationships between E–I balance and performance in psychophysical tasks applies neuromodulation techniques such as transcranial direct current stimulation (tDCS) (Ding et al., 2016; Loui, Hohmann, & Schlaug, 2010; Mathys et al., 2010; Ragert, Vandermeeren, Camus, & Cohen, 2008; Rogalewski, Breitenstein, Nitsche, Paulus & Knecht, 2004b; Spiegel, Byblow, Hess, & Thompson, 2013).

Transcranial direct current stimulation (tDCS) is a non-invasive technique that can modulate E–I balance in both human (Krause et al., 2013; Nitsche & Paulus, 2001) and animal subjects (Bindman, Lippold, & Redfearn, 1962; Márquez-Ruiz et al., 2012). Transcranial direct current stimulation delivers low intensity (2 mA or less) direct current to targeted cortical areas via two electrodes of opposite current polarities, one is placed on the scalp overlying the cortical region of interest, while the other is placed in a "reference" location, such as the cheek, or over a distal or proximal cortical location (Berryhill, Wencil, Coslett, & Olson, 2010; Im et al., 2012; Tseng, Iu, & Juan, 2018). Anodal-tDCS, in which the active electrode is positively charged, increases neural excitability (Nitsche & Paulus, 2000), while cathodal-tDCS, in which the active electrode is negatively charged, decreases the neural excitability of the "stimulated" area (Nitsche, Nitsche, et al., 2003). For instance, MRS studies have found a reduction of gamma-aminobutyric acid (GABA) (inhibitory transmitter) following anodal-tDCS and a reduction of the levels of both GABA and glutamate (excitatory transmitter) following cathodal-tDCS (Stagg et al., 2009) in human subjects. These changes in neural excitability have been confirmed by measurements of transcranial magnetic stimulation (TMS)-elicited motor evoked potentials (MEPs) (Kirimoto et al., 2011; Nitsche & Paulus, 2000, 2001; Pellicciari, Brignani, &

Miniussi, 2013) and visual evoked potentials (VEPs) (Accornero et al., 2007; Antal et al., 2004; Antal, Nitsche, & Paulus, 2006; Antal, Varga, et al., 2004). Unlike in active mode of tDCS (anodal- and cathodal-tDCS), where current is delivered for the whole duration of the stimulation (i.e., 10 min), the current in sham-tDCS is delivered to the brain region of interest for only a brief period of time (~30 seconds), mimicking the sensation of the active mode to blind participants about the stimulation type they are receiving (Gandiga et al., 2006; Palm et al., 2013). The effects of such a transient period of stimulation have been suggested to induce no observable changes in cortical excitability (Nitsche et al., 2008; Nitsche et al., 2005; Siebner et al., 2004).

Whether psychophysical task performance can be altered by tDCS is of interest for two reasons. Firstly, it can assist in interpreting differences in psychophysical task performance in different clinical groups in terms the underlying neurophysiology. Indeed, atypical auditory and visual perceptions in autism and schizophrenia have been measured by performance of psychophysical tasks, with some reports of autistic spectrum condition (ASC) individuals having enhanced auditory pitch discrimination (Bonnel et al., 2010; Bonnel et al., 2003) and superior visual orientation discrimination (Dickinson, Bruyns-Haylett, et al., 2016) compared to neurotypical individuals. Schizophrenic subjects, however, typically have poorer pitch discrimination (Javitt & Sweet, 2015; Rabinowicz, Silipo, Goldman, & Javitt, 2000) and impaired orientation discrimination 2016 (Shaw et al., 2019; Whitlow, 2016) compared to neurotypical individuals. This atypical perceptual performance in both autism and schizophrenia has been attributed to disrupted E–I balance, but with sometimes opposing, equivocal findings in different studies (Bonnel et al., 2010; Dickinson, Bruyns-Haylett, et al., 2016; Javitt & Sweet, 2015; Whitlow, 2016). Thus, a clearer understanding of how performance is related to E–I balance is required, and this understanding can be obtained by manipulating performance with tDCS. Secondly, attempting to alter performance with tDCS can assist in understanding which paradigms and parameters lead to the efficacy of tDCS, as psychophysical tasks are easier to theoretically link to E–I balance (which tDCS alters) than are more complicated cognitive tasks.

In the case of tDCS and perceptual tasks, cathodal-tDCS has been shown to disrupt pitch perception (Mathys et al., 2010) and tactile discrimination (Rogalewski et al., 2004b) and to enhance motion discrimination (Antal, Nitsche, et al., 2004). Surprisingly, as far as I am aware no researchers have investigated whether tDCS can alter performance on visual orientation discrimination tasks (ODTs), a task with clear links to visual cortical inhibition (Edden et al., 2009). During the ODT, participants were presented pairs of consecutive visual vertical or oblique gratings and were asked to indicate whether the secondly presented grating had been rotated clockwise or anticlockwise compared to the first presented grating (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009). The ODT comprises two orientation conditions based on the first grating orientation (vertical = 0° and oblique = 45°). Performance in the vertical condition is typically better than that in the oblique condition (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2014; Edden et al., 2009; Tibber et al., 2006), likely due to more visual cortical neurons being tuned to cardinal (vertical or horizontal) orientations compared to oblique ones (Appelle, 1972); this difference in performance is known as the "oblique effect".

The ODT is a task that should be susceptible to manipulation by tDCS, as performance in the task has been linked to E–I balance. For instance, topical application of GABA agonists in V1 in animal models increases the orientation tuning of visual cortical neurons (Li et al., 2008), whereas GABA antagonists decrease orientation tuning (Katzner et al., 2011; Sillito, 1975, 1979; Sillito et al., 1980). Furthermore, in human subjects, magnetic resonance spectroscopy (MRS) measurements of GABA concentration in V1 correlate with actual ODT performance (Edden et al., 2009). Despite the evidence linking increased inhibition with enhanced ODT performance, enhanced performance in subjects with ASC has been found (Dickinson, Bruyns-Haylett, et al., 2016), as well as in those with higher autistic traits (Dickinson et al., 2015; Dickinson et al., 2014). The notion of increased inhibition in autism is opposite to that previously thought, with many investigators interpreting differences in performance in other visual tasks, such as binocular rivalry (Freyberg et al., 2015), as caused by increases in excitation (see (Dickinson, Jones, et al.,

2016) for a review). As such, the relationship between ODT performance and E–I balance may require further investigation.

Thus in this study, a series of experiments were performed to investigate whether manipulating E–I of the primary visual cortex (V1) using tDCS could affect performance on the ODT. An identical ODT was used to that used in previous studies that found a difference in performance in ASC (Dickinson, Bruyns-Haylett, et al., 2016) and correlations between GABA concentration in V1 and ODT performance (Edden et al., 2009). The ODT consisted of both cardinal and oblique conditions. It was hypothesized that anodal-tDCS would impair performance in the ODT, whereas cathodal-tDCS would improve performance in the ODT based on previous studies suggesting a positive correlation between increased inhibition in the visual cortex and ODT performance (Dickinson, Bruyns-Haylett, et al., 2016; Edden et al., 2009; Nguyen et al., 2016). Improvements in performance between groups of subjects have been easier to observe in paradigms with oblique stimuli (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2014) rather than cardinal stimuli (Brock, Xu, & Brooks, 2011). This relative ease is thought to be due to the "easier-to-judge" cardinal stimuli resulting in a floor effect. As such, it was suspected that hypothesised elevations in performance following cathodal-tDCS would be easier to observe for the oblique condition than for the cardinal (vertical) condition and that decrements in performance would be easier to observe in the cardinal condition.

Method

Orientation discrimination task

Orientation discrimination threshold was measured using a two-alternative forced choice (2AFC) with an adaptive staircase procedure based on the work of Edden et al. (2009),

which has been previously used by (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2014). The task was programmed in MatLab 2016B (The MathWorks Inc., Natick, MA, 2000) with PsychToolbox (Brainard & Vision, 1997); Figure 2.1 illustrates the task design. In each trial, a circular reference and a targeting grating (diameter 4°; spatial frequency three cycles per degree; contrast 99%; mean luminance 83 cd/m^2) were sequentially presented for 350 ms with a 500 ms fixation between them. The task consisted of two orientation conditions based on the reference grating orientation (vertical = 0° and oblique = 45°). In each condition, there were two staircases based on the stimulus' rotation direction (clockwise and anticlockwise).

The staircases used the method of one-up three-down procedures converging on 79% accuracy (Leek, 2001). On the first trial of each staircase, the target grating is initially rotated 5 degrees from the reference grating, which can be easily detected. The orientation difference between the target and reference grating is then reduced until the participant makes an incorrect response in judging the orientation difference for a single trial. At this point, the staircase reverses and the difference between the two gratings increases until the participant makes correct responses for three consecutive trials, at which another reversal is triggered, and the orientation difference decreases. Initially, the step size is one degree, changing by 75 % following each reversal (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2014).

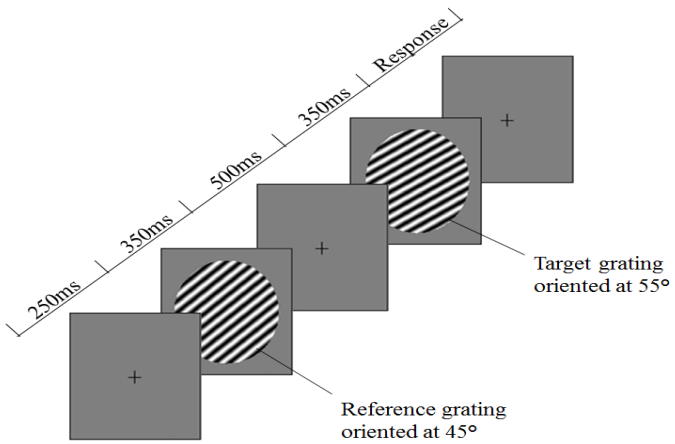


Figure 2.1. Schematic illustration of the orientation discrimination task. The figure is reprinted with permission from (Dickinson et al., 2014).

Participants were instructed to sit comfortably on a chair with a distance of 57 cm between their heads and the monitor. A black circular aperture was positioned over the monitor to eliminate any external cues of orientation provided by the monitor edges. Participants were instructed to judge whether the secondly presented grating (the target grating) had been tilted either clockwise or anti-clockwise compared to the firstly presented grating (reference grating) using right and left arrow keys. In a practice run, participants completed 10 trials for each of the four staircases. In the experimental run, however, participants completed 140 trials for each staircase, if they did not converge after eight reversals, the run would terminate. Depending on the experiment, the last six or four reversals of each staircase were used to calculate discrimination thresholds after discarding the first two reversals, which were considered practice trials. Thresholds of vertical and oblique conditions were calculated separately by averaging the left and right staircases of each condition (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2014).

Main exclusion criteria

Three general exclusion criteria were applied for all experiments. One regarded the unsuccessful completion of the possible six to eight reversals (eight reversals for Experiment 1 and six to eight reversals for Experiments 2, 3, and 4) for each condition in any orientation discrimination task (ODT) session's run. Thus, in Experiment 1, participants whose performance did not reach eight reversals in the first session were not invited to undertake the second session. Thirty-three percent of participants did not reach eight reversals and were thus not invited to the second session. Therefore, this criterion was modified in the subsequent experiments from eight to six reversals, and participants who failed to reach six reversals in each staircase were not invited for further sessions (Experiment 2) and were also excluded from the analysis. Inspection of the data (and the previous data, (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Dickinson et al., 2014) suggests that six reversals is sufficient to calculate a reliable threshold.

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

Transcranial direct current stimulation

A battery-driven constant generator (TCT research, Hong Kong) was used to generate direct current via two saline-solution-soaked sponge electrodes. One electrode (5 × 5 cm) was placed over the primary visual occipital cortex (V1) corresponding to Oz according to the international 10–20 Electrode Placement System (Jasper, 1958; Klem et al., 1999). To

locate Oz, the distance from the nasion to the inion was measured, and then 10% of this total distance from the inion was used or Oz location. The other electrode (5 × 7 cm) was placed over the left cheek to avoid confounding effects that might be generated by stimulating an additional brain region (Berryhill et al., 2010; Im et al., 2012; Tseng et al., 2018) (Figure 2.2).

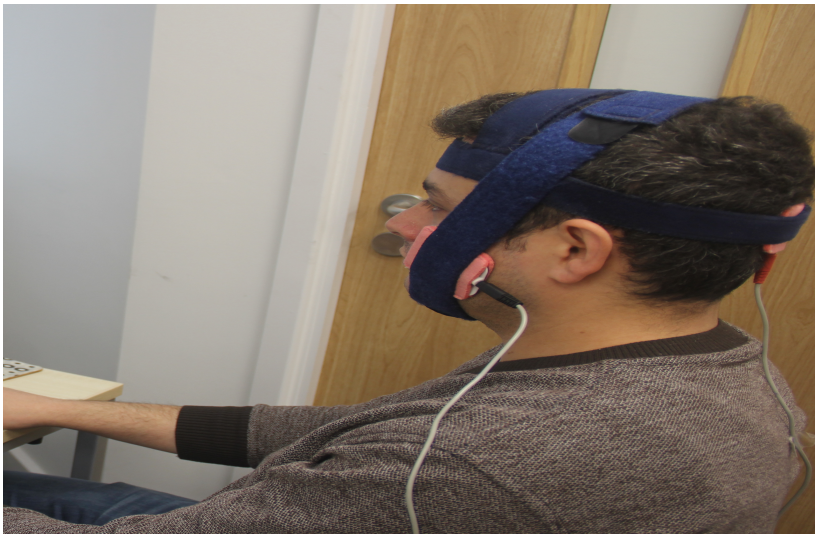


Figure 2.2. Illustration of the monopolar montage (Oz, left check) used in all the transcranial direct current stimulation (tDCS) experiments of this thesis. This picture is for illustrative purposes only.

Previous studies have confirmed the efficacy of transcranial direct current stimulation (tDCS) for visual cortex stimulation at this locus (Antal, Kincses, Nitsche, & Paulus, 2003a, 2003b; Antal et al., 2001, 2006; Ding et al., 2016); and see (Antal & Paulus, 2008) for review). The stimulation intensity gradually increases over 30 s until it reaches 2 mA to minimize the possibility of adverse sensations (Nitsche, Liebetanz, et al., 2003), and it lasts for 10 min. Durations of 9–13 min off line tDCS have been found to induce aftereffects lasting up to 90 min (Kuo et al., 2013; Nitsche, Nitsche, et al., 2003; Nitsche & Paulus, 2001), which easily covers the duration of the entire ODT, including self-directed break

periods (~25-minute total maximum duration). However, 1 mA has been shown sufficient to produce functionally relevant changes in inhibition and excitation in the visual system (Antal, Kincses, Nitsche, Bartfai, & Paulus, 2004); see (Antal et al., 2006) for review). In some brain regions such as the frontal lobe, 2 mA is required to elicit an effect in cognitive tasks (Iyer et al., 2005). As such, 2 mA was chosen to ensure that the chances of observing the effects of tDCS were maximized (Marshall et al., 2016). Furthermore, the stimulation intensity of 2 mA has also been found effective in inducing changes in the cortical excitability of occipital cortex in a polarity-dependent manner indicated by changes in performance in various visual perception tasks (Ding et al., 2016; Mancini, Bolognini, Haggard, & Vallar, 2012; Peters et al., 2013; Richard, Johnson, Thompson, & Hansen, 2015).

Experiment 1: Initial Examination of the Effect of tDCS on ODT Performance

Overview

An initial experiment was conducted to examine the effects of tDCS on ODT performance. Human participants were invited to participate in a two-session experiment with a 1-week interval between sessions. In each session, participants received 10 min of tDCS (sham-tDCS in the first session and active-tDCS in the second session (anodal or cathodal)), then two runs of the ODT with an average 2-min interval between the runs.

Participants

Thirty male undergraduate students at the Psychology Department of King Saud University (KSU) participated in the first of two tDCS sessions. Participants had normal or corrected-to-normal vision with no history of neurological disorders (e.g., epilepsy, head injuries, or migraines). Participants received course credits for participation in the study. The study was fully approved by the ethics committee of the Department of Psychology at The University of Sheffield and received written approval from the Psychology Department of KSU to conduct the study in that department.

Procedures

Participants provided a written consent form to take part in the study at the beginning of each session. Participants received 10 min of occipital tDCS (sham-tDCS in the first session and active-tDCS in the second). Participants performed a practice run of the ODT followed by two runs of the ODT with a self-timed break between them (1–3 min). During the session, participants were repeatedly asked to notify the experimenter when they were uncomfortable so that the experimental session could be terminated. At the end of the session, participants were requested to complete an adverse effects questionnaire (Brunoni et al., 2011) and a post-stimulation ratings form (including pain, attention, and fatigue) (Galea et al., 2009) (Table 2.1). This step was to examine whether there were any differences based on stimulation experience between active and sham-tDCS. Although sham-tDCS has been suggested and widely used as a placebo control condition (Dinn et al., 2017; Gandiga et al., 2006; Palm et al., 2013), recent findings have suggested that sham-tDCS may not be a very effective placebo control tool, as the stimulation experience

of active-tDCS differs from that of sham-tDCS (Kessler et al., 2012; Turi et al., 2019). The interval between the first and second session was 7 days (Figure 2.3).

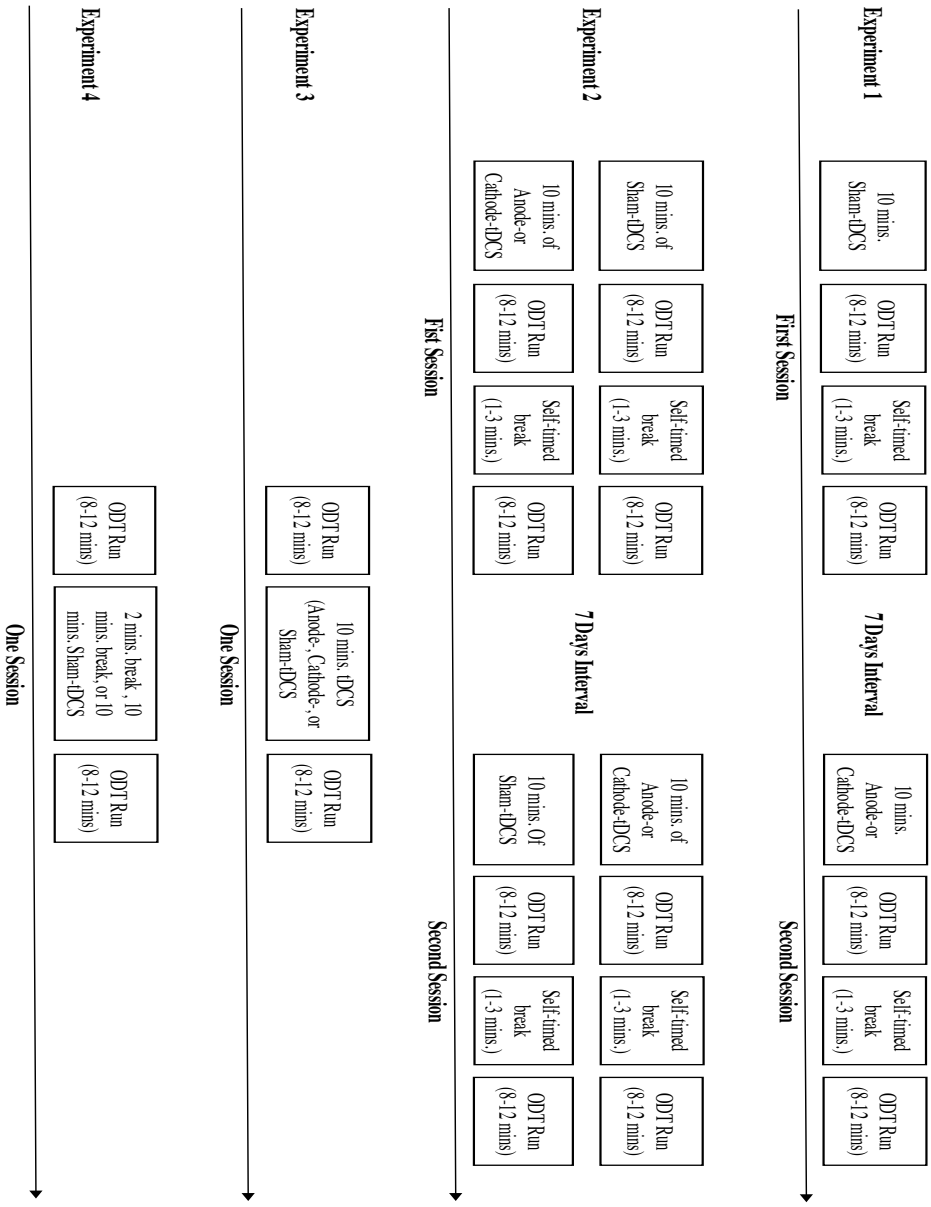


Figure 2.3. Schematic diagram of the design of each experiment.

Results

Ten of 30 participants were excluded from the analysis because of unsuccessful completion of eight reversals. Additionally, one participant did not show up for the second session. Thus, data from 19 participants were used in the analysis. All participants received sham-tDCS in first session, while 10 participants (age, M = 21.19, SD = 1.7) received anodal-tDCS, and 9 participants (age, M = 20.7, SD = 1.4) received cathodal-tDCS in the second session (Table 2. 1).

The thresholds for vertical and oblique ODT in each session were calculated separately by averaging the two runs' thresholds. Data were analysed using a repeated-measures analysis of variance (ANOVA) treating ODT condition (vertical, oblique) and session (sham-tDCS, active-tDCS) as within-subject variables, and tDCS type (anodal-tDCS, cathodal-tDCS) as a between-subject variable. All statistical analyses were performed using SPSS version 24 for Mac (IBM SPSS, Armonk, New York).

The results show a main effect of condition (F(1, 17) = 109.376, p < .0001), with ODT thresholds being significantly lower in the vertical condition (M = 1.81, SD = 0.20) compared to the oblique condition (M = 7.01, SD = 0.56). In addition, there was a main effect of session type (F(1, 17) = 6.593, p = .020) with ODT thresholds being significantly lower in the second active tDCS session (M = 4.12, SD = 0.36) compared to the first sham-tDCS one (M = 4.71, SD = 0.36). A significant interaction was found between condition and session (F(1, 17) = 6.231, p = .023), as well as a trend towards interaction between condition, session, and tDCS type (F(1, 17) = 4.113, p = .059). Pairwise comparison analyses showed that only the threshold of the oblique condition was significantly lower at the second (i.e., active-tDCS) session (M = 6.50, SD = 0.60) compared to the first (i.e., sham-tDCS) session (M = 7.53, SD = 0.60) (p = .013).

Although, no main effect of tDCS type was found ($F(1, 17) = 3.419$, $p = .82$), pairwise comparisons indicated that the reduction in threshold was only statistically significant for the oblique condition of cathodal-tDCS (($M = 7.35$, $SD = 2.88$) vs ($M = 8.90$, $SD = 2.78$)), ($p = .010$), not of anodal-tDCS (($M = 5.66$, $SD = 2.66$) vs ($M = 6.16$, $SD = 2.41$)), ($p = .341$) (Figure 2.4). Additionally, pairwise comparisons showed that the oblique threshold in the first session (sham-DCS) was significantly statistically lower in the subjects that subsequently received anodal-tDCS ($M = 6.16$, $SD = 2.41$) compared to those that subsequently received cathodal-tDCS ($M = 8.90$, $SD = 2.78$), $F(1, 17) = 5.303$, $p = .034$.

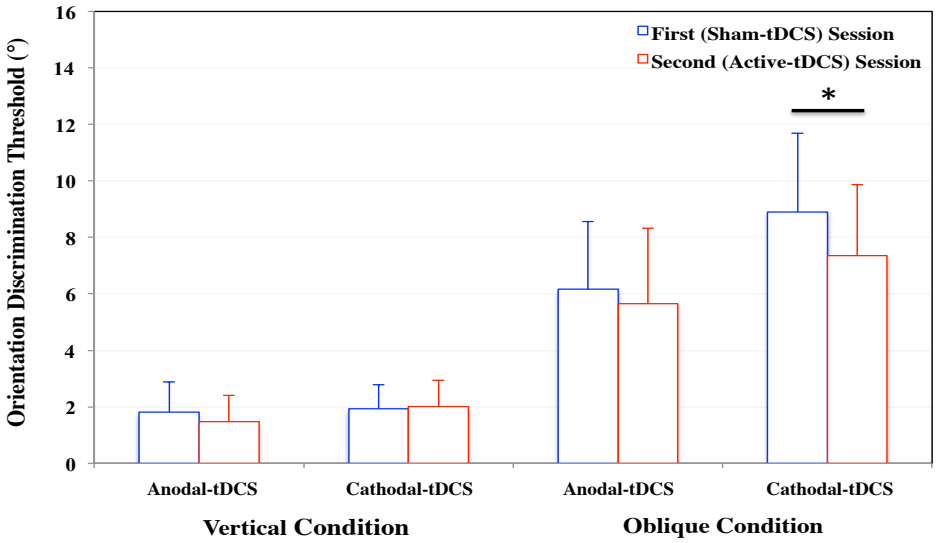


Figure 2.4 Mean orientation discrimination threshold of Experiment 1 (degrees, decreased threshold is associated with increased performance) following tDCS. All groups received sham-tDCS in first session and active-tDCS (either anodal-, or cathodal-tDCS) in second session. Anodal-tDCS was given to 10 participants, while cathodal-tDCS was given to 9 participants. Error bars represent standard deviation. *$p < .05$

Discussion

Examining tDCS effects on ODT performance, Experiment 1 showed a significant effect of the cathodal-tDCS on the oblique condition of the ODT performance. This finding is in agreement with previous studies' suggestions that higher neural inhibition may be related to superior performance of the ODT (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Dickinson et al., 2014). However, the anodal-tDCS group had a lower oblique threshold ($M = 6.16$, $SD = 2.41$) compared to that of the cathodal-tDCS group in the sham "baseline" condition ($M = 8.90$, $SD = 2.78$). This difference in threshold could have spuriously resulted in the observed differences after the active-tDCS condition. These "baseline" differences may be a result of the relatively small sample size used. Thus, increasing the study sample size could reduce baseline differences between anodal- and cathodal-tDCS in ODT performance. Therefore, it was decided that an additional experiment with a larger sample size and a counterbalanced design was necessary (see Experiment 2, below).

Furthermore, a counterbalanced design was required to minimize the effects of a "session" ("practice") effect as, in Experiment 1, all participants received sham-tDCS in the first session and active-tDCS in the second session. Although the data suggested an effect of cathodal-tDCS, it is difficult to attribute performance improvement specifically to tDCS, as the performance of all groups showed a trend towards improvement in the second session, regardless of tDCS type (anodal- versus cathodal-tDCS).

Experiment 2: A Replication of Experiment 1 with a Larger Sample Size and Counterbalanced Design

Overview

Experiment 1 suggested an effect of cathodal-tDCS on performance in the oblique condition of the ODT. This finding is consistent with previous suggestions of a correlation between increased inhibition and enhanced performance on oblique OTD (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Dickinson et al., 2014). However, an additional two-session experiment was conducted to replicate the findings of Experiment 1 with a bigger sample size and a completely counterbalanced randomized sham or active tDCS order. This step was necessary in order to make a definitive conclusion as to whether cathodal-tDCS increases performance in the oblique condition of OTD.

Participants

Forty-eight healthy volunteers from the University of Sheffield with normal or corrected-to-normal vision participated in this two-session tDCS study. Participants had no history of neurological disorders (e.g., epilepsy, head injuries, and migraines). Twenty-four of the participants were first-year psychology students and received credits for participation. The remaining participants were recruited from the students- and staff-volunteering email list of the University of Sheffield, and they received a £7 gift voucher for participation in each session. Participants provided a written consent form at the beginning of each session. The study was fully approved by the ethics committee of the Department of Psychology at The University of Sheffield.

Procedures

The task and procedures were identical to those described for Experiment 1, with the exception that subjects were randomly assigned to one of four conditions. Each condition consisted of two sessions in which the subjects received either active or sham-tDCS. The interval duration between the first and second session was 7 days (Figure 2.3). Counterbalancing tDCS types resulted in four tDCS "order" conditions (first and second session): anodal-sham, cathodal-sham, sham-anodal, and sham-cathodal. These conditions were collapsed based on tDCS type to anodal- and cathodal-tDCS (i.e. for initial analyses of tDCS effects, anodal-sham and sham-anodal tDCS orders were combined together to form the anodal-tDCS group, while cathodal-sham and sham-cathodal orders were combined to form the cathodal-tDCS group).

Results

Thirteen participants were excluded from analysis due to unsuccessful completion of 6 reversals in one of the session. Additionally, 3 participants did not show up for the second session. Thus, data from 32 participants were used in the analysis.

The anodal-tDCS type group consisted of 17 participants. Eight participants (male = 3; age, $M = 23$, $SD = 8.05$) received anodal-tDCS in the first session and sham-tDCS in the second session (anodal-sham), while 9 participants (male = 3; age, $M = 27$, $SD = 10.4$) received sham-tDCS first and anodal-tDCS in the second session (sham-anodal). Similarly, the cathodal-tDCS type group consisted of 15 participants. Seven participants (male = 1; age, $M = 24.4$, $SD = 13.9$) received cathodal-tDCS in the first session and sham-tDCS in

the second session (cathodal-sham), while 8 participants (male = 2; age, $M = 23.4$, $SD = 7.9$) received sham-tDCS first and cathodal-tDCS in the second session (sham-cathodal) (Table 2.1).

The thresholds for vertical and oblique conditions for each session were calculated separately by averaging the two runs' thresholds. First, a repeated measure ANOVA was conducted to examine the effects of tDCS on the performance of vertical and oblique orientation discrimination. Condition type (vertical vs oblique) and session type (active vs sham) were treated as within-subject variables, while tDCS type (anodal-tDCS vs cathodal-tDCS) was treated as a between-subject variable. There was a main effect of condition ($F(1, 30) = 331.528$, $p < .0001$). As expected, thresholds were lower on the vertical condition compared to the oblique condition. However, in contrast to Experiment 1, there was no main effect of session type ($F(1, 30) = 0.130$, $p = .721$), nor was there a main effect for tDCS type ($F(1, 30) = 0.128$, $p = .723$ (Figure 2.5).

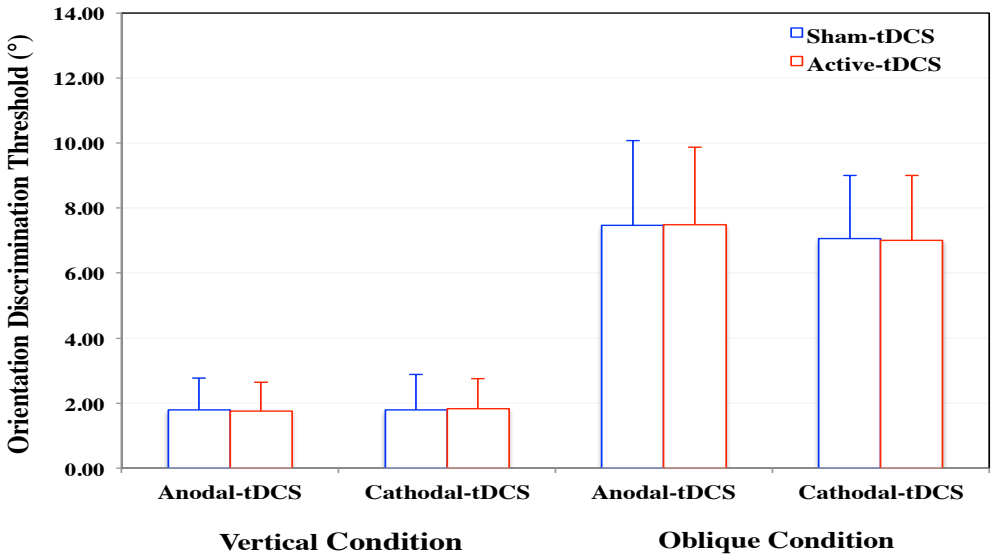


Figure 2.5. Mean orientation discrimination threshold of Experiment 2 (degrees, decreased threshold is associated with increased performance) following sham and active transcranial direct current stimulation (tDCS) regardless of session order. Participants receiving anodal-tDCS in either the first or second session are combined together, and participants receiving cathodal-tDCS in first or second session are combined together. Therefore, anodal-tDCS consisted of 17 participants while cathodal-tDCS consisted of 15 participants. Error bars represent standard deviation.

As Experiment 1 suggested ODT performance improvement in the second session over the first, the current data set was also analysed in terms of session order. Thus, a repeated ANOVA analysis was conducted to investigate whether there was any performance improvement in the second session compared to the first, regardless of tDCS order condition. Condition (vertical vs oblique) and session order (first vs second) were treated as within-subject variables, while tDCS type order (anodal-sham, cathodal-sham, sham-anodal, and sham-cathodal) was treated as a between-subject variable.

The results demonstrate a significant effect of condition ($F(1, 28) = 331.895$, $p < .0001$). As expected, thresholds were significantly lower in the vertical condition compared to oblique one. Furthermore, a main effect of session was found ($F(1, 28) = 23.373$, $p < .0001$). Thresholds were significantly lower in the second session ($M = 4.32$, $SD = 0.29$) compared to the first session ($M = 4.72$, $SD = 0.25$). Additionally, there was a significant interaction between condition and session order ($F(3, 28) = 16.972$, $p < .0001$). Pairwise comparison showed that only the threshold of the oblique condition was significantly lower at the second session ($M = 6.90$, $SD = 0.43$) compared to the first session ($M = 7.61$, $SD = 0.38$), ($p < .0001$), whereas no difference was found for the vertical condition ($p > .05$). Although there was no main effect of tDCS type order ($F(3, 28) = 1.70$, $p = .916$) or a significant interaction between condition (vertical vs oblique), session order (first vs second), and tDCS type order (anodal-sham, cathodal-sham, sham-anodal, and sham-cathodal), ($F(3, 28) = .328$, $p = .805$), a further pairwise comparison was conducted to check whether ODT performance improvement that occurred in the second session was limited to specific tDCS type order. The result showed that oblique performance of all tDCS type order was statistically significantly improved in the second session compared to first session: anodal-sham ($p = .050$), cathodal-sham ($p = .013$), sham-anodal ($p = .039$), and sham-cathodal ($p = .003$) (Figure 2.6).

