

# Neural modulation of the human visual cortex

by

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### **Author's Declaration**

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

## Abstract

Neuroplasticity is a phenomenon that refers to the brain's ability to reorganize, strengthen, and form neural connections, a process that becomes increasingly more difficult with age. Gamma amino-butyric acid (GABA), the primary inhibitory neurotransmitter in the brain, is thought to gate neuroplasticity, with increasing concentrations related to the closure of the critical period of development. As a result, the modulation of neuroplasticity and GABA concentration may have implications in the recovery and rehabilitation of neural functions.

This research addresses neuroplasticity in the visual cortex by applying rapid visual stimulation and non-invasive brain stimulation using both physiological and psychophysical outcome measures. One fundamental mechanism of neuroplasticity is known as long-term potentiation (LTP), a synaptic strengthening mechanism characterized by changes in cortical physiology and underlies the processes of learning and memory formation. While LTP can be induced in animal models of the brain through invasive electrical stimulation, recent studies have demonstrated LTP-like effects induced by rapid visual stimulation. Another technique that modulates neuroplasticity is non-invasive brain stimulation. Anodal transcranial direct current stimulation (a-tDCS) has been reported to decrease GABA concentration in the motor cortex, while a form of magnetic stimulation, continuous theta-burst stimulation (cTBS) has the opposite effect. Cortical GABA concentration is measured directly using magnetic resonance spectroscopy (MRS) an imaging technique that quantifies neural metabolites within a small region of interest. Binocular rivalry—a phenomenon wherein perception alternates stochastically when two different images are shown to each



eye—has been directly and indirectly associated with visual cortex GABA concentration, which poses the question of whether binocular rivalry dynamics can be used as an indirect measure of GABA concentration.

First, we tested the hypothesis that rapid monocular visual stimulation would increase the dominance of the stimulated eye during a binocular rivalry task. Unexpectedly, we found that rapid monocular visual stimulation strengthens the non-stimulated eye, a result which was not explained by adaptation, suggesting that the shift in dominance towards the non-stimulated eye may result from a homeostatic gain control mechanism.

Secondly, we investigated the effects of two opposing forms of non-invasive brain stimulation, a-tDCS and cTBS, on binocular rivalry dynamics. We hypothesized that a reduction of GABA using a-tDCS would result in an increase in binocular rivalry alternation rates, while cTBS would have the opposite effect. Although binocular rivalry alternation rates did not change with either stimulation method, duration of mixed perception increased significantly following cTBS. An increase in the inhibitory neurotransmitter GABA may translate to a reduction in neural noise, a complement to the phenomenon of stochastic resonance where increased neural noise may increase the detection of weak signals.

Finally, we investigated the effects of a-tDCS on visual cortex GABA and glutamate concentration. Although many studies report a reduction in motor cortex GABA concentration following a-tDCS, our results showed that visual cortex GABA concentration remained the same. Unexpectedly, we found a trend for an increase in glutamate following active a-tDCS, supporting the possibility that a-tDCS effects the visual cortex and motor cortex differently.

It is evident that there are many complex mechanisms that gate plasticity, and that modulating neuroplasticity is not as simple as we may have thought. Understanding these mechanisms, however, and the effects of modulatory techniques such as rapid visual stimulation and non-invasive brain stimulation on visual cortex plasticity, will provide a foundation for improving the recovery and rehabilitation potential of neurodevelopmental disorders and brain damage.

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## **Dedication**

For my loving mother and father.

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# Chapter 1

## Introduction

### 1.1 Overview of the Visual System

The human brain is a complex and dynamic structure that governs everything from our thoughts and behaviours, to our vision and perception. The normal development and function of the human visual system, as well as other neural systems, is highly dependent on early childhood experiences. While the eye is the light-sensing organ that interacts with the world physically, the processing, understanding, and interpretation of everything we see occurs in the complex neural networks of the brain.

When light enters the eye, it is captured by photoreceptor cells in the retina, then transmitted as an electrical signal to the brain. Retinal ganglion cells encode the features of the visual world such as colour, contrast, and motion, before conducting the information in three distinct pathways to the lateral geniculate nucleus (LGN) in the thalamus, as well

as forming other minor pathways to other brainstem structures. The parvocellular (P) pathway is generally sensitive to high spatial and low temporal frequencies, and is thought to relay colour information (Braddick and Atkinson, 2011; Derrington and Lennie, 1984; Merigan and Maunsell, 1993). In contrast, the magnocellular (M) pathway is sensitive to low spatial and high temporal frequencies, and is understood to relay luminance, contrast, and motion information to the brain (Gordon and McCulloch, 1999; Gori et al., 2015). Finally, the koniocellular (K) pathway is believed to be heterogenous, transmitting both colour and motion information (Derrington and Lennie, 1984; Hendry and Reid, 2000; Merigan and Maunsell, 1993). All three pathways primarily process and relay organized visual information mostly between the LGN and the primary visual cortex. LGN connectivity is complex and involves an estimated 90% more feedback cells than feedforward (Artal, 2017), demonstrating the role of both the LGN and V1 as the main cortical region for the next stage of visual processing.

The primary visual cortex, commonly referred to as V1, is only the first step in cortical visual processing. Information is relayed to extrastriate regions as either the dorsal stream or ventral stream pathway. The M pathway typically leads into the dorsal stream to process spatial information and motion perception, known as the “where” pathway. The P pathway leads into the ventral stream, encompassing visual areas V2 and V4, and is primarily responsible for form perception, known as the “what” pathway (Simic and Rovet, 2016).

In accordance with animal and human studies, visual functions become adult-like and fully developed at different rates (Daw, 1998; Simic and Rovet, 2016). Generally, more complex visual functions that require higher cortical processing take longer to mature

than visual functions that are processed at early cortical sites, such as motion and colour perception (Braddick, 1996; Hyvarinen et al., 2014; Leat et al., 2009). Throughout early childhood development, each visual function develops rapidly during a specific time of heightened plasticity, known as the critical period (Hooks and Chen, 2007; Power and Schlaggar, 2016). During this period, visual experience is essential for normal structural and functional development, such that deprivation or little input throughout this time will result in abnormal vision. Several studies on the critical period of visual functions in mice were compiled by Hooks and Chen (2007) to illustrate the timeline of development and demonstrate that there is a small window of high plasticity in early life specific to each function. This process of development is thought to be similar to that of humans, which lasts for a relatively short period of time. Studies have found varying evidence for the closure of the critical period in animal models depending on the visual function, ranging from approximately three to nine months in cats (Daw, 1998; Wiesel and Hubel, 1963), to four to five weeks in rats and mice (Fagiolini et al., 1994; Gordon and Stryker, 1996). In humans, the closure of the critical period for most visual functions is thought to be around five years of age (Bui Quoc and Milleret, 2014).

The concept of the critical period was first suggested by Hubel and Wiesel, where they discovered that visual deprivation in the early development of kittens led to altered cortical organization and response, whereas the same deprivation later in life had no effect (Wiesel and Hubel, 1963). Ocular dominance—the relative response of visual cortex neurons to input from each eye—was significantly weakened for the eye that was deprived during the critical period. This led to the discovery of a period of heightened plasticity, where visual stimulation is necessary for normal cortical and functional development in both animals

and humans.

### 1.1.1 Binocular Vision - Normal and Abnormal Development

Humans, and many other species have binocular vision, the ability to create a single image from two slightly displaced visual inputs. When processed as a single image, a sense of depth and a measure of distance is made possible. Visual input from each eye remains separated in early visual processing as both the LGN and the input layers of the primary visual cortex are systematically organized as right eye and left eye layers (LGN) and columns (layer 4B of V1) (Blake, 2001; Casagrande and Boyd, 1996; Parker and Cumming, 2001). While some evidence suggests that binocular rivalry is processed in the LGN (Haynes, 2005), there is evidence that integrating information from both eyes occurs early in the upper and lower layers of the primary visual cortex where cells respond to signals from both eyes equally (Dougherty et al., 2019).

Equal visual stimulation to both eyes in early development is essential for normal binocular vision to mature (Spiegel et al., 2017; Wiesel and Hubel, 1963). If one eye is deprived of stimulation for an extended period of time or receives little to no visual information during the critical period, long-lasting binocular deficits can result. Amblyopia, a neurodevelopmental disorder in which the lack of a clear visual input from one eye disrupts the typical development of visual cortex processing, is an example of the abnormal binocular vision that can result, and is prevalent in 1-4% of the adult population (Levi et al., 2015; McKean-Cowdin et al., 2013; MEPEDS, 2009; Williams et al., 2008). Long-lasting effects impacting many aspects of normal vision, such as visual acuity, stereoacuity, and

contrast sensitivity can occur as a result of untreated amblyopia prior to the closure of the critical period of development (Burke and Barnes, 2006). Studies have looked at the effects of early abnormal binocular visual input in humans, as well as treatments to reverse the effects of abnormal development or strengthen structural and functional neural networks, including visual perceptual learning (Levi and Li, 2009), binocular games and training (Hess et al., 2014; Hess et al., 2010; Li et al., 2014), and occlusion therapy of the amblyopic or deprived eye (Lunghi et al., 2016; Ramamurthy and Blaser, 2018). The success of these treatments relies on the brain's potential and ability to learn and adapt.

## 1.2 Neuroplasticity

The human brain has a remarkable ability to form, reorganize, and strengthen neural connections throughout early development. This phenomenon is known as neuroplasticity and can be classified as either structural or functional changes of the brain. Structural plasticity refers to physical changes in the connections or formation of neurons, as well as changes in the relative amount of grey matter (Demarin et al., 2014; Pascual-Leone et al., 2011; Shaw, 2013). One example of structural plasticity is neurogenesis, the process of generating new neuronal cells, which occurs extensively throughout childhood and may continue into adulthood, albeit at a slower rate (Rakic, 2001). Functional plasticity, on the other hand, refers specifically to changes in the strength of neural connections without any anatomical changes of neural wiring (Butz et al., 2009). More broadly, functional plasticity includes the brain's ability to learn or recover function from neurodevelopmental disorders such as amblyopia, or following brain damage in later adulthood (Finger and Almlil, 1985;

Horton et al., 2017). Changes in neural function are typically related to repeated activity within a circuit, known as activity-dependent plasticity (Butz et al., 2009).

Children can learn, understand, and adapt to the world around them in extraordinary ways as their brain grows and develops, and as approximately one million neural synapses are added every second from the third trimester to about 2 years of age (Levitt and Eagleson, 2018). This remarkable extent of growth and development allows for the recovery of neural function in children, particularly during critical periods (Hooks and Chen, 2007; Power and Schlaggar, 2016; Wiesel and Hubel, 1963). This complex phenomenon of neuroplasticity was previously thought to cease in adulthood. Specifically, the belief was that neural connections were hardwired after a certain age. However, recent discoveries have demonstrated that there is potential for neuroplasticity in adulthood—albeit to a lesser degree—allowing for changes, and recovery of neural connections later in life (El Mallah et al., 2000; Kupfer, 1957; Maino, 2012; Park and Bischof, 2013). Further investigation has looked into modulating neuroplasticity in adults with visual stimulation (Abuleil et al., 2019; Kirk et al., 2010; Teyler et al., 2005), auditory stimulation (Clapp et al., 2005a; Zahle et al., 2007), aerobic exercise (Zhou et al., 2017), and non-invasive brain stimulation techniques (Antal et al., 2006; Nitsche et al., 2008). Understanding how to harness and strengthen neuroplasticity in adults has been the focus of recent research in animal models as well as humans, with the goal of playing a role in recovery and rehabilitation of neural functions.

### 1.2.1 Mechanisms of Neuroplasticity

Although the process of learning and memory formation is not fully understood, Hebbian plasticity is a widely accepted mechanism for how information is created and solidified in neurons within the brain. In his book, *Organization of Behaviour*, Donald Hebb, a Canadian psychologist states:

When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased. (Hebb, [1949](#))

The theory of cognition and learning explains that neural circuits can be strengthened over time with repeated stimulation, summarized by Carla Shatz as neurons that fire together, wire together (Cooper, [2005](#); Pincus, [2008](#); Power and Schlaggar, [2016](#); Shatz, [1992](#)). Following Hubel and Wiesel's findings on visual plasticity in cats (Hubel and Wiesel, [1962](#)), a complementary statement to Hebb's finding was extended:

When the presynaptic axon of cell A repeatedly and persistently fails to excite the postsynaptic cell B while cell B is firing under the influence of other presynaptic axons, metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is decreased. (Stent, [1973](#))

In other words, connections and synapses are weakened if neuronal activity is not correlated. These fundamental concepts of strengthening and weakening synapses provide an

explanation for two phenomena, namely long-term potentiation and long-term depression, respectively.