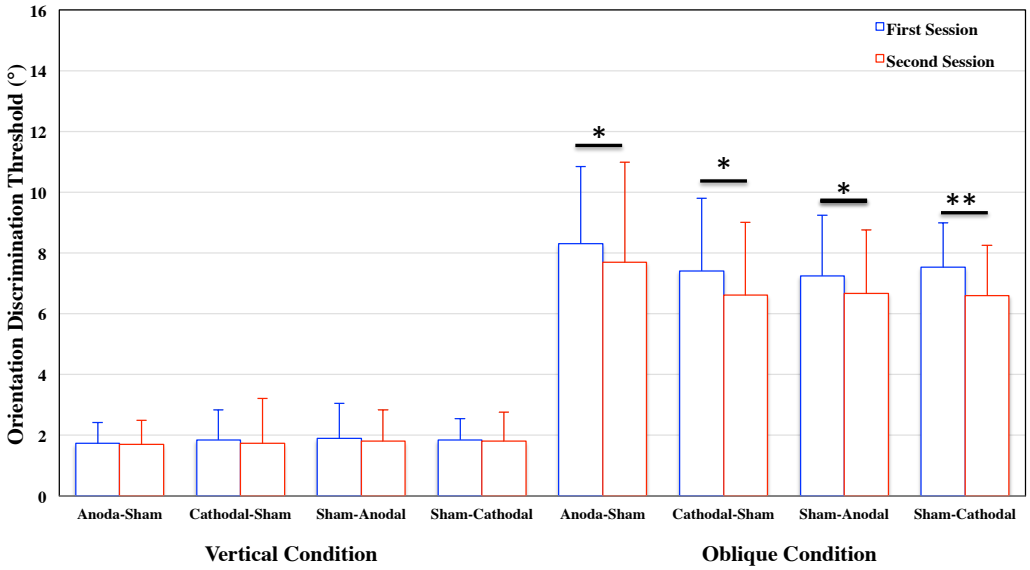


Figure 2.6. Mean orientation discrimination threshold of Experiment 2 (degrees, decreased threshold is associated with increased performance) in session 1 and session 2. Anodal-sham consisted of 8 participants, cathodal-sham consisted of 7 participants, sham-anodal consisted of 9 participants, and sham-cathodal consisted of 8 participants. Error bars represent standard deviation. *$p < .05$, **$p < .01$.

These data suggest a robust session "practice" effect, which could mask any putative effects of tDCS, making the evaluation of tDCS effects on ODT performance difficult. A possible solution was to develop an experimental design with less "practice-related" improvement. Therefore, to facilitate this, the putative practice effect was further examined in the data from both Experiment 1 and 2. Data from 51 participants (Experiment 1 and 2 data combined) were analysed using repeated measures ANOVA in order to track the emergence of the putative practice effect on ODT performance over the four runs that were completed in two sessions (two runs per session). Condition (vertical vs oblique) and run (first, second, third, and fourth) were treated as within-subject variables. Main effects of condition ($F(1, 50) = 380.172$, $p < .0001$) and run ($F(1, 50) = 9.411.172$, $p < .0001$) were found. As expected, performance was better in the vertical compared to oblique condition. A significant interaction was also found between condition and run ($F(1, 50) = 6.620$, $p < .0001$). Pairwise comparisons showed a significant decrease (improved performance) in the oblique condition threshold between first and third run ($p < .0001$), first and fourth run ($p = .001$), second and third run ($p = .002$), and second and fourth run ($p = .035$).

However, there was no significant difference in performance in the vertical or oblique condition between any two runs within a single session ($p > .05$). There was also some evidence of improvement in the vertical condition threshold between first and third run ($p = .031$).

Discussion

Re-examining tDCS effects on ODT performance, Experiment 2 failed to replicate Experiment 1's finding of a positive effect of cathodal-tDCS on oblique ODT performance. However, the occurrence of a robust improvement in the second session, regardless of tDCS type or order, could have masked tDCS effects from being observed. To inform an experimental design with limited performance improvements related to session ("practice") effects, further analysis of the combined data of Experiment 1 and 2 was conducted to investigate where within the two sessions of two runs the "practice effect" emerged; it appeared between the second and third runs. Thus, in the subsequent experiment, tDCS was given between two runs of a single session, with the aim of being able to evaluate tDCS effects on performance of the ODT without interference from practice effects.

Experiment 3: Re-examining Transcranial Direct Current Stimulation Effects on Orientation Discrimination Task Performance in a Limited Practice Effect Experimental Design)

Overview

The failure of Experiment 2 to replicate the finding of Experiment 1 was possibly caused by the transcranial direct current stimulation (tDCS) effect being masked by session-related "practice" effects. Further analysis of Experiment 1 and 2 data revealed that no observable practice effect occurred between the two runs of a single session. Therefore, in the current experiment, participants attended a single session consisting of two runs of an orientation discrimination task (ODT), with tDCS applied before the second run. This experimental design was anticipated to allow the effects of tDCS to be observed because of limited performance improvements between two ODT runs within one session.

Participants

Eighty-nine healthy volunteers from the University of Sheffield with normal or corrected-to-normal vision participated in this one-tDCS session study. None of the participants had a history of neurological disorders (e.g., epilepsy, head injuries, or migraines). Twenty-seven of the participants were first-year psychology students, and received credits for participation. The rest were recruited from the students and staff-volunteering list of the University of Sheffield and received a £7-gift voucher for participation in the study. Two participants had also participated in Experiment 2. Participants provided a written consent form at the beginning of the experimental session. The study was fully approved by the ethics committee of the Department of Psychology at The University of Sheffield.

Procedures

The same tasks and procedures of Experiment 2 were used in this experiment, with the exception of the number of sessions and runs that each participant completed. Participants were invited for one session comprising two ODT runs. After providing a written consent form to take part in the study, participants performed a practice run of the ODT followed by the first run. Participants were then randomly assigned to one of three tDCS type groups, which were anodal-, cathodal-, or sham-tDCS. Even though sham-tDCS has been shown to induce no observable changes in cortical excitability (Nitsche et al., 2008; Siebner et al., 2004), the polarity of sham-tDCS was counterbalanced in this experiment to avoid any potential neurobiological effects of the 30-s stimulation (Fonteneau et al., 2019). After 10 min tDCS (2 mA) stimulation, participants performed a second run of the ODT and then completed the adverse effect and post-stimulation ratings questionnaires (Table 2.1).

Results

During the stimulation duration, four participants notified the experimenter of experiencing uncomfortable sensations (scale pain) caused by the tDCS; in these cases, the experimental session was immediately terminated, and these subjects were excluded from analysis.

Data from 71 participants (anodal-tDCS ($N = 24$, male = 10, age $M = 24$, $SD = 7.2$), cathodal-tDCS ($N = 24$, male = 10; age, $M = 22.2$, $SD = 4.9$), and sham-tDCS ($N = 23$, male = 9; age, $M = 23.4$, $SD = 6.1$)) were used in the analysis (Table 2.1). Data from 13 participants were excluded because their thresholds in any condition of the ODT were two standard deviations above their tDCS type group mean. An additional participant was excluded because they did not receive tDCS due to headwear (e.g. hair extensions).

Data were analysed using repeated-measures analysis of variance (ANOVA). Condition (vertical vs oblique) and run (first vs second) were the within-subjects variables, while tDCS type (anodal-, cathodal-, or sham-tDCS) was the between-subject variable.

There was a main effect of condition ($F(1, 68) = 639.675$, $p < .0001$). As expected, thresholds were significantly lower for the vertical condition ($M = 1.63$, $SD = 0.11$) compared to the oblique condition ($M = 6.81$, $SD = 0.25$). Surprisingly, there was also a main effect of run ($F(1, 68) = 51.916$, $p < .0001$). Thresholds were significantly lower (indicating increased performance) in the second run ($M = 3.80$, $SD = 0.16$) compared to the first run ($M = 4.64$, $SD = 0.18$).

Additionally, a significant interaction was found between condition and run (F1, 68) = 35.762, $p < .0001$). Pairwise comparisons showed that only the thresholds for the oblique condition were significantly reduced in the second run ($p < .0001$), and not those of the vertical condition ($p = .066$). Although there was no significant interaction between condition, run, and tDCS type ($F(2, 68) = 1.199$, $p = .308$) and no main effect of tDCS type, ($F(2, 68) = 0.792$, $p = .457$), further pairwise comparisons were conducted to check whether the statistically significant performance improvement in oblique condition ($p < .0001$) and the trend towards performance improvement in the vertical condition ($p = .066$) occurred for all tDCS types (anodal-, cathodal-, and sham-tDCS). The result indicated a significant performance improvement in oblique condition for all tDCS type ($p < .0001$). Additionally, the result showed that only the vertical thresholds of cathodal-tDCS were significantly reduced (better performance) in the second run, compared to the first run ($p = .009$). However, no such vertical ODT performance improvement in the second run was found for anodal-tDCS ($p = .98$) or sham-tDCS ($p = .60$) (Figure 2.7).

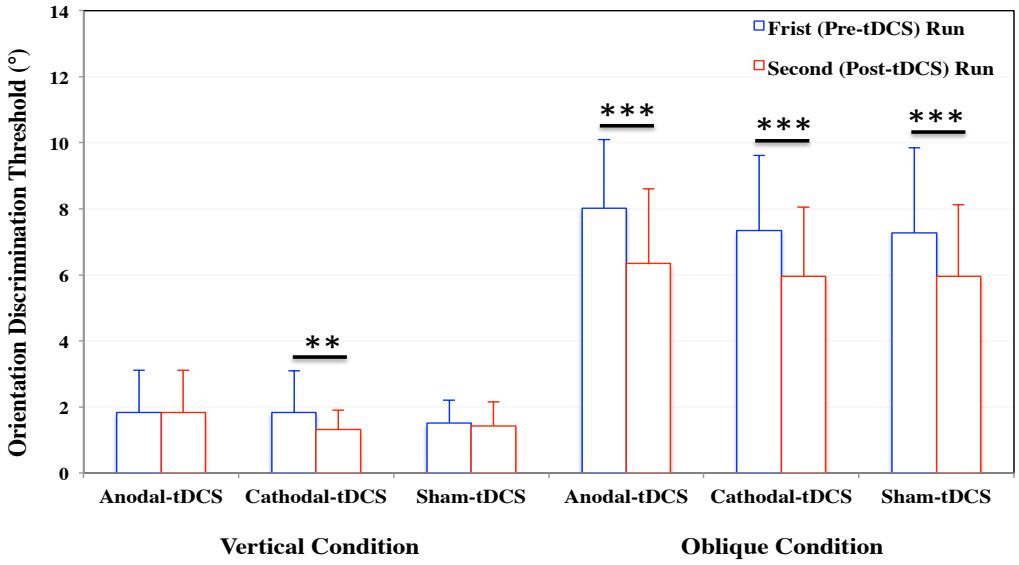


Figure 2.7. Mean orientation discrimination threshold of Experiment 3 (degrees, decreased threshold is associated with increased performance) before and following 10 min transcranial direct current stimulation (tDCS). Participants received tDCS between 2 runs of the ODT. Anodal-tDCS consisted of 24 participants, cathodal-tDCS consisted of 24 participants, and sham-tDCS consisted of 24 participants. Error bars represent standard deviation. $^{**}p < .01$, $^{***}p < .0001$.

Discussion

Examining tDCS effects on ODT performance, this one session of 2 ODT runs confirmed the finding of Experiment 2 of no observable effect of tDCS on ODT performance. However, unlike in Experiments 1 and 2, it appeared that there was an observed improvement in performance of the ODT between the first and second run. As some form of tDCS had been applied in all conditions (anodal-, cathodal-, and sham-tDCS), the improvement in performance in the second run could be caused by a generic placebo effect of tDCS. Another difference between the current experiment and previous studies (Experiments 1 and 2, as well as previously published studies: (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Dickinson et al., 2014) was that the use of tDCS

between the two runs required an increased delay time between the two runs (10 min rather than ~ 2 min) to deliver the tDCS, raising the possibility that this increased duration between runs could have also resulted in an improvement in performance. Thus, a further experiment was necessary to investigate these two possible causes of the unexpected improvement in ODT performance between the two runs.

Experiment 4: Examining the Possible Causes of Improved ODT Performance: Placebo Effect or Temporal Duration between Runs

Overview

The unexpected performance improvement in the second ODT run of Experiment 3 was hypothesized to result from either the extended delay period between the two runs compared to previous experiments (Experiments 1 and 2) and published studies (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Dickinson et al., 2014), or a general placebo effect of tDCS. To distinguish between these two possible causes of such performance improvement, the current experiment again required participants to attend one session comprising two runs of the ODT. Each participant was randomly assigned to one of three in-between run conditions, in which that participant received 10 min (sham-tDCS), 10 min (no-tDCS), or 2 min (no-tDCS) delay period between the two runs.

Participants

Forty-seven male undergraduate students at the Psychology Department of KSU participated in this one experimental session study. Participants had normal or corrected-to-normal vision with no history of neurological disorders (e.g., epilepsy, head injuries, or migraines). Participants received course credits for participation in the study. The study was fully approved by the ethics committee of the Department of Psychology at The University of Sheffield, and it received a written approval from the Psychology Department of KSU to conduct the study at their department.

Procedures

The same task and procedures of Experiment 2 were used in this experiment, with only one difference regarding tDCS type. Participants were invited for one session comprised of two runs of the ODT. After providing a written consent form to take part in the study, participants performed a preliminary practice run of the ODT, followed by the first true run. Participants were then randomly assigned to one of three conditions: receiving 10 min of sham-tDCS between the two runs or having either no-tDCS with a 10-min delay or 2-min delay between runs (Figure 2.3). Similar to Experiment 3, the polarity of sham-tDCS was counterbalanced in this experiment to avoid any potential neurobiological effects of the 30-s stimulation (Fonteneau et al., 2019), even though sham-tDCS has been shown to induce no observable changes in cortical excitability (Nitsche et al., 2008; Siebner et al., 2004).

Results

One participant in the middle of the first run notified the experimenter that they were feeling fatigued, so the experimental session was immediately terminated. Data from 41 participants—sham-tDCS ($N = 14$; age, $M = 20.8$, $SD = 1.5$), 10-min delay ($N = 13$; age, $M = 20.9$, $SD = 1.5$), and 2-min delay ($N = 14$; age, $M = 20.6$, $SD = 0.7$)—were used in the analysis (Table 2.1). This analysis excluded the data of 6 participants: 4 due to unsuccessful completion of six reversals, 1 due to their thresholds being two standard deviations above their group's mean, and 1 because of a participant who did not complete the task due to feeling unwell.

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

There were main effects of both condition ($F(1, 38) = 287.793$, $p < .0001$) and run ($F(1, 38) = 6.186$, $p = .017$). As expected, thresholds were significantly lower for the vertical condition compared to the oblique condition as well as for the second run compared to first run. Additionally, significant interactions were found between run and delay condition group ($F(2, 38) = 3.910$, $p = .029$) and between ODT condition (oblique, vertical) and run ($F(1, 38) = 7.665$, $p = .009$). Pairwise comparisons analysis showed that only sham-tDCS thresholds were significantly lower in the second run compared to the first run ($p = .001$). Another pairwise comparison analysis showed that only thresholds of oblique condition were significantly lower at the second session compared to the first session ($p = .005$). However, there was no main effect of delay condition group ($F(2, 38) = .363$, $p = .698$). Although there was no main effect of delay condition group ($F(2, 38) = .363$, $p = .698$) or a significant interaction between condition run and delay condition group, ($F(2, 38) = 2.111$, $p = .135$), a further pairwise comparison was conducted to check whether ODT performance improvement of sham-tDCS occurred in both the vertical condition and the

oblique condition. The result showed that only oblique performance of sham-tDCS was statistically significantly improved in the second run compared to first run ($p < .0001$). However, no such performance improvement of sham-tDCS was found in the vertical condition of the second run ($M = 1.95$, $SD = 0.28$) compared to the first run ($M = 2.47$, $SD = 0.25$), $p = .073$ (Figure 2.8).

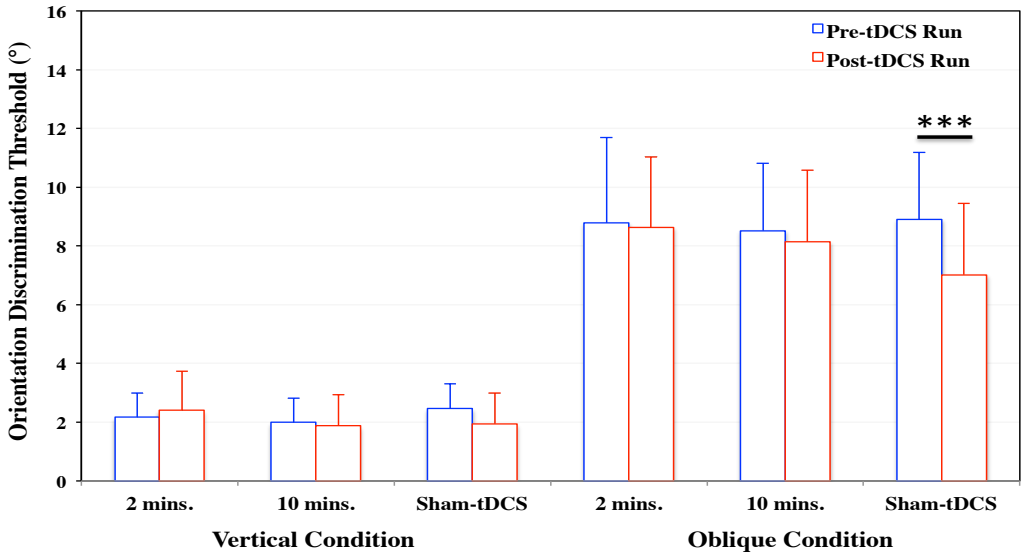


Figure 2.8. Mean orientation discrimination threshold of Experiment 4 (degrees, decreased threshold is associated with increased performance) before and following 10 min sham transcranial direct current stimulation (tDCS), 10-min delay, and 2-min delay. 14 participants received 10-min Sham-tDCS between the two ODT runs, 13 participants had 10-min delay between the two ODT runs, and 14 participants had 2-min delay between the two ODT runs. Error bars represent standard deviation. ***$p < .0001$.

Experiment	tDCS Type (Session 1, Session 2)	Participants (Male/Female)	Age (M, SD)	tDCS Side effects
Experiment 1	(Sham-tDCS, Anodal-tDCS)	(10/0)	(M=21.19, SD=1.7)	Neck Pain (N=1)
	(Sham- tDCS, Cathodal-tDCS)	(9/0)	(M=20.7, SD=1.4)	None
Experiment 2	(Sham-tDCS, Anodal-tDCS)	(3/6)	(M=27, SD=10.4)	None
	(Anodal-tDCS, Sham-tDCS)	(3/5)	(M=23, SD=8.05)	None
	(Sham-tDCS, Cathodal-tDCS)	(2/6)	(M=23.4, SD=7.9)	None
	(Cathodal-tDCS, Sham-tDCS)	(1/6)	(M=24.4, SD=13.9)	Burning sensation (N=1), Sleepiness (N=1)
Experiment 3	(Anodal-tDCS, NA)	(10/14)	(M=24, SD=7.2)	Skin redness (N=2), Sleepiness (N=1)
	(Cathodal-tDCS, NA)	10/14)	(M=22.2, SD=4.9)	None
	(Sham-tDCS, NA)	(9/13)	(M=23.4, SD=6.1)	Scalp pain (N=1)
Experiment 4	(Sham-tDCS, NA)	(14/0)	(M=20.8, SD=1.5)	Itching (N=1), Fatigue (N=1)
	(10 mins., NA)	(13/0)	(M=20.9, SD=1.5)	N.A
	(2 mins., NA)	(14/0)	(M=20.6, SD=0.7)	N.A

Table 2.1 Number of session and transcranial direct current stimulation (tDCS) condition for each experiment. Participants' number, sex, and age for each experiment's groups. tDCS side effects. Experiment 1 and 2 comprise 2 sessions. At the beginning of each session, participants received 10 min tDCS then conducted 2 orientation discrimination task (ODT) runs. However, Experiments 3 and 4 comprise 1 session where participants received tDCS or had 10-min delay or 2-min delay between the two ODT runs. In Experiments 3, four participants notified the experimenter about uncomfortable sensations (scalp pain) caused by the tDCS during the stimulation time, as such the experimental session was immediately terminated, and these subjects were excluded from analysis and from the table above. The stimulation experience of participants in each of the first 3 experiments did not significantly differ for active or sham-tDCS in terms of pain, attention, and fatigue based on the post-stimulation ratings ($p > .05$). Similarly, in the post-stimulation questionnaire, more than 70% of the participants received sham-tDCS in Experiment 4 thought or believed that they had received a real (active) stimulation.

Discussion

Experiment 4 examined whether a generic placebo effect of the tDCS temporal duration between the runs required to deliver tDCS caused the unexpected performance improvement in the ODT found in Experiment 3. Experiment 4 found that ODT performance was significantly improved in sham-tDCS alone, and not improved in subject assigned to conditions with no-tDCS (2-min delay, 10-min delay). This robust performance improvement following sham-tDCS suggests a placebo effect of tDCS on the ODT.

General Discussion

The effects of tDCS on ODT performance were investigated in four experiments. As expected from previous studies, the thresholds for the vertical condition were significantly lower (indicating increased performance) than for the oblique condition in all of the experiments. Consequently, compared to vertical thresholds, oblique thresholds were much more susceptible to change in all of the experimental paradigms. Experiment 1 findings suggested a possible enhancement of oblique ODT performance caused by cathodal-tDCS. This finding was re-examined in Experiment 2 with a larger sample size and carefully counter balanced randomized design. This was to eliminate any ordering effects (as Experiment 1 active-tDCS was always administered in the second session) that could have resulted in a false positive result Experiment 1. The results of Experiment 2 suggested no effect of tDCS on ODT performance. However, analysis of the data in terms of session order suggested a significant improvement in the second session, regardless of

experimental manipulation; thus, it was speculated that any tDCS effects would have been masked by the session-related practice effects. As such, an experiment was designed to eliminate the possible influence of practice effects. Further examination of data from Experiments 1 and 2 combined suggested that practice effects did not occur within the two runs of each session, but between the two sessions (i.e. between Runs 2 and 3). As such, Experiment 3 used a single session of two runs of the ODT with tDCS applied between the two runs. The data successfully replicated the finding in Experiment 2 that there was no effect of tDCS on ODT performance. However, unexpectedly, a strong performance improvement occurred in the second run. This improvement could have been due to either an increased temporal delay (10 min compared to about 1–3 min) between the two runs (during which tDCS was administered) or because of a generic placebo effect of tDCS on ODT performance, as some form of tDCS was always administered between the two runs (anodal-, cathodal-, or sham-tDCS). Experiment 4 investigated these two possible causes of performance improvement in a one-session experiment of two ODT runs. In this experiment, participants were randomly assigned to three groups with 10 min of sham-tDCS, and no-tDCS with time delays of 10 min, or 2 min between the two runs. The result of Experiment 4 confirmed that the unexpected performance improvement in the second ODT run resulted from a placebo tDCS effect rather than the extended delay period. Only the ODT performance of the sham-tDCS group was significantly improved in the second run whereas no such improvements were found in the groups of participants receiving no-tDCS. Taken together, the current study did not observe any reliable evidence for an effect of active tDCS on ODT performance, but instead found a strong placebo effect of tDCS that lead to increased ODT performance.

Orientation discrimination task performance of participants in the four experiments varied based on condition (oblique versus horizontal). In line with previous studies (Dickinson, Bruyns-Haylett, et al., 2016; Edden et al., 2009; Shafai, Armstrong, Iarocci, & Oruc, 2015), ODT performance is better on the vertical ODT compared to that on oblique condition. This condition effect is known as an oblique effect (Appelle, 1972) and is attributed to a higher sensitivity of neurons in the visual cortex to vertical and horizontal

visual stimuli (cardinal) compared to oblique stimuli (Furmanski & Engel, 2000; Vogels & Orban, 1985).

Additionally, based on the findings of Experiments 1 and 2, ODT performance improved in the second session compared to the first session. Consistent with a previous study from Shiu and Pashler (1992), this improvement occurs without any feedback being given. It is also a condition-dependent improvement, since it is greater on the oblique condition compared to the vertical condition. This is similar to the findings of (Song et al., 2010; Vogels & Orban, 1985), where training on line orientation discrimination led to an improvement in the oblique condition performance but not in the vertical and horizontal conditions. This improvement is suggested to be due to an increase of neural sensitivity to obliquely orientated stimuli (Schoups, Vogels, & Orban, 1995; Vogels & Orban, 1985), which may be too high initially for those associated with vertically and horizontally oriented stimuli to expect any further increase, due to the ceiling effect.

Despite any session-related practice effects on ODT performance in Experiment 1, a strong positive effect of cathodal-tDCS ODT performance was found. This finding was in line with a previous suggestion that there may be a correlation between increased neural inhibition in the primary visual (occipital) cortex and superior ODT performance (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Dickinson et al., 2014). However, there were two important limitations of Experiment 1 that required further investigation before one could conclude that cathodal-tDCS could increase OD performance. One possible limitation was related the small sample size, which, unfortunately, is not uncommon in tDCS studies. According to a meta-analysis study examining tDCS effects on various cognitive tasks in healthy human participants, the average sample size is 14.6 for studies with between-subjects design, and 17.9 for studies with within-subjects design (Medina & Cason, 2017), which is similar to that used here. Thus, although the sample size for Experiment 1 was small, the small sample size is not uncommon in the literature. Therefore, these findings may have implications for the interpretation of tDCS studies. Small sample size influences the estimation of effect size (Gelman & Carlin, 2014) and increases the likelihood that individual variability in baseline

performance can result in differences in mean values of groupings of subjects even when subjects are randomly assigned to experimental conditions. For instance, the oblique ODT threshold at the first baseline session of Experiment 1 was ($M = 6.16$, $SD = 2.41$) for those subjects assigned to the anodal-tDCS condition and was ($M = 8.90$, $SD = 2.78$) for those assigned to the cathodal-tDCS conditions. This difference in baseline performance between the groups of subjects could influence the overall findings of the study. For instance, the use of tDCS in other cognitive domains has found that low baseline performance in a task was found to be a predictor of subsequent improvement (McConathey et al., 2017) produced by tDCS. Another limitation concerning Experiment 1 finding was related to the lack of randomization of "sham- and active-tDCS order", which is not uncommon in a single- or multiple-session tDCS studies in both healthy and clinical population (DosSantos et al., 2014; Mancuso et al., 2016; Salimpour & Shadmehr, 2014; Spielmann, Van De Sandt-Koenderman, Heijenbrok-Kal, & Ribbers, 2018). All participants received sham-tDCS in the first session and either anodal- or cathodal-tDCS on the second session. The non-randomized tDCS type order made it difficult to distinguish tDCS effects from improvements in performance that were simply due to repeated attempts at the task ("practice effect"). Both groups treated with anodal and cathodal-tDCS performed better in the second session than in the first session.

To rule out the possibility of a false positive in Experiment 1, Experiment 2 was conducted with a larger sample size and a randomized "tDCS type order". Subjects were randomly assigned to one of four groups (anodal-sham, cathodal-sham, sham-anodal, sham-cathodal) and completed two sessions (two runs of the ODT on each session) with a 7-day interval between sessions. This experiment failed to replicate Experiment 1's finding of a positive effect of cathodal-tDCS on improving the oblique ODT performance, but instead showed a robust session-related practice effect. Orientation discrimination task performance in the second session demonstrated an improvement irrespective of stimulation type. In Experiment 2, this practice effect was even observed when subjects received anodal-tDCS in the first session and sham-tDCS in the second session. Given that there are several reports of anodal-tDCS blocking the occurrence of perceptual learning (Matsushita, Andoh, & Zatorre, 2015, 2017; Peters et al., 2013), this consistency suggests that the

practice effect observed in this paradigm is extremely robust. Such a robust practice effect might hinder or mask the tDCS effects from being detected. Similarly, anodal-tDCS effects were not observed on performance in trained tasks, but enhanced performance in untrained tasks' performance (Filmer, Lyons, Mattingley, & Dux, 2017). Thus, an experimental design of the ODT with minimum practice effects was necessary for examining tDCS effect on ODT performance. Further examination of Experiments 1 and 2 data revealed that practice effects did not occur between two ODT runs of the same session. Thus, one experimental session of two runs might allow tDCS effects on ODT performance to be detected.

Experiment 3 with one-session of two ODT runs replicated the findings of Experiment 2 that there was no observed effect of tDCS on ODT performance. Although the null finding of tDCS effects on ODT performance could be related to the tDCS protocol, this is unlikely. Notwithstanding, tDCS effects can vary based on many factors, such as location of electrode, time, intensity, and duration of stimulation (Nitsche et al., 2008). For instance, extended tDCS may lead to effects on neural excitability in the opposite direction of what is expected. Indeed, 20 min of cathodal-tDCS can actually increase neural excitability (Batsikadze et al., 2013) compared to the expected decreases that occur with shorter durations (e.g. 9 min (Batsikadze et al., 2013; Nitsche, Nitsche, et al., 2003)). However, the 10 min used here is a common duration (Antal, Kincses, Nitsche, Bartfai, & Paulus, 2004; Antal et al., 2003b; Antal et al., 2001) and is known to produce the expected changes in cortical excitability in V1 depending on whether stimulations is cathodal or anodal. The 10 min duration chosen here has been shown to produce up to 90 min of after effects, a duration far longer than the runs of the ODT completed after tDCS (Kuo et al., 2013; Nitsche, Nitsche, et al., 2003; Nitsche & Paulus, 2001); see (Antal et al., 2006), for review). Furthermore, whereas it is common to obtain anodal-excitation and cathodal-inhibition effects in studies of motor cortex, it is not as common to find neural inhibition effects of cathodal-tDCS as compared to neural excitation effects of anodal-tDCS in some cognitive domains (Jacobson, Koslowsky, & Lavidor, 2012), possibly because of difference in the cortices' structures (Antal et al., 2006). Nevertheless, the expected direction of cortical excitability changes elicited by tDCS has been reported in cortices

associated with higher cognitive functions (i.e., frontal lobe functions) (Iyer et al., 2005). Furthermore, in the case of the visual system, V1 has been shown to respond to tDCS in a similar fashion to M1 (Antal, Kincses, Nitsche, Bartfai, & Paulus, 2004; Antal et al., 2003b; Antal et al., 2001); see (Antal et al., 2006) for review). In the case of the current intensity, although 1 mA has been shown to be sufficient to produce functionally relevant changes in inhibition and excitation in the visual system (Antal, Kincses, Nitsche, Bartfai, & Paulus, 2004); see (Antal et al., 2006) for review), in some brain regions such as the frontal lobe, 2 mA is required to elicit an effect in cognitive tasks (Iyer et al., 2005). As such, in the current study, 2 mA was chosen to ensure that the chances of observing the effects of tDCS were maximised (Marshall et al., 2016). To summarise, the duration, intensity, and location of tDCS were chosen to maximize the effects of tDCS, and thus these parameters were unlikely to have resulted in the null findings observed.

Although being deliberately designed to avoid practice effects, the results of Experiment 3, surprisingly and unexpectedly, found a robust improvement in the post-stimulation run, regardless of whether active or sham-tDCS was given. There were two possible explanations for such an improvement. One was related to the interval time between the runs. Whereas participants in Experiments 1 and 2 conducted the two runs of the ODT with an average of 2 min interval time between runs, participants in Experiment 3 conducted the two runs of the ODT with 10 min interval between the two runs (to provide the time required to administer the tDCS). Thus, the improvement might be a result of the resting time between the runs. This is a reasonable possibility, since time after practice has been suggested to be crucial for perceptual learning (Bönstrup et al., 2019; Dewar, Alber, Cowan, & Della Sala, 2014; Schoups et al., 1995). It is suggested that performance improvement on a simple visual task (i.e., vernier acuity task [VAT]) occurs within 60 min of the task performance. While performing another task within 60 min of performing VAT disrupted VAT performance improvement, performing another task after 60 min did not disrupt VAT performance improvement (Seitz et al., 2005). Another explanation for the observed improvement was that the improvement might be a result of a placebo effect of tDCS, since all conditions received some form of tDCS (anodal-, cathodal-, or sham-tDCS). While many tDCS studies tend to use sham-tDCS as a placebo control condition

(Dinn et al., 2017; Gandiga et al., 2006), it can be difficult to distinguish the placebo effect from the stimulation effect (Fields & Levine, 1984), and an inclusion of a no-treatment (i.e., no-tDCS) can be important to evaluate the size of a possible placebo effect (Aslaksen, Vasylenko, & Fagerlund, 2014), since sham-tDCS alone is insufficient for the estimation of placebo effect size (Benedetti, Rainero, & Pollo, 2003).

Thus Experiment 4 examined both the putative placebo effect of tDCS and the possible effect of duration of interval between ODT runs on performance. Participants completed two runs of ODT and received 10 min sham-tDCS between the runs or had either 2 min or 10-min delay period between the runs with no-tDCS. Experiment 4 confirmed that the improvement observed in the prior experiments was a result of a placebo effect of tDCS. The sham-tDCS group was the only group whose performance improved in the second run of the ODT compared to those of no-tDCS. Although typical tDCS studies do not allow investigation of generic tDCS placebo effects, there are instances of similar placebo effects of tDCS modulating clinical and cognitive outcomes (Aslaksen et al., 2014; Cortese, Nowicky, Lopez de Heredia, & Belci, 2017; Egorova et al., 2015; Loo et al., 2018; Schambra, Bikson, Wager, DosSantos, & DaSilva, 2014; Turi et al., 2018). Sham-tDCS has been reported to reduce pain threshold (Loo et al., 2018; Schambra et al., 2014) and improve depression symptoms (Aslaksen et al., 2014; Egorova et al., 2015). For instance, Aslaksen et al. (2014) found a strong reduction in pain threshold with groups of participants receiving active- and sham-tDCS compared to those in a no-tDCS "group". Similarly, Loo et al. (2010) found that depression scores of depressed patients improved following multiple sessions of sham-tDCS. Such placebo effects may modulate neural activity given the findings of neuroimaging studies (using functional magnetic resonance imaging [fMRI] and positron emission tomography [PET]) of robust changes in neural activity in addition to reduction in clinical symptoms following the administration of placebo treatment (Mayberg et al., 2002; Wager, 2005; Wager et al., 2004). The placebo-related changes in behavioural and neurophysiological responses might reflect high-level top-down cognitive processes such as anticipation and expectation (Diederich & Goetz, 2008; Schambra et al., 2014; Skyt et al., 2018). Accordingly, it has been suggested that placebo effects influence only subjectively measured outcomes (Diederich & Goetz, 2008;

Schambra et al., 2014). Inconsistently, placebo effects of tDCS on the performance of an objectively measured low-level perceptual task (i.e., ODT) were found. This finding is partially consistent with previous studies' findings of placebo-related changes in outcomes of objective measures (i.e., working memory task, reward-based learning task) (Foroughi, Monfort, Paczynski, McKnight, & Greenwood, 2016; Turi et al., 2018; Turi, Mittner, Paulus, & Antal, 2017). For instance, performance in a reward-based learning task was robustly enhanced (impaired) by a combination of sham-tDCS, conditioning, and positive (negative) suggestive verbal instruction (Turi et al., 2018; Turi et al., 2017). Similarly, efficacy of training in a dual n-back task was enhanced by instruction-induced placebo (Foroughi et al., 2016). Unlike these studies, the finding of placebo effects of tDCS on the ODT occurred here the in absence of an explicitly suggestive instruction about the expected effects of tDCS on ODT performance. Investigating neurophysiological mechanisms underlying the placebo effects of tDCS could increase the understanding of the actual effects of tDCS and may also have potential benefits for health and cognition. For instance, if active- and sham-tDCS have a similar effect on reducing pain perception and orientation discrimination thresholds, then sham-tDCS may become a useful tool, especially for those with neurological disorders (i.e., epilepsy), without the complexities of inferring the effects of active-tDCS with neural activity.