### 1.2.2 Long-Term Potentiation

A fundamental mechanism of neural plasticity and a widely accepted example of Hebbian plasticity is known as long-term potentiation (LTP) (Cooper, 2005). LTP is a synaptic strengthening mechanism underlying learning and memory formation, a process which encompasses structural as well as functional changes of neural networks (Bliss and Lomo, 1973; Cooper, 2005; Nicoll, 2017). In 1973, Bliss and Lomo unequivocally demonstrated the phenomenon of LTP by measuring changes in synaptic amplitude in the rabbit hippocampus following electrical stimulation (Bliss and Lomo, 1973). Following the discovery of LTP, it quickly became apparent that there must be different forms of LTP, depending on the region of the brain, the neurons involved and the type of input the neuron receives (Blundon and Zakharenko, 2008; Nicoll, 2017).

#### 1.2.2.1 Physiology of LTP

The induction of LTP is typically assessed physiologically by directly measuring synaptic activity and increases in molecules within the brain (Nicoll, 2017). Many studies over the years contributed to the understanding of the mechanisms which underly LTP, and have generally concluded that LTP is associated with the excitatory neurotransmitter glutamate as well as changes in the expression of the glutamate receptors alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) and N-methyl D-aspartate (NMDA) (Hasan et



al., 2013; Nicoll, 2017; Ouardouz and Sastry, 2000). Additionally, there is evidence for structural and functional changes in the presynaptic neuron (Bliss and Collingridge, 2013; Emptage et al., 2003; Ward et al., 2006) as well as the postsynaptic neuron (Harvey and Svoboda, 2007; Lee et al., 2009; Tønnesen et al., 2014) as measures of the induction and expression of LTP. Inducing LTP in the brain is thought to begin a cascade of physiological events that act on the specific neural circuit and result in long-lasting changes in the expression of glutamate, receptor sensitivity and even the size of the neuron indicating strength of the circuit (see Nicoll, 2017 for a full review).

#### 1.2.2.2 LTP in Animals

LTP has been demonstrated extensively in animal models, cellularly, molecularly, and behaviourally (Bliss and Lomo, 1973; Cooke and Bliss, 2006; Eckert et al., 2013). LTP induction in an animal model can be used to understand the neurochemical changes that occur in the brain. For instance, a study with rats proved that high frequency electrical stimulation to the dentate gyrus resulted in increased activity of that particular neural circuit (Abraham et al., 2002). Further investigation demonstrated that this phenomenon occurred in different areas of the brain including the cerebral neocortex (Fox, 2002), the hippocampus (Bliss and Lomo, 1973), the motor cortex (Hasan et al., 2013), and the visual cortex (Eckert et al., 2013).

The translation of LTP from animal models to humans is a more recent venture (Clapp et al., 2012). Since direct electrical stimulation of a neuron is a largely invasive technique in animal models, attempts to induce LTP non-invasively led to the discovery that the same

effect can be achieved by rapid visual stimulation in animal models, referred to as a photic tetanus (Heynen and Bear, 2001; Zhang et al., 2000). This allowed for the non-invasive translation of LTP induction to human subjects.

### 1.2.2.3 LTP in Humans

Earlier research demonstrated the possible induction of LTP in isolated human cortical tissue (Beck et al., 2000; Chen et al., 1996); however, investigating changes in vivo are relatively recent with the advancement of research and technology. While there are imaging techniques that allow for the quantification of metabolites within a particular region of the brain in vivo, assessing changes in receptors and cascades is not as easily accessible in humans. As a result, evoked potentials including visual evoked potentials (VEPs) have been used to assess the electrical changes in a human brain following rapid visual stimulation (Teyler et al., 2005). Specifically, an increase in VEP amplitude of the N1b component was found following 2 minutes of rapid visual stimulation (Teyler et al., 2005). While this result suggests an increase in cortical activity and possibly increased plasticity, it is referred to as an LTP-like phenomenon, as direct changes in chemical activity are not measured. The study by Teyler et al. (2005) was the first to demonstrate the non-invasive induction of LTP in the visual cortex, as measured by changes in VEP amplitudes. The assumption is that changes in the neurochemistry are similar to that of previous studies in animal models, although the behavioural and perceptual effects of rapid visual stimulation remain unclear.

### 1.2.3 Neuroplasticity in the Human Visual Cortex

The human visual system responds to its surrounding environment at a cellular and molecular level, a concept known as experience-dependent plasticity (Karmarkar and Dan, 2006). The relationship between visual input and neural changes has proven important to understanding the physiology and mechanisms of neuroplasticity, particularly because of its potential role in recovery and rehabilitation of memory and neural functions in humans (Särkämö et al., 2014). While it is widely accepted that children generally have higher plasticity than adults, the mechanisms and changes that occur with age are not quite understood. Similarly, the neural changes that occur into older adulthood remain a mystery. Various manipulations to the visual system have been used in humans to understand how to increase plasticity in adults, such as rapid visual stimulation (Klöppel et al., 2015; Lahr et al., 2014; Norman et al., 2007; Teyler et al., 2005), visual perceptual learning (Fahle and Poggio, 2002; Furmanski et al., 2004; Maertens and Pollmann, 2005) and visual deprivation (Lunghi et al., 2015a; Lunghi et al., 2011; Lunghi et al., 2015b). Such visual manipulations may strengthen neural connections through the mechanism of LTP, weaken neural connections through the opposing mechanism of long-term depression (LTD), or result in short-term effects caused by visual adaptation.

#### 1.2.3.1 Adaptation

Visual adaptation refers to the temporary change in visual sensitivity to a perceived stimulus or image, and the aftereffects that follow (Webster, 2015). Typically, sensitivity to a particular stimulus is reduced following prolonged viewing of a high-contrast image

(Webster, 2011). A key characteristic of adaptation is its specificity; the strength of the effect is specific to colour, orientation, form and motion (Kohn, 2007; Webster, 2015). Additionally, studies have demonstrated that this short-term form of plasticity lasts approximately as long as the period of perception (Bağgöze et al., 2018; Greenlee et al., 1991).

Since both long-term potentiation and adaptation are experience-dependent forms of plasticity, it has been difficult to discern the two phenomena both physiologically and mechanistically (Harris et al., 2012; McGovern et al., 2012). This suggests a possible interaction between LTP and adaptation, since both act on similar neural mechanisms but create opposite perceptual effects (McGovern et al., 2012). Although the differences and characteristics of both mechanisms are still under investigation, both phenomena play a key role in understanding the mechanisms of plasticity in humans.

### **1.2.3.2 Amblyopia as a Model of Neuroplasticity**

The perceptual and behavioural effects of neuroplasticity are often studied using amblyopia as a model. Amblyopia is a neurodevelopmental disorder in which the lack of a clear visual input from one eye disrupts the typical development of visual cortex structure and function. In the past, amblyopia, as well as other developmental disorders, were deemed permanent if not treated during the critical period, due to the presumed lack of plasticity in the brain (Burke and Barnes, 2006). However, recent visual techniques and processes of visual manipulation demonstrate the potential for the reorganization and strengthening of neuronal connections to occur well past the critical period of development. These methods

provide new approaches to treatment and rehabilitation of amblyopia applicable to both children and adults. Since amblyopia results in binocular deficits, it has been commonly used as a model for understanding the development of binocular vision in both children and adults (Birch, 2013; Levi and Polat, 1996).

Amblyopia can develop as a result of deprivation, a complete lack of visual input to one eye throughout early development. However, the more common causes of amblyopia in human children are strabismus, an eye turn resulting in the misalignment of images from each eye, and/or anisometropia, a large, uncorrected difference in refractive error between the two eyes early in life (Holmes and Clarke, 2006). In each case, structural and functional changes take place within the visual cortex (Dai et al., 2019; Lu et al., 2019; Shatz and Stryker, 1978; Yang et al., 2019).

Not only does amblyopia result in reduced visual acuity in the amblyopic eye, there are also several other deficits including but not limited to reduced contrast sensitivity, reduced fixation stability, and reduced stereoacuity (Kanonidou, 2011; Levi, 2006; Li et al., 2007; Webber, 2018). If detected in childhood, typically before the age of 9, amblyopia is conventionally treated by patching the non-amblyopic eye, or fellow eye, to encourage the development of the amblyopic eye. Some patients recover completely, while most may recover some binocular function and improve slightly in visual acuity, or show no improvements at all (Mintz-Hittner and Fernandez, 2000; West and Williams, 2016).

Since the brain was once thought to be ‘hard-wired’ later in life, adults are typically untreated, as improvement was considered impossible. With a deeper understanding of neuroplasticity in recent years and the discovery that neurons can strengthen and form

new connections in adults, treatments for adults with amblyopia are becoming increasingly popular (Dahlmann-Noor, 2016; Gao et al., 2018; Hess et al., 2014; Hess et al., 2010; Hess and Thompson, 2015). The success of these new treatments of amblyopia depends on the extent of structural and functional changes in the brain to alter perception for prolonged periods of time, which are thought to be modulated by changes in chemicals within the brain.

## 1.3 Neurotransmitters and Plasticity

The dynamic response of the brain to visual input occurs, in part, from the changes in chemicals known as neurotransmitters that control the communication between two neurons. There are several types of neurotransmitters that either encourage neurons to fire (excitatory neurotransmitters), or inhibit neurons from firing (inhibitory neurotransmitters), each needing to be present in certain concentrations for normal functioning throughout life. As a result, neurotransmitter concentration is thought to play a role in the changes in plasticity that occur from childhood to adulthood.

### 1.3.1 GABA and Glutamate

The two primary inhibitory and excitatory neurotransmitters in the brain are gamma-aminobutyric acid (GABA) and glutamate, respectively. GABA is thought to play a role in the increasing difficulty for the maturing brain to form new neural connections or strengthen existing connection (Levelt et al., 2011). As a result, GABA has been as-

sociated with the evident decrease of neural plasticity in young adults (Baroncelli et al., 2011; Sale, 2010). Glutamate is the precursor of GABA, and therefore both neurotransmitters are closely connected in a cycle mediated by the enzyme glutamic acid decarboxylase (GAD) (Meldrum, 2000; Petroff, 2002). A homeostatic balance between excitatory and inhibitory neurotransmitters, namely GABA and glutamate, is thought to be essential for normal brain function (Fox and Stryker, 2017).

It is important to note, however, that the complexity of the GABAergic and glutamatergic neural network is not fully understood. Modulating GABA/glutamate concentration in humans has proven to be complicated as many components of each system—such as the neurotransmitter itself, its’ receptors, and the many enzymes and protein factors that modulate their expression—may be altered through different methods and techniques (Petroff, 2002).

### 1.3.1.1 GABA and the Critical Period

How plastic the brain can be changes from childhood into adulthood. The critical period of neural development is commonly used to understand the correlation between plasticity and cortical GABA concentration (Figure 1.1). Changes in GABA concentration have been found to influence the critical period. Specifically, reducing GABA function delays the onset of the critical period (Chen et al., 2001; Fagiolini et al., 2003; Morales et al., 2002; Mower, 1991) while increasing GABA function, either directly or indirectly, promotes the onset of the critical period at an earlier time (Fagiolini et al., 2004; Huang et al., 1999; Iwai et al., 2003). The first experiment to discover this phenomenon in 1998

showed that genetically reducing the synthesis of GABA in mice prevented the onset of the critical period of ocular dominance plasticity, the window of time during which the strength of the neural response to input from each eye can be altered (Fagiolini and Hensch, 2000; Hensch et al., 1998). Therefore, it is hypothesized that a particular threshold of GABA concentration is required to trigger the onset of the critical period of a particular function, and a higher threshold closes it (Fagiolini and Hensch, 2000; Hooks and Chen, 2007). Although the critical period closes after a short period of heightened plasticity, there is still potential for change and strengthening of neural connections throughout adolescence and adulthood. The extent to which plasticity exists in young and early adulthood and the exact mechanisms that slow it down are not clear and investigating these mechanisms will provide insight into new treatments for recovery and rehabilitation in later years.

### **1.3.1.2 Assessing GABA Concentration in Humans**

While there are several techniques to assess GABA function in animal models and isolated cortical tissue, the most common method for quantifying GABA concentration in the human brain is by magnetic resonance spectroscopy (MRS) (Muthukumaraswamy et al., 2009; Stagg et al., 2009b; van Loon et al., 2013). This imaging technique can quantify GABA and glutamate concentrations in a particular region of the brain. Most studies demonstrate the functional and behavioural changes that occur following GABA modulation in the motor cortex (Lagas et al., 2016; Patel et al., 2019). Although MRS is commonly used, it is expensive and time consuming. As a result, finding an indirect or behavioural measurement of GABA concentration would be useful.



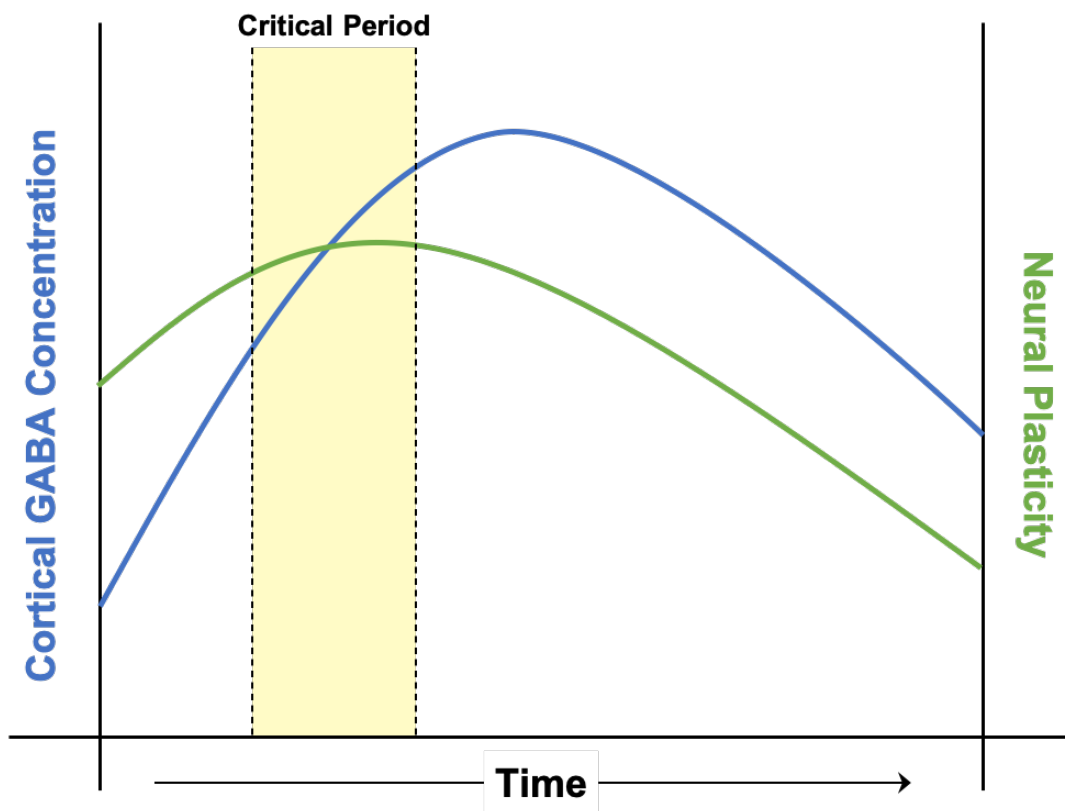


Figure 1.1: A schematic representation of the hypothesized overall increase in GABA concentration and decrease of neural plasticity in humans. Figure inspired by Hensch and Quinlan Hensch and Quinlan (2018).

**1.3.1.2.0.1 Binocular Rivalry as an Indirect Measure of GABA** Despite its many capabilities, the brain can resort to a state of bistable perception when presented with conflicting images in each eye. Binocular rivalry occurs when two different images are presented to each eye, resulting in stochastic changes from one percept to the other, as each eye competes for dominance. The nature of the perceptual switching under such conditions has fascinated researchers over the years and provided a method to study the neural correlates of binocular vision, as well as conscious awareness (Lumer et al., 1998;

Rees et al., 2002; Wunderlich et al., 2005). Since binocular rivalry appears to involve several neural correlates and seems to be processed in different areas along the visual pathway, it is inferred that the changes in the dynamics of binocular rivalry from childhood into adulthood will mature behaviourally in a similar manner to the neural correlates involved.

GABA has been correlated with binocular rivalry alternation rates in young adults (van Loon et al., 2013). Specifically, higher GABA is correlated with slower alternation rates during binocular rivalry. However, whether this correlation is robust is unclear, as a recent study found the opposite effect (Pitchaimuthu et al., 2017). Young adults are found to have higher GABA concentration than children (Levelt et al., 2011; Levelt and Hubener, 2012; Sale, 2010). This is consistent with changes in binocular rivalry alternation rates from childhood into adulthood—alternation rates decrease while GABA concentration (inhibition) increases. However, there is evidence for a continued increase of GABA concentration in older adulthood (Pitchaimuthu, 2017), as well as evidence for the opposite (Gao et al., 2013; Hua et al., 2008). Within-subject variations of GABA concentration may be a factor. A recent magnetic resonance spectroscopy (MRS) study in young and older adults found a significant decline in GABA concentration in older adults within the right striatum only, suggesting non-uniform changes of GABA across the brain (Hermans et al., 2017). As a result, it is still unclear whether the apparent decrease in binocular rivalry alternation rates is related to an increase or decrease in GABA concentration.

### 1.3.2 Magnetic Resonance Spectroscopy

Magnetic resonance imaging (MRI) is a widely used technique for understanding brain structure and function. MRI relies on a large magnet and the signals from protons to form detailed images of the brain and monitor functional as well as metabolic changes that occur over time, in response to visual stimulation, or even during rest (Lv et al., 2018; Shen, 2015; Van Der Graaf, 2010). Two commonly used analyses to understand brain function and dynamics are magnetic resonance spectroscopy and resting-state functional connectivity.

Magnetic resonance spectroscopy (MRS) is a technique that uses an MRI to quantify metabolites within a small region of the brain, or volume of interest (VOI). Spectra are obtained from the human brain based on the characteristic response of the metabolite to the magnet, from which the concentration is determined (Van Der Graaf, 2010; Figure 1.2). Resting state data shows the function of neural networks at rest, whereas functional imaging shows the neural response while performing a task. These imaging techniques give insight into the neurochemical and functional changes that occur within the brain and allow for a better understanding of neuroplasticity in humans.

#### 1.3.2.1 MRS and Neuroplasticity

The structural and functional changes that occur in the brain can be studied using various imaging techniques. Since neurotransmitter concentration is associated with changes in neuroplasticity, a common method of studying neuroplasticity in humans is through MRS. Quantifying GABA and glutamate within a region of the brain can reveal changes

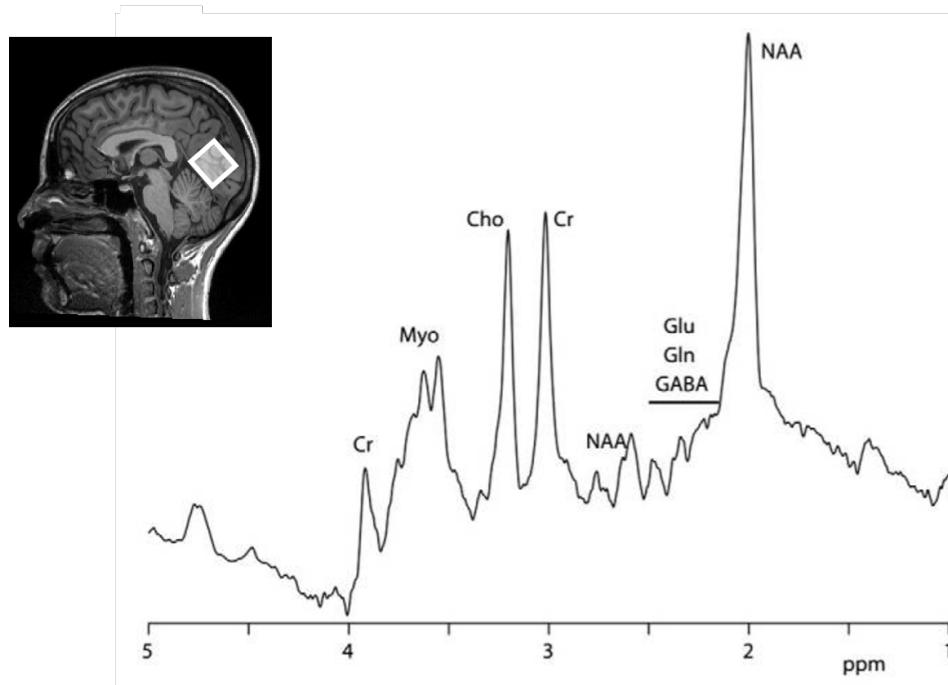


Figure 1.2: Representation of voxel of interest and edited spectrum output. Each metabolite has a distinct peak at a specific frequency (parts per million, ppm). The y-axis represents the signal intensity. The quantification of each metabolite is determined as the area under the peak. Reprinted from *Progress in Nuclear Magnetic Resonance Spectroscopy*, 60, Nicolaas A.J. Puts and Richard A.E. Edden, *In vivo magnetic resonance spectroscopy of GABA: A methodological review*, page 18, Copyright (2012), with permission from Elsevier (see section 6.4)

that occur either as a result of age, or by techniques that directly or indirectly modulate neurochemicals. MRS has been used to investigate neuroplasticity and the chemicals potentially associated with the age-related reduction of neuroplasticity.

### 1.3.3 Modulation of GABA

Since GABA has been strongly linked to neuroplasticity and the opening and closure of the critical period, modulating GABA concentrations has been a focus of recent research to understand the effects on brain rehabilitation and recovery. Studies using animal models have demonstrated the effects of GABA modulation on plasticity. In particular, decreasing GABA using pharmacological or environmental manipulations in adult rats resulted in enhanced visual cortex plasticity (Maddock et al., 2016; Sale et al., 2007; Vetencourt et al., 2008). Since such invasive techniques are difficult to replicate in humans, other methods are sought out for similar effects. For instance, as mentioned above, rapid visual stimulation was previously found to have LTP-like effects understood as an increase in plasticity, and therefore theoretically an influence on GABA concentration. However, this has yet to be confirmed. One recent method commonly used to modulate GABA is non-invasive brain stimulation.

### 1.3.4 Non-Invasive Brain Stimulation

Recent non-invasive methods of GABA modulation in human subjects include electrical and magnetic stimulation. Although it is still unclear whether these techniques do indeed effect GABA concentration, studies with animal models, and more recently humans, suggest that such techniques do, in fact, alter brain neurochemistry and functionality in some way (Stagg and Nitsche, 2011; Valero-Cabr e et al., 2017). Electrical and magnetic brain stimulation methods create an electric field in different ways and influence the brain

differently; however, they have been used in similar ways to modify brain and behaviour.

#### 1.3.4.1 Electrical Stimulation

Electrical stimulation relies on a weak electrical current that runs between two or more electrodes positioned on the head. There are several different ways that the current can be delivered to the brain, such as direct-current, alternating current, or random noise, each having a different influence on the brain (Vosskuhl et al., 2018). Transcranial direct current stimulation (tDCS) is the most commonly used technique and involves delivering a low amplitude current to a particular region of the brain using electrode sponges (Fertonani and Miniussi, 2016; Hurley and Machado, 2017; Jamil and Nitsche, 2017; Wilke et al., 2017). Two electrodes (an anode and a cathode) are positioned on the head and a weak electric current (typically 1-2mA) runs through them. Anodal tDCS (a-tDCS), in which the anode is placed over the region of interest, increases the excitability of a particular region of the brain possibly by decreasing GABA concentration (Antonenko et al., 2017a; Heise et al., 2014; Jamil and Nitsche, 2017). In contrast, cathodal tDCS (c-tDCS), in which the cathode is placed over the region of interest, decreases excitability by decreasing glutamate, the GABA antagonist within the brain.