In conclusion, this study, with four experiments, showed no effects of offline tDCS applied over the primary visual (occipital) cortex for 10 min with an intensity of 2 mA on the performance of the ODT. While the finding of Experiment 1 was suggestive of a positive effect of cathodal-tDCS on the oblique ODT performance, Experiments 2 and 3 failed to replicate it and instead suggested a placebo effect of tDCS on the performance. The tDCS placebo effect is confirmed in Experiment 4 by comparing performance of group receiving sham-tDCS with that of groups receiving no-tDCS. Thus, the current study demonstrates a novel positive placebo effect of tDCS on ODT performance. Additionally, it further confirms the important role of sample size to detect a true effect of tDCS and of replication in ensuring a findings' validity. Furthermore, this study points to the importance of including a no-tDCS group in order to evaluate a possible placebo effect of tDCS independently of the stimulation effects. Future studies should consider investigating the

neurophysiological mechanisms of tDCS with the same protocols and task used in the current study to examine whether the expected anodal-excitation and cathodal-inhibition effects occur in such experimental designs.

Chapter 3 : Effects of Transcranial Direct Current Stimulation on Peak Gamma Frequency and Visual Evoked Potential: Transcranial Direct Current Stimulation with Electroencephalogram

Abstract

Cortical excitation–inhibition (E–I) balance has been suggested to be reflected in peak gamma frequency elicited by visual stimulus and visual evoked potential (VEP) amplitude. For instance, it has been hypothesized that increased peak gamma frequency indicates an increased inhibition relative to excitation, whereas the abnormally high amplitudes of VEPs indicate hyperexcitability. This chapter investigates whether peak gamma frequency and amplitudes of VEP components (N1 and P2) can be modulated using transcranial direct current stimulation (tDCS), as tDCS has been shown to modulate E–I balance. The motivation for this investigation was the findings of Chapter 2, specifically the lack of causal relationships between manipulating cortical E–I balance in visual cortex using tDCS and orientation discrimination task (ODT) performance, a perceptual task with clear link to E–I balance. Healthy human participants completed two runs of an electroencephalogram (EEG) task that has been shown to elicit strong gamma frequency oscillations and clear VEP activity. Between the runs, participants were randomly assigned to three tDCS conditions (anodal-, cathodal-, and sham-tDCS) or received no-tDCS. Transcranial direct current stimulation 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 peak gamma frequency and VEP amplitudes using repeated measures ANOVAs. The results of both metrics showed a main effect of EEG task run (pre-tDCS vs post-tDCS). For instance, peak gamma frequency significantly increased in the second run of the EEG task while VEP amplitudes significantly decreased. However, no main effects of tDCS were found in both metrics. Possible explanations for the absence of tDCS effect are discussed.

Introduction

As mentioned in Chapter 1, excitation–inhibition (E–I) balance plays a crucial role in cognition and behaviour (Edden et al., 2012; Yizhar et al., 2011). Disruption in E–I balance has been suggested to be implicated in neurological disorders (e.g., autism, schizophrenia, and migraine) (Baroncelli et al., 2011; Bertone, Mottron, Jelenic, & Faubert, 2005; Coghlan et al., 2012; Dickinson, Jones, et al., 2016; Nguyen et al., 2016; Rubenstein & Merzenich, 2003). Such a disruption in E–I balance has been indirectly inferred from performance in visual psychophysical tasks (i.e., Binocular Rivalry Task, orientation discrimination task [ODT]) (Dickinson, Bruyns-Haylett, et al., 2016; Freyberg et al., 2015; Nguyen et al., 2016; Robertson, Kravitz, Freyberg, Baron-Cohen, & Baker, 2013; Robertson, Ratai, & Kanwisher, 2016; Sysoeva et al., 2016). Performance in these psychophysical tasks has been shown to be associated with the resting-state gamma-aminobutyric acid (GABA) concentration levels in the primary visual cortex (V1) (Edden et al., 2009; Kurcyus et al., 2018; van Loon et al., 2013). For instance, it has been shown that across subjects higher resting-state GABA concentration level in the visual cortex has been shown to significantly associate with slower perceptual dynamics (van Loon et al., 2013) and enhanced orientation discriminability (Edden et al., 2009).

Although the performance in the ODT has been found to be associated with cortical E–I balance (indicated by GABA) (Edden et al., 2009), a series of experiments in Chapter 2 using tDCS, a non-invasive neuromodulation technique shown to modulate the main excitatory and inhibitory transmitters (Krause et al., 2013; Stagg et al., 2009), to investigate the causal relationship between E–I balance and ODT performance observed no effects of occipital tDCS on ODT performance other than a placebo effect. The failure to observe any effects of tDCS on ODT performance did not rule out the possibility that tDCS might induce changes in cortical E–I balance that were not reflected in the task performance. As such, this chapter aims to investigate this possibility by evaluating the effects of occipital tDCS with identical protocols and montages to that of Chapter 2 on

basic neurophysiological markers of E–I balance in visual cortex, such as visually induced peak gamma frequency and VEP amplitudes (N1 and P2). 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, E–I balance has been indirectly inferred from the peak frequency of the gamma band (30–90 Hz) (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015). Neural oscillatory activity in the gamma band has been suggested to result from the interactions between pyramidal excitatory cells and inhibitory GABAergic interneurons (Brunel, 2003; Börgers & Kopell, 2003). Consistent with this finding, peak gamma frequency has been shown to positively correlate with increased resting-state GABA concentration level in V1 (Edden et al., 2009; Kujala et al., 2015; Muthukumaraswamy et al., 2009). However, this relationship could not be confirmed in the work of Cousijn et al. (2014), possibly because of methodological differences concerning, for example, type of MRS sequences and sample size (Cousijn et al., 2014; Kujala et al., 2015). In addition, peak gamma frequency has also been shown to inversely associate with blood-oxygenation-level dependent (BOLD) response measured by functional MRI (Muthukumaraswamy et al., 2009). Such an association possibly reflects the level of an E–I balance, given the findings of a negative correlational relationship between fMRI BOLD response and GABA concentration (Donahue et al., 2010; Kurcyus et al., 2018; Muthukumaraswamy et al., 2009). Additionally, pharmacological manipulation of GABA receptors has been shown to influence 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). These findings are unexpected, however, based on findings of a positive correlation GABA and peak gamma frequency (Edden et al., 2009; Kujala et al., 2015; Muthukumaraswamy et al., 2009), suggesting that the direction of the relationship between cortical inhibition and peak gamma frequency requires more investigation. In addition, peak gamma frequency has also been found to be associated with performance in psychophysical tasks such binocular rivalry and the ODT, which have been shown to correlate with resting-state GABA concentration level (Edden et al., 2009; van Loon et al., 2013). For instance, higher gamma frequency was found to be associated

with slower perceptual dynamics (Fesi & Mendola, 2015) and enhanced orientation discriminability (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).

Similar to neural oscillations at gamma frequency, neural oscillation at alpha frequency band (8-12 Hz) has also been suggested to reflect cortical E-I balance (Klimesch, Sauseng, & Hanslmayr, 2007; Lozano-Soldevilla, 2018; Mayhew, Ostwald, Porcaro, & Bagshaw, 2013; Romei, Rihs, Brodbeck, & Thut, 2008). One line of evidence supporting this comes from findings of studies showing that the activity of excitatory and inhibitory transmitters implicated in the generations of such neural oscillations in animals and humans (Lozano-Soldevilla et al., 2014; Lőrincz, Kékesi, Juhász, Crunelli, & Hughes, 2009; Schreckenberger et al., 2004). For instance, pharmacological manipulations of the activity of excitatory and inhibitory interneurons have been shown to modulate the activity of alpha oscillations (Ahveninen et al., 2007; Muthukumaraswamy et al., 2015). Additionally, increased and decreased of the alpha oscillations has been suggested to indicate a state of inhibited or enhanced cortical excitability, respectively (Jensen & Mazaheri, 2010; Romei et al., 2007). Also, alpha activity has been suggested to play a role in information processing (Anderson & Ding, 2011; Klimesch, 2012; Pfurtscheller, Neuper, & Mohl, 1994; Sauseng et al., 2005). For instance, alpha activity decreases in the brain regions contralateral to the attention direction whereas it increases in the brain regions ipsilateral to attention direction. These changes in alpha activity are thought to work as a gating mechanism as irrelevant information gets inhibited to increase the efficacy of processing the relevant information (Anderson & Ding, 2011). This selective suppression to irrelevant information associated with increased alpha activity reflects an inhibitory functional role of alpha oscillations (Jensen & Mazaheri, 2010). Additionally, alpha activity has been shown to associate with gamma activity (Osipova, Hermes, & Jensen, 2008; Spaak, Bonnefond, Maier, Leopold, & Jensen, 2012; Voytek et al., 2010; Zazio, Schreiber, Miniussi, & Bortoletto, 2019). For instance, an increase of alpha power associates with a reduction in gamma frequency power (Spaak et al., 2012; Zazio et al., 2019). Although alpha activity can be indirectly indicative index of cortical E-I balance (Lozano-Soldevilla, 2018), this

chapter mainly focused on investigating the links between neural oscillations at gamma frequency band given previous studies findings of an association between peak gamma frequency on the one hand and GABA concentration levels in visual cortex and ODT thresholds on the other hand (Dickinson, Bruyns-Haylett, et al., 2016; Edden et al., 2009; Muthukumaraswamy et al., 2009; Shaw et al., 2019).

Similar to peak gamma frequency, VEP activity has been suggested to reflect the summation of excitatory and inhibitory postsynaptic potentials (EPSP, IPSP, respectively) (Purpura, 1959; Zemon et al., 1980). Accordingly, VEP amplitudes have used to indicate E–I balance (Aloisi, Marrelli, Porto, Tozzi, & Cerone, 1997; Andrade, Butler, Peters, Molholm, & Foxe, 2016; Ding et al., 2016; Gawel et al., 1983; Kennard et al., 1978; Nguyen et al., 2016; Sokol, 1983). 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, VEP amplitudes have been shown to be modulated by pharmacological manipulations of GABA activity in animal and human models (Daniels & Pettigrew, 1975; Hudnell & Boyes, 1991; Kraut et al., 1990; Schafer et al., 1984; 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 amplitudes of VEP components (Aloisi et al., 1997; Nguyen et al., 2016; Zemon et al., 1980; Zeneroli et al., 1981).

As detailed in the introduction, tDCS is a way to modulate cortical E–I balance (Antonenko et al., 2017; Clark, Coffman, Trumbo, & Gasparovic, 2011; Kim et al., 2014; Krause et al., 2013; Stagg et al., 2009). Although tDCS over the visual cortex has been used to attempt to modulate neural oscillatory activity in the visual cortex at the gamma

frequency band (Antal, Varga, et al., 2004; Hanley et al., 2016; Marshall et al., 2016; Wiesman et al., 2018; Wilson et al., 2017), findings are equivocal. For instance, anodal-tDCS was found to increase gamma frequency power while cathodal-tDCS decreased it (Antal, Varga, et al., 2004). An additional study also reported that anodal-tDCS increased gamma frequency power compared to sham-DCS but left peak gamma frequency unchanged (Wilson et al., 2017). Additionally, cathodal-tDCS was shown to reduce the spontaneous gamma frequency compared to both sham- and anodal-tDCS (Wiesman et al., 2018). However, several studies failed to find any effects of occipital tDCS in modulating neural activity at the gamma frequency (Hanley et al., 2016; Marshall et al., 2016). This inconsistency might result from differences in tasks and tDCS montages and parameters (Nitsche et al., 2008; Woods et al., 2016). For instance, Hanley et al. (2016) and Marshall et al. (2016) used a tDCS montage with a short distance between the target and reference electrode (Oz, Cz), increasing the risk of the current shunting effects (Bikson et al., 2010; Miranda et al., 2006). However, Wiesman et al. (2018) and Wilson et al. (2017) used a montage with a longer distance between the target and reference electrode (Oz, right frontal cortex), satisfying the recommendation of a 4-cm placement to avoid such effects (Moliadze et al., 2010; Rush & Driscoll, 1968). Additionally, Hanley et al. (2016) and Marshall et al. (2016) administered tDCS during a visual task (online tDCS) while Wiesman et al. (2018) and Wilson et al. (2017) administered tDCS before the visual task (offline tDCS). Such a difference might contribute to the discrepancy between these studies' findings, given the brain-state dependency of tDCS effects (Bocci et al., 2014; LLi et al., 2017; Li et al., 2019). As such, offline tDCS with a monopolar tDCS montage (Oz, left cheek) was used to attempt to modulate peak gamma frequency induced by a visual EEG task, shown previously to elicit clear and reliable gamma response (Milne et al., 2018; Milne et al., 2019). This task was anticipated to allow the observation of putative changes in peak gamma frequency produced by tDCS, based on previous findings of a robust difference in peak gamma frequency between individuals with and without ASC when a similar visual task was used (Dickinson, Bruyns-Haylett, et al., 2016).

Similarly, effects of occipital tDCS on VEP amplitudes have been investigated, but with inconsistent results (Accornero et al., 2007; Antal, Kincses, Nitsche, Bartfai, & Paulus,

2004; Antal et al., 2006; Siniatchkin et al., 2011). For instance, Antal et al. (2004) found that anodal-DCS increased VEP-N75, while cathodal-tDCS decreased it, with observation of no such robust effects of tDCS on VEP-P100. Inconsistent with that study, P100 amplitude was found to be modulated by tDCS in a polarity-dependent manner as anodal-tDCS decreased VEP P100, while cathodal-tDCS increased it (Accornero et al., 2007). However, Bocci et al. (2014) reported that anodal-tDCS increased the amplitudes of both VEP-P1 and VEP-N1, which is consistent with the findings of Ding et al. (2016) and Siniatchkin et al. (2011) that anodal-tDCS increased the amplitude of VEP ((N75- P100), (N80- P100)), while cathodal-tDCS decreased it (Ding et al., 2016; Siniatchkin et al., 2011). Again, the discrepancy could possibly be attributed to methodological differences (i.e., tDCS protocol and montage, tasks being used) (Nitsche et al., 2008; Woods et al., 2016). For instance, while Antal et al. (2004) used a bipolar tDCS montage (Oz, Cz) with a striped pattern visual stimuli, Accornero et al. (2007) used a monopolar tDCS montage (Oz, posterior neck-base) with pattern-reversal checkerboard stimuli. Given the inconsistent findings of occipital tDCS effects on neural activity (i.e., gamma frequency oscillations, VEP activity), further investigation is needed to resolve this discrepancy and uncover the potential outcomes of tDCS.

Using identical protocols and montages to those used in Chapter 2, the current study aimed to investigate the effects of occipital tDCS on peak gamma frequency and VEP components amplitudes (N1 and P2) measured by electroencephalogram (EEG). As gamma frequency and VEP activity 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), an EEG task that has been shown to elicit strong peak gamma frequency and clear VEP activity was used (Milne et al., 2018; Milne et al., 2019). It was hypothesised 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). Additionally, it was expected 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).

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). Thirteen of the participants had participated in previous studies, and the rest were new participants. The new participants were asked to complete a 12–15-min visual ODT 25–30 min before the EEG acquisition. Detailed information about the ODT was provided in the method section of Chapter 2. Moreover, detailed information about the ODT data collected in this experiment is presented in Chapter 4.

Participants received a £10–12 gift voucher for participation. Participants gave written informed consent at the beginning of each session. The study received full ethical approval from the Department of Psychology University of Sheffield ethics committee.

Transcranial direct current stimulation

Identical to Chapter 2, 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 10–20 electrode placement system (Jasper, 1958; Klem et al., 1999). The efficacy of transcranial direct current stimulation (tDCS) over the occipital cortex has been reported previously (Antal, Kincses, Nitsche, & Paulus, 2003a, 2003b; Antal, Nitsche, & Paulus, 2001; Antal et al., 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 has been relatedly used in previous tDCS studies (Berryhill et al., 2010; Hsu et al., 2011; Nasseri et al., 2015; Reinhart et al., 2017).

A duration of 10 min offline tDCS was used in this study, given previous studies' findings that 9–13 min offline tDCS has an aftereffect lasting up 90 min after the termination of the stimulation (Kuo et al., 2013; Nitsche, Nitsche, et al., 2003; Nitsche & Paulus, 2001). Such an aftereffect of tDCS covers the duration of resetting the EEG equipment (3–7 min) and the EEG task (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. 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). However, with sham-tDCS, the current was delivered for only 30 s, 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).

Electroencephalogram task

Apparatus

Electroencephalogram (EEG) data were collected using 64 electrodes BioSemi ActiveTwo system (Biosemi Instrumentation BV, Amsterdam, The Netherlands) at a sampling rate of 2048 Hz. The electrodes were placed in accordance with the international 10/20 system (Jasper, 1958; Klem et al., 1999). Electroencephalogram 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 below +/–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.

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 in 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 check subtended .4 degrees of visual angle.

In each run, participants were asked to sit comfortably on a chair with a distance of 57 cm between their heads and the monitor and were asked to keep movement to a minimum. Participants were instructed to fixate on a red dot appearing on the centre of the monitor.

The static black and white checkerboard stimulus repeatedly appeared on the centre of the monitor for an average of 2000ms (1500-2500ms) with the inter-stimulus interval (ISI) of 1500–2500 ms (mean=2000 ms).

Participants were asked to press the spacebar when the checkerboard disappeared in order to maintain attention. Participants have presented 200 trials, divided equally into two blocks with a self-timed break between these blocks (1–3 min). Participants were asked to respond in the first block using their right hand, and in the second block using their left hand. Each run lasted 12–15 min, depending on the duration of participants' break between the run's two blocks (Figure 3.1).

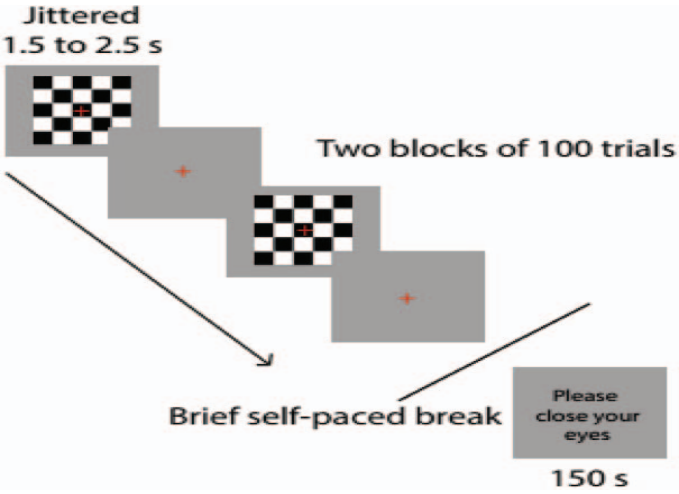


Figure 3.1 Schematic diagram of the electroencephalogram (EEG) task. This figure is reprinted with permission from (Milne et al., 2019).

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. Participants completed the EEG task in a light-dimmed electrically shielded room.

At the end of the experimental session, participants were asked to complete questionnaires assessing tDCS's adverse effects (Brunoni et al., 2011) and post-stimulation ratings of pain, attention, and fatigue (Galea et al., 2009). This step was to evaluate to what extent participants' experience of active-tDCS (anodal and cathodal) would differ from that of participants of sham-tDCS, given the findings of recent studies suggesting that sham-tDCS may be less effective in blinding participants to the stimulation mode (active vs sham) based on participants' stimulation experiences. 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).

Transcranial direct current stimulation electroencephalogram setting

After the end of the first run of the electroencephalogram (EEG) task, the EEG amplifier was switched off, and the EEG electrode wires were disconnected from the EEG amplifier. 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 transcranial direct current stimulation (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 (Figure 3.2 A and B). Afterward, tDCS was switched on for 10 min, starting in a ramp-up like fashion over the first 30 s until it reached 2 mA. At the end of the tDCS 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.). An approximate duration of 5 minutes (3–7 min) lapsed 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.

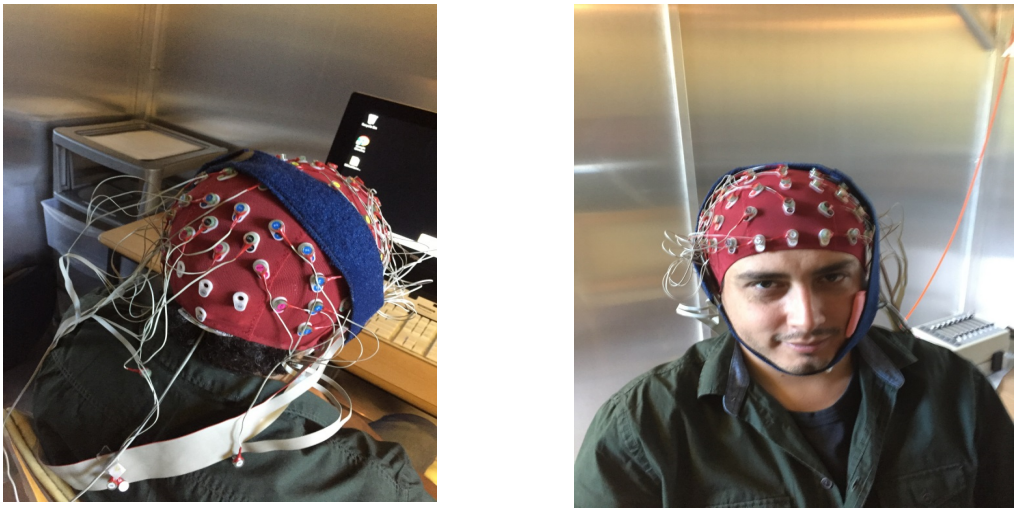


Figure 3.2 A and B. Illustration of the combination of transcranial direct current stimulation (tDCS) with electroencephalogram (EEG). These pictures are for illustrative purposes only.

Electroencephalogram analysis

Similar to previous studies (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015), continuous EEG data were sampled online at 1024 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 used a high pass filter of 1 Hz 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, Dworetzky, & Schomer, 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 3. 1).

tDCS type Group	Pre-tDCS Run (Removed EEG channels)				Pre-tDCS Run (Removed EEG channels)			
	M	Min.	Max.	*SD*	*M*	Min.	Max.	*SD*
Anodal-tDCS	3	1	7	2.14	3.82	1	9	2.89
Cathodal-tDCS	3.55	1	9	2.73	4.00	1	10	3.29
Sham-tDCS	3.73	1	9	2.15	3.36	2	7	1.69
10-min delay with no-tDCS	4.55	1	11	3.39	4.36	1	11	3.26

Table 3.1 Removed electroencephalogram (EEG) channels of pre- and post-transcranial direct current stimulation (tDCS) runs for each for the tDCS type group. 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 group ($p > .05$).

Then, continuous EEG data were segmented into epochs from 200 ms prior to the stimulus onset to 1,500. The number of epochs 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 3. 2).

tDCS type Group	Pre-tDCS Run (Remained Epochs)				Post-tDCS Run (Remained Epochs)			
	M	Min.	Max.	*SD*	*M*	Min.	Max.	*SD*
Anodal-tDCS	192.82	178	199	6.68	192.64	186	199	4.59
Cathodal-tDCS	189.00	163	200	12.97	189.82	165	200	10.43
Sham-tDCS	181.82	145	197	18.91	180.64	151	197	14.66
10-min delay with no-tDCS	183.55	157	199	13.56	183.09	156	200	13.82

Table 3.2 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 ($p > .05$).

Independent component analysis for the time-frequency analysis

Electroencephalogram signals recorded from the scalp can be generated from neural activity and environmental (e.g., noise from power line interference) or biological sources (e.g., eye movements, blinks, and muscle activity) (Luck, 2014; Tatum et al., 2011; Teplan, 2002). The non-neural environmental and biological sources of EEG are considered artefacts and can be problematic. For instance, power line interference produces noise at 50 Hz throughout the EEG signals (Correa, Laciar, Patiño, & Valentinuzzi, 2007; Reddy & Narava, 2013). Similarly, eye saccades have been linked to changes in EEG power in the gamma frequency range (30–90 Hz) between 200–300 ms after the onset of the stimulus (Reva & Aftanas, 2004; Yuval-Greenberg, Tomer, Keren, Nelken, & Deouell, 2008). Such artefacts could negatively affect the frequency and time range of this study's interest. Thus, in a manner identical that of previous studies (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015), a signal-blind source separation technique known as

independent component analysis (ICA) (Makeig, Jung, Bell, Ghahremani, & Sejnowski, 1997) was used to isolate the neural responses to the visual stimulus from other artefacts' activity (Jung et al., 2000). ICA can decompose data into either spatially or temporally independent components (Anemüller, Duann, Sejnowski, & Makeig, 2006). The spatial ICA is commonly used with fMRI signals (Erhardt et al., 2011) whereas the temporal ICA is commonly used in EEG data (Chatzichristos, Davies, Escudero, Kofidis, & Theodoridis, 2018). As such, in this chapter, 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.

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 contentious 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 *"Encephalogram 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 tomography of all components. Any ICA components with focal activity in the occipital cortex were selected, leading to up to four ($M = 2.89$, $SD = .72$) components being selected for each participant in the pre-tDCS run and up to five components in the post-tDCS run ($M = 280$, $SD = .85$), irrespective of tDCS groups (anodal-, cathodal-, sham-, 10-min delay with no-tDCS). The selected components 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, Chen, Tsoi, & Sergejew, 1997). The time-frequency analysis was performed via in-house MATLAB script that was developed by Torrence and Compo (1998) identical to that used previously (Dickinson, Bruyns- Haylett, et al., 2016; Dickinson et al., 2015). Any components with no- or unclear event-related dynamics were excluded, (Figure 3.3)

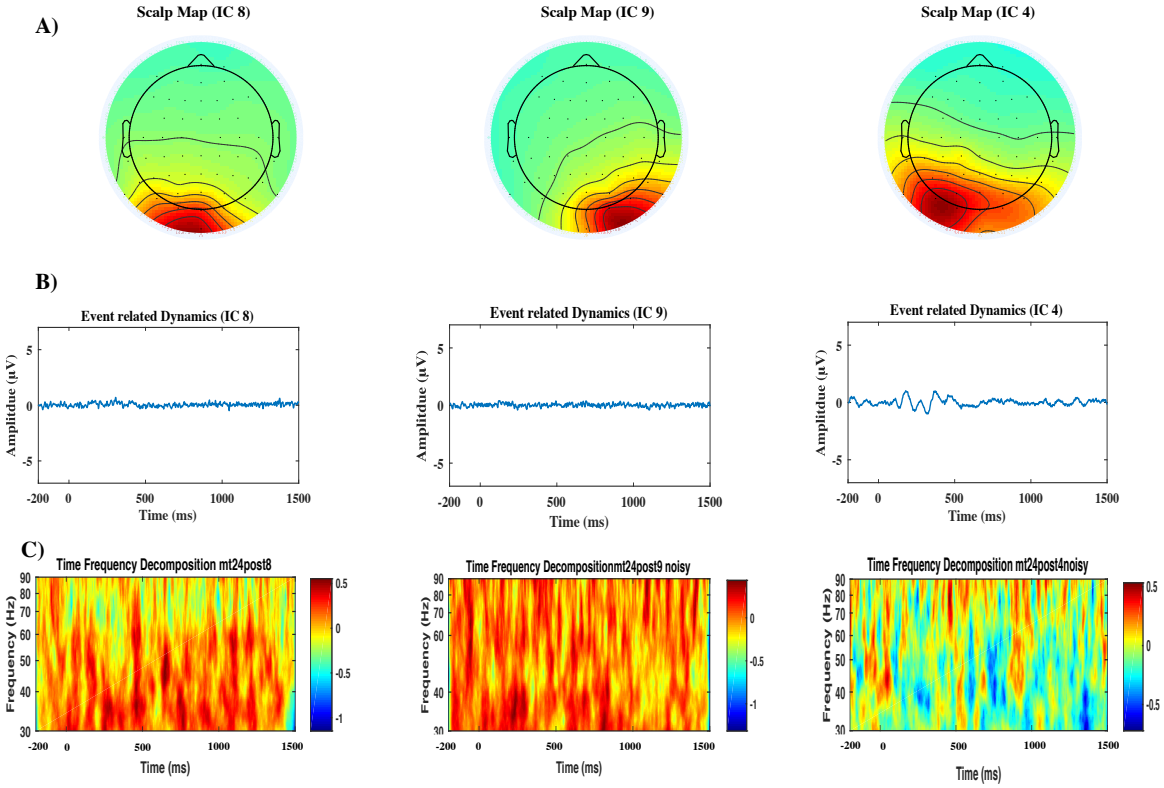


Figure 3.3. Illustrations of excluded IC components due to non-clear event-related dynamics and unclear induced gamma activity for one participant. A) Illustrates the scalp maps of IC components with activity in visual cortex for one participant. B) Illustrates the event-related dynamics of the three IC components for one participant. C) Illustrates induced gamma activity of the three IC components for one participant.

From the remaining components of the pre- and post- tDCS run, the best matching pairs of components from the pre- and post-tDCS sharing similar distinct event-related dynamics

for each participant were selected. Finally, a single component 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 pairs for a participant, a single component pair was selected based on the clarity of the sustained visually induced changes in gamma band power, (Figure 3.4).

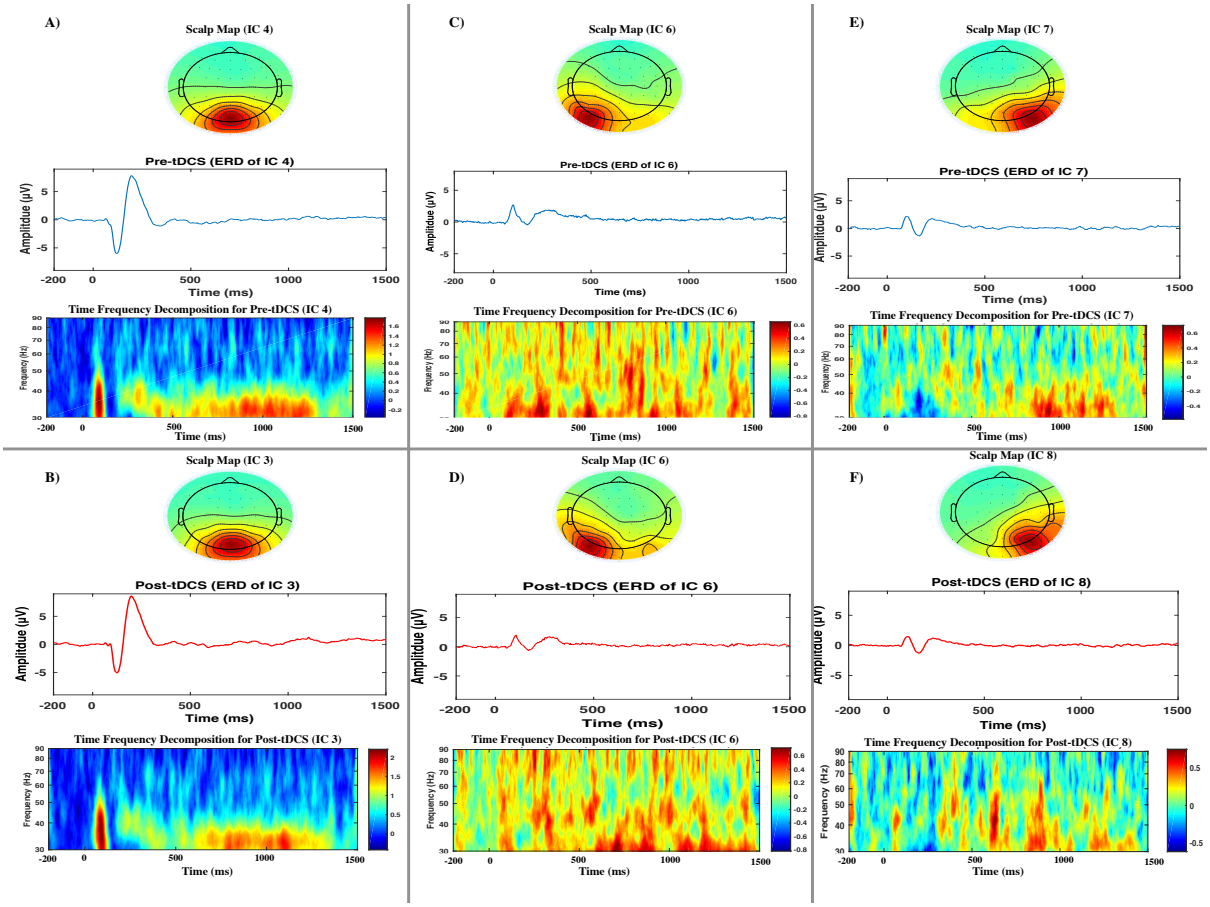


Figure 3.4. illustrations of ICA components selections for one participant pre- and post-tDCS. A, C, and E illustrate scalp map, event-related dynamics, and induced gamma activity of IC components pre-tDCS for one participant. B, D, and F illustrate scalp map, event-related dynamics, and induced gamma 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 a 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 component pair from pre- and post-tDCS run for each participant based on their VEP similarity and the clarity of the induced gamma activity, a repeated

measures analysis of variance (ANOVA) was performed to examine tDCS effects on induced gamma frequency.

To summarise, the initial step was to check the scalp tomography 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 components with no clear event-related dynamics with IC components of the other EEG data set for the same participant. The second reason is that IC components with clear event-related dynamics have unclear induced gamma frequency, (Figure 3.3). After IC components 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 IC components 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, (Figure 3.4).

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 ICA components 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, Moore, & Jevrejeva, 2004; K. Müller et al., 2004). The complex Morlet wavelet consists of a complex exponential modulated by a Gaussian, $\omega_0 = 6$; where ω_0 is 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), 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 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. Such analysis contains, in addition to induced gamma activity, the power changes of evoked gamma responses.

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 subsequent matrix's maxima provides the maximum increase in evoked power in gamma frequency band (30-90 Hz) following stimulus presentation (Figure 3.5A). Thus, to obtain a better estimate of induced gamma activity, the power changes of evoked responses at gamma frequency band is subtracted from the induced gamma activity (Figure 3.5B). Before the subtraction, however, the wavelet transforms are rescaled between zeros to unity as the induced wavelet transform has power changes with variable magnitudes to the signal wavelet transform. The selection of the subsequent matrix's maxima provides the maximum increase in induced power in gamma frequency band following the presentation of the stimulus. Thus, the wavelet transforms were performed on each trials (epoch) for each subject, then these trials were averaged in order to increase the signal to noise ratio (SNR). A Gaussian non-linear least squares curve was 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 (Figure 3.5C).

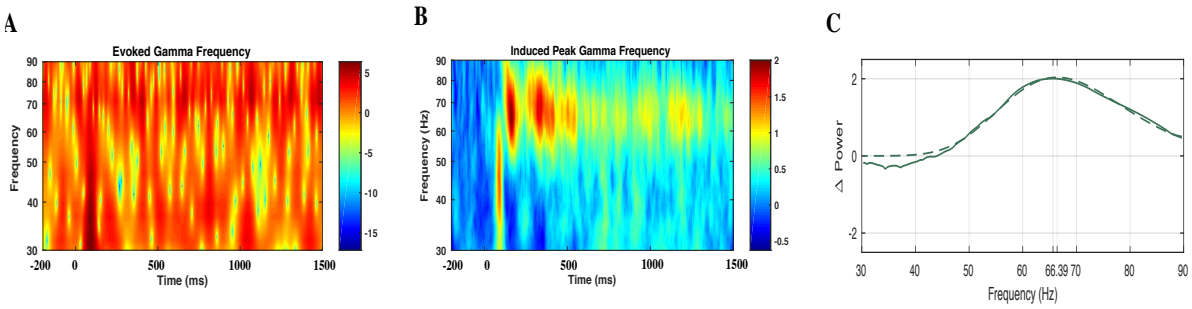


Figure3.5. Illustrations of full gamma activity, induced gamma frequency, and power changed at gamma frequency band of an independent component of a single participant. (A) Time frequency decomposition of full gamma activity activity, including evoked and induced activity for an independent component of one participant. (B) Time frequency decomposition of induced gamma frequency for an independent component of one participant. (C) The total power change at each frequency (solid line) and the curve-fitted total power change at gamma frequency (dashed line) for an independent component of one participant.

Visual evoked potentials of the occipital cortex (Oz)

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 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 (Figure 3.11). This method of selecting time windows for evoked potential events is commonly used (Hanslmayr et al., 2005; Kissler, Herbert, Winkler, & Junghofer, 2009; Milne et al., 2018).

Results

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. The stimulation experience of participants also did not significantly differ between active- and sham-tDCS ($p > .05$). In addition, the stimulation experience of participants for active- and sham-tDCS did not significantly differ in terms of pain, attention, and fatigue based on the post-stimulation ratings ($p > .05$). 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).

Several participants were excluded from the analysis due to excessive noise in their EEG signals with no clear induced gamma activity (N=4), had peak amplitudes of VEP components (N1, P2) deviating from the mean by more than 3 standard deviations (N=1), technical issues related to tDCS connection (N=1), and uncomfortable tingling sensation of tDCS (N=1). Additionally, three participants were ineligible to participate in the EEG task due to headwear (e.g. hair extensions) ($N = 2$) or being on medication ($N = 1$), and they were therefore excluded from the analysis. 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, $M = 29.38$, $SD = 7.50$).

Time-frequency analysis

Two repeated measures ANOVA analyses were performed to investigate effects of tDCS on the activity of induced gamma frequency (peak gamma frequency, gamma frequency power). All statistical analyses were performed using SPSS version 24 for Mac (IBM SPSS, Armonk, New York).

First, data were analysed using a repeated measures ANOVA, treating tDCS-type groups as a between-subjects variable and treating peak gamma frequency, including peak gamma frequency pre-tDCS gamma frequency pre-tDCS post-tDCS as within-subjects variables.

A main effect of peak gamma frequency was found, ($F(1, 35) = 7.927$, $p = .008$). Pairwise comparisons showed 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, $SE = 2.07$), (Figure 3.6A).

However, no significant interaction between peak gamma frequency and tDCS- type groups was found, ($F(3, 35) = .746$, $p = .53$), nor main effect of tDCS- type groups ($F(3, 35) = .711$, $p = .55$), (Figure 3.7A and Figure 3.8).

Second, data were analysed using a repeated measures ANOVA, treating tDCS-type groups as a between-subjects variable and treating gamma frequency power pre-tDCS and post-tDCS as within-subjects variables.

No main effect of gamma frequency power was found ($F(1, 35) = .757$, $p = .390$), (Figure 3.6B). Additionally, no significant interaction between gamma frequency power and tDCS-type groups was found, ($F(3, 35) = .982$, $p = .41$), nor main effect of tDCS- type groups ($F(3, 35) = .464$, $p = .71$), (Figure 3.7B).

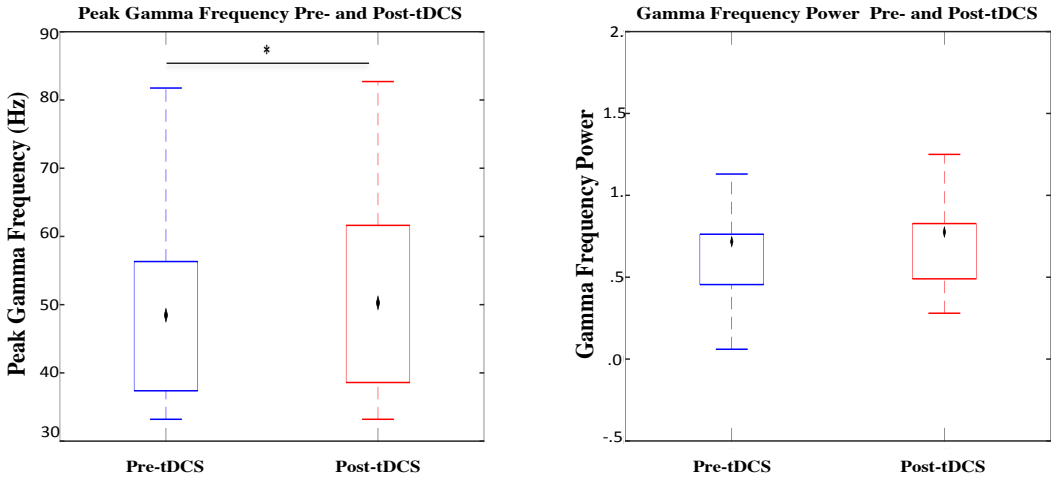


Figure 3.6 A and B. Box plots demonstrating the mean and standard error of the neurophysiological measures pre- and post-transcranial direct current stimulation (tDCS) for all the tDCS type groups. A) Box plots demonstrating peak gamma frequency pre- and post-tDCS for all the tDCS type groups. B) Box plots demonstrating gamma power frequency pre- and post-tDCS for all the tDCS type groups. * $p = .008$.

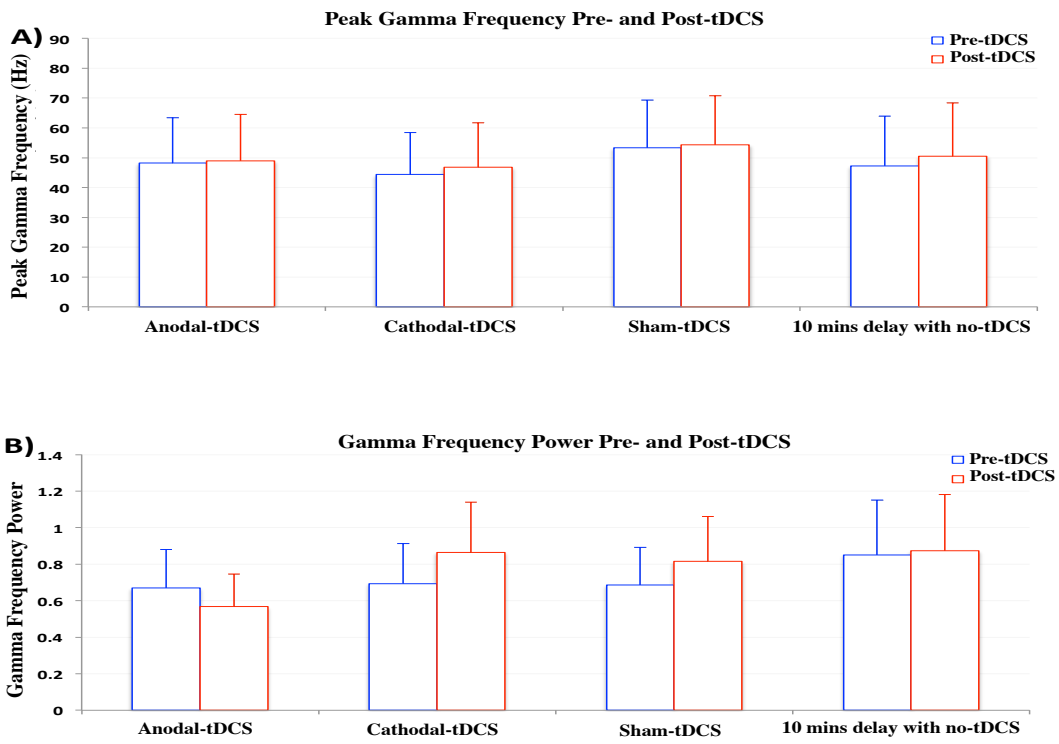
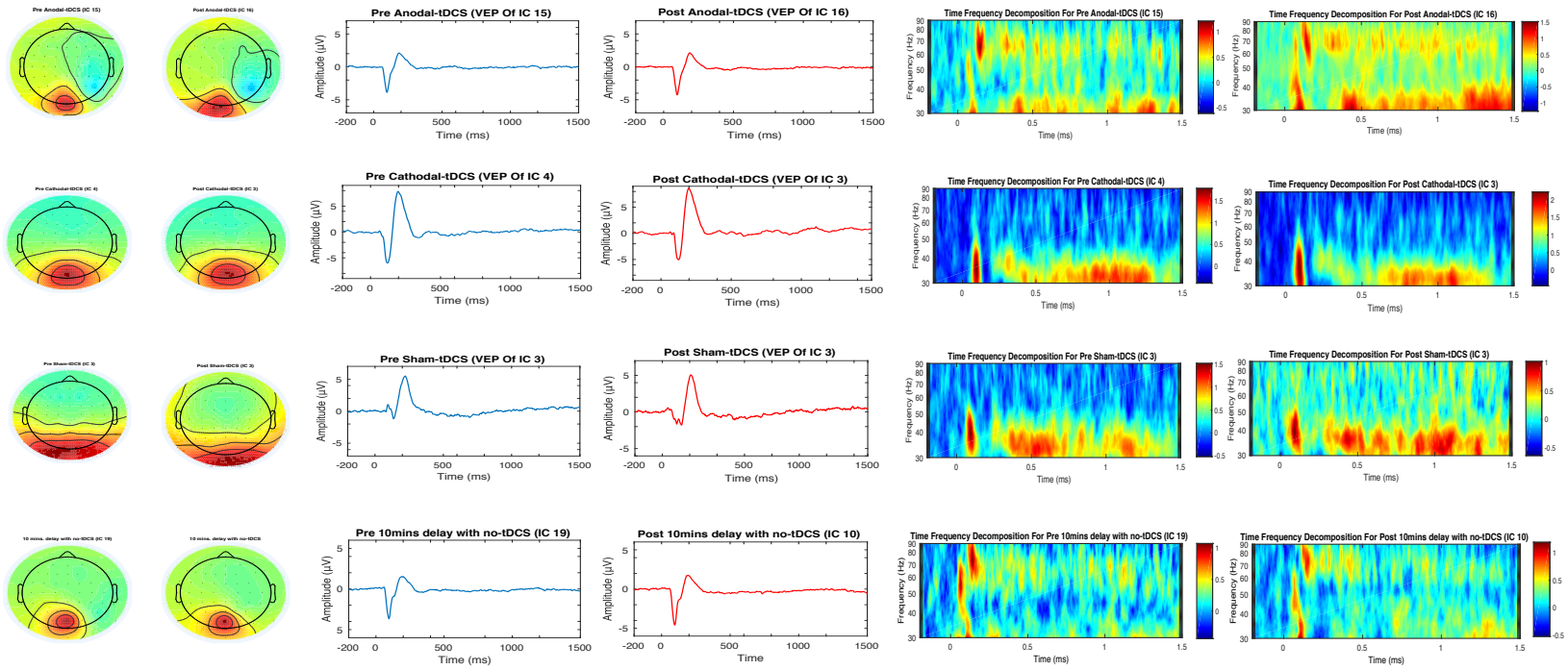


Figure 3.7 A and B. Bar charts demonstrating the mean and standard error of induced gamma frequency oscillations (peak and power) pre-transcranial direct current stimulation (tDCS) (blue line) and post-tDCS (blue line) for each of the tDCS-type groups (anodal-, cathode-, sham-, and 10-min delay with 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).



"Figure 3.8. 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)."

Visual evoked potential analysis

Data were analysed using a repeated measures ANOVA, treating tDCS-type groups as a between-subjects variable and peak amplitudes of visual evoked potential (VEP) components (N1 and P2) and runs (pre- and post-tDCS) as within-subjects variables.

There were main effects of peak amplitudes of VEP components (N1 and P2) ($F(1, 35) = 35.644$, $p < .0001$) and run (pre-tDCS and post-tDCS) ($F(1, 35) = 5.474$, $p = .025$). The peak amplitude of P2 was significantly higher ($M = 13.13$ μV, $SE = 1.03$) than the peak amplitude of N1 ($M = 5.76$ μV, $SE = .75$). Additionally, the peak amplitude of VEP components (N1 and P2) was significantly lower in the second (post-tDCS) run ($M = 9.00$ μV, $SE = .68$) compared to the first run ($M = 9.89$ μV, $SE = .69$).

To evaluate whether the run-related reduction occurred for both N1 and P2, a *post hoc* analysis was performed. The result showed that only N1 component was significantly reduced in the second (post-tDCS) run ($M = 5.27$ μV, $SE = .73$) compared to the first (pre-tDCS) run ($M = 6.24$ μV, SE = .81), $p = .015$. However, no such significant reduction occurred for P2 in the second run ($M = 12.73$ μV, $SE = 1.07$) compared to the first (pre-tDCS) run ($M = 13.53$ μV, $SE = 1.07$)), $p = .148$ (Figure 3.9).

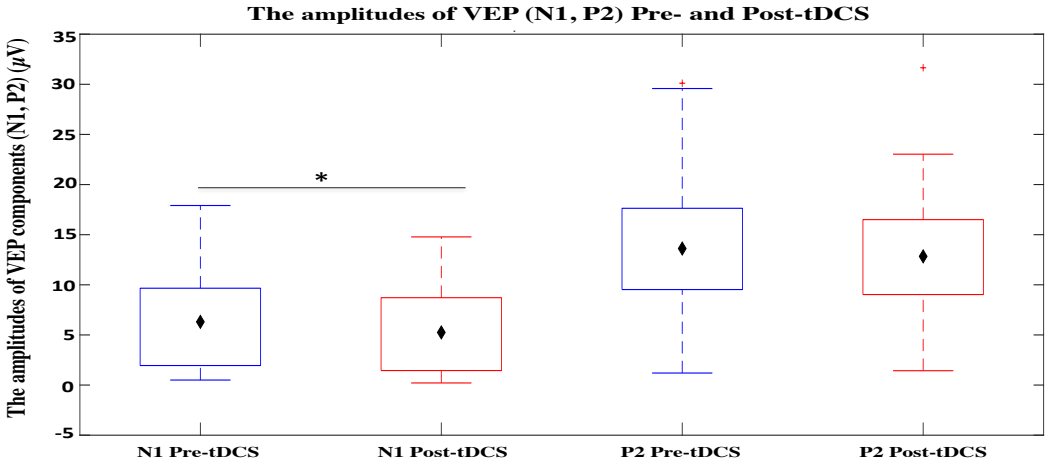


Figure 3.9. Box plots demonstrating the means and standard error of the amplitudes of visual evoked potential (VEP)-N1 and P2 pre- and post-transcranial direct current stimulation (tDCS) for all tDCS-type groups (anodal-, cathodal-, sham-, and 10-min delay with no-tDCS). * p = .015.

Additionally, there were neither significant interactions nor main effects for tDCS-type groups ($F(3, 35) = .375$, $p = .771$) (Figure 3.10 and Figure 3.11).

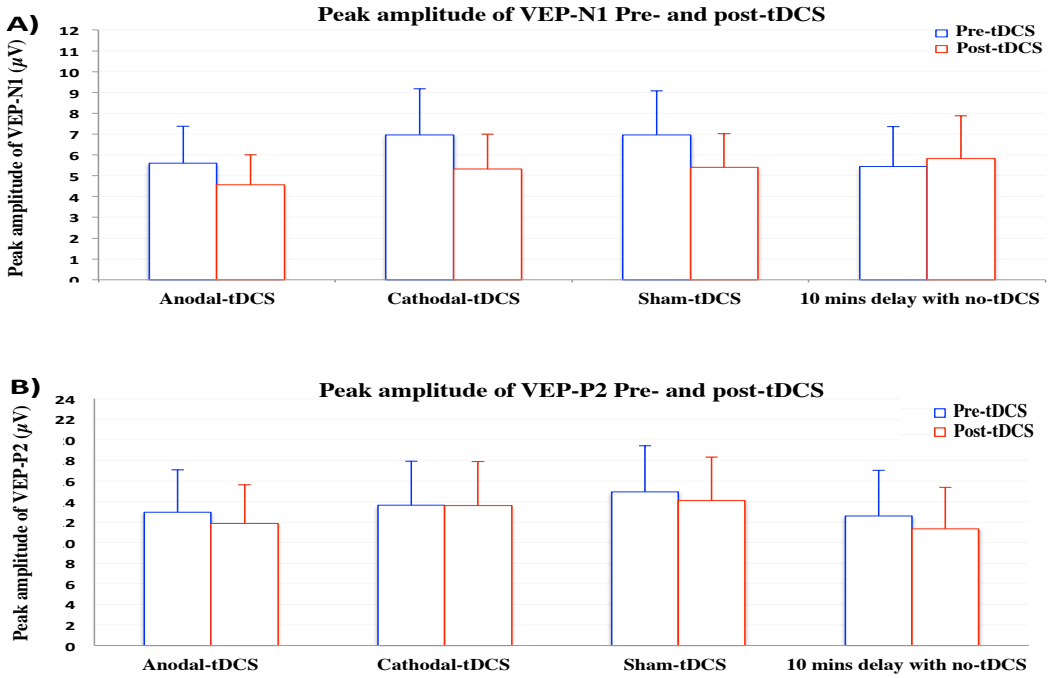


Figure 3.10 A and B. Bar charts demonstrating the mean and standard error of the amplitudes of visual evoked potential (VEP)-N1 and P2 pre-transcranial direct current stimulation (tDCS) (blue line) and post-tDCS (red line) for each of the tDCS-type groups (anodal-, cathodal-, sham-, and 10-min delay 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 going between 175 ms and 250 ms post-stimulus onset.

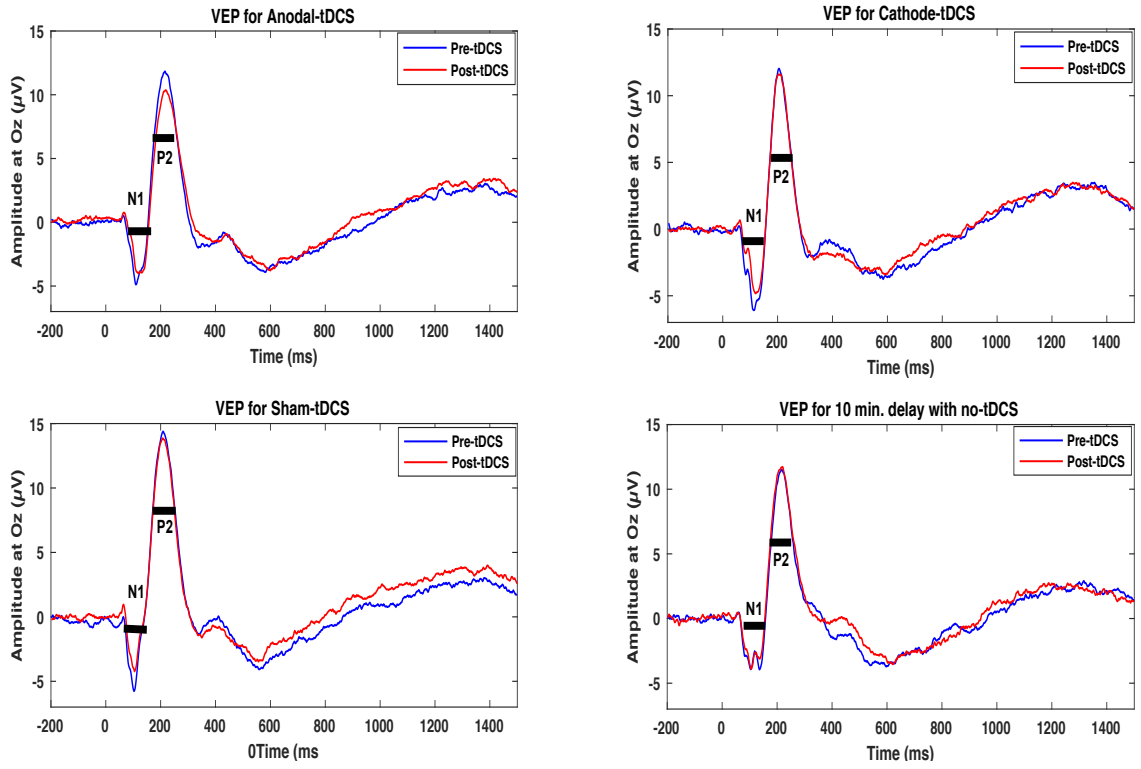


Figure 3.11. Grand-averaged visual evoked potential (VEP) waveforms in response to the checkerboard stimulus for each of the transcranial direct current stimulation (tDCS) type groups pre-tDCS (blue line) and post-tDCS (red line). A) VEP waveforms for anodal-tDCS pre-tDCS (blue line) and post-tDCS (red 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.

Discussion

In this chapter, the effects of offline tDCS in modulating induced gamma frequency (peak gamma frequency and gamma frequency power) and the amplitudes of VEP components (N1 and P2) were investigated. Participants completed two runs of an EEG task in a dim-light room while EEG data were collected. During the EEG task, participants were instructed to fixate on a red dot appearing on the centre of a monitor while a black and white chalkboard stimulus was repeatedly presented. Between the two runs of the EEG task, there was an interval of approximately 20 minutes during which participants randomly received anodal-tDCS, cathodal-tDCS, sham-tDCS, or had 10-min delay with no-tDCS. The statistical analyses of the time-frequency and VEP amplitude metrics revealed a main effect of EEG task run (pre-tDCS vs post-tDCS) on both induced gamma frequency (peak gamma frequency and gamma frequency power) and amplitude of VEP components (N1 and P2). For example, induced gamma frequency robustly increased in the second run (post-tDCS) compared to the first (pre-tDCS) run of the EEG task. Further analysis showed that only peak gamma frequency, but no gamma frequency power, significantly increased in the second (post-tDCS) run compared to the first (pre-tDCS) run of the EEG task. Similarly, but in the opposite direction, the amplitude of VEP components robustly decreased in the second (post-tDCS) run compared to the first (pre-tDCS) run of the EEG task. Further analysis showed that only VEP-N1 amplitude, but no VEP-P2 amplitude, significantly decreased in the second (post-tDCS) run compared to the first (pre-tDCS) run of the EEG task. Additionally, the statistical analyses of both metrics of time-frequency and VEP amplitude revealed no main effects of tDCS in modulating either induced gamma frequency or the amplitude of VEP components (N1 and P2). Possible explanations for the observation of no effects of tDCS in induced gamma frequency and the amplitude of VEP components (N1 and P2) are discussed below.

Unlike previous studies finding no robust difference in neural activity (i.e., peak gamma frequency and VEP amplitude) between three-point recordings in a single session (Ding et al., 2016; Magazzini et al., 2016; Muthukumaraswamy et al., 2013), robust changes in both

induced gamma frequency and VEP amplitudes related to the EEG task repetition were observed, irrespective of tDCS type groups. For instance, peak gamma frequency significantly increased in the second run (post-tDCS) of the EEG task compared to the first (pre-tDCS) run. Additionally, the amplitude of VEP-N1 significantly decreased in the second run (post-tDCS) of the EEG task compared to the first (pre-tDCS) run. Such an increase in peak gamma frequency and reduction in N1 may also indicate increased cortical inhibition, given the findings of animal and human studies suggesting a positive correlation between GABA concentration and peak gamma frequency (Edden et al., 2009; Kujala et al., 2015; Muthukumaraswamy et al., 2009), but an inverse 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).

The EEG task run-related changes observed in neural activity (i.e., increase in peak gamma frequency, reduction in VEP amplitudes) could be attributed to habituation. Habituation, a well-documented phenomenon, can be defined as a reduction in responses resulting from stimulus repetition (Rankin et al., 2009; Thompson & Spencer, 1966). While the underlying mechanisms of habituation are not fully understood, the balance of E–I has been suggested to play a role in normalizing habituation (Ambrosini et al., 2016; Brighina, Palermo, & Fierro, 2009; Coppola et al., 2013; Mulleners, Chronicle, Palmer, Koehler, & Vredeveld, 2001). For instance, reduced habituation in migraine has been thought to be associated with downregulation of GABA (Brighina et al., 2009). Such reduced habituation has been reflected in the lack of VEP amplitude reduction over stimulus repetition (Afra, Cecchini, De Pasqua, Albert, & Schoenen, 1998; Coppola et al., 2015; Schoenen, 1996). Manipulating neural excitability using electrical brain stimulation such as repetitive transcranial magnetic stimulation (rTMS) and tDCS has been reported to influence habituation (Bohotin et al., 2002; Fumal et al., 2006; Siniatchkin et al., 2011; Viganò et al., 2013). For instance, it has been shown that increased habituation of individuals with migraines occurred following excitatory rTMS that initially increased VEP amplitude, while inhibitory rTMS decreased habituation of healthy individuals after inducing decrement in VEP amplitude (Bohotin et al., 2002). Likewise, tDCS has been shown to modulate habituation in a polarity-dependent manner as anodal-DCS increased

habituation after increasing VEP amplitude, whereas cathodal-tDCS decreased habituation after reducing VEP amplitude (Siniatchkin et al., 2011). A possible explanation for such stimulation-related habituation has been suggested to reflect an adaptive mechanism for regulating E–I balance (Brighina et al., 2009; Siniatchkin et al., 2011). In accordance with the putative role of E–I balance in habituation, the current study's findings of the EEG run-related neural changes in peak gamma frequency and VEP-N1 amplitude may reflect increased cortical inhibition relative to excitation in the visual cortex. Although habituation is usually reflected in a response reduction (e.g., reduced VEP amplitude) (Megela & Teyler, 1979; Thompson & Spencer, 1966; Wastell & Kleinman, 1980), increased peak gamma frequency may reflect reduced neural activity (e.g., increased inhibition), given the findings of a positive association between peak gamma frequency and GABA concentration levels in V1 (Edden et al., 2009; Kujala et al., 2015; Muthukumaraswamy et al., 2009).

Another possible explanation of the EEG task run-related changes may be related to attention. Attention has been known to modulate gamma frequency band activity (Bauer, Stenner, Friston, & Dolan, 2014; Koelewijn et al., 2013; M. M. Müller, Gruber, & Keil, 2000; Ray, Niebur, Hsiao, Sinai, & Crone, 2008; Tallon-Baudry, Bertrand, Hénaff, Isnard, & Fischer, 2004) and VEP amplitude (Di Russo & Spinelli, 1999; Eason, 1981; Eason, Harter, & White, 1969). For instance, attention towards visual stimuli increases gamma frequency oscillations before the onset of the visual stimulus (Tallon-Baudry et al., 2004), but decreases them afterwards (Bauer et al., 2014; Tallon-Baudry et al., 2004). Similarly, attention towards visual stimuli has been shown to increase the amplitude of VEP compared to inattention (Di Russo & Spinelli, 1999; Eason, 1981). However, such a possibility that the EEG task run-related changes are due to attention modulations would unlikely be the case, as the EEG task used in the current study employed a technique maintaining participants' attention throughout the task (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015). During the task, participants were asked to conduct a simple but continuous action related to stimulus appearance (pressing the spacebar when the stimulus disappeared). While it could be argued that the task demand could be fulfilled even when fixating on the peripheral field around the fixation point, such a possibility

could result, for example, in a reduction of VEP amplitude in both runs (Hoshiyama & Kakigi, 2001), eliminating the possibility that the reduction could be caused by a fixation on the peripheral field of the stimulus location.

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 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 changes in visual peak gamma frequency following 20-min anodal-tDCS with an intensity of 2 mA compared to sham-tDCS (Wilson et al., 2017). 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 strongly was found to reduce the gamma frequency power (Hanley et al., 2016) and increase the local amplitudes of gamma frequency compared to sham-tDCS (Wilson et al., 2017). However, cathodal-tDCS was found to decrease spontaneous gamma frequency compared to anodal- and sham-tDCS (Wiesman et al., 2018). Inconsistent with other studies, Marshall et al. (2016) and Medina and Cason (2017) found no tDCS effects on gamma frequency band activity. Similarly, the current study, consistent also with Wilson et al. (2017), observed no effects of tDCS in modulating peak gamma frequency. Given the the established relationship between gamma and alpha activity (Osipova et al., 2008; Spaak et al., 2012; Voytek et al., 2010; Zazio et al., 2019), it is unlikely that alpha activity could be altered by tDCS, as both peak gamma frequency and gamma frequency power were not affected by tDCS.

As an associational relationship 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 has investigated whether VEP could be modulated using tDCS. Although several studies have investigated whether tDCS effects over the visual cortex 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 robust 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 no robust effects of tDCS observed in modulating peak gamma frequency and VEP amplitudes, several factors related to task (e.g., properties of visual stimulus) and tDCS configurations (e.g., montage and parameter) have been suggested to play important role in the efficacy of tDCS (Medina & Cason, 2017; Thair et al., 2017). However, such suggested factors would unlikely account for the absence of tDCS effects in modulating neural activity (peak gamma frequency, amplitudes of VEP N1 and P2 components). Effects of tDCS on occipital cortex have been observed with high contrast visual stimulus (Wiesman et al., 2018), monopolar montage (e.g., occipital cortex-cheek) (Reinhart et al., 2016), and 30 min after the application of 10-min tDCS with an intensity of 2 mA (Ding et al., 2016). A 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). As tDCS was administered (approximately 5 min) after the first run of the EEG task, it may be possible that the post task-induced neural oscillations changes lasted to the time of stimulation (Barnes, Bullmore, & Suckling, 2009; Duff et al., 2008; Henz, John, Merz, & Schöllhorn, 2018), diminishing the potential tDCS effects. tDCS effects have been suggested to depend on the state of the brain during the stimulation (Bocci et al.,

2014; Filmer et al., 2014; Li et al., 2017; Moloney & Witney, 2013; Siebner et al., 2004). Evidence supports this claim can be seen in the different effects of tDCS on the VEP amplitude and habituation of individuals with and without migraine (Brighina, Piazza, Daniele, & Fierro, 2002; Siniatchkin et al., 2011). For instance, VEP amplitude and habituation of individual without migraine were modulated in a polarity-dependent manner, as anodal-tDCS increased both VEP amplitude and habituation, while cathodal-tDCS did the opposite. However, no such effects of tDCS on VEP amplitude and habituation of individuals with migraines occurred (Siniatchkin et al., 2011), possibly because of low cortical pre-activation level (Bohotin et al., 2002). An additional support to the brain-state dependency of tDCS effects comes from findings of studies combining tDCS with repetitive transcranial magnetic stimulation (rTMS). For instance, pairing anodal-tDCS with excitatory rTMS has shown to reduce neural excitability in the visual cortex, while pairing cathodal-tDCS with inhibitory rTMS increases it (Bocci et al., 2014). A similar brain-state-related reverse polarity effects of tDCS has also been observed in the motor cortex (Siebner et al., 2004). To reduce the possible interference of post-task brain state and tDCS, future studies examining tDCS effects on VEP and peak gamma frequency should consider multiple session design instead of a single session, given the high reliability of peak gamma frequency and VEP activity over time (Joost, Bach, & Schulte-Mönting, 1992; Sarnthein, Andersson, Zimmermann, & Zumsteg, 2009; Tan, Gross, & Uhlhaas, 2016).

Despite the growing interest in investigating tDCS effects in the neural activity of the human brain using electrophysiological techniques such as EEG and MEG, there has not yet been any EEG-tDCS study examining tDCS effects on neural oscillatory activity of V1 (i.e., peak gamma frequency or VEP amplitudes) based on the best of my knowledge. The current study, therefore, is the first EEG-tDCS study to examine the effects of offline occipital tDCS in modulating peak gamma frequency in addition to VEP amplitudes. The current study showed the possibility of using ICA in a within-subject design. As running separate ICA decompositions would more likely cause differences in ICA components ordering and scalp topography (Delorme & Makeig, 2004), using the event-related dynamics of ICA components in addition to the source location can be useful for best

matching corresponding pairs of ICA components from two EEG task runs or sessions. Although running one ICA for the two runs of EEG for each single participant eliminates the possibility of choosing two different ICA components representing different aspects of brain activity, it was decided to run two separate Independent component analyses for each subject. Running two separate ICA for the pre- and post-tDCS EEG data set of each participant reduced the possible influence of either the pre- or post-tDCS data in playing a major role of generating the IC components given the possibility that tDCS may induce robust changes in the neural activity observed. Additionally, stimulating visual cortex using tDCS required removing some EEG electrodes during the tDCS stimulation period and returning them for the post tDCS recording, which in turn might result in slight changes in electrodes' site in addition to the possibility of requiring removal of different 'noisy' electrodes from the pre- and post-tDCS EEG data set. As such running two separate ICA 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, analysis of two separate ICA by selecting the best matched IC components from two data sets were found to not statistically differ from that of the one ICA combining the two data sets (Arbabshirani, Havlicek, Kiehl, Pearlson, & Calhoun, 2013).

The current study has two limitations regarding participant type and sample size. For instance, 13 participants had participated in previous experiments of ours, while the rest were new participants. The new participants conducted approximately 12–15 min visual ODT task 25–30 min before the first EEG task run. Subsequent One-way ANOVA analyses were conducted to assess whether there were any robust differences in induced gamma frequency and VEP activity of the pre-tDCS EEG run between the new participants (N=26) and those who had participated in previous experiments (N=13). For instance, peak gamma frequency of the new participants (M=47.16, SE=2.11) did not significantly differ from that of old participants (M=51.04, SE=4.54), $F(1,37)=.792$, $p=.379$. Also, gamma frequency power of the new participants (M=.68, SE=.088) did not significantly differ from that of old participants (M=.78, SE=.14), $F(1,37)=.355$, $p=.555$. Similarly, VEP-N1 of the new participants (M=6.04, SE=.93) did not significantly differ from that of old

participants (M=6.82, SE=1.46), F(1,37)=.220, p=.642. Additionally, VEP-P2 of the new participants (M=12.74, SE=1.16) did not significantly differ from that of old participants (M=15.37, SE=2.01), F(1,37)=1.470, p=.233. Additionally, although the relatively small sample size of the current study was sufficient to detect the EEG task-run related changes, it may not have had the sufficient power to detect effects of tDCS between groups given that each group consisted of 8–11 participants. However, such a limitation is not uncommon in tDCS studies and has been suggested to explain the inconsistent findings of tDCS effects on cognition (Medina & Cason, 2017).

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). During EEG acquisition, participants were repeatedly presented a black and white checkerboard stimulus known to elicit strong gamma frequency oscillations and VEP amplitudes and were instructed to press a spacebar key when the stimulus disappeared. The result is robust increase in peak gamma frequency and reduction in VEP-N1 amplitude in the second (post-tDCS) run compared to the first (tDCS-pre) run, irrespective of the tDCS type groups. However, no effects of tDCS were found in modulating peak gamma frequency and the amplitudes of VEP components (N1 and P2) in V1. The current study is the first to examine the effects of offline tDCS on both VEP and peak gamma frequency using EEG. Furthermore, it demonstrates the usefulness of ICA components' VEP in selecting pairs of components from different runs (pre-, post-tDCS run). Future tDCS-EEG studies using within-subject design should consider having two or multiple separate sessions with a larger sample size to avoid the post-task destabilized brain state and to increase the detectability of small effects of tDCS.