There are several mechanisms that are thought to underly the effects of tDCS. The physiological changes underlying the effect of tDCS is dependent on the shift in the polarity of neurons. The current flows from the anode to the cathode and must also flow through the neurons to have an effect. Early work in animal models demonstrates an excitatory effect on the neurons under the anode, and an inhibitory effect on the neurons under the

cathode, likely by depolarizing and hyperpolarizing, respectively (Bikson et al., 2004; Jamil and Nitsche, 2017)

One mechanism of tDCS on the brain is thought to involve the modulation of GABA concentration as seen in studies on the motor cortex. Specifically, studies have found a significant reduction in motor cortex GABA concentration following a-tDCS (Kim et al., 2014; Patel et al., 2017) and prolonged changes in GABA that lasted approximately one hour (Patel et al., 2019). Other studies found increased cortical excitability following a-tDCS (Nitsche and Paulus, 2001) and increased motor learning (Stagg et al., 2011a), all attributed to a reduction in GABA concentration. In the visual cortex, electrical stimulation has an effect on behavioural measures, such as contrast sensitivity (Battaglini et al., 2020; Ding et al., 2016) and depth perception (Behrens et al., 2017; Castaño-Castaño et al., 2019a; Spiegel et al., 2013b). However, the effects on the visual cortex may not be as pronounced and direct as those observed for the motor cortex (Lang et al., 2007). Variations across studies in electrode placement, stimulation intensity, and duration of stimulation make it difficult to compare results within and across regions of the brain, which may account for the wide range of results and issues of replicability of studies within the field (DaSilva et al., 2011).

#### **1.3.4.2 Magnetic Stimulation**

Transcranial magnetic stimulation (TMS) involves the induction of low electromagnetic current using a magnetic coil over a particular region of the brain. TMS is thought to result in long-lasting changes to the brain. Depending on the pattern and parameters of

stimulation, TMS can either increase or decrease cortical excitability (Mix et al., 2010; Valero-Cabré et al., 2017). A common and relatively effective pattern of stimulation is known as repetitive TMS, wherein pulses are administered rapidly and repeatedly within a short period of time. Two patterns of repetitive TMS are intermittent theta-burst stimulation (iTBS) and continuous theta-burst stimulation (cTBS), which modulate excitability in opposite directions (Mix et al., 2010; Valero-Cabré et al., 2017). iTBS increases motor cortex excitability using bursts of high frequency stimulation typically separated by 200ms intervals, while cTBS consists of rapid pulses for short periods of time, decreasing cortical excitability (Di Lazzaro et al., 2008). Although the way in which TMS exerts its effect on the brain is not fully understood, it is thought to have a similar mechanism as LTP or LTD (Klomjai et al., 2015). Interestingly, the effects of TMS and which neurons the protocol may influence depend on the region of the brain being stimulated and the profile of the neurons present in that region (Castrillon et al., 2020). This implies that different regions of the brain may respond differently to similar protocols, calling for further investigation in each particular region of the brain.

## 1.4 Summary

Modifying cortical excitability is thought to have long-term effects on functional and behavioural measures. Studies on the motor cortex have demonstrated the rehabilitation effects of electrical and magnetic stimulation (Hendricks et al., 2003; Kim et al., 2014; Nitsche and Paulus, 2001; Patel et al., 2017; Stagg et al., 2011b). Additionally, visual stimulation has been demonstrated to increase visual evoked potential amplitudes, indi-



cating a possible increase in plasticity (Norman et al., [2007](#); Teyler et al., [2005](#)). Further investigation is required to understand whether or not these techniques of neural modulation have an effect on the visual cortex and visual function.

# Chapter 2

## Objectives and Rationale

The brain has a remarkable capacity to form and strengthen neural connections during early childhood development. As the brain matures, however, neuroplasticity becomes increasingly difficult, thought to be associated, in part, with an increase in GABA concentration. Consequently, increasing neuroplasticity in adults for the purpose of recovery and rehabilitation of behaviour and function may be achieved by increasing cortical excitability and/or modulating GABA concentration in the brain. Long-term potentiation (LTP), a mechanism of neuroplasticity which underlies learning and memory formation, can be induced through rapid visual stimulation of a high contrast image, and is thought to increase plasticity of the visual cortex (Teyler et al., 2005). Non-invasive brain stimulation, such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) are techniques that have been found to modulate GABA concentration in the motor cortex; specifically, anodal tDCS (a-tDCS) decreases GABA while continuous theta burst stimulation (cTBS) increases GABA (Heise et al., 2014; Kim et al., 2014; Stagg

et al., 2009a; Stagg et al., 2009b). Whether or not tDCS and TMS have the same effect on visual cortex GABA concentration is not yet known. In order to investigate the effects of these modulatory techniques, visual cortex GABA concentration must be measured. A possible indirect and behavioural method to measure GABA concentration is binocular rivalry, a phenomenon that occurs when two different images are shown to each eye. Previously, GABA concentration has been associated with binocular rivalry alternation rates (van Loon et al., 2013). A direct measure of GABA concentration can be achieved using magnetic resonance spectroscopy (MRS), an imaging technique that quantifies GABA in a particular region of the brain.

The objective of my research is to investigate the effects of current neural modulation techniques on visual cortex GABA concentration in the adult brain.

**Project 1:** To explore the behavioural effects of rapid visual stimulation by investigating whether monocular rapid visual stimulation has an LTP-like effect on binocular rivalry dynamics in young adults.

**Project 2:** To investigate the effects of a-tDCS and cTBS—techniques which have opposite effects on GABA concentration—on binocular rivalry dynamics in young adults.

**Project 3:** To investigate the effects of a-tDCS on visual cortex GABA concentration by measuring visual cortex GABA concentration using MRS before and after a-tDCS in young healthy adults.

Projects 1 and 2 were completed in tandem and led to project 3 in order to provide a more direct answer to the modulation of visual cortex GABA concentration (Figure 2.1).

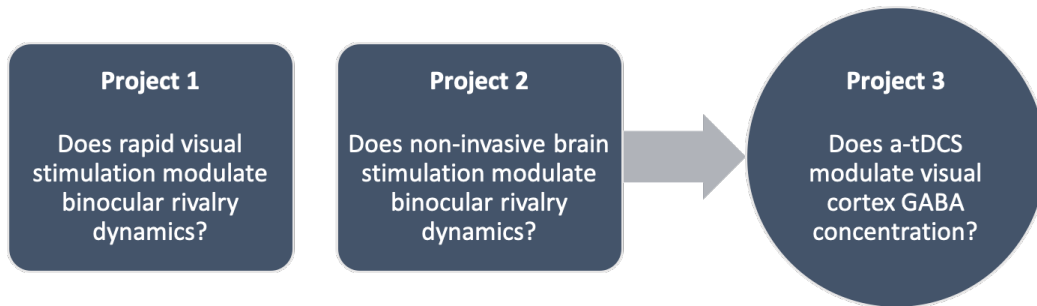


Figure 2.1: Timeline and rationale of projects.

## 2.1 Hypotheses

**Project 1:** Monocular rapid visual stimulation will cause the stimulated eye to dominate in binocular rivalry as a result of an LTP-like increase in excitability of neurons driven by the stimulated eye.

**Project 2:** A-tDCS will cause an increase in mixed percept duration as a result of reduced GABA concentration of the primary visual cortex. cTBS will have the opposite effect.

**Project 3:** A-tDCS will reduce visual cortex GABA concentration.

# Chapter 3

## Modulation of binocular rivalry with rapid monocular visual stimulation

### 3.1 Overview

Rapid visual stimulation can increase synaptic efficacy by repeated synaptic activation. This long-term potentiation-like (LTP-like) effect can induce increased excitability in the human visual cortex. To examine the effect of rapid visual stimulation on perception, we tested the hypothesis that rapid monocular visual stimulation would increase the dominance of the stimulated eye in a binocular rivalry task. Participants ( $n = 25$ ) viewed orthogonal 0.5 cpd gratings presented in a dichoptic anaglyph to induce binocular rivalry. Rivalry dynamics (alternation rate, dominance, and mixed percept durations) were recorded before and after 2 min of rapid monocular stimulation (9Hz flicker of one grat-

ing) or a binocular control condition (9Hz alternation of the orthogonal gratings viewed binocularly). Rapid monocular stimulation did not affect alternation rates or mixed percept duration. Unexpectedly, rivalry dominance of the stimulated eye was significantly reduced. A further experiment revealed that this effect could not be explained by monocular adaptation. Together, the results suggest that rapid monocular stimulation boosts dominance in the non-stimulated eye, possibly by activating homeostatic interocular gain control mechanisms.

## 3.2 Introduction

Long-term potentiation (LTP) is the process of strengthening synaptic efficacy through repeated activation. This fundamental mechanism of neuroplasticity involves a cascade of cellular and molecular changes and underpins the processes of learning and memory formation (Bliss and Collingridge, 1993; Bliss and Lomo, 1973). Early research revealed that rapid electrical stimulation of presynaptic cells within the rabbit hippocampus induced a lasting increase in the response amplitude of postsynaptic cells (Bliss and Lomo, 1973). Subsequent studies demonstrated similar effects (Bröcher et al., 1992) and characterized the neurochemical changes that occurred as a result of the stimulation (Hayashi2000; Teyler and DiScenna, 1987). These changes included a rise in postsynaptic calcium, the release of glutamate, and the activation of N-methyl-D-aspartate (NMDA) receptors (Malenka and Nicoll, 1999). While LTP is typically induced using electrical stimulation *in vitro*, similar effects (a strengthening of neural responses following stimulation) have been reported in the visual cortex using rapid visual stimulation in adult rats (Frenkel et al., 2006; Heynen

and Bear, 2001) and in humans (Clapp et al., 2005b; Normann et al., 2007; Teyler et al., 2005).

In human adults, 2-minutes of rapid visual stimulation of a high-contrast checkerboard increased the amplitude of the N1b component of visual evoked potentials (VEPs) (Norman et al., 2007; Sanders et al., 2018; Teyler et al., 2005). Rapid visual stimulation, sometimes referred to as visual tetanus, has been delivered in a number of ways including 9Hz flicker of checkerboard or grating stimuli and 2 Hz pattern reversal of checkerboard stimuli (Norman et al., 2007; Teyler et al., 2005). To account for the effect of visual adaptation that can reduce visual cortex excitability and VEP amplitude (Blakemore and Campbell, 1969), most studies of rapid visual stimulation include a period of eye closure that at least matches the duration of rapid visual stimulation (Magnussen and Greenlee, 1985). The effect of rapid visual stimulation on VEP amplitude is stimulus specific (Ross et al., 2008; Vassilev et al., 1994), reliant on NMDA receptors in animal models (Clapp et al., 2006a), and may also involve an increase in glutamate receptor expression (Eckert et al., 2013), suggesting that it involves an LTP-like mechanism.

The majority of studies on rapid visual stimulation in humans have used electrophysiology or neuroimaging to measure visual cortex excitability before and after stimulation (Sanders et al., 2018). Therefore, the perceptual effects of rapid visual stimulation, if any, are not well understood. This is an important issue. If the LTP-like changes in cortical excitability induced by rapid visual stimulation can modulate perception, rapid visual stimulation may have therapeutic applications. For example, repetitive transcranial magnetic stimulation of the visual cortex can transiently improve visual functions such as contrast sensitivity in adults with amblyopia, a neurodevelopmental disorder of vision (Clavagnier

et al., 2013; Thompson et al., 2008; Tuna et al., 2020). Like rapid visual stimulation, the effects of repetitive transcranial magnetic stimulation on cortical excitability likely involve LTP-like mechanisms (Hoogendam et al., 2010). Therefore, rapid visual stimulation may have similar effects and, unlike repetitive transcranial magnetic stimulation, can be delivered to the thalamocortical inputs from just one eye. This property may make repetitive visual stimulation particularly well suited for the treatment of amblyopia, which is characterized by a large imbalance in the neural response generated by each eye (Barnes et al., 2001).

Two preliminary studies have reported behavioural effects of rapid visual stimulation. Beste et al. observed improved luminance discrimination following 40 minutes of 20 Hz rapid visual stimulation, whereas Clapp et al. observed a reaction time improvement, but no change in response accuracy, during a checkerboard detection task following 2 minutes of 9Hz stimulation (Beste et al., 2011; Clapp et al., 2012). In this experiment we further explore the behavioural effects of rapid visual stimulation by investigating the effect of monocular rapid visual stimulation on binocular rivalry.

Binocular rivalry is a form of bistable perception wherein conflicting monocular images stochastically compete for dominance when viewed dichoptically. The resulting percept can involve periods of complete perceptual dominance by one eye, and periods of a mixed percept whereby images are superimposed or each eye dominates in different regions of the visual field (piecemeal) (Wilson et al., 2001). In individuals with normal binocular vision, the periods of perceptual dominance are relatively equal between the two eyes. However, the relative dominance of each eye during binocular rivalry can be modulated by presenting stimuli with features such as size (Kang, 2009), colour (Stalmeier and de Weert,



1988), luminance (Hong and Shevell, 2008), orientation (Holmes et al., 2006) and spatial frequency (Fahle, 1982), that differ between the two eyes.