Chapter 4 : Performance in Orientation Discrimination Task Can Be Predicted by Peak Gamma Frequency and Visual Evoked Potential N1 Peak Amplitude

Abstract

Excitation–inhibition (E–I) balance has been indirectly inferred from psychophysical measures (i.e., performance in orientation discrimination task [ODT]) and neurophysiological measures (i.e., gamma frequency oscillations, amplitudes of visual evoked potential (VEP) due to their association with gamma-aminobutyric acid (GABA), the major inhibitory transmitter. Although previous studies have found a correlation between enhanced ODT performance and higher peak gamma frequency, the relationship between ODT performance and VEP activity has not yet been explored. Therefore, the current chapter aims to replicate and extend upon previous findings by investigating to what extent ODT performance in the vertical or oblique condition could be predicted by both gamma frequency activities (peak gamma frequency and gamma frequency power) and amplitudes of VEP components (N1 and P2). The main motivation for this investigation was the findings of Chapters 2 and 3 that no causal relationships between manipulating cortical E–I balance in visual cortex using transcranial direct current stimulation (tDCS) and ODT performance, gamma frequency activities, and VEP amplitudes were observed. Forty-nine participants completed an ODT comprising a vertical and oblique condition and an EEG task that has shown to elicit strong peak gamma frequency and VEP activity. The results of multiple linear regression analyses assessing the relationship between performance in conditions of ODT (vertical, oblique) and the neurophysiological measures (induced gamma frequency and amplitudes of VEP components) showed that only performance in the oblique condition but not in the vertical

condition of the ODT could highly be predicted by neurophysiological measures. Enhanced performance in the oblique ODT is associated with higher peak gamma frequency and/or lower VEP-N1 peak amplitude. This finding is consistent with and provides additional support to previous studies suggesting an association between increased cortical inhibition (indicated by enhanced performance in the ODT), higher peak gamma frequency, and lower VEP-N1 amplitude.

Introduction

Atypical visual perception in individuals with neurological and neurodevelopmental disorders (i.e., autism spectrum conditions [ASC], schizophrenia [SCZ], and migraine) has been hypothesised to stem from disruption in the cortical excitation–inhibition (E–I) balance (Chen, Norton, & Ongur, 2008; Franklin, Sowden, Burley, Notman, & Alder, 2008; Franklin et al., 2010; Shaw et al., 2019; Shepherd, 2000; Tibber et al., 2006; Yoon et al., 2010). Evidence supporting such hypotheses comes from psychophysical task performance suggested to indirectly reflect E–I balance (e.g., orientation discrimination task [ODT], binocular rivalry, and surround suppression (Dickinson, Bruyns-Haylett, et al., 2016; Edden et al., 2009; Freyberg et al., 2015; Nguyen et al., 2016; Tibber et al., 2006; Yoon et al., 2010). Performance in such psychophysical tasks has been found to be associated with gamma-aminobutyric acid (GABA), a major inhibitory transmitter, as measured by magnetic resonance spectroscopy (MRS) (Edden et al., 2009; Kurcyus et al., 2018; van Loon et al., 2013). For instance, Edden et al. (2009) found that performance in the ODT is associated with resting-state GABA concentration level in the visual cortex. Enhanced performance in the vertical and oblique condition of ODT is associated with higher GABA concentration in the visual cortex, although the association was only statistically significant for the relationship between oblique ODT performance and GABA. The lack of the significant relationship between vertical ODT and GABA possibly caused

by a ceiling effect, as vertical ODT thresholds were very low (Dickinson et al., 2014). The association between ODT performance and resting-state GABA concentration in the visual cortex is consistent with findings of animal studies showing causal relationships between the neural selectivity of cortical cells to particular orientations and GABA activity (Katzner et al., 2011; Leventhal et al., 2003; Li et al., 2008; Sillito, 1975). For instance, administering GABA agonist increases neural selectivity of specific orientations (Leventhal et al., 2003; Li et al., 2008), whereas GABA antagonist decreases it (Katzner et al., 2011; Sillito, 1975). Accordingly, performance in the ODT has been suggested to be a useful indicator of cortical E–I balance in the visual cortex (Dickinson, Jones, et al., 2016).

Similar to ODT performance, peak gamma frequency has also been suggested to indicate cortical E–I balance (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009; Fesi & Mendola, 2015; Kujala et al., 2015; Muthukumaraswamy et al., 2009; Sysoeva et al., 2016). Gamma oscillation activities have been suggested to arise from the dynamic interaction between pyramidal excitatory and inhibitory interneuron cells (Brunel & Wang, 2003; Buzsáki & Wang, 2012; Börgers & Kopell, 2003), and that lower E–I ratio can result in higher gamma oscillation (Brunel & Wang, 2003). Consistent with these findings, MRS studies found a positive association between GABA concentration and peak gamma frequency (Edden et al., 2009; Kujala et al., 2015; Muthukumaraswamy et al., 2009), although such a finding could not be replicated in the work of Cousijn et al. (2014), possibly due to methodological differences (i.e., types of MRS sequence) (Ding et al., 2016; Kujala et al., 2015). Additionally, magnetoencephalography (MEG) and electroencephalogram (EEG) studies have shown peak gamma frequency to be significantly associated with ODT performance (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015). Similar to the relationship between performance in the vertical and oblique condition of the ODT and resting-state GABA concentration level in the visual cortex (Edden et al., 2009), Dickinson, Bruyns-Haylett, et al. (2016) and Dickinson et al. (2015) found that only oblique ODT performance, but not vertical ODT performance, is statistically significantly associated with peak gamma frequency. Enhanced oblique ODT performance's correlation with higher peak gamma frequency is in the same direction as the association between ODT performance and GABA concentration level (Edden et al.,

2009). Accordingly, higher peak gamma frequency has been suggested to indicate increased cortical inhibition in the occipital cortex (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009).

Similar to gamma frequency oscillations, visual evoked potential (VEP) activity has been suggested to reflect the summation of excitatory and inhibitory post-synaptic potentials (EPSP, IPSP, respectively) of cortical cells (Purpura, 1959; Zemon et al., 1980). Consistent with this suggestion, animal and human models have shown that pharmacological manipulations of GABA activity lead to robust changes in VEP amplitudes (Daniels & Pettigrew, 1975; Hudnell & Boyes, 1991; Kraut et al., 1990; Rockstroh et al., 1991; Schafer et al., 1984; Zemon et al., 1980; Zemon, Kaplan, et al., 1986; Zeneroli et al., 1981). For instance, using an extracellular recording technique, Daniels & Pettigrew (1975) found an effect of manipulation GABA activity pharmacologically on the cortical cells of cats, as spontaneous and visually evoked responses of complex and hypercomplex cells increased following the administration of GABA antagonist. Such post-GABA antagonist changes in cortical cells were associated with a reduction in the selectivity of stimulus features (i.e. orientation and direction) (Daniels & Pettigrew, 1975). This finding is consistent with previous studies' findings of an association between GABA activity and cortical cells' selectivity for stimulus features (Katzner et al., 2011; Leventhal et al., 2003; Li et al., 2008; Sillito, 1975). Additionally, application of GABA agonist in rats decreased the amplitude of VEP-N1 and increased that of VEP-P2 (Zeneroli et al., 1981), whereas the application of GABA antagonist in cats increased the VEP-N1 amplitude and decreased that of VEP-P2 (Zemon et al., 1980). However, the findings of human studies investigating the effects of pharmacological manipulations of GABA activity on VEP amplitudes have been inconsistent. For instance, while Rockstroh et al. (1991) found that administration of GABA agonist induced robust changes on VEP-P100 amplitudes, no such changes on VEP amplitudes were observed following similar pharmacological manipulations of GABA activity (Bartel, Blom, & Van der Meyden, 1988; Hammond & Wilder, 1985; Loughnan, Sebel, Thomas, & Rutherfoord, 1987). Although this discrepancy suggests further investigation of the association between GABA activity and VEP amplitudes, atypical VEP amplitudes have been considered as indirect indications of disrupted cortical E–I

balance (Ashjazadeh & Varavipour, 2015; Gawel et al., 1983; Kennard et al., 1978; Nguyen et al., 2016; Porciatti, Bonanni, Fiorentini, & Guerrini, 2000; Sand, Zhitniy, White, & Stovner, 2008; Sokol, 1983). For instance, it has been suggested that high VEP amplitudes reflect cortical hyperexcitability (Boylu et al., 2010; Nguyen et al., 2016; Sand et al., 2008) while small VEP amplitudes reflect increased cortical inhibition (Moon & Lim, 2009; Sokol, 1983). In accordance with these findings and suggestions of animal and human studies, measuring VEP amplitudes may be a useful tool to indirectly indicate cortical E–I balance.

Although ODT performance, gamma frequency activities, and amplitudes of VEP have been thought, mainly based on correlational studies, to reflect cortical E–I balance (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Dickinson et al., 2014; Kennard et al., 1978; Muthukumaraswamy et al., 2009; Nguyen et al., 2016; Stagg et al., 2009), Chapters 2 and 3 found no causal relationships between cortical E–I balance in visual cortex, which was manipulated by transcranial direct current stimulation (tDCS) and assessed by both psychophysical (ODT performance) and neurophysiological measures (peak gamma frequency and VEP amplitudes). Such a lack of causal relationship between E–I balance and these psychophysical and neurophysiological measures motivates the current investigation into the correlational associations between these variables (ODT, peak gamma frequency, and VEP amplitudes). Such investigation can provide additional evaluation of these measures as being indirect indicators of E–I balance. Such evaluation may be of great importance, given the inconsistent findings regarding the relationships between GABA concentration level and both peak gamma frequency (Cousijn et al., 2014; Edden et al., 2009; Muthukumaraswamy et al., 2009) and VEP amplitudes (Hammond & Wilder, 1985; Loughnan et al., 1987; Rockstroh et al., 1991). Additionally, although the relationship between ODT performance and peak gamma frequency has been investigated previously (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009), there has been no study yet, that I am aware of, investigating the relationship between ODT performance and VEP amplitudes, aside from studies assessing the effects of perceptual training on ODTs on visual event-related potential (ERP) (Song, Peng, Li, et al., 2007; Song, Peng, Lu, et al., 2007; Song et al., 2010).

Using multiple linear regression analyses, the relationships between ODT performance were investigated, along with gamma frequency activity and VEP amplitudes, to determine to what extent ODT performance could be predicted by these neurophysiological measures. To measure the vertical and oblique thresholds, an ODT that has been used previously by Dickinson, Bruyns-Haylett, et al. (2016), Dickinson et al. (2015), and Dickinson et al. (2014) and is similar to that used by Edden et al. (2009). Given that gamma frequency oscillations and VEP activity are sensitive to particular features of stimulus (i.e., size, contrast, and frequency) (Bach & Ullrich, 1997; Busch et al., 2004; Korth & Nguyen, 1997; Schadow et al., 2007), an EEG task that has been shown to elicit strong gamma frequency and VEP activities (Milne et al., 2018; Milne et al., 2019) was used. As ODT performance, peak gamma frequency, and VEP amplitudes are associated with GABA activity (Edden et al., 2009; Muthukumaraswamy et al., 2009; Zemon et al., 1980; Zeneroli et al., 1981), it was expected that ODT performance would be predicted by these neurophysiological measures. Additionally, based on various previous studies (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009), it was expected that enhanced ODT performance would be associated with a higher peak gamma frequency. Furthermore, based on the associations between ODT performance and GABA concentration (Edden et al., 2009) and between GABA activity and amplitudes of VEP-N1 and P2 components (Zemon et al., 1980; Zeneroli et al., 1981), it was expected that enhanced ODT performance would be associated with a lower VEP-N1 amplitude and a higher VEP-P2 amplitude.

Method

Data of this study are the same as reported in the tDCS-EEG experimental study (Chapter 3). These data were collected before the application of tDCS. As mentioned in the

participant section of Chapter 3, participants completed an approximately 12–15-min ODT (including practise and an actual run of the ODT) 25–30 min before the EEG acquisition, unless they had completed the ODT in previous experiments (Chapter 2).

Detailed descriptions of the study methods are reported in Chapters 2 and 3

Detailed discrimination of the ODT is provided in Chapter 2. Moreover, detailed descriptions of the following topics are provided in Chapter 3: participants, EEG task, apparatus, procedures, EEG analysis, independent component analysis (ICA) for the time-frequency analysis, selection of the ICA components for the time-frequency analysis, time-frequency analysis, visual evoked potentials of the occipital cortex (Oz).

Result

Data from 12 out of 49 participants were excluded from the analyses because they did not meet one or more of the inclusion criteria. For instance, four participants had an ODT threshold of more than two standard deviations away from the ODT thresholds' means of the group. Furthermore, four participants had extensive noise in their EEG data signals, and one participant had amplitudes of VEP components (N1 and P2) deviating from the mean by more than three standard deviations. Additionally, three participants were not eligible to participate in the EEG task due to headwear (e.g. hair extensions) ($N = 2$) or due to being on medication ($N = 1$). Thus, the data of 37 participants (13 female, 24 male:

mean age 28.32, range = 19–52) were used for the analysis. Descriptive statistics of vertical and oblique orientation discrimination thresholds and neurophysiological measures (peak gamma frequency, gamma power frequency, VEP-N1 amplitude, and VEP-P2 amplitude) are shown in Table 4.1. All statistical analyses were performed using SPSS version 24 for Mac (IBM SPSS, Armonk, New York).

Variables	Mean	Standard Deviation
Vertical ODT threshold (°)	1.55	0.81
Oblique ODT threshold (°)	7.13	2.02
Peak gamma frequency (Hz)	50.21	13.75
Gamma frequency power	0.80	0.50
The amplitude of VEP-N1 (μv)	6.12	4.55
The amplitude of VEP-P2 (μv)	13.67	6.60

Table 4.1 Means and standard deviations of psychophysical (vertical and oblique orientation discrimination thresholds) and neurophysiological measure (peak gamma frequency. gamma frequency power, visual evoked potential (VEP)-N1 amplitude, and VEP-P2 amplitude).

First, whether ODT performance would differ based on condition (vertical, oblique) was investigated using a paired samples *t*-test. The result showed a significant performance difference based on condition ($t(36) = -17.70$, $p < .0001$). Orientation discrimination task thresholds for the vertical condition ($M = 1.55°$, $SD = .81°$) were significantly lower than that of the oblique condition ($M = 7.13°$, $SD = 2.02°$) (Figure 4.1).

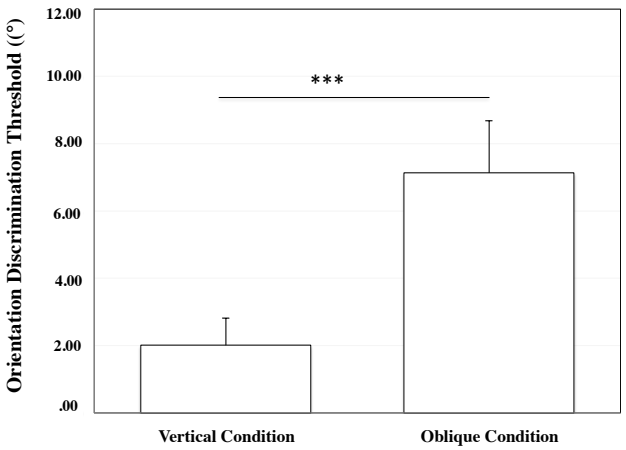


Figure 4.1. Orientation discrimination thresholds of vertical and oblique condition (in degrees). ***$p < .0001$.

Second, bivariate correlation analyses were conducted to evaluate the relationship between ODT thresholds for vertical and oblique condition and the personal characteristics of the participants (sex, age, and handedness). Any of the personal characteristics with statistically significant correlations with ODT performance would be treated as a covariate variable in the further multiple regression analyses. However, the correlation analyses did not indicate any significant relationship between ODT thresholds for the vertical and oblique condition and any of the personal characteristics (*ps* < .05).

Third, whether performance on vertical condition of the ODT could be predicted based on neurophysiological measures (peak gamma frequency, gamma power frequency, VEP-N1 peak amplitude, and VEP-P2 peak amplitude) was investigated using multiple linear regression analysis. The results revealed a statistically insignificant regression equation ($F(4, 32) = 1.03$, $p = .407$), with an $R^2 = .114$ (Table 4.2). Additionally, none of the neurophysiological measures was a significant coefficient in the regression model, suggesting that none of these neurophysiological measures statistically significantly predicts performance on vertical condition of the ODT (Figure 4.2). This result

Table 4.2 Summary of multiple linear regression analysis for neurophysiological measures predicting performance on vertical condition of orientation discrimination task (ODT).

Variable	B	SE B	β	t	P
Peak Gamma Frequency (Hz)	-0.011	0.011	-0.18	-1.01	0.322
Gamma Frequency Power	-0.169	0.331	-0.10	-0.51	0.613
Amplitude of VEP-N1 (μv)	0.048	0.03	0.27	1.617	0.116
Amplitude of VEP-P2 (μv)	0.011	0.023	0.09	0.47	0.644

Note. $R^2 = .114$ ($N = 37$, $p = .407$).

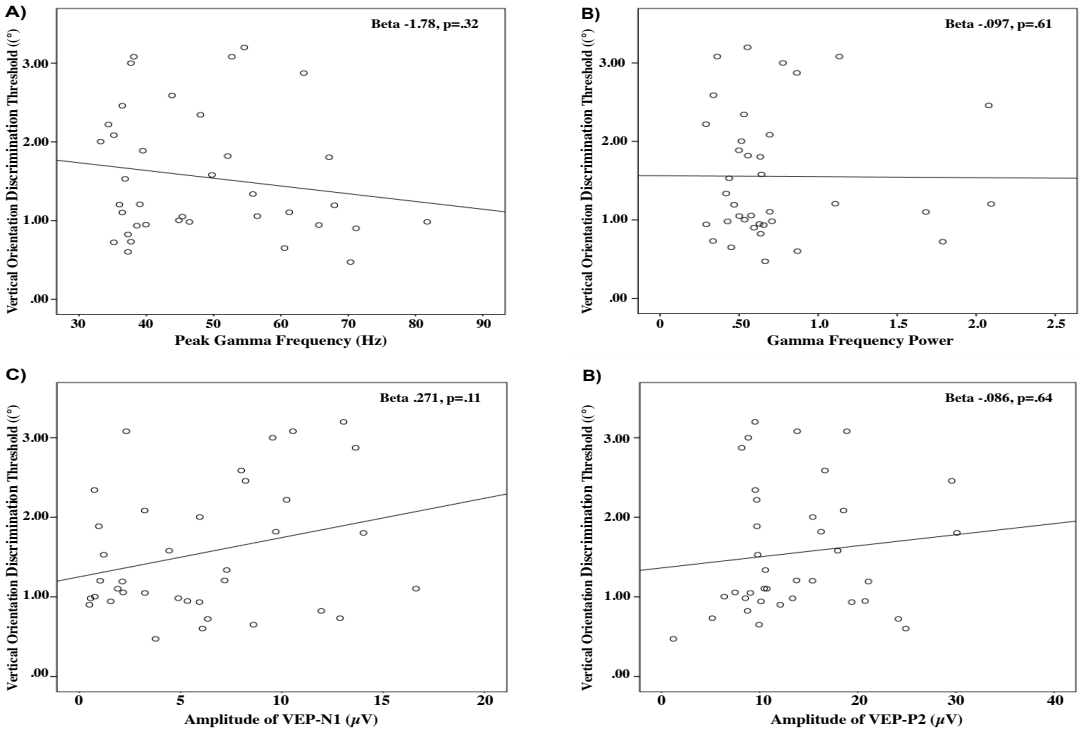


Figure 4.2. Prediction of vertical orientation discrimination task (ODT) performance by the neurophysiological measures. A) Peak gamma frequency does not statistically significantly predict performance in the vertical condition of ODT, $p < .05$. B) Gamma frequency power does not statistically significantly predict performance in the vertical condition of ODT, $p < .05$. C) VEP-N1 peak amplitude does not statistically significantly predict performance in the vertical condition of ODT, $p < .05$. D) VEP-P2 peak amplitude does not statistically significantly predict performance in the vertical condition of ODT, $p < .05$.

Fourth, whether performance on the oblique condition of the ODT could be predicted based on neurophysiological measures (peak gamma frequency, gamma power frequency, the amplitude of VEP-N1, and the amplitude of VEP-P2) was investigated using multiple linear regression analysis. The result revealed a statistically significant regression equation ($F(4, 32) = 4.45$, $p = .006$), with an $R^2 = .357$ (Table 4.3). Approximately 36% of the variance in oblique ODT performance can be accounted for by the combination of the four neurophysiological measures. Only peak gamma frequency and peak amplitude of VEP-N1 component statistically significantly predict ODT performance (($\beta = -.46$, $t(32) = -3.07$, $p = .004$), ($\beta = .39$, $t(32) = 2.72$, $p = .011$), respectively). Individuals with higher peak gamma frequency and/or lower amplitude of VEP-N1 are expected to have lower ODT thresholds (enhanced performance). Although no other neurophysiological measures statistically significantly predict ODT performance, VEP-P2 approached significance as a predictor of performance on the oblique condition of the ODT ($\beta = -.29$, $t(32) = -1.82$, $p = .079$), as higher VEP-P2 peak amplitudes are expected to be associated with lower oblique thresholds (Figure 4.3).

Table 4.3 Summary of multiple leaner regression analysis for neurophysiological measures predicting performance on oblique condition of ODT.

Variable	B	SE B	β	t	P
Peak Gamma Frequency (Hz)	-0.07	0.02	-0.46	-3.07	0.004
Gamma Frequency Power	-0.14	0.70	-0.03	-0.2	0.843
Peak of VEP (N1) Component (μv)	0.17	0.06	0.39	2.72	0.011
Peak of VEP (P2) Component (μv)	-0.09	0.05	-0.29	-1.82	0.079

Note. $R^2 = .357$ ($N = 37$, $p = .006$).

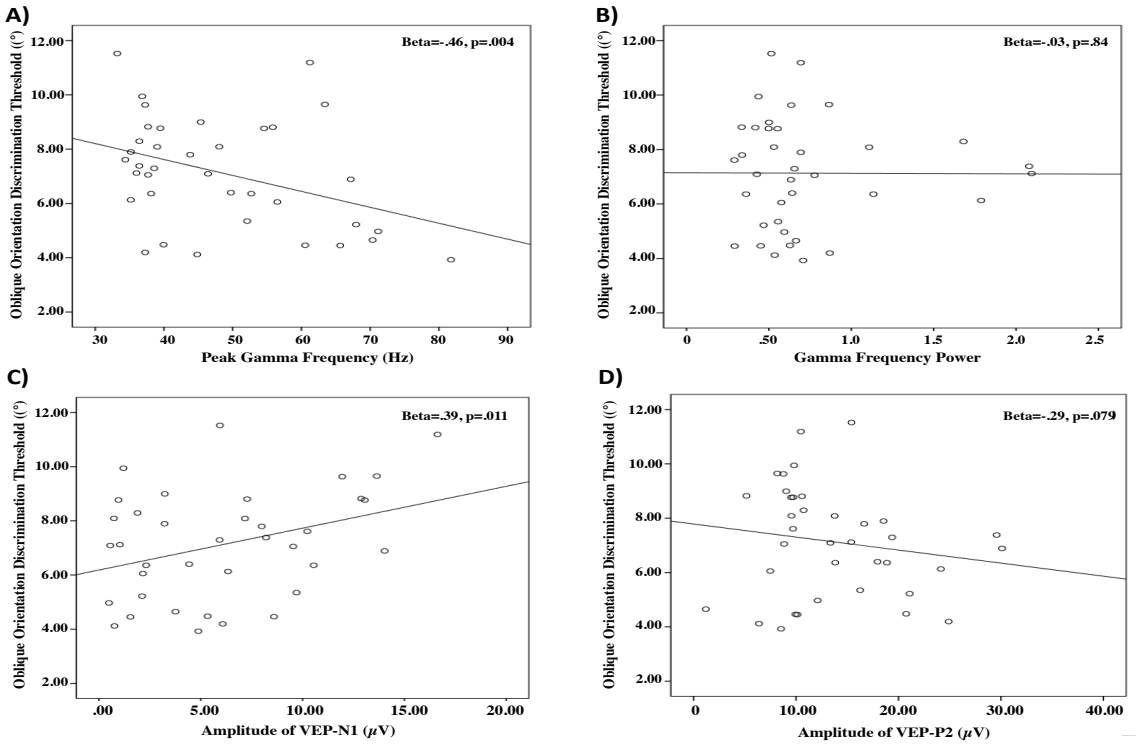


Figure 4.3. Prediction of oblique orientation discrimination task (ODT) performance by the neurophysiological measures. A) Peak gamma frequency statistically significantly predicts performance in the oblique condition of ODT, $p = .004$. B) Gamma frequency power does not statistically significantly predict performance in the oblique condition of ODT, $p < .05$. C) VEP-N1 peak amplitude statistically significantly predicts performance in the oblique condition of ODT, $p = .011$. D) VEP-P2 peak amplitude approaches significance as a predictor of performance in the oblique condition of ODT, $p = .079$.

Discussion

The current study has investigated the relationship between performance in the ODT and neurophysiological measures (peak gamma frequency, gamma frequency power, VEP-N1 amplitude and VEP-P2 amplitude) as to what extent ODT performance in the vertical and oblique condition could be predicted by these neurophysiological measures. Participants completed an ODT consisting of a vertical and oblique condition and an EEG task previously shown to elicit strong gamma frequency oscillations and VEP activities. Performance in the ODT differed based on condition, as ODT thresholds were statistically significantly lower for the vertical condition than for the oblique condition, replicating the well-known phenomenon of oblique effect (Appelle, 1972; Dickinson et al., 2014; Edden et al., 2009; Tibber et al., 2006). Additionally, it was found that performance in the vertical condition of the ODT could not be predicted by neurophysiological measures, due possibly to a ceiling effect reflected in very low thresholds preventing any potential relationship between ODT performance and neurophysiological measures from being detectable (Dickinson et al., 2014). Additionally, as expected, it was found that performance in the oblique condition of the ODT can be strongly predicted by the neurophysiological measures, especially by peak gamma frequency and VEP-N1 peak amplitude. Higher peak gamma frequency and/or lower VEP-N1 amplitude is associated with enhanced performance in the oblique condition of the ODT. This finding successfully replicates previous findings of an relationship between performance in the oblique condition of the ODT and peak gamma frequency (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009) and extends them by finding a new link between enhanced performance in oblique condition of the ODT and lower VEP-N1 amplitude. This finding supports the suggested relationship between cortical inhibition (indicated by ODT performance) and both peak gamma frequency and the amplitude of VEP-N1 (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009; Kujala et al., 2015; Zemon et al., 1980; Zeneroli et al., 1981).

As expected, performance in the ODT was significantly better (lower thresholds) for the vertical condition, as compared to the performance of the oblique condition, consistent with a large body of research (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Dickinson et al., 2014; Edden et al., 2009; Tibber et al., 2006). The robust difference in ODT performance between vertical and oblique condition reflects the oblique effect (Appelle, 1972). It has been suggested that the neural selectivity of cardinal orientations (i.e., horizontal, vertical) is higher than that of oblique orientation (Huang et al., 2006; Li, et al., 2003; Mansfield, 1974; Yu & Shou, 2000), resulting in better discrimination for cardinally oriented objects compared to obliquely oriented objects.

Consistent with previous studies of the insignificant relationship between vertical ODT thresholds and GABA concentration levels in the occipital cortex of humans (Edden et al., 2009), the current investigation finds that performance in vertical ODT condition cannot be predicted by neurophysiological measures. This finding is also consistent with previous MEG and EEG studies' findings of no correlations between vertical ODT performance and peak gamma frequency measured (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009). A possible explanation for such an insignificant relationship has been suggested to be a ceiling effect on the vertical condition of the ODT (Dickinson et al., 2014). Therefore, the low vertical ODT threshold may prevent any possible relationship between vertical ODT performance and neurophysiological measures (i.e., gamma frequency oscillations and VEP activities).

As expected, the current investigation found that performance in the oblique condition of the ODT is highly predictable with neurophysiological measures, especially peak gamma frequency and VEP-N1 amplitude. Similar to previous studies' findings of an association between performance in the oblique condition of ODT and peak gamma frequency (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009), higher peak gamma frequency is highly expected to be associated with enhanced oblique ODT performance (lower thresholds). This finding is consistent with the finding of an association between enhanced oblique ODT performance and increased resting-state GABA concentration levels in the visual cortex (Edden et al., 2009), given the positive

relationship between GABA and both enhanced oblique ODT performance (Edden et al., 2009) and higher peak gamma frequency (Edden et al., 2009; Kujala et al., 2015; Muthukumaraswamy et al., 2009). Additionally, it was found that lower VEP-N1 amplitude is highly expected to be associated with enhanced oblique ODT performance. This finding is consistent with animal models' findings of an association between GABA activity and VEP-N1 amplitude (Zemon et al., 1980; Zeneroli et al., 1981), given the relationship between GABA concentration and oblique ODT performance (Edden et al., 2009). For instance, the application of GABA agonist (antagonist) decreased (increased) VEP-N1 amplitude (Zemon et al., 1980; Zeneroli et al., 1981). Such manipulations of GABA activity have been shown to affect the neural selectivity of cortical cells to stimulus features (i.e., orientation, direction). For instance, administration of GABA agonist (antagonist) enhanced (impaired) the selectivity of cortical cells for stimulus orientations (Katzner et al., 2011; Li et al., 2008; Sillito, 1975). In relation to GABA activity, the finding that oblique ODT performance is associated with higher peak gamma frequency and/or lower amplitude of VEP-N1 supports the suggested links between cortical inhibition (indicated by ODT thresholds) and both peak gamma frequency and the amplitude of VEP-N1 (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Dickinson et al., 2014; Edden et al., 2009).

Although the current investigation finds that only peak gamma frequency and VEP-N1 peak amplitude can accurately predict performance in the oblique condition of the ODT, VEP-P2 peak amplitude approached significance as a predictor of oblique ODT performance. In light of the relationship between GABA and performance in the oblique condition of the ODT (Edden et al., 2009), the direction of the relationship between VEP-P2 peak amplitude and performance in the oblique condition of the ODT is consistent with the findings of animal models (Zemon et al., 1980; Zeneroli et al., 1981). For instance, the application of GABA agonist (antagonist) increased (decreased) the amplitude of VEP-P2 (Zemon et al., 1980; Zeneroli et al., 1981). One possible explanation for the insignificant predictability of VEP-P2 for ODT performance may be related to the orientation of the visual stimulus being used, given that P2 peak amplitude has been shown to depend on the stimulus orientation (Song, Peng, Li, et al., 2007; Song, Peng, Lu, et al., 2007; Song et al.,

2010). For instance, while perceptual training on the cardinal condition of the ODT led to a reduction in N1 peak amplitude, it left P2 peak amplitude unchanged (Song et al., 2010). However, perceptual training on the oblique condition of the ODT led to a reduction in N1 peak amplitude and increase in P2 peak amplitude (Song, Peng, Li, et al., 2007; Song, Peng, Lu, et al., 2007; Song et al., 2010). Thus, it seems possible that having the stimulus oriented cardinally limited the detectability of any variances in P2 peak amplitude associated with ODT performance, resulting in insignificance.

As peak gamma frequency and VEP-N1 amplitude have shown to be associated with GABA concentration and activity (Edden et al., 2009; Muthukumaraswamy et al., 2009; Zemon et al., 1980; Zeneroli et al., 1981) and were found in the current study to accurately predict performance in the oblique condition of the ODT, a subsequent Pearson's correlation analysis was conducted to assess the relationship between peak gamma frequency and VEP-N1 peak amplitude. The result showed no statistically robust correlational relationship between these two neurophysiological measures ($r = .022$, $N = 37$, $p = .899$, two-tailed test). This finding is consistent with several reports suggesting different neural generators of the visually induced gamma frequency and VEP activity (Sannita, Carozzo, Fioretto, Garbarino, & Martinoli, 2007; Sannita, Lopez, Piras, & Di Bon, 1995). It is also possible that the insignificant relationship between peak gamma frequency and VEP-N1 amplitude is due to the difference in the time window of occurrence between peak gamma frequency (~200–400 ms post-stimulus onset) and VEP-N1 peak amplitude (80–155 ms post-stimulus onset). Such differences between peak gamma frequency and VEP-N1 amplitude in the time window of their occurrence might reflect differences in cognitive functions (Menon & Crottaz-Herbette, 2005). For instance, early neural responses occurring between 100 and 200 ms following the onset of the stimulus (i.e., N1 peak amplitude) have been suggested to reflect early cognitive processes (i.e., sensory processes) (Sirel Karakaş & Başar, 1998; Olofsson, Nordin, Sequeira, & Polich, 2008). On the other hand, late neural responses occurring 250 ms after the onset of the stimulus (i.e., peak gamma frequency) have been suggested to reflect late cognitive processes (i.e., perceptual processes) (Engel, Fries, & Singer, 2001). Additionally, it has been suggested that early and late neural responses follow different processing approaches.

For instance, early neural responses are processed in a bottom-up manner, while later neural responses are processed in a top-down manner (Engel et al., 2001; Menon & Crottaz-Herbette, 2005; Olofsson et al., 2008). These differences between peak gamma frequency and VEP-N1 amplitude in the occurrence time window, function, and processing approaches might explain the lack of significant correlational relationships between these two neurophysiological measures.

In light of the growing interest in investigating the relationships between psychophysical and neurophysiological measures as indirect indicators of E–I balance (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009; Rokem et al., 2011; Song et al., 2017; Yoon et al., 2010), the current study provides additional support to the suggested relationship between cortical inhibition (indicated by ODT thresholds) and both peak gamma frequency and VEP-N1 amplitude. While the relationship between ODT performance and peak gamma frequency has been shown in the work of Dickinson, Bruyns-Haylett et al. (2016), Dickinson et al (2015), and Edden et al. (2009), the current study extends the investigation to include amplitudes of VEP components (N1 and P2), given the suggestion that VEP amplitudes indicate cortical E–I balance (Ashjazadeh & Varavipour, 2015; Daniels & Pettigrew, 1975; Nguyen et al., 2016). The result is consistent with these previous studies' findings of a relationship between enhanced oblique ODT performance and higher peak gamma frequency (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009). As expected based on animal research (Zemon et al., 1980; Zeneroli et al., 1981) in relation to the association between GABA concentration and ODT performance (Edden et al., 2009), the current investigation finds a relationship between enhanced oblique ODT performance and lower VEP-N1 amplitude. Although the current study identifies an interesting relationship between cortical inhibition (indicated by ODT performance) and both peak gamma frequency and VEP-N1 peak amplitude, a possible limitation of the study is related to that a portion of participants ($N = 13$) who completed the OTD 5–7 months earlier than the day of the EEG task, while the reset completed it 25–30 min before the EEG task. However, subgroup analysis examining such a possibility revealed no statistically significant difference in

neurophysiological measures between participants based on time of conducting the ODT (several months pre-EEG task versus 25–30 min pre-EEG task) ($p < .05$).