In this study, we induced binocular rivalry by dichoptically presenting orthogonal, sinusoidal gratings. Dichoptic presentation was achieved using red/green anaglyphs. The aim of our first experiment was to determine suitable grating parameters. Specifically, we aimed to identify a stimulus configuration that generated minimal time spent in mixed perception and stable alternation rates across trials. In our second experiment, we used this stimulus to assess whether monocular rapid visual stimulation modulates binocular rivalry dynamics and/or dominance durations in individuals with normal binocular vision, based on previous work showing that rapid visual stimulation induces LTP-like effects in human visual cortex (Clapp et al., 2006b; Normann et al., 2007; Ross et al., 2008; Sanders et al., 2018; Teyler et al., 2005). Our hypothesis was that rapid monocular visual stimulation would strengthen the cortical response to inputs from the stimulated eye and that this would increase the relative time spent perceiving the stimulus presented to the stimulated eye during binocular rivalry (i.e. increase the perceptual dominance of the stimulated eye). In a third experiment, we measured binocular rivalry before and after viewing a monocular static grating as a test of monocular visual adaptation.

### 3.3 Materials and Methods

Three experiments were performed. Experiment 1 investigated the parameters for the binocular rivalry stimulus. Experiment 2 measured the effect of rapid monocular stimulation on binocular rivalry dynamics. A subset of participants from Experiment 2 completed

a third experiment to determine whether adaptation could explain the results of Experiment 2.

### **3.3.1 Experiment 1: Stimulation parameters for binocular rivalry**

#### **3.3.1.1 Participants**

Nine adults (age range: 21-28 years; 5 female) with self-reported normal binocular vision participated in a 1-hour binocular rivalry experiment. All participants were informed of the nature of the study before participation and provided written informed consent. The project was approved by the University of Waterloo Research Ethics Committee (ORE #30537; May 2016).

#### **3.3.1.2 Stimuli and protocol**

Orthogonally oriented sinusoidally modulated gratings were presented dichoptically (57cm viewing distance) within a circular field subtending 6.1 degrees of visual angle on a gamma corrected 24" Asus<sup>®</sup> 3D monitor. Relatively large gratings were used because this study was the first step in a program of research that will extend to participants with reduced vision caused by amblyopia. Participants with amblyopia may struggle to see small stimuli. Dichoptic presentation was achieved using red/green anaglyph glasses with less than 5% crosstalk. The space average contrast levels of the gratings were matched (0.5; calculated as the difference between the luminance of the coloured stripes and the

black bars used in each grating divided by their sum) using a Chroma Meter CS-100<sup>®</sup> photometer through the anaglyphic filters. photometer with measurements made through the anaglyphic filters (mean luminance: red = 8.4 cd/m<sup>2</sup>; green = 32.9 cd/m<sup>2</sup>). Using a computer keyboard, participants continuously reported whether they perceived the grating presented to the left eye (left eye dominant), the grating presented to the right eye (right eye dominant), or a mixed percept of both gratings. Specifically, a keyboard key was allocated to each percept. Participants held down the key corresponding to their current percept and switched keys when their percept changed. The total duration of each percept as well as the number of alternations (a change from one percept to another) were analyzed.

Participants completed 40 x 60s randomly sequenced trials—5 trials for each combination of two grating orientation pairs (45/135° vs. 90/180°) and 4 spatial frequencies (0.5, 1, 1.5 or 2 cycles per degree); the spatial frequency of the gratings presented to each eye within a trial was always identical.

### **3.3.1.3 Analysis**

Binocular rivalry alternation rates were calculated for each trial separately by dividing the number of alternations (defined as any change in percept) by the total presentation time. Alternation rate calculations included mixed percepts. Alternation rates across all five trials were then averaged for each set of stimulus parameters. The cumulative duration of mixed percepts was also analysed. Ocular dominance indices were calculated for each participant as (time spent viewing with right eye minus time spent viewing with left eye

divided by total time spent viewing right eye and left eye percepts) to investigate the effect of spatial frequency and orientation on ocular dominance.

Data were tested for normality using the Shapiro-Wilk paired-samples assumption test. Normally distributed data were analysed using repeated measures ANOVA and post-hoc paired t-tests. Skewed data were analysed using the Friedman test and post-hoc Wilcoxon signed-rank test. We anticipated skewed data across all experiments because the distributions were bounded. Repeated measures ANOVAs or Friedman tests with factors of orientation (90/180 vs. 45/135) and spatial frequency (0.5 vs. 1.0 vs. 1.5 vs. 2.0 cpd) were conducted separately for alternation rate, mixed duration, and the absolute ocular dominance index. To determine whether stimulus orientation or spatial frequency affected the stability of binocular rivalry dynamics across trials, each participant's standard deviation across trials for each combination of orientation and spatial frequency was calculated for alternation rate. Repeated measures ANOVAs with factors of orientation and spatial frequency were conducted on the standard deviation data. Following convention in the field, a p-value of less than 0.05 was considered statistically significant.

### **3.3.2 Experiment 2: Binocular rivalry following rapid monocular stimulation**

#### **3.3.2.1 Participants**

Twenty-five adults (mean age 25, range 19-33) with normal binocular vision based on stereopsis of  $\leq 40$  arc sec (The Fly Stereo Acuity Test<sup>®</sup> Vision Assessment Corporation)

and normal or corrected-to-normal vision (0.1 logMAR or better in each eye) participated in the rapid monocular stimulation experiment. Exclusion criteria included any neurological condition or the use of psychoactive drugs. All participants were informed of the nature of the study before participation and provided written informed consent. The project was approved by the University of Waterloo Research Ethics Committee (ORE #30537; May 2016).

### **3.3.2.2 Rivalry stimulus**

The stimulus spatial frequency and orientation pair determined in experiment 1 (0.5cpd, 45/135°) was chosen for this experiment. Viewing conditions and the method of reporting binocular rivalry percepts were identical to experiment 1. Three 60-second trials of binocular rivalry were recorded before and after rapid monocular stimulation.

### **3.3.2.3 Study design**

We used a modified version of the rapid monocular stimulation protocol described by Teyler and colleagues Teyler et al. (2005) (Figure 3.1). Within a repeated measures design, participants completed two study conditions on separate days: a rapid monocular visual stimulation condition, and a binocular control condition. Upon the first visit, participants completed either the rapid monocular stimulation condition or the binocular control condition, assigned randomly. Rapid monocular stimulation involved monocular viewing of only one of the two gratings that made up the binocular rivalry stimulus flickering on and off (50% duty cycle, on: high contrast grating on a luminance-matched grey surround; off:

uniform grey field) at 9Hz for 2 minutes. The stimulated eye was randomly selected for each participant. The stimulated eye was stimulated with the same grating orientation that was presented to that eye during the pre and post stimulation binocular rivalry measures because the LTP-like effects of rapid visual stimulation are stimulus specific. Participants wore red/green glasses during the rapid monocular stimulation. The binocular control condition was identical except that the two gratings that made up the binocular rivalry stimulus were alternated in the center of the monitor at 9 Hz and viewed binocularly (no red/green glasses). In both the rapid monocular stimulation and binocular control conditions, the two minutes of visual stimulation was followed by two minutes of eye closure to minimize adaptation effects. Binocular rivalry measures were recorded before stimulation (pre) and after eyelid closure (post).

#### **3.3.2.4 Analysis**

The binocular rivalry measures were alternation rate, time spent in mixed perception, and ocular dominance index (all calculated as in experiment 1). Alternation rates and time spent in mixed perception across all three trials were averaged for each condition. An ocular dominance index was calculated for each participant based only on the duration of left eye dominant and right eye dominant percepts. Mixed percepts were not included in this analysis. In the rapid monocular stimulation condition this index was defined as: stimulated eye dominance duration minus non-stimulated eye dominance duration divided by the total time for the percepts of the stimulated eye and non-stimulated eye; in the binocular control condition the ratio was calculated in the same way based on the eye randomly selected for stimulation in the monocular condition.

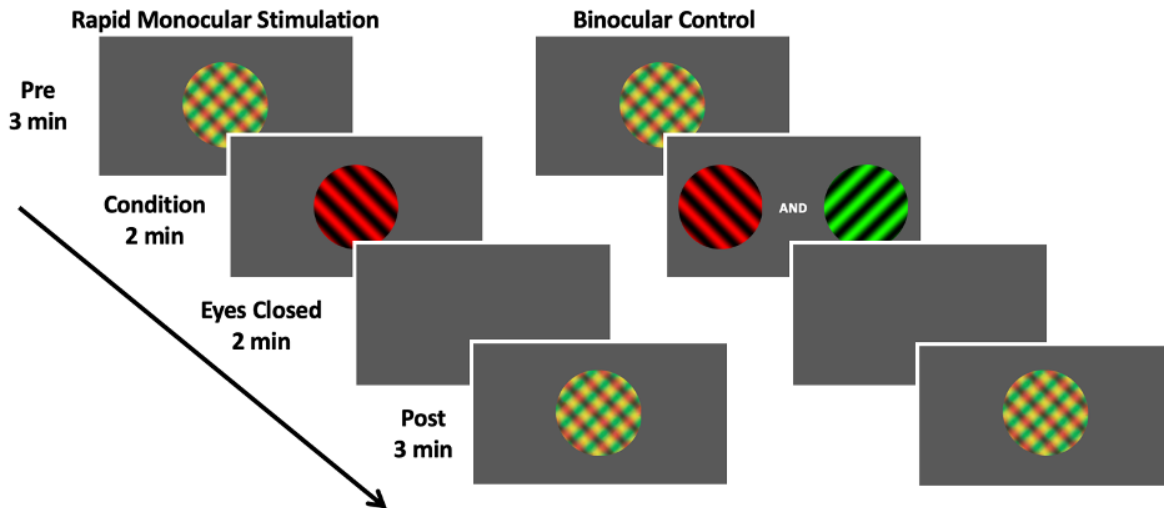


Figure 3.1: Schematic representation of Experiment 2 protocol. Plaid stimuli indicate binocular rivalry testing. In the rapid monocular stimulation condition, one the of the gratings that made up the plaid was presented monocularly and flickered at 9Hz. The stimulated eye (and therefore the red or green colour of the grating) was randomised. In this figure, the red grating is shown as an example. In the control binocular condition, the two gratings that made up the binocular rivalry stimulus were alternated at 9 Hz at the center of the screen and were viewed binocularly.

Data were analyzed using parametric or non-parametric tests depending on normality as in experiment 1. ANOVAs or Freidman tests with factors of Condition (rapid monocular stimulation vs. control) and Time (pre vs. post stimulation) were conducted separately for alternation rate, mixed duration, and ocular dominance indices. Post-hoc testing was conducted using paired t-tests or the Wilcoxon signed-rank test.

### 3.3.3 Experiment 3: Binocular rivalry following monocular adaptation

#### 3.3.3.1 Participants and methods

A subset of participants that completed experiment 2 who consented to and were available for additional testing (N=12) completed experiment 3 on a separate day several months after completing experiment 2. Experiment 3 was a post-hoc experiment designed to investigate whether monocular adaptation could explain the results of experiment 2. The pre and post measurements of binocular rivalry used in experiment 3 were identical to those used in experiment 2. The monocular adaptation between these tests was a static monocular presentation of one of the gratings (red or green) that made up the binocular rivalry stimulus for 2 minutes. The static grating was presented to the same eye (left or right) that had been exposed to rapid monocular stimulation in experiment 2. As in experiment 2, participants closed their eyes for 2 minutes following adaptation (Figure 3.2).

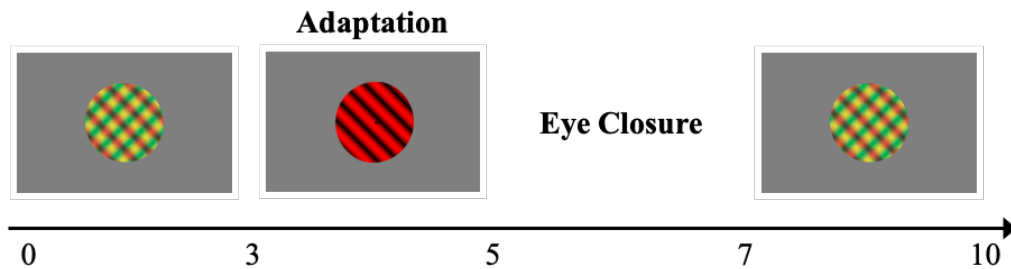


Figure 3.2: Schematic representation of Experiment 3 protocol. Plaid stimuli indicate binocular rivalry testing. For each participant, the same grating used in the rapid monocular stimulation condition was shown as a static image in the adaptation condition.