In conclusion, the current study has investigated whether performance in a vertical and oblique condition of the ODT can be predicted by neurophysiological measures (i.e., peak amplitude, peak gamma frequency and gamma frequency power, VEP-N1 peak amplitude and VEP-P2 peak amplitude). While neurophysiological measures cannot predict performance in the vertical condition of the ODT, they accurately predict performance in the oblique condition of the ODT. Specifically, higher peak gamma frequency and/or lower VEP-N1 amplitude are expected to be associated with enhanced performance on the oblique condition of the ODT (lower thresholds). This finding provides additional support to the suggested relationship between cortical inhibition (indicated by ODT thresholds) and these neurophysiological measures, and thus supports the usefulness of these measures as indirect indicators of E–I balance. The current study is the first to show the link between ODT performance and both peak gamma frequency and VEP-N1 peak amplitude. Future studies should consider examining such relationships using psychophysical tasks that have clear links to E–I balance (e.g., binocular rivalry and contrast sensitivity task) to further expand the understanding of such links between E–I balance, psychophysical, and neurophysiological measures.

Chapter 5 : General Discussion

Motivation for Research

The research reported in this thesis attempts to examine the causal relationship between cortical excitation–inhibition (E–I) balance and psychophysical orientation discrimination task (ODT) performance and neurophysiological measures (gamma frequency oscillations and amplitudes of visual evoked potential [VEP]). The limited number of studies investigating the causal relationship between E–I balance and psychophysical and neurophysiological measures motived this thesis. Indeed, relationships between human cortical E–I balance and these kinds of measures have mainly been based on correlational studies (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Dickinson et al., 2014; Kennard et al., 1978; Muthukumaraswamy et al., 2009; Nguyen et al., 2016; Shaw et al., 2019; Stagg et al., 2009). As mentioned in previous chapters, a growing body of research suggests a link between cortical E–I imbalance and atypical cognitive processes (Dickinson, Bruyns-Haylett, et al., 2016; Freyberg et al., 2015; Rokem et al., 2011; Shepherd, 2000; Sysoeva et al., 2016; Tibber et al., 2006; Wilkinson et al., 2008; Yoon et al., 2010; Yoon et al., 2009). Evidence to support this suggestion comes mostly from correlational studies (Dickinson, Bruyns-Haylett, et al., 2016; Freyberg et al., 2015; Yoon et al., 2010), employing psychophysical (i.e., ODT (Dickinson et al., 2014; Shaw et al., 2019; Sysoeva et al., 2016; Tibber et al., 2006) and/or neurophysiological measures (i.e., gamma frequency oscillations, VEP activities) (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Nguyen et al., 2016; Sand et al., 2008; Shaw et al., 2019). Such psychophysical and neurophysiological measures have been shown to be associated with the concentration and activity of gamma-aminobutyric acid (GABA), the major inhibitory transmitter (Edden et al., 2009; Kujala et al., 2015; Muthukumaraswamy et al., 2009; Zemon et al., 1980; Zeneroli et al., 1981). For instance, performance in an ODT has been suggested to indicate cortical inhibition (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2014; Edden et al., 2009; Shaw et al., 2019; Sysoeva et al., 2016; Tibber et al., 2006), given the relationship between increased resting-state GABA concentration

levels in the visual cortex of humans and enhanced oblique ODT performance. Such relationship between ODT performance and GABA concentration is consistent with the findings of animal studies examining the effects of pharmacological manipulations of GABA activity on neural selectivity of stimulus features (i.e., orientation) (Katzner et al., 2011; Leventhal et al., 2003; Li et al., 2008; Sillito, 1975). Similarly, being positively associated with GABA concentration (Kujala et al., 2015; Muthukumaraswamy et al., 2009), higher peak gamma frequency has been suggested to reflect increased cortical inhibition (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015) (see (Dickinson, Jones, et al., 2016) for a review). Similar to peak gamma frequency, VEP amplitudes have also been suggested to reflect cortical E–I balance (Kennard et al., 1978; Nguyen et al., 2016; Sand et al., 2008), in light of animal research findings of an association between GABA activity and VEP amplitudes (Zemon et al., 1980; Zeneroli et al., 1981). For instance, in the same direction of the effects of GABA antagonist on the VEP N1 and P2 components of animal models (Zemon et al., 1980), the higher amplitude of VEP-N1 and lower amplitude of VEP-2 of humans has been suggested to reflect cortical hyperexcitability (Gawel et al., 1983). Therefore, using methods to allow for causal inferences of the correlation-based suggestions of an association between disruption in E–I balance and atypical cognitive processes could provide a deeper understanding of the relationship between E–I and cognition.

One method to investigate the causal relationship between E–I balance and cognition is to modulate E–I balance and measure the effect of this modulation on cognition. One tool to modulate E–I balance is transcranial direct current stimulation (tDCS) (Clark et al., 2011; Krause et al., 2013; Stagg et al., 2009). Transcranial direct current stimulation has been suggested to modulate cortical excitability in a polarity-dependent manner, as anodal-tDCS increases cortical excitability while cathodal-tDCS increases cortical inhibition (Nitsche, Nitsche, et al., 2003; Nitsche & Paulus, 2000). The effects of tDCS have been shown in different brain regions, such as the motor, auditory, somatosensory, and visual cortex (Antal et al., 2003a; Mathys et al., 2010; Nitsche & Paulus, 2000, 2001; Rogalewski, Breitenstein, Nitsche, Paulus, & Knecht, 2004a). Such effects are reflected in changes in behavioural (i.e., contrast sensitivity, motion detection thresholds) (Antal, Nitsche, et al.,

2004; Antal et al., 2001; Ding et al., 2016) and/or neurophysiological measures (i.e., neural oscillation frequency, VEP activities) (Antal, Varga, et al., 2004; Ding et al., 2016; Wiesman et al., 2018; Wilson et al., 2017). Additionally, the effects of tDCS can last after the cessation of the stimulation. For instance, it has been shown that 9–13 min of tDCS produces an aftereffect lasting up to up to 90 min (Kuo et al., 2013; Nitsche, Nitsche, et al., 2003; Nitsche & Paulus, 2001). Thus, tDCS seems an ideal tool to investigate the causal relationship between E–I balance and cognition using psychophysical and neurophysiological measures with clear links to E–I balance, such as ODT, peak gamma frequency, and VEP amplitudes.

In this thesis, causal relationships between cortical E–I balance in the visual cortex, which was manipulated by tDCS, and both psychophysical and neurophysiological measures were investigated in a series of experiments. First, four experiments were conducted to thoroughly examine whether manipulation of cortical E–I balance using 2 mA of occipital tDCS for 10 min would result in robust changes in ODT performance (Chapter 2). Although no robust changes in ODT performance related to tDCS were observed, other than a placebo effect, an additional experiment combining tDCS-EEG was conducted to evaluate whether robust neurophysiological changes (indicated by gamma frequency oscillation and VEP amplitudes, N1 and P2) would be observed following the same protocol of tDCS used in the behavioural experiments (Chapter 3). This step was to examine the possibility that tDCS might induce robust neurophysiological changes in the visual cortex, which might not be reflected in observable changes in ODT performance. However, the results revealed robust changes in neither gamma frequency oscillation nor VEP amplitudes (N1 and P2) following the application of tDCS. As no effects of modulating cortical E–I balance using tDCS were observed in either psychophysical (Chapter 2) or neurophysiological outcomes (Chapter 3), the relationship between these psychophysical and neurophysiological was assessed (Chapter 4) to determine to what extent performance in vertical and oblique conditions of the ODT could be predicted by gamma frequency oscillations and amplitudes of VEP components (N1 and P2). It was found, as expected, that oblique ODT performance, but not vertical ODT performance, can highly be predicted by these neurophysiological measures. Higher peak gamma frequency

and/or lower VEP-N1 amplitude are associated with enhanced oblique performance. A detailed summary of each chapter's findings is provided in the following sections of this general discussion chapter.

Summary of Findings

Summary of findings of Chapter 2

In the first study, the effects of tDCS on ODT performance was investigated in four experiments. During the ODT, participants were presented consecutive pairs of grating and were asked to judge whether the second (target) grating tilted clockwise or anti-clockwise compared to the first (reference) grating. The ODT comprised vertical and oblique conditions, depending on the orientation of the reference grating. In the vertical condition, the reference grating was orientated at 0°, while in the oblique condition, the reference grating was oriented at 90°. The ODT was based on the work of Edden et al. (2009) and has been previously used by Dickinson, Bruyns-Haylett et al. (2016), Dickinson et al. (2015), and Dickinson et al. (2014). Transcranial direct current stimulation montages and protocols were kept the same for all experiments. The target electrode (5 × 5 cm) was placed over the occipital cortex at Oz (international 10–20 system), while the reference electrode (5 × 7 cm) was placed over the left cheek for 10 min with an intensity of 2 mA. The protocol and montage of tDCS used in this thesis have been shown to be effective in modulating behavioural (i.e., visual perception tasks) and neurophysiological outcomes (i.e., VEP amplitudes) (Ding et al., 2016; Peters et al., 2013; Richard et al., 2015).

The four experiments had slight methodological differences (i.e., number of sessions, between single- and two-session experiment), the timing of tDCS (i.e., pre-ODT runs,

between ODT runs). For instance, the first two experiments had two sessions with an interval of 7 days while the remaining experiments had a single session. Each session in all experiments had two runs of the ODT. Additionally, while participants of experiments with two sessions (Experiment 1 and 2) received tDCS then completed two runs of the ODT with a self-timed break (~2 minutes) between the runs, participants of experiments with a single session (Experiments 3 and 4) received tDCS between two runs of the ODT. Each run of the ODT lasted 8–12 min.

In Experiment 1, participants received sham-tDCS in the first session but active-tDCS (anodal- or cathodal-tDCS) in the second session. The result showed main effects of task condition (vertical, oblique) and session (first, second). The performance was better for the vertical condition of the ODT than for oblique condition. Additionally, the performance was better in the second session than in the first session. Although no main effect of tDCS was found, the investigation of a trend towards a significant interaction between task condition, session, and tDCS type (anodal- vs cathodal-tDCS) revealed that only robust performance improvement was observed in the oblique condition of the ODT for those who received cathodal-tDCS. Such a finding of a robust performance improvement in the oblique condition of the ODT following cathodal-tDCS is consistent with the suggested relationship between enhanced performance in the ODT and increased inhibition (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2014; Edden et al., 2009); however, another experiment with a larger sample size and randomized tDCS types (active anodal- and cathodal-tDCS vs sham-tDCS) between sessions was required to confirm this initial finding.

Experiment 2, with a larger sample size and randomized tDCS types (active anodal- and cathodal- tDCS vs sham-tDCS) between sessions was conducted to replicate the findings of Experiment 1. In the first session of Experiment 2, half of the participants received active-tDCS (anodal- or cathodal-tDCS), while the rest received sham-tDCS. However, in the second session, participants who had received sham-tDCS in the first session received active-tDCS (anodal- or cathodal-tDCS), while the rest received sham-tDCS. After the stimulation, participants completed the two runs of the ODT with a self-timed break (~2

minutes). Similar to Experiment 1's results, Experiment 2's results showed a main effect of task condition (vertical vs oblique), as the performance was better for vertical compared to oblique. However, no main effects of session type (active vs sham) or tDCS type (anodal- vs cathodal-tDCS) were found. Another analysis was conducted to evaluate the session-related effects. The results demonstrated main effects of task condition and session, as performance was better in the vertical condition than in the oblique condition of the ODT, as well as in the second session compared to the first session. However, no main effect of tDCS types was found. Further analysis revealed that robust performance improvement in the oblique condition of the ODT occurred for both anodal- and cathodal-tDCS groups regardless of the session type (active vs sham). This finding contradicts previous studies' suggestions that anodal-tDCS blocks perceptual learning consolidation (Matsushita et al., 2015; Peters et al., 2013). Such a strong session-related effect might mask any potential effects of tDCS on ODT performance. Thus, an experimental design with minimum perceptual learning was needed to ensure that the absence of tDCS effect in modulating performance in the ODT was not due to session-induced perceptual learning. Therefore, previous data (Experiment 1 and 2) was analysed to track performance improvement between and within sessions. The result showed that robust performance improvement occurs only in between-sessions runs (i.e., between the first run of the first session and both first and second run of the second session), but not within-session runs (i.e., between the first and second run of the first or second session).

Thus, Experiment 3 with a single session was conducted to re-evaluate tDCS effects on ODT performance. Participants received tDCS (anodal-, cathodal-, or sham-tDCS) between two runs of the ODT. The result revealed a main effect of task condition, as the performance was better in the vertical condition than in the oblique condition of the ODT. Additionally, a main effect of the ODT run is found, as the performance was better in the post-tDCS run than in the pre-tDCS run. This finding is surprising, given the results of the analyses of previous data tracking performance improvement between- and within-session runs, and it is inconsistent with previous studies' findings of no performance difference between two runs of the ODT within a single session (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Dickinson et al., 2014). Two possibilities were generated to

explain such unexpected improvement in the post-tDCS (second) run. The first possibility was related to an increase in the temporal duration between the two runs from approximately 2 minutes to approximately 10 minutes, given the crucial role of resting time following practice in perceptual learning (Bönstrup et al., 2019; Dewar et al., 2014; Schoups et al., 1995). The second possibility was that this performance improvement might result from a placebo effect of tDCS, given the occurrence of robust performance improvement following all types of tDCS, including sham-tDCS.

Therefore, Experiment 4 was conducted to examine whether the robust performance improvement in the post-tDCS (second) run of the ODT observed in Experiment 3 was caused by the increased temporal duration between the two runs, allowing for consolidation of perceptual learning or due to a placebo effect of tDCS. In a single session experiment, participants randomly had a 2-min or 10-min break between runs of the ODT with no-tDCS, or they received sham-tDCS between the two runs of the ODT. The result showed main effects of the task condition and run. The performance was better in the vertical condition of the ODT compared to oblique condition. In addition, the performance was better in the second run of the ODT than in the first run. While there was no main effect of the delay condition group (2 min with no-tDCS, 10 min with no-tDCS, or sham-tDCS), a further analysis investigating the significant interaction between run and delay condition group revealed that ODT performance was only significantly improved in the second run of the ODT for the group receiving sham-tDCS. This finding confirmed that the unexpected robust ODT performance improvement observed in the second run of the ODT in Experiment 3 resulted mostly from a placebo effect of tDCS rather than increased temporal duration between the runs.

Summary of findings of Chapter 3

Although the investigations of the causal relationship between E–I balance and ODT performance did not reveal any actual tDCS effects on ODT performance other than a placebo effect (Chapter 2), such null findings of actual tDCS effect in ODT performance were not enough to rule out the possibility that active tDCS might alter neural activity (i.e., peak gamma frequency, VEP amplitudes) without producing any observable changes at the behavioural level. It was hypothesised that anodal-tDCS would decrease peak gamma frequency, whereas cathodal-tDCS would increase it, based on the work of Dickinson, Bruyns-Haylett et al. (2016), Dickinson et al. (2015), and Edden et al. (2009). Additionally, it was hypothesised that anodal-tDCS would increase VEP-N1 amplitude and decrease VEP-P2, whereas cathodal-tDCS would have the opposite effects, in accordance with animal-model findings of increased (reduced) amplitude of VEP-N1 and reduced (increased) amplitude of P2 following the administration of GABA antagonist (agonist) (Zemon et al., 1980; Zeneroli et al., 1981). To investigate the effects of tDCS in modulating gamma frequency oscillations and VEP amplitudes, a tDCS-EEG experiment was conducted. In this experiment, participants completed 12–15 the ODT (including practice and actual run of the ODT), unless they had completed it in previous experiments. After that, participants completed two runs of an EEG task, shown to elicit a strong peak gamma frequency and VEP activity (Milne et al., 2018; Milne et al., 2019). The interval between the completion of the ODT and the start of EEG data collection was approximately 20 minutes. During the EEG task, participants were asked to maintain fixation on a red dot appearing on the centre of a monitor where black and white checkerboard stimulus appeared repeatedly. Participants were instructed to press the spacebar key when the checkerboard stimulus disappeared. The run of the EEG task lasted up to 15 min, including a self-timed break. Between the two runs of EEG task, participants randomly received tDCS (anodal-, cathodal-, or sham-tDCS) or had a 10-min break with no-tDCS. The results of two separate analyses of variance (ANOVAs) assessing the effects of tDCS on gamma frequency oscillations (peak gamma frequency and gamma frequency

power) and VEP amplitudes (N1 and P2) showed no main effect of tDCS in modulating either peak gamma frequency or amplitudes of VEP components (N1 and P2). However, EEG task repetition-related changes were observed in both analyses. For instance, peak gamma frequency robustly increased in the second (post-tDCS) run of the EEG task, while the amplitudes of VEP components decreased. The null findings of actual tDCS effects on both peak gamma frequency and VEP amplitudes are consistent with the previous findings of no main effects of actual tDCS in modulating performance in the ODT.

Summary of findings of Chapter 4

Although the findings of Chapters 2 and 3 investigating the effects of tDCS on psychophysical (ODT) and neurophysiological measures (peak gamma frequency and gamma frequency power, as well as VEP amplitudes of N1 and P2) failed to support the suggestion that tDCS modulates E–I balance (Clark et al., 2011; Krause et al., 2013; Stagg et al., 2009), it was necessary to reassess the links between these psychophysical and neurophysiological measures as being indirect indicators of E–I balance to ensure the validity of this claim. To achieve this verification, an additional study was conducted to replicate previous findings of an association between ODT and peak gamma frequency and to expand upon them by including the amplitudes of VEP components (N1 and P2) (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009). The question was of the extent to which ODT performance could be predicted by gamma frequency oscillations (peak gamma frequency, gamma power frequency) and amplitudes of VEP components (N1 and P2). It was hypothesized that increased peak gamma frequency, lower VEP-N1, and higher VEP-P2 would be associated with enhanced performance in the ODT (Dickinson, Bruyns-Haylett, et al., 2016; Edden et al., 2009; Zemon et al., 1980; Zeneroli et al., 1981). Data from this study were mainly the same as

those collected and analysed in the tDCS-EEG experiment (Chapter 3). As mentioned earlier, participants in the tDCS-EEG experiment completed an approximately 12–15-min ODT (including a practice run and actual run of the ODT) unless they had completed it previously (Chapter 2). After that, participants completed the EEG task. All the ODT and EEG task data included in this study were collected in the first (pre-tDCS) runs. The result of the linear multiple regressions showed that performance in the oblique condition of the ODT could highly be predicted by higher peak gamma frequency and/or lower VEP-N1. Additionally, VEP-P2 amplitude trended towards significance as a predictor of the oblique condition of ODT performance ($p = .079$). This result is successfully replicated previous studies finding an association between enhanced oblique ODT performance and higher peak gamma frequency (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009) and accords with animal and human research findings and suggestions that cortical inhibition can be inferred from amplitudes of VEP-N1 and P2 (Gawel et al., 1983; Zemon et al., 1980; Zeneroli et al., 1981). In relation to this finding of a strong association between cortical inhibition (as indicated by oblique ODT performance) and neurophysiological measures, the null findings of actual effects of tDCS in modulating ODT performance (Chapter 2) and both peak gamma frequency and amplitudes of VEP components (N1 and P2) (Chapter 3) do not support the suggested effects of tDCS in modulating E–I balance (Clark et al., 2011; Krause et al., 2013; Stagg et al., 2009).

Oblique effect in the orientation discrimination task

Consistent with previous studies (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2014; Shafai et al., 2015; Sysoeva et al., 2016; Tibber et al., 2006), the results of the four experiments show that performance in the orientation discrimination task (ODT) was better for the vertical condition, as compared to the oblique condition. Such poor performance in

the oblique condition of the ODT compared to vertical one is referred to as an "oblique effect" (Appelle, 1972). Such performance differences between the vertical and oblique condition of the ODT have been suggested to reflect orientation selectivity, where neural cells are selectively more sensitive and responsive to particular orientations (i.e., cardinal). For instance, it has been shown that more neural cells of the primary visual cortex (V1) respond to vertical and horizontal ordination, as compared to oblique orientation (Li, et al., 2003; Mansfield, 1974; Rose & Blakemore, 1974; Yu & Shou, 2000). Additionally, more neural cells have also been suggested to respond preferentially to cardinal (vertical, horizontal) orientation compared to oblique orientation (Katzner et al., 2011; Leventhal et al., 2003; Li et al., 2008; Sillito, 1975, 1979; Sillito et al., 1980). Neural tuning width for cardinal orientation has been shown to be narrower than that of oblique orientation (Li et al. 2003; Nelson et al., 1977; Orban & Kennedy, 1981). Although perceptual training has been shown to increase orientation selectivity (Schoups, Vogels, Qian, & Orban, 2001), the oblique effect was present even after intensive training that led to robust performance improvement in the oblique condition of line-ODT (Vogels & Orban, 1985).

Session effect on orientation discrimination task performance

In the first two experiments of two sessions (Chapter 2), a robust performance improvement in the second session was found. This orientation discrimination task (ODT) performance improvement was mainly driven by the improvement in the oblique condition of the ODT, as only robust performance improvement in the second session was observed in the oblique condition, but not in the vertical condition, of the ODT. This condition-dependent performance improvement is consistent with the findings of previous studies investigating the effects of training on ODT performance (Song et al., 2010; Vogels & Orban, 1985). For instance, intensive perceptual training was shown to induce robust

performance improvement only in the oblique condition of the ODT, but not in the cardinal (i.e., vertical and horizontal) conditions (Song et al., 2010; Vogels & Orban, 1985). Such a lack of inducing any observable changes in the cardinal condition of the ODT has been suggested to be caused by a ceiling effect. It is possible that the strong performance in the vertical condition in the first session left no space for any further performance improvement. Additionally, the session-related improvement was so strong that it occurred even following anodal-tDCS, which has been suggested to block perceptual learning (Matsushita et al., 2015, 2017; Peters et al., 2013).

Placebo effects of transcranial direct current stimulation

In Experiment 3 of a single session (Chapter 2), performance in the ODT robustly improved in the second run of the ODT. Such run-related improvement was inconsistent with previous studies (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Dickinson et al., 2014) and was unexpected, based on the analysis of previous data (Experiment 1 and 2) revealing that no robust performance improvement in oblique condition occurred within a session's runs of the ODT. Such unexpected run-related improvement was speculated to result from either increasing the time duration between ODT runs of Experiment 3 to 10 min compared to 2 min, as in Experiment 1 and 2, or a placebo effect of transcranial direct current stimulation (tDCS). Examining these two possibilities by assigning groups of participants to either short or long break between the runs of the ODT (2 min vs 10 min) with no-tDCS, while a third group received sham-tDCS between the runs of the ODT, Experiment 4 showed that performance improvement was only robust for the group receiving sham-tDCS. Such a finding confirms that the unexpected run-related performance found in Experiment 3 depends highly on a placebo

effect of tDCS and refutes the possible role of increasing duration in causing such an improvement.

In spite of a large body of research investigating the effects of tDCS, little attention has been paid to the placebo effects of tDCS in modulating behavioural and neurophysiological outcomes. A small number of studies have reported placebo effects of tDCS in modulating clinical and cognitive outcomes (Aslaksen et al., 2014; Cortese et al., 2017; Egorova et al., 2015; Loo et al., 2018; Schambra et al., 2014; Turi et al., 2018). For instance, sham-tDCS has been shown to reduce depression (Loo et al., 2018; Schambra et al., 2014) and pain perception (Aslaksen et al., 2014; Egorova et al., 2015). Such placebo effects may affect neurophysiological measures, as investigating placebo effects of pharmacological (i.e., drug) and non-pharmacological interventions (i.e., lotion) on depression and pain perception were found to cause observable changes in neural activity (Mayberg et al., 2002; Wager, 2005; Wager et al., 2004). For instance, a positron emission tomography (PET) study assessing effects of administering placebo drugs on depression showed that placebo effects produced robust brain changes in addition to clinical improvement in depression symptoms (Mayberg et al., 2002). Similarly, a functional magnetic resonance imagining (fMRI) study showed that placebo effects of lotion application resulted in a reduction in neural activity in pain-related brain regions in addition to reducing pain perception (Wager et al., 2004). Such placebo-induced behavioural and neurophysiological changes (Mayberg et al., 2002; Schambra et al., 2014; Wager, 2005; Wager et al., 2004) may reflect high-level top-down cognitive processes (i.e., anticipation and expectation) (Diederich & Goetz, 2008; Schambra et al., 2014).

Placebo effects have been suggested to influence subjective self-reported measures, but not objective ones (Schwarz & Büchel, 2015; Stewart-Williams & Podd, 2004). For instance, (Schwarz & Büchel, 2015) found a dissociation between placebo effects based on the type of measures being used, as either subjective or an objective measure. In their study, they manipulated participants' expectations of the effects of an intervention in modulating performance in a cognitive task. They found that inducing positive expectation about the effects of the intervention on a cognitive task performance enhanced the perceived effect

of the intervention on task performance, with no observable effects on the task performance (Schwarz & Büchel, 2015). This finding suggests that placebo effects modulate outcomes of subjective but not of objective measures. Inconsistent with this finding, several studies have found that objectively measured outcomes could be modulated by placebo effects (Foroughi et al., 2016; Turi et al., 2018; Turi et al., 2017): For instance, expected and perceived performance in a rewards-based learning task improved (impaired) following a combination of sham-tDCS, conditioning, and positive (negative) verbal instruction about the expected effect (Turi et al., 2018; Turi et al., 2017). Additionally, the efficacy of training in a working memory task (dual n-back task) was enhanced by instruction-induced placebo (Foroughi et al., 2016). Consistent with these findings of placebo effects manipulating performance in cognitive tasks, the results of Experiments 3 and 4 (Chapter 2) showed a robust placebo effect that enhanced performance in the ODT. Unlike previous studies reporting placebo effects of tDCS on subjectively measured outcomes or including an explicitly suggestive positive or negative instruction about the expected effects of tDCS on performance (Foroughi et al., 2016; Schwarz & Büchel, 2015; Turi et al., 2018; Turi et al., 2017), this study finds placebo effects on the performance of an objectively measured low-level perceptual task (ODT) in the absence of an explicitly suggestive instruction about the expected effects of tDCS on ODT performance.

Effects of perception of transcranial direct current stimulation on orientation discrimination task performance

As placebo effects have been linked to beliefs and expectations about the efficacy of the treatments or interventions (Mayberg et al., 2002; Schambra et al., 2014; Wager, 2005; Wager et al., 2004), whether orientation discrimination task (ODT) performance

improvement depended on participants' perceptions of the stimulations type they received, as either active- or sham-tDCS, was investigated using Experiment 3 data (Chapter 2). Participants at the end of each session were asked to indicate whether they thought they had received real or active-, or sham-DCS in the post-stimulation questionnaires (Galea et al., 2009). Based on their thoughts on the stimulation type they had received, and regardless of the actual stimulation they had received, participants were categorized into an active-tDCS group ($N = 54$) and sham-tDCS group ($N = 12$). Two paired sample *t*-test analyses were conducted to evaluate oblique ODT performance improvement pre- and post-tDCS for each group separately. For participants who thought that they had received active-tDCS (active group) regardless of the actual stimulation, the result showed a robust performance improvement in oblique condition of the ODT at the second (post-tDCS) run ($M = 6.80°$, $SD = 2.83°$) compared to the first (pre-tDCS) run ($M = 8.53°$, $SD = 2.94°$), ($p < .0001$). For participants who thought that they had received sham-tDCS (sham group) regardless of the actual stimulation, the result almost reached statistical significance ($p = .052$), as performance in the oblique condition of the ODT on the second (post-tDCS) run ($M = 6.30$, $SD = 1.94$) was better than was the first (pre-tDCS) run ($M = 7.35$, $SD = 2.14$). The statistical insignificance may be caused by the small sample size. Although the results are consistent with the findings of previous studies showing an association between perception of treatment or intervention and the expected behavioural outcomes, the results cannot rule out the possibility that placebo effects of tDCS could occur even in the absence of perception of tDCS.

Electroencephalogram task repetition-related changes in neural activity

The results of the electroencephalogram (EEG)-tDCS study (Chapter 4) showed EEG task repetition-related changes in VEP amplitudes and peak gamma frequency. For instance, N1

amplitude decreased in the second run compared to the first run of the EEG task. However, peak gamma frequency increased in the second run compared to the first run of the EEG task. Such changes possibly reflect the well-known phenomenon of habituation, where behavioural and neural responses to a repeated stimulus are reduced over time (Rankin et al., 2009; Thompson & Spencer, 1966). Normal habituation has been suggested to depend on balanced E–I ratio (Ambrosini et al., 2016; Brighina et al., 2009; Coppola et al., 2013). Furthermore, reduced habituation reflected in lack of VEP amplitude's reduction over stimulus repetition (Afra et al., 1998; Coppola et al., 2015) has been suggested to reflect down-regulation of GABA activity (Brighina et al., 2009). Evidence supporting such claims comes from brain stimulation studies showing that an excitatory repetitive transcranial magnetic stimulation (rTMS) initially increased VEP amplitude and increased habituation, while an inhibitory rTMS initially decreased VEP amplitude and decreased inhibition (Bohotin et al., 2002). Similar effects on habituation were also observed following the application of anodal- and cathodal-tDCS (Siniatchkin et al., 2011).

In accordance with the suggested relationship between habituation and inhibition (Brighina et al., 2009; Siniatchkin et al., 2011), the finding of increased peak gamma frequency and reduced N1 amplitude in the second run of the EEG task is more likely to indicate increased inhibition, given that both higher peak gamma frequency and lower N1 amplitude have been found to be associated with increased GABA concentration and activity (Edden et al., 2009; Muthukumaraswamy et al., 2009; Zemon et al., 1980; Zeneroli et al., 1981). Although habituation typically involves reduction in behavioural and neural responses, increased peak gamma frequency in the second run of the EEG task may reflect "an inverse habituation," given the suggestion that increased peak gamma frequency indicates increased inhibition (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009; Muthukumaraswamy et al., 2009).

Strengths of Experimental Work Presented in the Thesis

The strength of this thesis investigating the effects of modulating E–I balance using tDCS on outcomes of psychophysical and neurophysiological measure can be seen in three ways. The first is using psychophysical (i.e., ODT) and neurophysiological (i.e., peak gamma frequency and amplitudes of VEP components, N1 and P2) measures that have been shown to have clear links to E–I balance (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009; Zemon et al., 1980; Zeneroli et al., 1981). Associated with E–I balance, these psychophysical and neurophysiological measures are presumably more susceptible to being genuinely influenced by tDCS than are behavioural and personality measures lacking clear links to E–I balance. The second point is related to the verification of the potential causes behind the unexpected robust performance improvement between ODT runs within a single session found in Experiment 3 (Chapter 2). This step revealed a strong placebo effect of tDCS on ODT performance and pointed out the importance of including the no-tDCS group. Unfortunately, most tDCS studies do not include a no-tDCS group, making it very difficult to distinguish the placebo effects of tDCS from the actual effect of the stimulation (Fields & Levine, 1984), as sham-tDCS has been suggested to be insufficient to estimate the size of potential placebo effects of tDCS (Benedetti et al., 2003). The third point regards the combination of tDCS and EEG. Although several MEG studies have recently investigated the effects of tDCS on neural activity in the human visual cortex (Hanley et al., 2016; Marshall et al., 2016; Wiesman et al., 2018; Wilson et al., 2017), no EEG study, as far as I am aware, has been conducted yet to investigate effects of tDCS on the neural activity of the visual cortex. Additionally, this thesis showed that the independent component analysis (ICA) technique of EEG data could be very useful in a within-subject design, given that matched pairs of ICA components from the first (pre-tDCS) EEG run and second (post-tDCS) EEG run share similar distinct event-related dynamics and source localization.

Limitations of Experimental Work Presented in the Thesis

This thesis has three limitations. The first limitation is related to the sample type, as most of the participants for all the experiments were students. This homogeneity could possibly limit the generalizability of the findings. However, this limitation is unlikely to be problematic, given that cognitive and neurophysiological variables rather than personal and attitudinal variables were investigated in this thesis (Hanel & Vione, 2016). The second limitation is related to gender imbalanced samples. For instance, most of the participants in experiments conducted in Sheffield, UK, were female, although the gender ratio for each tDCS group for all experiments was balanced. Additionally, in the experiments conducted in Saudi Arabia, data from only male participants were collected, due to the lack of accessibility to female participants. The third limitation is related to the sample of EEG experiment having different experimental procedures. For instance, participants were asked to complete an approximately 12–15-minute ODT (including practice and actual run of the ODT) 25–30 min before conducting the two runs of the EEG task, unless they had completed the ODT in previous experiments. However, the results of an analysis conducted to investigate the effects of such a difference in procedures on neural activity (gamma frequency oscillations and VEP components amplitudes) showed that difference in experimental procedures did not have a robust impact on the outcomes of these neurophysiological measures.

Further Study

Future tDCS studies should consider including a no-tDCS group, as this step could help distinguish the real effect of tDCS from the placebo effect of tDCS. Although sham-tDCS

has been used widely to control for placebo effect, attributing performance difference between sham- and active-tDCS that have the same direction (i.e., both show enhanced performance) to an actual effect of tDCS may not be a valid inference, given the stronger sensations of active-tDCS compared to sham-tDCS (Kessler et al., 2012; Turi et al., 2019), possibly resulting in a stronger placebo effect of tDCS for active-tDCS than for sham-tDCS. Additionally, future studies should also investigate whether the tDCS placebo-induced enhanced performance in ODT performance is associated with changes in GABA concentration in the visual cortex, given the relationship between perceptual learning and GABA concentration level in the visual cortex (Garcia, 2017; Heba et al., 2015).

Conclusion

In this thesis, the effects of manipulating E–I balance using tDCS on the outcomes of psychophysical and neurophysiological measures were investigated. In Chapter 2 of this thesis, the effects of tDCS on ODT performance in a series of experiments were studied. Although the results found no main effect of tDCS types on ODT performance, a placebo effect of tDCS was suggested, as performance in the oblique condition of the ODT robustly improved following any type of tDCS (anodal-, cathodal-, or sham-tDCS). This suggestion was confirmed by the finding of a single session experiment including no-tDCS conditions in addition to sham-tDCS condition. The result revealed that performance in the oblique condition of the ODT was only strongly improved following sham-tDCS, while no such improvement was observed in conditions with no-tDCS. This finding supports the suggested placebo effect of tDCS in enhancing ODT performance observed in Experiment 3 (Chapter 2). Even though the investigation of tDCS effects on ODT performance did not reveal any actual effects of tDCS other than a placebo effect, it did not rule out the possibility that tDCS might produce neurophysiological changes that were not reflected in

psychophysical outcomes. Therefore, in Chapter 3 of this thesis, the effects of tDCS on induced gamma frequency oscillations (peak gamma frequency and gamma frequency power) and amplitudes of VEP components (N1 and P2) were investigated. Participants received tDCS (anodal-, cathodal-, or sham- tDCS) or had 10 min between two runs of an EEG task, shown to produce strong neural activity. Consistent with the findings of Chapter 2, no main effects of tDCS type were observed in both gamma frequency oscillations and the amplitudes of VEP components. Additionally, EEG task repetition-related changes were found in both gamma frequency oscillations and the amplitudes of VEP. For instance, peak gamma frequency robustly increased in the second run of the EEG task, while the amplitude of VEP-N1 decreased. The EEG task repetition-related changes of both peak gamma frequency and amplitude of VEP-N1 may reflect neural habituation and increased cortical inhibition. Given the suggestion that tDCS affects E–I balance, the lack of findings of any actual effects of tDCS on outcomes of psychophysical and neurophysiological measures suggested to reflect E–I balance made investigating the relationship between the psychophysical and neurophysiological measures necessary. This investigation was to ensure the validity of the claim that tDCS does not modulate E–I balance and to reassess the links between these measures thought to indirectly indicate E–I balance. Thus, Chapter 4 investigated the extent to which performance in the vertical and oblique condition of the ODT could be predicted by the neurophysiological measures (peak gamma frequency, gamma frequency power, amplitude of VEP-N1, and amplitude of VEP-N1P2). The result showed that only performance in the oblique condition of the ODT could highly be predicted by these neurophysiological measures. Only peak gamma frequency and VEP-N1 amplitude could significantly predict oblique ODT performance, as higher peak gamma frequency and/or lower amplitude of VEP-N1 is associated with enhanced performance in the oblique condition of the ODT. This finding successfully replicates and extends previous studies showing that in addition to higher peak gamma frequency, lower VEP-N1 amplitude is strongly associated with enhanced oblique ODT performance (Dickinson, Bruyns-Haylett, et al., 2016; Dickinson et al., 2015; Edden et al., 2009). Future studies should include a no-tDCS condition to present a better estimate of the size of the placebo effect. Additionally, future studies should investigate the placebo effects of tDCS on GABA concentration level in the visual cortex.

References

Abeles, M. (1991). *Corticonics: Neural circuits of the cerebral cortex*: Cambridge University Press.

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.

Adesnik, H. (2017). Synaptic mechanisms of feature coding in the visual cortex of awake mice. *Neuron, 95*(5), 1147-1159. e1144.

Afra, J., Cecchini, A. P., De Pasqua, V., Albert, A., & Schoenen, J. (1998). Visual evoked potentials during long periods of pattern-reversal stimulation in migraine. *Brain: a journal of neurology, 121*(2), 233-241.

Ahveninen, J., Lin, F.-H., Kivisaari, R., Autti, T., Hämäläinen, M., Stufflebeam, S., . . . Kähkönen, S. (2007). MRI-constrained spectral imaging of benzodiazepine modulation of spontaneous neuromagnetic activity in human cortex. *Neuroimage, 35*(2), 577-582.

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.

Ambrosini, A., Iezzi, E., Perrotta, A., Kisialiou, A., Nardella, A., Berardelli, A., . . . Schoenen, J. (2016). Correlation between habituation of visual-evoked potentials and magnetophosphene thresholds in migraine: A case-control study. *Cephalalgia, 36*(3), 258-264.

Anderson, J. S., Carandini, M., & Ferster, D. (2000). Orientation tuning of input conductance, excitation, and inhibition in cat primary visual cortex. *Journal of neurophysiology, 84*(2), 909-926.

Anderson, K., & Ding, M. (2011). Attentional modulation of the somatosensory mu rhythm. *Neuroscience, 180*, 165-180.

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.

Anemüller, J., Duann, J.-R., Sejnowski, T. J., & Makeig, S. (2006). Spatio-temporal dynamics in fMRI recordings revealed with complex independent component analysis. *Neurocomputing, 69*(13-15), 1502-1512.

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

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., Kruse, W., Kincses, T. Z., Hoffmann, K.-P., & Paulus, W. (2004). Direct current stimulation over V5 enhances visuomotor coordination by improving motion perception in humans. *Journal of cognitive neuroscience, 16*(4), 521-527.
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.
Antal, A., Varga, E. T., Kincses, T. Z., Nitsche, M. A., & Paulus, W. J. N. (2004). Oscillatory brain activity and transcranial direct current stimulation in humans. *15*(8), 1307-1310.
Antonenko, D., Schubert, F., Bohm, F., Ittermann, B., Aydin, S., Hayek, D., . . . Flöel, A. (2017). tDCS-induced modulation of GABA levels and resting-state functional connectivity in older adults. *Journal of Neuroscience*, 0079-0017.
Appelle, S. (1972). Perception and discrimination as a function of stimulus orientation: the" oblique effect" in man and animals. *Psychological bulletin, 78*(4), 266.
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.
Ardolino, G., Bossi, B., Barbieri, S., & Priori, A. (2005). Non‐synaptic mechanisms underlie the after‐effects of cathodal transcutaneous direct current stimulation of the human brain. *The Journal of physiology, 568*(2), 653-663.
Armstrong, R., & Cubbidge, R. (2014). The Eye and Vision: An Overview. In *Handbook of Nutrition, Diet and the Eye* (pp. 3-9): Elsevier.
Ashjazadeh, N., & Varavipour, B. (2015). Abnormalitites of Visual Evoked Potential in Migraine Patients. *Iranian Journal of Medical Sciences, 28*(2), 65-68.
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.
Atallah, B. V., & Scanziani, M. (2009). Instantaneous modulation of gamma oscillation frequency by balancing excitation with inhibition. *Neuron, 62*(4), 566-577.
Avella Gonzalez, O. (2014). Mechanisms of Cortical Oscillations: Waxing and waning, Resonance and Internetwork interactions.
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.
Bachtiar, V., Johnstone, A., Berrington, A., Lemke, C., Johansen-Berg, H., Emir, U., & Stagg, C. J. (2018). Modulating Regional Motor Cortical Excitability with Noninvasive Brain

Stimulation Results in Neurochemical Changes in Bilateral Motor Cortices. *Journal of Neuroscience, 38*(33), 7327-7336.
Barnes, A., Bullmore, E. T., & Suckling, J. (2009). Endogenous human brain dynamics recover slowly following cognitive effort. *PloS one, 4*(8), e6626.
Baroncelli, L., Braschi, C., Spolidoro, M., Begenisic, T., Maffei, L., & Sale, A. (2011). Brain plasticity and disease: a matter of inhibition. *Neural plasticity, 2011*.
Bartel, P., Blom, M., & Van der Meyden, C. (1988). Effects of single doses of diazepam, chlorpromazine, imipramine and trihexyphenidyl on visual-evoked potentials. *Neuropsychobiology, 20*(4), 212-217.
Bastani, A., & Jaberzadeh, S. (2012). Does anodal transcranial direct current stimulation enhance excitability of the motor cortex and motor function in healthy individuals and subjects with stroke: a systematic review and meta-analysis. *Clinical neurophysiology, 123*(4), 644-657.
Bastani, A., & Jaberzadeh, S. (2013). a-tDCS differential modulation of corticospinal excitability: the effects of electrode size. *Brain stimulation, 6*(6), 932-937.
Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M. F., & Nitsche, M. (2013). Partially non‐linear stimulation intensity‐dependent effects of direct current stimulation on motor cortex excitability in humans. *The Journal of physiology, 591*(7), 1987-2000.
Bauer, M., Stenner, M.-P., Friston, K. J., & Dolan, R. J. (2014). Attentional modulation of alpha/beta and gamma oscillations reflect functionally distinct processes. *Journal of Neuroscience, 34*(48), 16117-16125.
Başar, E., Başar-Eroglu, C., Karakaş, S., & Schürmann, M. (2001). Gamma, alpha, delta, and theta oscillations govern cognitive processes. *International journal of psychophysiology, 39*(2-3), 241-248.
Behrens, J. R., Kraft, A., Irlbacher, K., Gerhardt, H., Olma, M. C., & Brandt, S. A. (2017). Long-lasting enhancement of visual perception with repetitive noninvasive transcranial direct current stimulation. *Frontiers in cellular neuroscience, 11*, 238.
Benedetti, F., Rainero, I., & Pollo, A. (2003). New insights into placebo analgesia. *Current Opinion in Anesthesiology, 16*(5), 515-519.
Berlim, M. T., Van den Eynde, F., & Daskalakis, Z. J. (2013). Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Journal of psychiatric research, 47*(1), 1-7.
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.
Bikson, M., Brunoni, A. R., Charvet, L. E., Clark, V. P., Cohen, L. G., Deng, Z.-D., . . . Kappenman, E. S. (2018). Rigor and reproducibility in research with transcranial electrical stimulation: An NIMH-sponsored workshop. *Brain stimulation, 11*(3), 465-480.
Bikson, M., Datta, A., Rahman, A., & Scaturro, J. (2010). Electrode montages for tDCS and weak transcranial electrical stimulation: role of “return” electrode’s position and

size. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology, 121*(12), 1976.
Bikson, M., Inoue, M., Akiyama, H., Deans, J. K., Fox, J. E., Miyakawa, H., & Jefferys, J. G. (2004). Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. *The Journal of physiology, 557*(1), 175-190.
Bindman, L. J., Lippold, O., & Redfearn, J. (1962). Long-lasting changes in the level of the electrical activity of the cerebral cortex produced by polarizing currents. *Nature, 196*(4854), 584.
Bindman, L. J., Lippold, O., & Redfearn, J. (1964). The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long‐lasting after‐effects. *The Journal of physiology, 172*(3), 369-382.
Blake, R. (1989). A neural theory of binocular rivalry. *Psychological review, 96*(1), 145.
Bocci, T., Caleo, M., Tognazzi, S., Francini, N., Briscese, L., Maffei, L., . . . Sartucci, F. (2014). Evidence for metaplasticity in the human visual cortex. *Journal of neural transmission, 121*(3), 221-231.
Boggio, P. S., Ferrucci, R., Rigonatti, S. P., Covre, P., Nitsche, M., Pascual-Leone, A., & Fregni, F. (2006). Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. *Journal of the neurological sciences, 249*(1), 31-38.
Bohotin, V., Fumal, A., Vandenheede, M., Gerard, P., Bohotin, C., Maertens De Noordhout, A., & Schoenen, J. (2002). Effects of repetitive transcranial magnetic stimulation on visual evoked potentials in migraine. *Brain, 125*(4), 912-922.
Bonds, A. (1982). An “oblique effect” in the visual evoked potential of the cat. *Experimental Brain Research, 46*(1), 151-154.
Bonnel, A., McAdams, S., Smith, B., Berthiaume, C., Bertone, A., Ciocca, V., . . . Mottron, L. (2010). Enhanced pure-tone pitch discrimination among persons with autism but not Asperger syndrome. *Neuropsychologia, 48*(9), 2465-2475.
Bonnel, A., Mottron, L., Peretz, I., Trudel, M., Gallun, E., & Bonnel, A.-M. (2003). Enhanced pitch sensitivity in individuals with autism: a signal detection analysis. *Journal of cognitive neuroscience, 15*(2), 226-235.
Boylu, E., Domac, F., Kocer, A., Unal, Z., Tanridağ, T., & Us, O. (2010). Visual evoked potential abnormalities in migraine patients. *Electromyography and clinical neurophysiology, 50*(6), 303-308.
Brainard, D. H., & Vision, S. (1997). The psychophysics toolbox. *Spatial vision, 10*, 433-436.
Breitmeyer, B. G., & Ganz, L. (1976). Implications of sustained and transient channels for theories of visual pattern masking, saccadic suppression, and information processing. *Psychological review, 83*(1), 1.
Brighina, F., Palermo, A., & Fierro, B. (2009). Cortical inhibition and habituation to evoked potentials: relevance for pathophysiology of migraine. *The journal of headache and pain, 10*(2), 77.
Brighina, F., Piazza, A., Daniele, O., & Fierro, B. (2002). Modulation of visual cortical excitability in migraine with aura: effects of 1 Hz repetitive transcranial magnetic stimulation. *Experimental brain research, 145*(2), 177-181.
Brock, J., Xu, J. Y., & Brooks, K. R. (2011). Individual differences in visual search: Relationship to autistic traits, discrimination thresholds, and speed of processing. *Perception, 40*(6), 739-742.

Brunel, N. (2000). Dynamics of sparsely connected networks of excitatory and inhibitory spiking neurons. *Journal of computational neuroscience, 8*(3), 183-208.
Brunel, N. (2003). Dynamics and plasticity of stimulus-selective persistent activity in cortical network models. *Cerebral Cortex, 13*(11), 1151-1161.
Brunel, N., & Hakim, V. (1999). Fast global oscillations in networks of integrate-and-fire neurons with low firing rates. *Neural computation, 11*(7), 1621-1671.
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.
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.
Buzsáki, G., & Wang, X.-J. (2012). Mechanisms of gamma oscillations. *Annual review of neuroscience, 35*, 203-225.
Bönstrup, M., Iturrate, I., Thompson, R., Cruciani, G., Censor, N., & Cohen, L. G. (2019). A Rapid Form of Offline Consolidation in Skill Learning. *Current Biology*.
Börgers, C., & Kopell, N. (2003). Synchronization in networks of excitatory and inhibitory neurons with sparse, random connectivity. *Neural computation, 15*(3), 509-538.
Callan, D. E., Falcone, B., Wada, A., & Parasuraman, R. (2016). Simultaneous tDCS-fMRI identifies resting state networks correlated with visual search enhancement. *Frontiers in human neuroscience, 10*, 72.
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.
Capilla, A., Melcón, M., Kessel, D., Calderón, R., Pazo-Álvarez, P., & Carretié, L. (2016). Retinotopic mapping of visual event-related potentials. *Biological psychology, 118*, 114-125.
Chaieb, L., Antal, A., & Paulus, W. (2011). Transcranial alternating current stimulation in the low kHz range increases motor cortex excitability. *Restorative neurology and neuroscience, 29*(3), 167-175.
Chan, C., Hounsgaard, J., & Nicholson, C. (1988). Effects of electric fields on transmembrane potential and excitability of turtle cerebellar Purkinje cells in vitro. *The Journal of Physiology, 402*(1), 751-771.
Chatzichristos, C., Davies, M., Escudero, J., Kofidis, E., & Theodoridis, S. (2018). *Fusion of EEG and fMRI via soft coupled tensor decompositions.* Paper presented at the 2018 26th European Signal Processing Conference (EUSIPCO).
Chen, Y., Norton, D., & Ongur, D. (2008). Altered center-surround motion inhibition in schizophrenia. *Biological psychiatry, 64*(1), 74-77.
Chew, T., Ho, K.-A., & Loo, C. K. (2015). Inter-and intra-individual variability in response to transcranial direct current stimulation (tDCS) at varying current intensities. *Brain Stimulation, 8*(6), 1130-1137.

Chowdhury, S., & Rasmusson, D. J. J. o. n. (2003). Corticocortical inhibition of peripheral inputs within primary somatosensory cortex: the role of GABAA and GABAB receptors. *90*(2), 851-856.

Clark, V. P., Coffman, B. A., Trumbo, M. C., & Gasparovic, C. (2011). Transcranial direct current stimulation (tDCS) produces localized and specific alterations in neurochemistry: a 1H magnetic resonance spectroscopy study. *Neuroscience letters, 500*(1), 67-71.

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.

Cohen, M. X. (2017). Where does EEG come from and what does it mean? *Trends in neurosciences, 40*(4), 208-218.

Coppola, G., Bracaglia, M., Di Lenola, D., Di Lorenzo, C., Serrao, M., Parisi, V., . . . Schoenen, J. (2015). Visual evoked potentials in subgroups of migraine with aura patients. *The journal of headache and pain, 16*(1), 92.

Coppola, G., Parisi, V., Di Lorenzo, C., Serrao, M., Magis, D., Schoenen, J., & Pierelli, F. (2013). Lateral inhibition in visual cortex of migraine patients between attacks. *The journal of headache and pain, 14*(1), 20.

Correa, A. G., Laciar, E., Patiño, H., & Valentinuzzi, M. (2007). *Artifact removal from EEG signals using adaptive filters in cascade.* Paper presented at the Journal of Physics: Conference Series.

Cortese, A., Nowicky, A., Lopez de Heredia, L., & Belci, M. (2017). Effects of transcranial direct current stimulation (tDCS) on chronic pain in spinal cord injured patients.

Costa, T. L., Gualtieri, M., Barboni, M. T., Katayama, R. K., Boggio, P. S., & Ventura, D. F. (2015). Contrasting effects of transcranial direct current stimulation on central and peripheral visual fields. *Experimental Brain Research, 233*(5), 1391-1397.

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.

Creel, D. J. (2016). Visually evoked potentials by Donnell J. Creel. *Webvision: The Organization of the Retina and Visual System [Internet]*, 1-21.

Creutzfeldt, O. D., Fromm, G. H., & Kapp, H. (1962). Influence of transcortical dc currents on cortical neuronal activity. *Experimental neurology, 5*(6), 436-452.

Culham, J., He, S., Dukelow, S., & Verstraten, F. A. (2001). Visual motion and the human brain: what has neuroimaging told us? *Acta psychologica, 107*(1-3), 69-94.

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.

Declerck, A., Oei, L., Arnoldussen, W., & te Dorsthorst, M. (1985). Alterations in transient visual-evoked potentials induced by clonazepam and sodium valproate. *Neuropsychobiology, 14*(1), 39-41.

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of neuroscience methods, 134*(1), 9-21.

Dewar, M., Alber, J., Cowan, N., & Della Sala, S. (2014). Boosting long-term memory via wakeful rest: intentional rehearsal is not necessary, consolidation is sufficient. *PloS one, 9*(10), e109542.

Di Russo, F., & Spinelli, D. (1999). Spatial attention has different effects on the magno-and parvocellular pathways. *Neuroreport, 10*(13), 2755-2762.

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., Bruyns‐Haylett, M., Jones, M., & Milne, E. (2015). Increased peak gamma frequency in individuals with higher levels of autistic traits. *European Journal of Neuroscience, 41*(8), 1095-1101.

Dickinson, A., Jones, M., & Milne, E. (2014). Oblique orientation discrimination thresholds are superior in those with a high level of autistic traits. *Journal of autism and developmental disorders, 44*(11), 2844-2850.

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.

Dieckhöfer, A., Waberski, T. D., Nitsche, M., Paulus, W., Buchner, H., & Gobbelé, R. (2006). Transcranial direct current stimulation applied over the somatosensory cortex–differential effect on low and high frequency SEPs. *Clinical Neurophysiology, 117*(10), 2221-2227.

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., . . . 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.

DosSantos, M. F., Martikainen, I. K., Nascimento, T. D., Love, T. M., DeBoer, M. D., Schambra, H. M., . . . DaSilva, A. F. (2014). Building up analgesia in humans via the endogenous μ-opioid system by combining placebo and active tDCS: a preliminary report. *PLoS One, 9*(7), e102350.

Duff, E. P., Johnston, L. A., Xiong, J., Fox, P. T., Mareels, I., & Egan, G. F. (2008). The power of spectral density analysis for mapping endogenous BOLD signal fluctuations. *Human brain mapping, 29*(7), 778-790.

Eason, R. G. (1981). Visual evoked potential correlates of early neural filtering during selective attention. *Bulletin of the Psychonomic Society, 18*(4), 203-206.

Eason, R. G., Harter, M. R., & White, C. (1969). Effects of attention and arousal on visually evoked cortical potentials and reaction time in man. *Physiology & Behavior, 4*(3), 283-289.

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., . . . 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.

Engel, A. K., & Fries, P. (2010). Beta-band oscillations—signalling the status quo? *Current opinion in neurobiology, 20*(2), 156-165.

Engel, A. K., Fries, P., & Singer, W. (2001). Dynamic predictions: oscillations and synchrony in top–down processing. *Nature Reviews Neuroscience, 2*(10), 704.

Erhardt, E. B., Rachakonda, S., Bedrick, E. J., Allen, E. A., Adali, T., & Calhoun, V. D. (2011). Comparison of multi‐subject ICA methods for analysis of fMRI data. *Human brain mapping, 32*(12), 2075-2095.

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

Fields, H. L., & Levine, J. D. (1984). Placebo analgesia—a role for endorphins? *Trends in Neurosciences, 7*(8), 271-273.

Filmer, H. L., Dux, P. E., & Mattingley, J. B. (2014). Applications of transcranial direct current stimulation for understanding brain function. *Trends in neurosciences, 37*(12), 742-753.

Filmer, H. L., Lyons, M., Mattingley, J. B., & Dux, P. E. (2017). Anodal tDCS applied during multitasking training leads to transferable performance gains. *Scientific reports, 7*(1), 12988.

Fonteneau, C., Mondino, M., Arns, M., Baeken, C., Bikson, M., Brunoni, A. R., . . . Pascual-Leone, A. (2019). Sham tDCS: A hidden source of variability? Reflections for further blinded, controlled trials. *Brain stimulation*.

Foroughi, C. K., Monfort, S. S., Paczynski, M., McKnight, P. E., & Greenwood, P. (2016). Placebo effects in cognitive training. *Proceedings of the national Academy of Sciences, 113*(27), 7470-7474.

Franklin, A., Sowden, P., Burley, R., Notman, L., & Alder, E. (2008). Color perception in children with autism. *Journal of Autism and Developmental Disorders, 38*(10), 1837-1847.

Franklin, A., Sowden, P., Notman, L., Gonzalez‐Dixon, M., West, D., Alexander, I., . . . White, A. (2010). Reduced chromatic discrimination in children with autism spectrum disorders. *Developmental Science, 13*(1), 188-200.

Fresnoza, S., Christova, M., Feil, T., Gallasch, E., Körner, C., Zimmer, U., & Ischebeck, A. (2018). The effects of transcranial alternating current stimulation (tACS) at

individual alpha peak frequency (iAPF) on motor cortex excitability in young and elderly adults. *Experimental brain research, 236*(10), 2573-2588.
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.
Friedman-Hill, S., Maldonado, P. E., & Gray, C. M. (2000). Dynamics of striate cortical activity in the alert macaque: I. Incidence and stimulus-dependence of gamma-band neuronal oscillations. *Cerebral cortex, 10*(11), 1105-1116.
Fujimoto, S., Kon, N., Otaka, Y., Yamaguchi, T., Nakayama, T., Kondo, K., . . . Tanaka, S. (2016). Transcranial direct current stimulation over the primary and secondary somatosensory cortices transiently improves tactile spatial discrimination in stroke patients. *Frontiers in neuroscience, 10*, 128.
Fujimoto, S., Yamaguchi, T., Otaka, Y., Kondo, K., & Tanaka, S. (2014). Dual-hemisphere transcranial direct current stimulation improves performance in a tactile spatial discrimination task. *Clinical Neurophysiology, 125*(8), 1669-1674.
Fumal, A., Coppola, G., Bohotin, V., Gérardy, P.-Y., Seidel, L., Donneau, A.-F., . . . Schoenen, J. (2006). Induction of long-lasting changes of visual cortex excitability by five daily sessions of repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers and migraine patients. *Cephalalgia, 26*(2), 143-149.
Furmanski, C. S., & Engel, S. A. (2000). An oblique effect in human primary visual cortex. *Nature neuroscience, 3*(6), 535.
Furubayashi, T., Terao, Y., Arai, N., Okabe, S., Mochizuki, H., Hanajima, R., . . . Ugawa, Y. (2008). Short and long duration transcranial direct current stimulation (tDCS) over the human hand motor area. *Experimental brain research, 185*(2), 279-286.
Fuzessery, Z., & Hall, J. J. J. o. N. (1996). Role of GABA in shaping frequency tuning and creating FM sweep selectivity in the inferior colliculus. *76*(2), 1059-1073.
Galambos, R. (1992). A comparison of certain gamma band (40-Hz) brain rhythms in cat and man. In *Induced rhythms in the brain* (pp. 201-216): Springer.
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.
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.
Garcia, A. D. (2017). *Neural correlates of visual perceptual learning and inhibitory neurotransmitter in humans using magnetic resonance spectroscopy.* University of Birmingham,
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.
Gelman, A., & Carlin, J. (2014). Beyond power calculations: assessing type S (sign) and type M (magnitude) errors. *Perspectives on Psychological Science, 9*(6), 641-651.
Gieselmann, M., & Thiele, A. (2008). Comparison of spatial integration and surround suppression characteristics in spiking activity and the local field potential in macaque V1. *European Journal of Neuroscience, 28*(3), 447-459.
Goodale, M. A., & Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends in neurosciences, 15*(1), 20-25.

Goodale, M. A., & Westwood, D. A. (2004). An evolving view of duplex vision: separate but interacting cortical pathways for perception and action. *Current opinion in neurobiology, 14*(2), 203-211.
Gregory, S., Fusca, M., Rees, G., Schwarzkopf, D. S., & Barnes, G. (2016). Gamma frequency and the spatial tuning of primary visual cortex. *PloS one, 11*(6), e0157374.
Greinacher, R., Buhôt, L., Möller, L., & Learmonth, G. (2018). The time course of ineffective sham blinding during 1mA tDCS. *BioRxiv*, 462424.
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.
Hadjipapas, A., Lowet, E., Roberts, M., Peter, A., & De Weerd, P. (2015). Parametric variation of gamma frequency and power with luminance contrast: A comparative study of human MEG and monkey LFP and spike responses. *Neuroimage, 112*, 327-340.
Hammond, E. J., & Wilder, B. (1985). Effect of gamma‐vinyl GABA on human pattern evoked visual potentials. *Neurology, 35*(12), 1801-1801.
Hanel, P. H., & Vione, K. C. (2016). Do student samples provide an accurate estimate of the general public? *PloS one, 11*(12), e0168354.
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.
Hasenstaub, A., Shu, Y., Haider, B., Kraushaar, U., Duque, A., & McCormick, D. A. (2005). Inhibitory postsynaptic potentials carry synchronized frequency information in active cortical networks. *Neuron, 47*(3), 423-435.
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.
He, H.-y., & Cline, H. T. (2019). What Is Excitation/Inhibition and How Is It Regulated? A Case of the Elephant and the Wisemen. *Journal of Experimental Neuroscience, 13*, 1179069519859371.
Heba, S., Puts, N. A., Kalisch, T., Glaubitz, B., Haag, L. M., Lenz, M., . . . Schmidt-Wilcke, T. (2015). Local GABA concentration predicts perceptual improvements after repetitive sensory stimulation in humans. *Cerebral Cortex, 26*(3), 1295-1301.
Henz, D., John, A., Merz, C., & Schöllhorn, W. I. (2018). Post-task Effects on EEG Brain Activity Differ for Various Differential Learning and Contextual Interference Protocols. *Frontiers in human neuroscience, 12*, 19.
Herring, J. D., Esterer, S., Marshall, T. R., Jensen, O., & Bergmann, T. O. (2019). Low-frequency alternating current stimulation rhythmically suppresses gamma-band oscillations and impairs perceptual performance. *Neuroimage, 184*, 440-449.
Herrmann, C. S., Fründ, I., & Lenz, D. (2010). Human gamma-band activity: a review on cognitive and behavioral correlates and network models. *Neuroscience & Biobehavioral Reviews, 34*(7), 981-992.

Hicks, T., & Dykes, R. J. B. r. (1983). Receptive field size for certain neurons in primary somatosensory cortex is determined by GABA-mediated intracortical inhibition. *274*(1), 160-164.

Ho, K.-A., Taylor, J. L., Chew, T., Gálvez, V., Alonzo, A., Bai, S., . . . Loo, C. K. (2016). The effect of transcranial direct current stimulation (tDCS) electrode size and current intensity on motor cortical excitability: evidence from single and repeated sessions. *Brain stimulation, 9*(1), 1-7.

Hoshiyama, M., & Kakigi, R. (2001). Effects of attention on pattern-reversal visual evoked potentials: foveal field stimulation versus peripheral field stimulation. *Brain Topography, 13*(4), 293-298.

Houtgast, T. (1972). Psychophysical evidence for lateral inhibition in hearing. *The Journal of the Acoustical Society of America, 51*(6B), 1885-1894.

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

Huang, L., Shou, T., Chen, X., Yu, H., Sun, C., & Liang, Z. (2006). Slab-like functional architecture of higher order cortical area 21a showing oblique effect of orientation preference in the cat. *Neuroimage, 32*(3), 1365-1374.

Hubel, D. H. (1995). *Eye, brain, and vision*: Scientific American Library/Scientific American Books.

Hubel, D. H., & Livingstone, M. S. (1990). Color and contrast sensitivity in the lateral geniculate body and primary visual cortex of the macaque monkey. *Journal of neuroscience, 10*(7), 2223-2237.

Hubel, D. H., & Wiesel, T. N. (1968). Receptive fields and functional architecture of monkey striate cortex. *The Journal of physiology, 195*(1), 215-243.

Hubel, D. H., & Wiesel, T. N. (1974). Sequence regularity and geometry of orientation columns in the monkey striate cortex. *Journal of Comparative Neurology, 158*(3), 267-293.

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

Hussman, J. P. (2001). Letters to the editor: suppressed GABAergic inhibition as a common factor in suspected etiologies of autism. *Journal of autism and developmental disorders, 31*(2), 247-248.

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.

Isaacson, J. S., & Scanziani, M. (2011). How inhibition shapes cortical activity. *Neuron, 72*(2), 231-243.

Iyer, M., Mattu, U., Grafman, J., Lomarev, M., Sato, S., & Wassermann, E. (2005). Safety and cognitive effect of frontal DC brain polarization in healthy individuals. *Neurology, 64*(5), 872-875.

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.
Javitt, D. C., & Sweet, R. A. J. N. R. N. (2015). Auditory dysfunction in schizophrenia: integrating clinical and basic features. *16*(9), 535.
Jensen, O., Kaiser, J., & Lachaux, J.-P. (2007). Human gamma-frequency oscillations associated with attention and memory. *Trends in neurosciences, 30*(7), 317-324.
Jensen, O., & Mazaheri, A. (2010). Shaping functional architecture by oscillatory alpha activity: gating by inhibition. *Frontiers in human neuroscience, 4*, 186.
Jia, X., Xing, D., & Kohn, A. (2013). No consistent relationship between gamma power and peak frequency in macaque primary visual cortex. *Journal of Neuroscience, 33*(1), 17-25.
Joliot, M., Ribary, U., & Llinas, R. (1994). Human oscillatory brain activity near 40 Hz coexists with cognitive temporal binding. *Proceedings of the National Academy of Sciences, 91*(24), 11748-11751.
Joost, W., Bach, M., & Schulte-Mönting, J. (1992). Influence of mood on visually evoked potentials: a prospective longitudinal study. *International Journal of Psychophysiology, 12*(2), 147-153.
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.
Kaiser, G. (1994). A Friendly Guide to Wavelets, Birkhauser, Boston. In: MA.
Kang, E. K., & Paik, N.-J. (2011). Effect of a tDCS electrode montage on implicit motor sequence learning in healthy subjects. *Experimental & translational stroke medicine, 3*(1), 4.
Karakaş, S., & Başar, E. (1998). Early gamma response is sensory in origin: a conclusion based on cross-comparison of results from multiple experimental paradigms. *International Journal of Psychophysiology, 31*(1), 13-31.
Karakaş, S., Başar-Eroğlu, C., Özesmi, C., Kafadar, H., & Erzengin, Ö. Ü. (2001). Gamma response of the brain: a multifunctional oscillation that represents bottom-up with top-down processing. *International Journal of Psychophysiology, 39*(2-3), 137-150.
Katzner, S., Busse, L., & Carandini, M. (2011). GABAA inhibition controls response gain in visual cortex. *Journal of Neuroscience, 31*(16), 5931-5941.
Kehrer, C., Maziashvili, N., Dugladze, T., & Gloveli, T. (2008). Altered excitatory-inhibitory balance in the NMDA-hypofunction model of schizophrenia. *Frontiers in molecular neuroscience, 1*, 6.
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.
Khatoun, A., Asamoah, B., & Mc Laughlin, M. (2017). Simultaneously excitatory and inhibitory effects of transcranial alternating current stimulation revealed using selective pulse-train stimulation in the rat motor cortex. *Journal of Neuroscience, 37*(39), 9389-9402.

Kim, S., Stephenson, M. C., Morris, P. G., & Jackson, S. R. (2014). tDCS-induced alterations in GABA concentration within primary motor cortex predict motor learning and motor memory: a 7 T magnetic resonance spectroscopy study. *Neuroimage, 99*, 237-243.

Kirimoto, H., Ogata, K., Onishi, H., Oyama, M., Goto, Y., & Tobimatsu, S. J. C. N. (2011). Transcranial direct current stimulation over the motor association cortex induces plastic changes in ipsilateral primary motor and somatosensory cortices. *122*(4), 777-783.

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.

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.

Klimesch, W. (2012). Alpha-band oscillations, attention, and controlled access to stored information. *Trends in cognitive sciences, 16*(12), 606-617.

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: the inhibition–timing hypothesis. *Brain research reviews, 53*(1), 63-88.

Koelewijn, L., Dumont, J. R., Muthukumaraswamy, S. D., Rich, A. N., & Singh, K. D. (2011). Induced and evoked neural correlates of orientation selectivity in human visual cortex. *Neuroimage, 54*(4), 2983-2993.

Koelewijn, L., Rich, A. N., Muthukumaraswamy, S. D., & Singh, K. D. (2013). Spatial attention increases high-frequency gamma synchronisation in human medial visual cortex. *Neuroimage, 79*, 295-303.

Kondo, H. M., Pressnitzer, D., Shimada, Y., Kochiyama, T., & Kashino, M. (2018). Inhibition-excitation balance in the parietal cortex modulates volitional control for auditory and visual multistability. *Scientific reports, 8*(1), 14548.

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.

Kremláček, J., Kuba, M., Chlubnová, J., & Kubová, Z. (2004). Effect of stimulus localisation on motion-onset VEP. *Vision Research, 44*(26), 2989-3000.

Kubová, Z., Kuba, M., Spekreijse, H., & Blakemore, C. (1995). Contrast dependence of motion-onset and pattern-reversal evoked potentials. *Vision research, 35*(2), 197-205.

Kujala, J., Jung, J., Bouvard, S., Lecaignard, F., Lothe, A., Bouet, R., . . . 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.

Kulikowski, J., McGlone, F., Kranda, K., & Ott, H. (1984). Are the amplitudes of visual evoked potentials sensitive indices of hangover effects after repeated doses of

benzodiazepines? In *Sleep, Benzodiazepines and Performance* (pp. 154-164): Springer.
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.
Kuo, M.-F., Paulus, W., & Nitsche, M. A. (2014). Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. *Neuroimage, 85*, 948-960.
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.
Laczó, B., Antal, A., Niebergall, R., Treue, S., & Paulus, W. (2012). Transcranial alternating stimulation in a high gamma frequency range applied over V1 improves contrast perception but does not modulate spatial attention. *Brain stimulation, 5*(4), 484-491.
Ladeira, A., Fregni, F., Campanhã, C., Valasek, C. A., De Ridder, D., Brunoni, A. R., & Boggio, P. S. (2011). Polarity-dependent transcranial direct current stimulation effects on central auditory processing. *PLoS One, 6*(9), e25399.
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.
Leek, M. R. (2001). Adaptive procedures in psychophysical research. *Perception & psychophysics, 63*(8), 1279-1292.
Leite, J., Gonçalves, Ó. F., Pereira, P., Khadka, N., Bikson, M., Fregni, F., & Carvalho, S. (2018). The differential effects of unihemispheric and bihemispheric tDCS over the inferior frontal gyrus on proactive control. *Neuroscience research, 130*, 39-46.
Leventhal, A. G., Wang, Y., Pu, M., Zhou, Y., & Ma, Y. (2003). GABA and its agonists improved visual cortical function in senescent monkeys. *Science, 300*(5620), 812-815.
Li, B., Peterson, M. R., & Freeman, R. D. (2003). Oblique effect: a neural basis in the visual cortex. *Journal of neurophysiology, 90*(1), 204-217.
Li, G., Yang, Y., Liang, Z., Xia, J., & Zhou, Y. (2008). GABA-mediated inhibition correlates with orientation selectivity in primary visual cortex of cat. *Neuroscience, 155*(3), 914-922.
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.
Li, L. M., Violante, I., Leech, R., Ross, E., Hampshire, A., Opitz, A., . . . Sharp, D. J. (2017). Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. *bioRxiv*, 179556.
Li, L. M., Violante, I. R., Leech, R., Ross, E., Hampshire, A., Opitz, A., . . . Sharp, D. J. (2019). Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. *Human brain mapping, 40*(3), 904-915.
Li, W., & Gilbert, C. D. (2017). Perceptual Learning: Neural Mechanisms.
Liebetanz, D., Nitsche, M. A., Tergau, F., & Paulus, W. (2002). Pharmacological approach to the mechanisms of transcranial DC‐stimulation‐induced after‐effects of human motor cortex excitability. *Brain, 125*(10), 2238-2247.