### 3.3.3.2 Analysis

Two analyses were conducted. First, the results from the rapid monocular stimulation and control conditions in experiment 2 were reanalysed using only data from the subset of participants who completed experiment 3 to test whether the main finding from experiment 2 (reduced ocular dominance index for the stimulated eye in the rapid monocular stimulation condition but not the control condition) was present in the smaller sample. Wilcoxon signed-rank tests were used to compare the ocular dominance indices pre vs. post stimulation in the rapid monocular stimulation and control conditions. Second, a Wilcoxon signed-rank test was conducted on the data collected in experiment 3 to compare ocular dominance indices pre vs. post static visual adaptation of one eye.

## 3.4 Results

### 3.4.1 Experiment 1

For alternation rates, a repeated measures ANOVA showed no significant effects of Grating Orientation ( $p > 0.05$ ; Figure 3.3A). However, a main effect of Grating Spatial Frequency was observed ( $F_{1,8} = 4.194$ ,  $p = 0.016$ ,  $\eta^2$ ; Figure 3.3B, Table 3.1). ). Alternation rates were slowest at 0.5 cpd. Alternation rates for the 0.5 cpd stimulus differed significantly from the 1 cpd ( $t_8 = -3.617$ ,  $p = 0.007$ , Cohen's  $d = -1.206$ ) and 1.5 cpd ( $t_8 = -3.485$ ,  $p = 0.008$ , Cohen's  $d = -1.1.62$ ) stimuli, but not the 2 cpd stimulus ( $t_8 = -1.597$ ,  $p = 0.149$ , Cohen's  $d = -0.532$ ). No significant effects of Grating Orientation or Grating Spatial

Frequency were observed for mixed duration or for the standard deviations of alternation rate (all  $F > 3.903$ , all  $p > 0.069$ ). Absolute values of ocular dominance indices were not normally distributed. As a result, the Friedman test was conducted and showed no significant effect of Grating Orientation ( $F_1 = 0.130$ ,  $p = 0.716$ , Kendall's  $W = -567.8$ ) or Grating Spatial Frequency ( $F_1 = 2.641$ ,  $p = 0.062$ , Kendall's  $W = -21.9$ ) on ocular dominance index. Based on these results, a spatial frequency of 0.5 cpd was chosen for experiment 2 because this spatial frequency induced the slowest alternation rates. The oblique orientations (45/135) were chosen for experiment 2 arbitrarily.

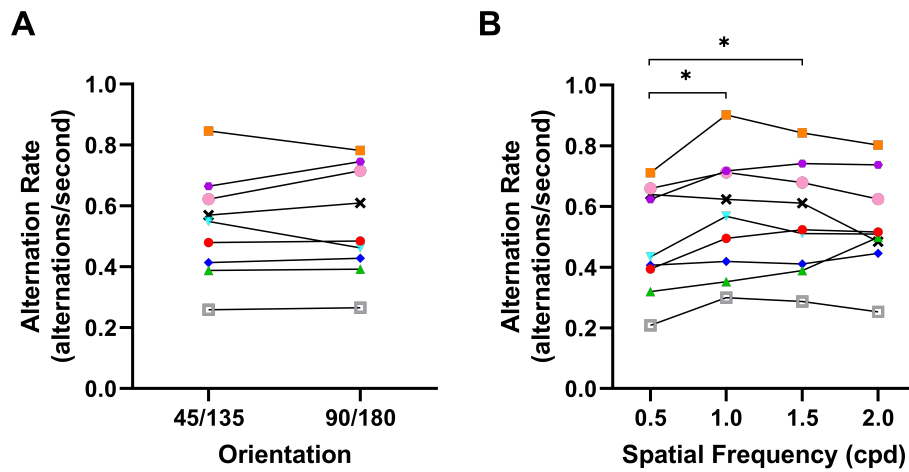


Figure 3.3: Rivalry alternation rates for experiment 1. (A) Orientation with the mean alternation rates for each individual participant collapsed across spatial frequency. (B) Spatial frequency with mean alternation rates for each individual participant collapsed across orientation. Each color signifies a different participant ( $n = 9$ ). (\*) indicates significant differences for post hoc paired t-tests  $p < 0.05$ .

Table 3.1: Experiment 1 - Effects of stimulus parameters on binocular rivalry

Spatial Frequency	Alternation Rate* (Hz)	Mixed Percept Duration* (time/60s)	Absolute Ocular Dominance Index*
0.5cpd	0.49 ( $\pm 0.18$ )	0.06 ( $\pm 0.02$ )	0.11 ( $\pm 0.07$ )
1.0cpd	0.57 ( $\pm 0.19$ )	0.10 ( $\pm 0.03$ )	0.11 ( $\pm 0.04$ )
1.5cpd	0.56 ( $\pm 0.18$ )	0.12 ( $\pm 0.04$ )	0.16 ( $\pm 0.10$ )
2.0cpd	0.54 ( $\pm 0.16$ )	00.13 ( $\pm 0.04$ )	0.20 ( $\pm 0.16$ )

(\*) grand mean between subjects followed by the mean of the within subjects' standard deviations.

### 3.4.2 Experiment 2

Neither alternation rates nor ocular dominance indices were normally distributed. Therefore, nonparametric statistics were adopted. The median values  $\pm$  interquartile ranges for measures of rivalry dynamics pre and post rapid monocular stimulation were  $\pm 0.24$  Hz and  $0.56 \pm 0.24$  Hz for alternation rates (Figure 3.4),  $8.46 \pm 10.13$  s and  $11.96 \pm 12.33$  s for time spent in mixed perception (Figure 3.5), and  $0.02 \pm 0.12$  and  $-0.05 \pm 0.08$  for ocular dominance indices (Figure 3.6). For the binocular control condition, medians pre and post stimulation were  $0.65 \pm 0.28$  and  $0.61 \pm 0.27$  for alternation rates,  $12.51 \pm 11.71$  s and  $13.71 \pm 13.95$  s for time spent in mixed perception, and  $-0.01 \pm 0.09$  and  $-0.02 \pm 0.16$  for ocular dominance indices. Rapid monocular stimulation did not alter binocular rivalry alternation rates (Freidman test: no effect of Condition [rapid monocular stimulation vs. binocular control];  $F_1 = 3.137$ ,  $p = 0.081$ , Kendall's  $W = -17.9$ ), or the duration of mixed percepts (Freidman test: no effect of Condition [rapid monocular stimulation vs. binocular control];  $F_1 = 3.229$ ,  $p = 0.077$ , Kendall's  $W = -18.1$ ). However, rapid monocular stimulation shifted the ocular dominance index in favour of the non-stimulated eye (Freidman

test: significant effect of Condition [rapid monocular stimulation vs. binocular control];  $F_1 = 5.332$ ,  $p = 0.025$ , Kendall's  $W = -18.8$ ). The effect was associated with a significant shift in ocular dominance index towards the non-stimulated percept following the rapid monocular stimulation condition (post hoc Wilcoxon signed-rank test,  $W = 248.0$ ,  $p = 0.005$ ,  $r = 0.653$ ; Figure 3.6). In other words, rapid monocular stimulation decreased the time spent viewing the percept for the stimulated eye relative to that for the non-stimulated eye. There was no change in ocular dominance index for the binocular control condition ( $W = 134.5$ ,  $p = 0.668$ ,  $r = -0.103$ ).

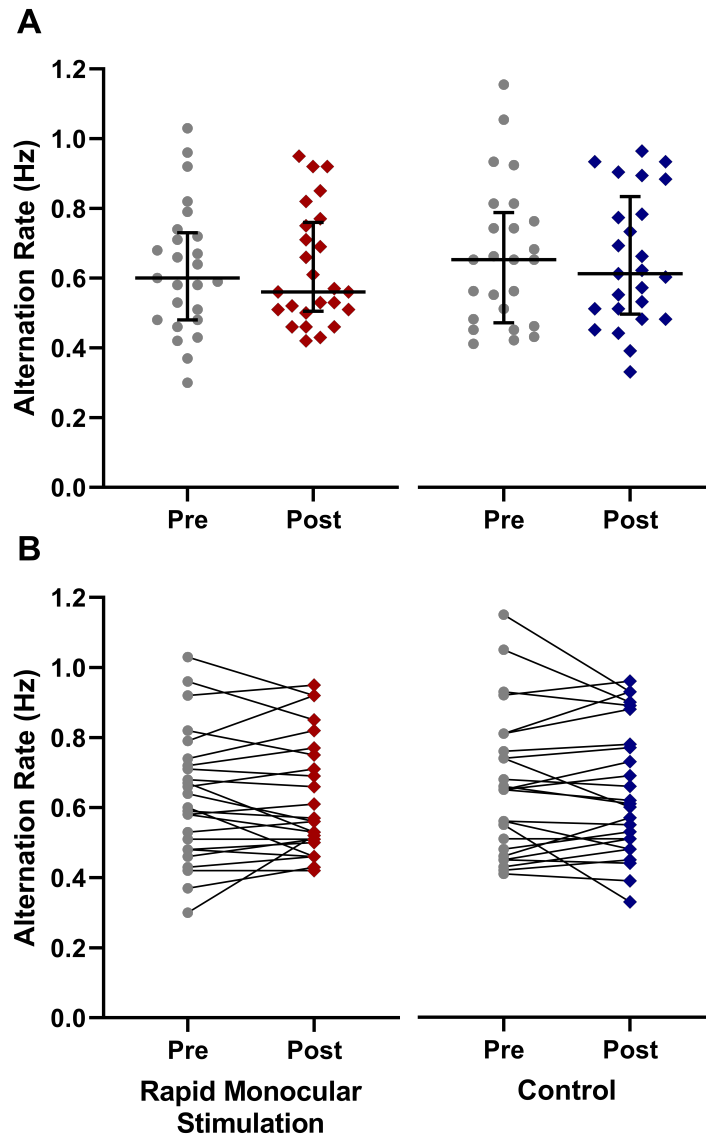


Figure 3.4: Individual alternation rates for the rapid monocular stimulation and binocular control conditions in experiment 2 presented as scatter (A) and line (B) plots. Solid horizontal lines in panel A denote medians; error bars = IQR.

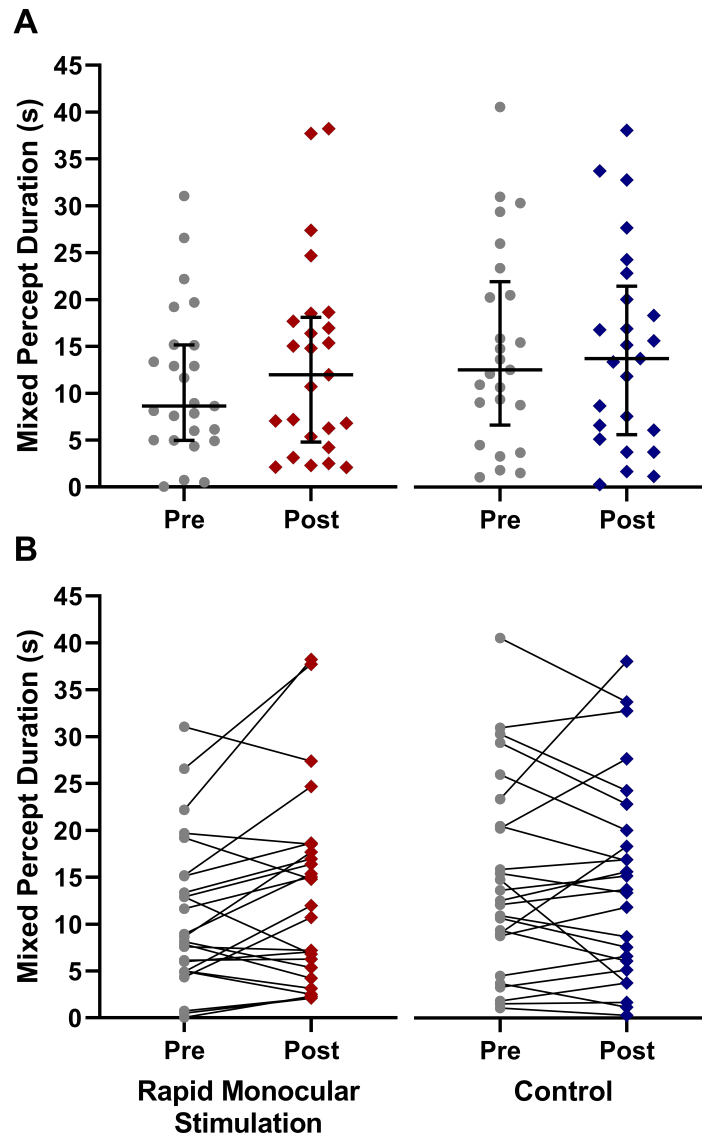


Figure 3.5: Time in mixed perception for the rapid monocular stimulation and binocular control conditions from experiment 2 presented as scatter (A) and line (B) plots as in figure 3.4

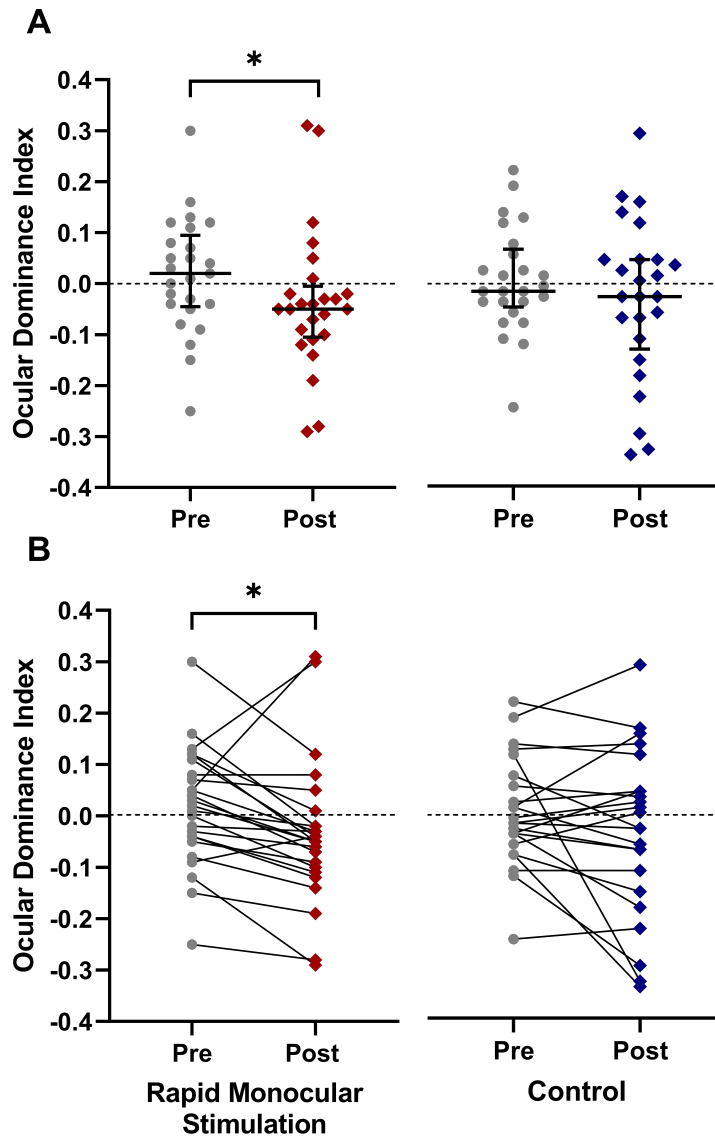


Figure 3.6: Median ocular dominance indices for the rapid visual stimulation and binocular control conditions in experiment 2 presented as scatter (A) and line (B) plots as in figure 3.4. Negative values indicate decreased dominance for the stimulated eye.

### 3.4.3 Experiment 3

Experiment 3 data were not normally distributed. For the subgroup from experiment 2 who also completed experiment 3, monocular adaptation did not alter ocular dominance ( $W = 30.0$ ,  $p = 0.838$ ,  $r = 0.091$ ). Importantly, this subgroup did show a significant shift in ocular dominance towards the non-stimulated eye following rapid monocular stimulation, similar to that of the full cohort in experiment 2 ( $W = 66.0$ ,  $p = 0.004$ ,  $r = 1.000$ ; Figure 3.7). This subgroup also showed no effect of the binocular control condition from their experiment 2 data ( $W = 32.0$ ,  $p = 0.610$ ,  $r = -0.179$ ).



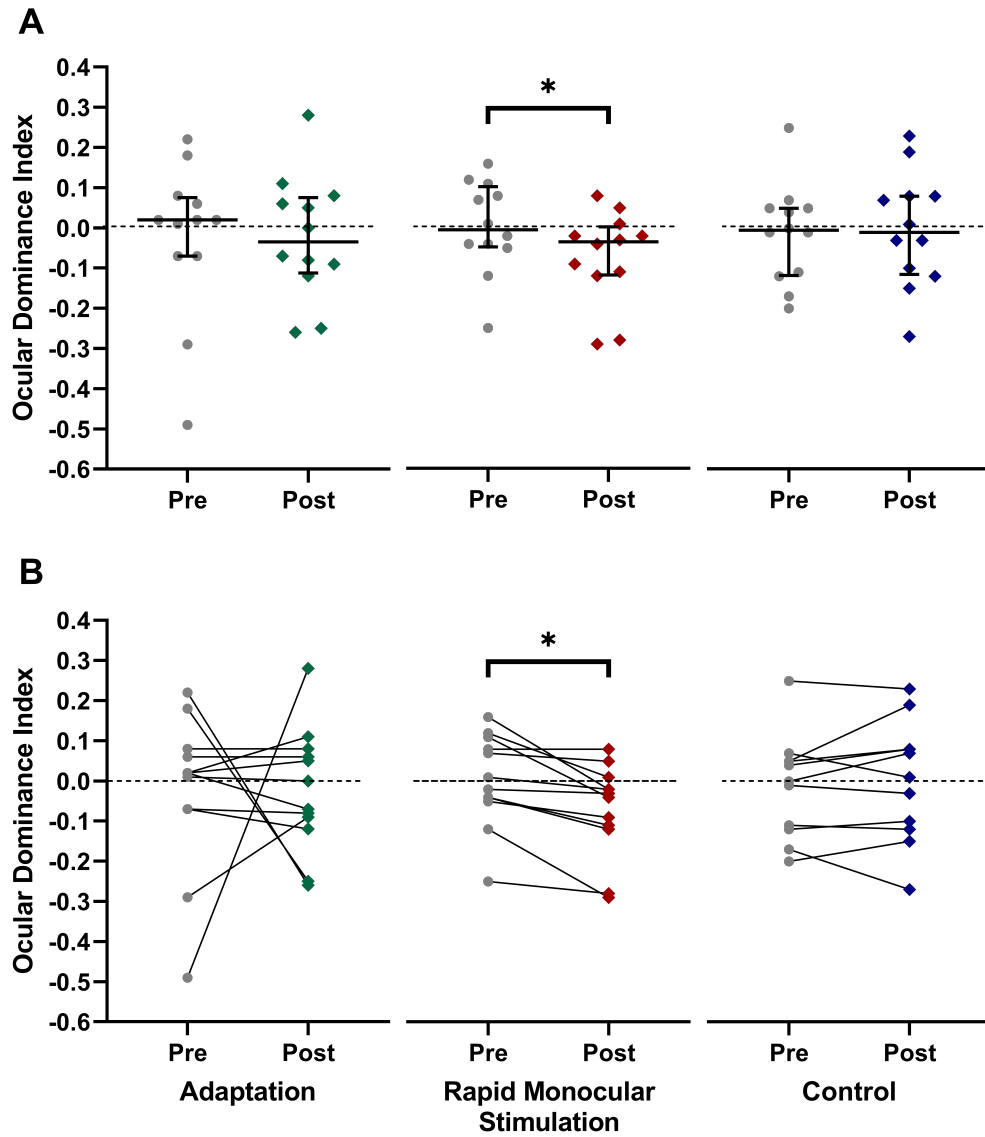


Figure 3.7: Ocular dominance indices for participants who completed both experiment 2 and experiment 3 ( $n = 12$ ) presented as scatter (A) and line (B) plots as in figure 3.4. Negative values indicate reduced dominance for the stimulated/adapted eye.

## 3.5 Discussion

The primary aim of this study was to assess whether rapid monocular stimulation of one eye would increase the dominance of that eye during binocular rivalry. Unexpectedly, we observed the opposite effect; rapid monocular stimulation reduced the relative dominance of the stimulated eye during binocular rivalry.

How might we explain this unexpected result? The simplest explanation is that rapid monocular stimulation caused retinal or cortical adaptation resulting in reduced dominance of the stimulated eye during binocular rivalry. Following previous work (Teyler et al., 2005), our rapid monocular stimulation protocol was designed to minimize adaptation effects by providing a period of eye closure directly after the rapid visual stimulation that was the same duration as the rapid visual stimulation itself (2 minutes). Generally, a period of adaptation lasts as long as the stimulation (Başgöze et al., 2018; Greenlee et al., 1991). However, it is still possible that adaptation played a role in our results. Therefore, we conducted a third experiment on a subset of participants from experiment 2 who were available and willing to complete further testing. This experiment revealed that simply adapting one eye to one of the gratings that made up the binocular rivalry stimulus did not alter ocular dominance. Although the sample size for this experiment was smaller than for the main experiment and therefore had less power to detect small shifts in ocular dominance, there was no trend observed to indicate adaptation. Together, the use of a period of eye closure within our rapid monocular stimulation protocol and the results of experiment 3 argue against adaptation as an explanation of our unexpected result.

An alternative explanation is that rapid visual stimulation of one eye may not have generated the expected LTP-like effects but rather a long-term depression-like effect (LTD). Although increased cortical excitability is the most commonly reported effect of visual stimulation (Clapp et al., 2006a; de Gobbi Porto et al., 2015; Kirk et al., 2010; Teyler et al., 2005), decreased or inconsistent changes in cortical activity have also been reported. These include a reduced visual cortex BOLD response post-stimulation (Lahr et al., 2014) and reduced VEP amplitude in young adults post stimulation (Abuleil et al., 2019). The reason that some studies show LTP-like and others show LTD-like results is not clear; however, this pattern of results does suggest that visual stimulation effects are inconsistent (Sanders et al., 2018). LTD-like changes following visual stimulation would be consistent with our observation of relatively reduced binocular rivalry dominance for the eye that received rapid monocular stimulation.

One additional possible explanation for decreased dominance following rapid monocular stimulation is suggested by recent studies that have explored the effect of short-monocular occlusion on binocular rivalry dominance. After one eye is occluded for a period of time, that eye has a relatively increase in dominance during binocular rivalry once the occlusion is removed (Lunghi et al., 2011; Min et al., 2018). This effect does not require occlusion of the deprived eye. Induced suppression of one eye or the presentation of lower contrast images to one eye for as little as 3 minutes also increases that eye's binocular rivalry dominance (Kim et al., 2017). Other image degradation manipulations such as the presentation of pink noise (Bai et al., 2017) or spatial scrambling of one eye's image also result in increased dominance of the deprived eye over the eye exposed to normal visual stimulation (Ramamurthy and Blaser, 2018; Zhou et al., 2014). The effects of short-term monocular occlusion also extend

to participants with amblyopia, a disorder characterized by chronic perceptual dominance of the fellow eye over the amblyopic eye (Li et al., 2011). Occlusion of the amblyopic eye strengthens the contribution of that eye to binocular vision once the occlusion is removed (Chadnova et al., 2017; Lunghi et al., 2011; Lunghi et al., 2016; Lunghi et al., 2019; Zhou et al., 2013; Zhou et al., 2019).

Possible mechanisms underlying the ocular dominance shift induced by short-term monocular occlusion include a change in neural interocular gain control resulting from a large imbalance in the input from each eye to cortical processing (Lunghi et al., 2011; Zhou et al., 2013). This change is associated with reduced visual cortex GABA concentration (Lunghi et al., 2015a) and may involve both feedforward and feedback pathways (Ramamurthy and Blaser, 2018).

The effect of monocular deprivation on binocular rivalry typically requires a longer period of deprivation than two minutes (Lunghi et al., 2015b). However, it is possible that LTP-like changes in visual cortex induced by monocular rapid visual stimulation drive a more rapid plastic change. In particular, we postulate that the strengthening of the cortical response to the stimulated eye generated by our monocular rapid stimulation protocol rapidly activated the same homeostatic mechanisms that underpin short-term monocular occlusion effects. In other words, the reduced binocular rivalry dominance of the stimulated eye was not a direct effect of the rapid monocular stimulation but was caused by the relative deprivation of the non-stimulated eye.