Liu, C.-S., Bryan, R., Miki, A., Woo, J., Liu, G., & Elliott, M. (2006). Magnocellular and parvocellular visual pathways have different blood oxygen level–dependent signal time courses in human primary visual cortex. *American Journal of Neuroradiology, 27*(8), 1628-1634.

Livingstone, M., & Hubel, D. (1988). Segregation of form, color, movement, and depth: anatomy, physiology, and perception. *Science, 240*(4853), 740-749.

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

Loo, C. K., Sachdev, P., Martin, D., Pigot, M., Alonzo, A., Malhi, G. S., . . . Mitchell, P. (2010). A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. *International Journal of Neuropsychopharmacology, 13*(1), 61-69.

Loughnan, B., Sebel, P., Thomas, D., & Rutherfoord, C. (1987). Evoked potentials following diazepam or fentanyl. *Anaesthesia, 42*(2), 195-198.

Loui, P., Hohmann, A., & Schlaug, G. (2010). *Inducing disorders in pitch perception and production: a reverse-engineering approach.* Paper presented at the Proceedings of Meetings on Acoustics 159ASA.

Lozano-Soldevilla, D. (2018). On the physiological modulation and potential mechanisms underlying Parieto-occipital alpha oscillations. *Frontiers in computational neuroscience, 12*, 23.

Lozano-Soldevilla, D., ter Huurne, N., Cools, R., & Jensen, O. (2014). GABAergic modulation of visual gamma and alpha oscillations and its consequences for working memory performance. *Current Biology, 24*(24), 2878-2887.

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

Lőrincz, M. L., Kékesi, K. A., Juhász, G., Crunelli, V., & Hughes, S. W. (2009). Temporal framing of thalamic relay-mode firing by phasic inhibition during the alpha rhythm. *Neuron, 63*(5), 683-696.

Magazzini, L., Muthukumaraswamy, S. D., Campbell, A. E., Hamandi, K., Lingford‐Hughes, A., Myers, J. F., . . . 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.

Magazzini, L., & Singh, K. D. (2018). Spatial attention modulates visual gamma oscillations across the human ventral stream. *NeuroImage, 166*, 219-229.

Magri, C., Schridde, U., Murayama, Y., Panzeri, S., & Logothetis, N. K. (2012). The amplitude and timing of the BOLD signal reflects the relationship between local field potential power at different frequencies. *Journal of Neuroscience, 32*(4), 1395-1407.

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.

Mancini, F., Bolognini, N., Haggard, P., & Vallar, G. J. J. o. C. N. (2012). tDCS modulation of visually induced analgesia. *24*(12), 2419-2427.

Mancuso, L. E., Ilieva, I. P., Hamilton, R. H., & Farah, M. J. (2016). Does transcranial direct current stimulation improve healthy working memory?: a meta-analytic review. *Journal of Cognitive Neuroscience, 28*(8), 1063-1089.

Mann, E. O., & Paulsen, O. (2007). Role of GABAergic inhibition in hippocampal network oscillations. *Trends in neurosciences, 30*(7), 343-349.
Mansfield, R. (1974). Neural basis of orientation perception in primate vision. *Science, 186*(4169), 1133-1135.
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.
Martinovic, J. (2014). Magno-, Parvo-, Koniocellular Pathways. *Encyclopedia of color science and technology*, 1-5.
Mathys, C., Loui, P., Zheng, X., & Schlaug, G. J. F. i. p. (2010). Non-invasive brain stimulation applied to Heschl's gyrus modulates pitch discrimination. *1*, 193.
Matsunaga, K., Nitsche, M. A., Tsuji, S., & Rothwell, J. C. (2004). Effect of transcranial DC sensorimotor cortex stimulation on somatosensory evoked potentials in humans. *Clinical Neurophysiology, 115*(2), 456-460.
Matsushita, R., Andoh, J., & Zatorre, R. J. (2015). Polarity-specific transcranial direct current stimulation disrupts auditory pitch learning. *Frontiers in Neuroscience, 9*, 174.
Matsushita, R., Andoh, J., & Zatorre, R. J. (2017). Direct Current Stimulation Disrupts Consolidation of Auditory Pitch Discrimination Learning. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 10*(1), e2.
Matthews, N., & Welch, L. (1997). Velocity-dependent improvements in single-dot direction discrimination. *Perception & psychophysics, 59*(1), 60-72.
Mayberg, H. S., Silva, J. A., Brannan, S. K., Tekell, J. L., Mahurin, R. K., McGinnis, S., & Jerabek, P. A. (2002). The functional neuroanatomy of the placebo effect. *American Journal of Psychiatry, 159*(5), 728-737.
Mayhew, S. D., Ostwald, D., Porcaro, C., & Bagshaw, A. P. (2013). Spontaneous EEG alpha oscillation interacts with positive and negative BOLD responses in the visual–auditory cortices and default-mode network. *Neuroimage, 76*, 362-372.
McConathey, E. M., White, N. C., Gervits, F., Ash, S., Coslett, H., Grossman, M., & Hamilton, R. H. (2017). Baseline performance predicts tdcs-mediated improvements in language symptoms in primary progressive aphasia. *Frontiers in human neuroscience, 11*, 347.
McDermott, T. J., Wiesman, A. I., Mills, M. S., Spooner, R. K., Coolidge, N. M., Proskovec, A. L., . . . Wilson, T. W. (2019). tDCS modulates behavioral performance and the neural oscillatory dynamics serving visual selective attention. *Human brain mapping, 40*(3), 729-740.
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.
Megela, A. L., & Teyler, T. J. (1979). Habituation and the human evoked potential. *Journal of Comparative and Physiological Psychology, 93*(6), 1154.
Meinecke, D. L., & Peters, A. (1987). GABA immunoreactive neurons in rat visual cortex. *Journal of Comparative Neurology, 261*(3), 388-404.
Menon, V., & Crottaz-Herbette, S. (2005). Combined EEG and fMRI studies of human brain function. *Int Rev Neurobiol, 66*, 291-321.
Meredith, J. T., & Celesia, G. G. (1982). Pattern-reversal visual evoked potentials and retinal eccentricity. *Electroencephalography and Clinical Neurophysiology, 53*(3), 243-253.

Mihaylova, M. S., Hristov, I., Racheva, K., Totev, T., & Mitov, D. (2015). Effect of extending grating length and width on human visually evoked potentials. *Acta Neurobiol Exp, 75*, 293-304.

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*.

Miranda, P. C., Lomarev, M., & Hallett, M. (2006). Modeling the current distribution during transcranial direct current stimulation. *Clinical neurophysiology, 117*(7), 1623-1629.

Molero-Chamizo, A., Bailén, J. R. A., Béjar, T. G., López, M. G., Rodríguez, I. J., Lérida, C. G., . . . Vega, M. J. R. (2018). Poststimulation time interval-dependent effects of motor cortex anodal tDCS on reaction-time task performance. *Cognitive, Affective, & Behavioral Neuroscience, 18*(1), 167-175.

Moliadze, V., Antal, A., & Paulus, W. (2010). Electrode-distance dependent after-effects of transcranial direct and random noise stimulation with extracephalic reference electrodes. *Clinical Neurophysiology, 121*(12), 2165-2171.

Moloney, T. M., & Witney, A. G. (2013). Transcranial direct current stimulation (tDCS) priming of 1 Hz repetitive transcranial magnetic stimulation (rTMS) modulates experimental pain thresholds. *Neuroscience letters, 534*, 289-294.

Monier, C., Chavane, F., Baudot, P., Graham, L. J., & Frégnac, Y. (2003). Orientation and direction selectivity of synaptic inputs in visual cortical neurons: a diversity of combinations produces spike tuning. Neuron 37: 663–680.

Monte-Silva, K., Kuo, M.-F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2013). Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain stimulation, 6*(3), 424-432.

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

Mori, T., Takeuchi, N., Suzuki, S., Miki, M., Kawase, T., & Izumi, S.-I. (2016). Anodal transcranial direct current stimulation over the auditory cortex improved hearing impairment in a patient with brainstem encephalitis. *Journal of International Medical Research, 44*(3), 760-764.

Mucke, S., Manahilov, V., Strang, N. C., Seidel, D., Gray, L. S., & Shahani, U. J. J. o. v. (2010). Investigating the mechanisms that may underlie the reduction in contrast sensitivity during dynamic accommodation. *10*(5), 5-5.

Mulleners, W., Chronicle, E., Palmer, J., Koehler, P., & Vredeveld, J. (2001). Suppression of perception in migraine evidence for reduced inhibition in the visual cortex. *Neurology, 56*(2), 178-183.

Murray, L. M., Edwards, D. J., Ruffini, G., Labar, D., Stampas, A., Pascual-Leone, A., & Cortes, M. (2015). Intensity dependent effects of transcranial direct current stimulation on corticospinal excitability in chronic spinal cord injury. *Archives of physical medicine and rehabilitation, 96*(4), S114-S121.

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., Shaw, A. D., Jackson, L. E., Hall, J., Moran, R., & Saxena, N. (2015). Evidence that subanesthetic doses of ketamine cause sustained disruptions of NMDA and AMPA-mediated frontoparietal connectivity in humans. *Journal of Neuroscience, 35*(33), 11694-11706.

Márquez-Ruiz, J., Leal-Campanario, R., Sánchez-Campusano, R., Molaee-Ardekani, B., Wendling, F., Miranda, P. C., . . . Delgado-García, J. M. (2012). Transcranial direct-current stimulation modulates synaptic mechanisms involved in associative learning in behaving rabbits. *Proceedings of the National Academy of Sciences, 109*(17), 6710-6715.

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.

Müller, M. M., Gruber, T., & Keil, A. (2000). Modulation of induced gamma band activity in the human EEG by attention and visual information processing. *International Journal of Psychophysiology, 38*(3), 283-299.

Müller, R., Göpfert, E., & Hartwig, M. (1985). Visual evoked potential studies on human cortical coding of the speed of movement of a grating pattern. *EEG-EMG Zeitschrift fur Elektroenzephalographie, Elektromyographie und verwandte Gebiete, 16*(2), 75-80.

Müller, R., Göpfert, E., Schlykowa, L., & Anke, D. (1990). The human motion VEP as a function of size and eccentricity of the stimulation field. *Documenta ophthalmologica, 76*(1), 81-89.

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.

Nelson, J., Kato, H., & Bishop, P. (1977). Discrimination of orientation and position disparities by binocularly activated neurons in cat straite cortex. *Journal of neurophysiology, 40*(2), 260-283.

Neustadter, E., Mathiak, K., & Turetsky, B. (2016). EEG and MEG probes of schizophrenia pathophysiology. In *The Neurobiology of Schizophrenia* (pp. 213-236): Elsevier.

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

Nitsche, M., Doemkes, S., Karakose, T., Antal, A., Liebetanz, D., Lang, N., . . . Paulus, W. (2007). Shaping the effects of transcranial direct current stimulation of the human motor cortex. *Journal of neurophysiology, 97*(4), 3109-3117.

Nitsche, M., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., . . . Paulus, W. (2003). Pharmacological modulation of cortical excitability shifts induced by

transcranial direct current stimulation in humans. *The Journal of physiology, 553*(1), 293-301.
Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., . . . 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., . . . 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. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of physiology, 527*(3), 633-639.
Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology, 57*(10), 1899-1901.
Nitsche, M. A., Seeber, A., Frommann, K., Klein, C. C., Rochford, C., Nitsche, M. S., . . . Antal, A. (2005). Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *The Journal of physiology, 568*(1), 291-303.
Olofsson, J. K., Nordin, S., Sequeira, H., & Polich, J. (2008). Affective picture processing: an integrative review of ERP findings. *Biological psychology, 77*(3), 247-265.
Orban, G. A., & Kennedy, H. (1981). The influence of eccentricity on receptive field types and orientation selectivity in areas 17 and 18 of the cat. *Brain research*.
Orekhova, E. V., Butorina, A., Sysoeva, O. V., Prokofyev, A., Nikolaeva, A., & Stroganova, T. A. (2015). Frequency of gamma oscillations in humans is modulated by velocity of visual motion. *American Journal of Physiology-Heart and Circulatory Physiology*.
Osipova, D., Hermes, D., & Jensen, O. (2008). Gamma power is phase-locked to posterior alpha activity. *PloS one, 3*(12), e3990.
Pal, G. K. (2001). *Textbook of practical physiology*: Orient Blackswan.
Palm, U., Reisinger, E., Keeser, D., Kuo, M.-F., Pogarell, O., Leicht, G., . . . Padberg, F. (2013). Evaluation of sham transcranial direct current stimulation for randomized, placebo-controlled clinical trials. *Brain stimulation, 6*(4), 690-695.
Pantazis, D., Fang, M., Qin, S., Mohsenzadeh, Y., Li, Q., & Cichy, R. M. (2018). Decoding the orientation of contrast edges from MEG evoked and induced responses. *NeuroImage, 180*, 267-279.
Pantev, C. (1995). Evoked and induced gamma-band activity of the human cortex. *Brain topography, 7*(4), 321-330.
Pappas, S. C., Ferenci, P., Schafer, D. F., & Jones, E. A. (1984). Visual evoked potentials in a rabbit model of hepatic encephalopathy: II. Comparison of hyperammonemic

encephalopathy, postictal coma, and coma induced by synergistic neurotoxins. *Gastroenterology, 86*(3), 546-551.
Pellegrino, G., Maran, M., Turco, C., Weis, L., Di Pino, G., Piccione, F., & Arcara, G. (2018). Bilateral Transcranial Direct Current Stimulation Reshapes Resting-State Brain Networks: A Magnetoencephalography Assessment. *Neural plasticity, 2018*.
Pellicciari, M. C., Brignani, D., & Miniussi, C. J. N. (2013). Excitability modulation of the motor system induced by transcranial direct current stimulation: a multimodal approach. *83*, 569-580.
Peters, M. A., Thompson, B., Merabet, L. B., Wu, A. D., & Shams, L. (2013). Anodal tDCS to V1 blocks visual perceptual learning consolidation. *Neuropsychologia, 51*(7), 1234-1239.
Pfurtscheller, G., Neuper, C., & Mohl, W. (1994). Event-related desynchronization (ERD) during visual processing. *International Journal of Psychophysiology, 16*(2-3), 147-153.
Porciatti, V., Bonanni, P., Fiorentini, A., & Guerrini, R. (2000). Lack of cortical contrast gain control in human photosensitive epilepsy. *Nature neuroscience, 3*(3), 259.
Priori, A., Berardelli, A., Rona, S., Accornero, N., & Manfredi, M. (1998). Polarization of the human motor cortex through the scalp. *Neuroreport, 9*(10), 2257-2260.
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.
Purpura, D. P., & McMurtry, J. G. (1965). Intracellular activities and evoked potential changes during polarization of motor cortex. *Journal of neurophysiology, 28*(1), 166-185.
Rabinowicz, E. F., Silipo, G., Goldman, R., & Javitt, D. C. J. A. o. g. p. (2000). Auditory sensory dysfunction in schizophrenia: imprecision or distractibility? *, 57*(12), 1149-1155.
Ragert, P., Vandermeeren, Y., Camus, M., & Cohen, L. G. (2008). Improvement of spatial tactile acuity by transcranial direct current stimulation. *Clinical Neurophysiology, 119*(4), 805-811.
Rankin, C. H., Abrams, T., Barry, R. J., Bhatnagar, S., Clayton, D. F., Colombo, J., . . . 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.
Ray, S., Niebur, E., Hsiao, S. S., Sinai, A., & Crone, N. E. (2008). High-frequency gamma activity (80–150 Hz) is increased in human cortex during selective attention. *Clinical Neurophysiology, 119*(1), 116-133.
Reddy, A. G., & Narava, S. (2013). Artifact removal from EEG signals. *International Journal of Computer Applications, 77*(13).
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., & Woodman, G. F. (2014). Causal control of medial–frontal cortex governs electrophysiological and behavioral indices of performance monitoring and learning. *Journal of Neuroscience, 34*(12), 4214-4227.

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.

Reva, N., & Aftanas, L. (2004). The coincidence between late non-phase-locked gamma synchronization response and saccadic eye movements. *International Journal of Psychophysiology, 51*(3), 215-222.

Richard, B., Johnson, A. P., Thompson, B., & Hansen, B. C. J. F. i. p. (2015). The effects of tDCS across the spatial frequencies and orientations that comprise the contrast sensitivity function. *6*, 1784.

Rivest, J., Boutet, I., & Intriligator, J. (1997). Perceptual learning of orientation discrimination by more than one attribute. *Vision Research, 37*(3), 273-281.

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.

Roche, N., Geiger, M., & Bussel, B. (2015). Mechanisms underlying transcranial direct current stimulation in rehabilitation. *Annals of physical and rehabilitation medicine, 58*(4), 214-219.

Rockstroh, B., Elbert, T., Lutzenberger, W., & Altenmüller, E. (1991). Effects of the anticonvulsant benzodiazepine clonazepam on event-related brain potentials in humans. *Electroencephalography and clinical neurophysiology, 78*(2), 142-149.

Rogalewski, A., Breitenstein, C., Nitsche, M. A., Paulus, W., & Knecht, S. (2004a). Transcranial direct current stimulation disrupts tactile perception. *European Journal of Neuroscience, 20*(1), 313-316.

Rogalewski, A., Breitenstein, C., Nitsche, M. A., Paulus, W., & Knecht, S. J. E. J. o. N. (2004b). Transcranial direct current stimulation disrupts tactile perception. *20*(1), 313-316.

Rokem, A., Yoon, J. H., Ooms, R. E., Maddock, R. J., Minzenberg, M., & Silver, M. A. (2011). Broader visual orientation tuning in patients with schizophrenia. *Frontiers in human neuroscience, 5*, 127.

Romei, V., Brodbeck, V., Michel, C., Amedi, A., Pascual-Leone, A., & Thut, G. (2007). Spontaneous fluctuations in posterior α-band EEG activity reflect variability in excitability of human visual areas. *Cerebral cortex, 18*(9), 2010-2018.

Romei, V., Rihs, T., Brodbeck, V., & Thut, G. (2008). Resting electroencephalogram alpha-power over posterior sites indexes baseline visual cortex excitability. *Neuroreport, 19*(2), 203-208.

Rose, D., & Blakemore, C. (1974). An analysis of orientation selectivity in the cat's visual cortex. *Experimental Brain Research, 20*(1), 1-17.

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.

Rush, S., & Driscoll, D. A. (1968). Current distribution in the brain from surface electrodes. *Anesthesia & Analgesia, 47*(6), 717-723.

Russo, R., Wallace, D., Fitzgerald, P. B., & Cooper, N. R. (2013). Perception of comfort during active and sham transcranial direct current stimulation: a double blind study. *Brain stimulation, 6*(6), 946-951.

Saiote, C., Turi, Z., Paulus, W., & Antal, A. (2013). Combining functional magnetic resonance imaging with transcranial electrical stimulation. *Frontiers in human neuroscience, 7*, 435.

Salimpour, Y., & Shadmehr, R. (2014). Motor costs and the coordination of the two arms. *Journal of Neuroscience, 34*(5), 1806-1818.

Sand, T., Zhitniy, N., White, L. R., & Stovner, L. J. (2008). Visual evoked potential latency, amplitude and habituation in migraine: a longitudinal study. *Clinical Neurophysiology, 119*(5), 1020-1027.

Sannita, W. G., Carozzo, S., Fioretto, M., Garbarino, S., & Martinoli, C. (2007). Abnormal waveform of the human pattern VEP: contribution from gamma oscillatory components. *Investigative ophthalmology & visual science, 48*(10), 4534-4541.

Sannita, W. G., Lopez, L., Piras, C., & Di Bon, G. (1995). Scalp-recorded oscillatory potentials evoked by transient pattern-reversal visual stimulation in man. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 96*(3), 206-218.

Sarnthein, J., Andersson, M., Zimmermann, M. B., & Zumsteg, D. (2009). High test–retest reliability of checkerboard reversal visual evoked potentials (VEP) over 8 months. *Clinical Neurophysiology, 120*(10), 1835-1840.

Sauseng, P., Klimesch, W., Stadler, W., Schabus, M., Doppelmayr, M., Hanslmayr, S., . . . Birbaumer, N. (2005). A shift of visual spatial attention is selectively associated with human EEG alpha activity. *European Journal of Neuroscience, 22*(11), 2917-2926.

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.

Schoenen, J. (1996). Deficient habituation of evoked cortical potentials in migraine: a link between brain biology, behavior and trigeminovascular activation? *Biomedicine & pharmacotherapy, 50*(2), 71-78.

Schoups, A., Vogels, R., Qian, N., & Orban, G. (2001). Practising orientation identification improves orientation coding in V1 neurons. *Nature, 412*(6846), 549.

Schoups, A. A., Vogels, R., & Orban, G. A. (1995). Human perceptual learning in identifying the oblique orientation: retinotopy, orientation specificity and monocularity. *The Journal of physiology, 483*(3), 797-810.

Schreckenberger, M., Lange-Asschenfeld, C., Lochmann, M., Mann, K., Siessmeier, T., Buchholz, H.-G., . . . Gründer, G. (2004). The thalamus as the generator and modulator of EEG alpha rhythm: a combined PET/EEG study with lorazepam challenge in humans. *Neuroimage, 22*(2), 637-644.

Schuhmann, T., Kemmerer, S. K., Duecker, F., De Graaf, T. A., Ten Oever, S., De Weerd, P., & Sack, A. T. (2019). Left parietal tACS at alpha frequency induces a shift of visuospatial attention. *BioRxiv*, 644237.

Schwarz, K. A., & Büchel, C. (2015). Cognition and the placebo effect–dissociating subjective perception and actual performance. *PloS one, 10*(7), e0130492.

Seitz, A. R., Yamagishi, N., Werner, B., Goda, N., Kawato, M., & Watanabe, T. (2005). Task-specific disruption of perceptual learning. *Proceedings of the National Academy of Sciences of the United States of America, 102*(41), 14895-14900.

Shafai, F., Armstrong, K., Iarocci, G., & Oruc, I. (2015). Visual orientation processing in autism spectrum disorder: No sign of enhanced early cortical function. *Journal of vision, 15*(15), 18-18.

Shaw, A. D., Knight, L., Freeman, T. C., Williams, G. M., Moran, R. J., Friston, K. J., . . . Singh, K. D. (2019). Oscillatory, Computational, and Behavioral Evidence for Impaired GABAergic Inhibition in Schizophrenia. *Schizophrenia Bulletin*.

Shepherd, A. (2000). Visual contrast processing in migraine. *Cephalalgia, 20*(10), 865-880.

Shiu, L.-P., & Pashler, H. (1992). Improvement in line orientation discrimination is retinally local but dependent on cognitive set. *Perception & psychophysics, 52*(5), 582-588.

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.

Sillito, A. (1975). The contribution of inhibitory mechanisms to the receptive field properties of neurones in the striate cortex of the cat. *The Journal of physiology, 250*(2), 305-329.

Sillito, A. (1979). Inhibitory mechanisms influencing complex cell orientation selectivity and their modification at high resting discharge levels. *The Journal of physiology, 289*(1), 33-53.

Sillito, A. M., Kemp, J. A., Milson, J. A., & Berardi, N. (1980). A re-evaluation of the mechanisms underlying simple cell orientation selectivity. *Brain research, 194*(2), 517-520.

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.

Siper, P. M., Zemon, V., Gordon, J., George-Jones, J., Lurie, S., Zweifach, J., . . . Buxbaum, J. D. (2016). Rapid and objective assessment of neural function in autism spectrum disorder using transient visual evoked potentials. *PloS one, 11*(10), e0164422.

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.

Sohal, V. S., & Rubenstein, J. L. (2019). Excitation-inhibition balance as a framework for investigating mechanisms in neuropsychiatric disorders. *Molecular psychiatry*, 1.

Sokol, S. (1983). Abnormal evoked potential latencies in amblyopia. *British Journal of Ophthalmology, 67*(5), 310-314.

Sokolov, A., Pavlova, M., Lutzenberger, W., & Birbaumer, N. (2004). Reciprocal modulation of neuromagnetic induced gamma activity by attention in the human visual and auditory cortex. *Neuroimage, 22*(2), 521-529.

Song, C., Sandberg, K., Andersen, L. M., Blicher, J. U., & Rees, G. (2017). Human occipital and parietal GABA selectively influence visual perception of orientation and size. *Journal of Neuroscience*, 3945-3916.

Song, Y., Peng, D., Li, X., Zhang, Y., Kang, J., Qu, Z., & Ding, Y. (2007). Neural correlates of short-term perceptual learning in orientation discrimination indexed by event-related potentials. *Chinese Science Bulletin, 52*(3), 352-357.

Song, Y., Peng, D., Lu, C., Liu, C., Li, X., Liu, P., . . . Ding, Y. (2007). An event-related potential study on perceptual learning in grating orientation discrimination. *Neuroreport, 18*(9), 945-948.

Song, Y., Sun, L., Wang, Y., Zhang, X., Kang, J., Ma, X., . . . Ding, Y. (2010). The effect of short-term training on cardinal and oblique orientation discrimination: An ERP study. *International Journal of Psychophysiology, 75*(3), 241-248.

Spaak, E., Bonnefond, M., Maier, A., Leopold, D. A., & Jensen, O. (2012). Layer-specific entrainment of gamma-band neural activity by the alpha rhythm in monkey visual cortex. *Current Biology, 22*(24), 2313-2318.

Spiegel, D. P., Byblow, W. D., Hess, R. F., & Thompson, B. J. N. a. n. r. (2013). Anodal transcranial direct current stimulation transiently improves contrast sensitivity and normalizes visual cortex activation in individuals with amblyopia. *27*(8), 760-769.

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.

Spielmann, K., Van De Sandt-Koenderman, W. M., Heijenbrok-Kal, M. H., & Ribbers, G. M. (2018). Comparison of Two Configurations of Transcranial Direct Current Stimulation for Treatment of Aphasia. *Journal of rehabilitation medicine, 50*(6), 527-533.

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

Stagg, C. J., & Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *The Neuroscientist, 17*(1), 37-53.

Stewart-Williams, S., & Podd, J. (2004). The placebo effect: dissolving the expectancy versus conditioning debate. *Psychological bulletin, 130*(2), 324.

Swettenham, J. B., Muthukumaraswamy, S. D., & Singh, K. D. (2009). The spectral properties of induced and evoked gamma oscillations in human early visual cortex to moving and stationary stimuli. *Journal of neurophysiology*.

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.

Tallon-Baudry, C., Bertrand, O., Hénaff, M.-A., Isnard, J., & Fischer, C. (2004). Attention modulates gamma-band oscillations differently in the human lateral occipital cortex and fusiform gyrus. *Cerebral Cortex, 15*(5), 654-662.

Tallon-Baudry, C., Bertrand, O., Peronnet, F., & Pernier, J. (1998). Induced γ-band activity during the delay of a visual short-term memory task in humans. *Journal of Neuroscience, 18*(11), 4244-4254.

Tan, H.-R., Gross, J., & Uhlhaas, P. (2016). MEG sensor and source measures of visually induced gamma-band oscillations are highly reliable. *NeuroImage, 137*, 34-44.

Tang, M. F., & Hammond, G. R. (2013). Anodal transcranial direct current stimulation over auditory cortex degrades frequency discrimination by affecting temporal, but not place, coding. *European Journal of Neuroscience, 38*(5), 2802-2811.

Tao, H. W., Li, Y.-t., & Zhang, L. I. (2014). Formation of excitation-inhibition balance: inhibition listens and changes its tune. *Trends in neurosciences, 37*(10), 528-530.

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

Tehovnik, E. J. (1996). Electrical stimulation of neural tissue to evoke behavioral responses. *Journal of neuroscience methods, 65*(1), 1-17.

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.

Tibber, M. S., Guedes, A., & Shepherd, A. J. (2006). Orientation discrimination and contrast detection thresholds in migraine for cardinal and oblique angles. *Investigative ophthalmology & visual science, 47*(12), 5599-5604.

Tobimatsu, S., Kurita-Tashima, S., Nakayama-Hiromatsu, M., Akazawa, K., & Kato, M. (1993). Age-related changes in pattern visual evoked potentials: differential effects of luminance, contrast and check size. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 88*(1), 12-19.

Tokimura, H., Di Lazzaro, V., Tokimura, Y., Oliviero, A., Profice, P., Insola, A., . . . Rothwell, J. (2000). Short latency inhibition of human hand motor cortex by somatosensory input from the hand. *The Journal of Physiology, 523*(2), 503-513.

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

Treutwein, B. J. V. r. (1995). Adaptive psychophysical procedures. *35*(17), 2503-2522.

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., Bjørkedal, E., Gunkel, L., Antal, A., Paulus, W., & Mittner, M. (2018). Evidence for Cognitive Placebo and Nocebo Effects in Healthy Individuals. *Scientific reports, 8*(1), 17443.

Turi, Z., Csifcsák, G., Boayue, N. M., Aslaksen, P., Antal, A., Paulus, W., . . . 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*.

Turi, Z., Mittner, M., Paulus, W., & Antal, A. (2017). Placebo intervention enhances reward learning in healthy individuals. *Scientific reports, 7*, 41028.

Uhlhaas, P. J., Roux, F., Rodriguez, E., Rotarska-Jagiela, A., & Singer, W. (2010). Neural synchrony and the development of cortical networks. *Trends in cognitive sciences, 14*(2), 72-80.

Uji, M., Wilson, R., Francis, S. T., Mullinger, K. J., & Mayhew, S. D. (2018). Exploring the advantages of multiband fMRI with simultaneous EEG to investigate coupling between gamma frequency neural activity and the BOLD response in humans. *Human brain mapping, 39*(4), 1673-1687.

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.

van Pelt, S., & Fries, P. (2013). Visual stimulus eccentricity affects human gamma peak frequency. *Neuroimage, 78*, 439-447.

van Pelt, S., Shumskaya, E., & Fries, P. (2018). Cortical volume and sex influence visual gamma. *NeuroImage, 178*, 702-712.

Viganò, A., D'Elia, T. S., Sava, S. L., Auvé, M., De Pasqua, V., Colosimo, A., . . . 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.

Vogels, R., & Orban, G. A. (1985). The effect of practice on the oblique effect in line orientation judgments. *Vision research, 25*(11), 1679-1687.

Voytek, B., Canolty, R. T., Shestyuk, A., Crone, N., Parvizi, J., & Knight, R. T. (2010). Shifts in gamma phase–amplitude coupling frequency from theta to alpha over posterior cortex during visual tasks. *Frontiers in human neuroscience, 4*, 191.

Wager, T. D. (2005). The neural bases of placebo effects in pain. *Current Directions in Psychological Science, 14*(4), 175-179.

Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., . . . Cohen, J. D. (2004). Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science, 303*(5661), 1162-1167.

Wagner, T., Fregni, F., Fecteau, S., Grodzinsky, A., Zahn, M., & Pascual-Leone, A. (2007). Transcranial direct current stimulation: a computer-based human model study. *Neuroimage, 35*(3), 1113-1124.

Wandell, B. A. (1995). *Foundations of vision*: Sinauer Associates.

Ward, L. M. (2003). Synchronous neural oscillations and cognitive processes. *Trends in cognitive sciences, 7*(12), 553-559.

Wastell, D. G., & Kleinman, D. (1980). Potentiation of the habituation of human brain potentials. *Biological psychology, 10*(1), 21-29.

Westheimer, G., & Lavian, J. (2013). Perceptual learning of orientation judgments in oblique meridians. *Attention, Perception, & Psychophysics, 75*(6), 1252-1259.

Whitlow, L. (2016). *An investigation of the link between cortical inhibition, neural oscillations and psychophysics in schizophrenia.* Cardiff University,

Whittington, M. A., Traub, R., Kopell, N., Ermentrout, B., & Buhl, E. (2000). Inhibition-based rhythms: experimental and mathematical observations on network dynamics. *International journal of psychophysiology, 38*(3), 315-336.

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.

Wilent, W. B., & Contreras, D. (2005). Dynamics of excitation and inhibition underlying stimulus selectivity in rat somatosensory cortex. *Nature neuroscience, 8*(10), 1364.

Wilkinson, F., Karanovic, O., & Wilson, H. (2008). Binocular rivalry in migraine. *Cephalalgia, 28*(12), 1327-1338.

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.

Woods, A. J., Antal, A., Bikson, M., Boggio, P. S., Brunoni, A. R., Celnik, P., . . . Kappenman, E. S. (2016). A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clinical Neurophysiology, 127*(2), 1031-1048.

Wu, G. K., Tao, H. W., & Zhang, L. I. (2011). From elementary synaptic circuits to information processing in primary auditory cortex. *Neuroscience & Biobehavioral Reviews, 35*(10), 2094-2104.

Xia, J., Tang, Y., Liang, Z., Yang, Y., Li, G., & Zhou, Y. (2013). GABA increases stimulus selectivity of neurons in primary visual cortices of cats chronically treated with morphine. *Neuroscience, 241*, 116-125.

Yang, B., Ma, X., Schweinhart, A. M., Wang, F., Sun, M., & Song, Y. (2012). Comparison of event-related potentials elicited by cardinal and oblique orientations with broad-band noise stimuli. *Vision research, 60*, 95-100.

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

Yoon, J. H., Maddock, R. J., Rokem, A., Silver, M. A., Minzenberg, M. J., Ragland, J. D., & Carter, C. S. (2010). GABA concentration is reduced in visual cortex in schizophrenia and correlates with orientation-specific surround suppression. *Journal of Neuroscience, 30*(10), 3777-3781.

Yoon, J. H., Rokem, A. S., Silver, M. A., Minzenberg, M. J., Ursu, S., Ragland, J. D., & Carter, C. S. (2009). Diminished orientation-specific surround suppression of visual processing in schizophrenia. *Schizophrenia Bulletin, 35*(6), 1078-1084.

Yu, H., & Shou, T. (2000). The oblique effect revealed by optical imaging in primary visual cortex of cats. *Sheng li xue bao:[Acta physiologica Sinica], 52*(5), 431-434.

Yuval-Greenberg, S., Tomer, O., Keren, A. S., Nelken, I., & Deouell, L. Y. (2008). Transient induced gamma-band response in EEG as a manifestation of miniature saccades. *Neuron, 58*(3), 429-441.

Zazio, A., Schreiber, M., Miniussi, C., & Bortoletto, M. (2019). Modelling the effects of ongoing alpha activity on visual perception: the Oscillation-based Probability of Response. *bioRxiv*, 752766.

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.