Our study had a number of limitations. As mentioned above, the sample size for experiment 3 was limited. Additional experiments with a larger sample size will be required

to fully explore the effect of monocular adaptation on binocular rivalry for our stimuli. Visible outliers in our sample (Figure 3.6) are likely due to the high individual variability and can be addressed with a larger sample size. Moreover, our stimulus was contrast balanced, and as a result, the luminance of each grating was different. This may influence binocular rivalry dynamics with a preference for the eye with higher luminance. However, it is more important to eliminate contrast differences, which typically have larger effects on binocular rivalry (Kulikowski, 1992). In addition, while the focus of our study was the effect of rapid monocular visual stimulation on binocular rivalry dynamics, further investigation is needed to identify the optimal visual stimulus parameters for the induction of LTP-like or LTD-like effects. Temporal frequency is likely to be a particularly important parameter. Electroencephalography (EEG) recordings may also provide further insight into the neural mechanisms driving the effect of rapid monocular visual stimulation on binocular rivalry. Additionally, we did not measure the optimal duration of monocular rapid visual stimulation for altering eye dominance in binocular rivalry or the length of time for which eye dominance was altered. It has previously been observed that 2 minutes of rapid visual stimulation increased VEP amplitudes while 10 minutes of stimulation had no effect (Norman et al., 2007). In addition, the effect of rapid visual stimulation on VEP/ERP amplitude has been reported to last for up to an hour or until the effect is measured using a slow 1Hz stimulus (Clapp et al., 2006a; Teyler et al., 2005). It is currently unknown whether these results also apply to the behavioural effects of rapid visual stimulation.

As a whole, our results raise the exciting possibility that rapid monocular stimulation can be used to rapidly induce eye dominance shifts. Potential applications of this technique

include the manipulation of ocular dominance in amblyopia. We are currently conducting studies that address this possibility.

## 3.6 Summary

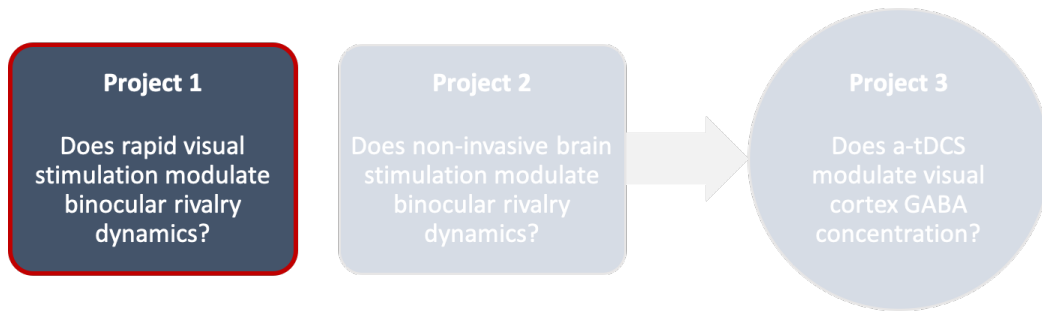


Figure 3.8: Project 1 diagram and rationale.

The primary aim of Project 1 was to investigate the effects of rapid monocular visual stimulation on binocular rivalry dynamics. LTP is a fundamental mechanism of neuroplasticity that underlies the processes of learning and memory formation. Recently, rapid visual stimulation has been reported to induce LTP-like effects in the human brain, measured as a change in VEP amplitude (Normann et al., 2007; Teyler et al., 2005); however, the perceptual effects of rapid visual stimulation are less understood. We hypothesized that rapid monocular visual stimulation will increase the dominance of the stimulated eye during a binocular rivalry task. Unexpectedly, we found a significant shift in ocular dominance towards the non-stimulated eye following two minutes of rapid monocular visual stimulation, a result which could not be explained by adaptation. Our findings support recent research with short-term monocular occlusion that report a surprising shift in ocular dominance towards the deprived eye (Chadnova et al., 2017; Lunghi et al., 2011; Zhou et al., 2015; Zhou et al., 2018) a result that can be explained by a possible homeostatic gain control mechanism.

Concurrently, we were also interested in the effects of non-invasive brain stimulation—techniques that can modulate cortical excitability—on binocular rivalry dynamics. Both rapid visual stimulation and non-invasive brain stimulation alter the neurophysiology of the brain, as seen through changes in VEP amplitudes and neurotransmitter concentration. Whether these changes translate behaviourally is still under investigation.



# Chapter 4

## Modulation of binocular rivalry with non-invasive stimulation of the visual cortex

### 4.1 Overview

Neuromodulation of the primary visual cortex using anodal transcranial direct current stimulation (a-tDCS) can alter visual perception and enhance neuroplasticity. However, the mechanisms that underpin these effects are currently unknown. When applied to the motor cortex, a-tDCS reduces the concentration of the inhibitory neurotransmitter gamma aminobutyric acid (GABA), an effect that has been linked to increased neuroplasticity. The aim of this study was to assess whether a-tDCS also reduces GABA-mediated inhibition

when applied to the human visual cortex. Changes in visual cortex inhibition were measured using binocular rivalry dynamics. Binocular rivalry has recently been advocated as a direct and sensitive measure of visual cortex inhibition whereby GABA agonists decrease mixed percept durations and agonists of the excitatory neurotransmitter acetylcholine increase mixed percepts. Our hypothesis was that visual cortex a-tDCS would increase mixed percepts during binocular rivalry by reducing GABA-mediated inhibition and increasing cortical excitation. In addition, we measured the effect of continuous theta-burst transcranial magnetic stimulation (cTBS) to the visual cortex on binocular rivalry dynamics. When applied to the motor cortex, cTBS increases GABA concentration and we therefore hypothesized that visual cortex cTBS would decrease mixed percept duration. Binocular rivalry dynamics were recorded before and after active and sham a-tDCS (N=15) or cTBS (N=15). A-tDCS had no effect. Contrary to our hypothesis, cTBS significantly increased mixed percepts during rivalry. These results suggest that the neurochemical mechanisms of non-invasive brain stimulation differ between the motor and visual cortices.

## 4.2 Introduction

Non-invasive brain stimulation techniques, such as anodal transcranial direct current stimulation (a-tDCS) have been used as an indirect method for modulating neural excitability and promoting neuroplasticity. When applied to the visual cortex, a-tDCS increases contrast sensitivity (Antal et al., 2001; Behrens et al., 2017; Ding et al., 2016; Spiegel et al., 2013a), improves visual acuity (Bocci et al., 2018; Reinhart et al., 2016), and enhances perceptual learning (Sczesny-Kaiser et al., 2016; Spiegel et al., 2013b) in patients with

amblyopia, a neurodevelopmental disorder that affects binocular vision, as well as controls. In addition to perceptual changes, studies have found reduced phosphene thresholds (Antal et al., 2003a; Antal et al., 2003b; Sczesny-Kaiser et al., 2016) and increased VEP amplitudes (Ding et al., 2016; Sczesny-Kaiser et al., 2016; Strigaro et al., 2015) following a-tDCS, which suggest physiological and neurochemical changes in the visual cortex that result in increased cortical excitability.

Although the mechanisms underlying the effects of a-tDCS on visual cortex are not known, the effects of a-tDCS on the motor cortex are attributed in part to modulation of inhibition mediated by the neurotransmitter gamma amino-butyric acid (GABA). Specifically, magnetic resonance spectroscopy measures indicate that a-tDCS reduces motor cortex GABA concentration (Antonenko et al., 2017b; Bachtiar et al., 2015; Heise et al., 2014; Kim et al., 2014; Patel et al., 2019; Patel et al., 2017; Stagg et al., 2009a). The effects of visual cortex a-tDCS on perception and visual function are consistent with reduced GABA levels. For example, visual phenomena that have been linked to GABA mediated inhibition such as an attenuated cortical response to inputs from the amblyopic eye in adults with amblyopia (Ding et al., 2016; Spiegel et al., 2013a), surround suppression (Spiegel et al., 2012) and lateral inhibition (Raveendran et al., 2020) can be modulated with a-tDCS.

In contrast to a-tDCS, continuous theta-burst stimulation (cTBS), a form of transcranial magnetic stimulation that can also alter visual perception (Clavagnier et al., 2013), has been found to increase GABA concentration in the motor cortex (Stagg et al., 2009b). cTBS, therefore, would be expected to have the opposite effect to a-tDCS on percepts that are influenced by GABA-mediated inhibition.

Binocular rivalry (BR) dynamics have recently been advectioned as a sensitive measure of GABA-mediated inhibition within the human visual cortex (Mentch et al., 2019). BR is a form of bistable perception wherein the brain alternately suppresses one eye over the other stochastically when each eye views a difference image. This phenomenon has been commonly used to investigate binocular function in the human brain (Blake and Logothetis, 2002; Kovács et al., 1996; Tong et al., 2006; Tong et al., 1998). Previous studies have found that BR dynamics in young adults are inversely correlated with the concentration of the primary inhibitory neurotransmitter in the brain known as gamma-aminobutyric acid (GABA) (Pitchaimuthu et al., 2017; Robertson et al., 2016; van Loon et al., 2013). Specifically, young adults with slower binocular rivalry alternation rates had a higher concentration of primary visual cortex GABA concentration, and high GABA concentration was correlated with mean perceptual dominance, defined as the time spent viewing either dominant percept (not mixed perception). Scientists have used various methods to manipulate neurotransmitter concentration in order to understand the role it plays in behavioural and functional mechanisms within the brain. For instance, cortical infusion of drugs such as benzodiazepines increase GABAergic inhibition within the brain and modulate visual function as demonstrated in adult rats (Sale et al., 2007). Most recently, a direct manipulation of GABA concentration in the human brain showed an effect on BR perceptual dominance (Mentch et al., 2019), wherein a small dose of a drug that increases GABAergic inhibition resulted in increased dominance percept duration in young adults as compared to a placebo. Additionally, reduced inhibition and increased excitation induced by the acetylcholine agonist donepezil increased mixed percept duration during binocular rivalry (Sheynin et al., 2020). Given this evidence, we used BR mixed

percept duration as a measure of cortical inhibition.

Whether brain stimulation indeed alters visual cortex GABA concentration as it does in the motor cortex is not yet known. Our study aimed to address this question. We hypothesized that visual cortex a-tDCS would reduce visual cortex GABA concentration resulting in increased mixed percept durations and visual cortex cTBS would have the opposite effect.

## **4.3 Materials and Methods**

### **4.3.1 Participants**

A total of thirty young adults with normal or corrected-to-normal vision (0.1 LogMAR or better in each eye) participated in one of the two within-subject design experiments: fifteen in the a-tDCS experiment (control and sham, mean age 25, median age 24, range 22-30, 11 female) and fifteen in the cTBS experiment (control and sham, mean age 24, median age 24, range 22-29, 7 female). Participants with abnormal binocular vision history and those taking psychoactive drugs were excluded. All participants were informed of the nature of the study before participation and provided written informed consent. The project was approved by the University of Waterloo Research Ethics Committee (ORE #30537).

### 4.3.2 Stimulus

Dichoptic, orthogonally oriented ( $45^\circ$  and  $135^\circ$ ) sinusoidally modulated red/green gratings (0.5 cycles per degree,  $6.1^\circ$  of visual angle) were presented on a 24" Asus<sup>®</sup> 3D monitor. Participants wore shutter glasses to view the stimulus. The contrast of the gratings was matched using a Chroma Meter CS-100<sup>®</sup> photometer (mean luminance: red =  $8.4 \text{ cd/m}^2$ ; green =  $32.9 \text{ cd/m}^2$ ). Stimuli were viewed from 57cm using a chin rest. Participants reported perceiving the  $45^\circ$  grating only, the  $135^\circ$  grating only or a mixture of both (piece-meal or superimposition percepts) by holding down a computer keyboard key and switching keys as the percept changed.

### 4.3.3 Anodal transcranial direct current stimulation (a-tDCS)

Two 5x7 cm electrode sponges were placed on the scalp, the anode at international 10-20 electrode system position Oz and the cathode at Cz. Each tDCS electrode was placed inside a saline-soaked sponge. A-tDCS was delivered at 2mA for 15 minutes in addition to a 30-second ramp-up and 30-second ramp-down period using a NeuroConn<sup>®</sup> DC-Stimulator MC-8. The sham condition consisted only of the ramp-up and ramp-down periods. Participants were masked to the stimulation condition. The experimenter could not be masked due to the limitations of the equipment software; however, sessions were randomly sequenced prior to the start of data collection. For both active and sham conditions, six 60-second trials of binocular rivalry were recorded before, during, 5 minutes, and 30 minutes post stimulation (Figure 4.1A).

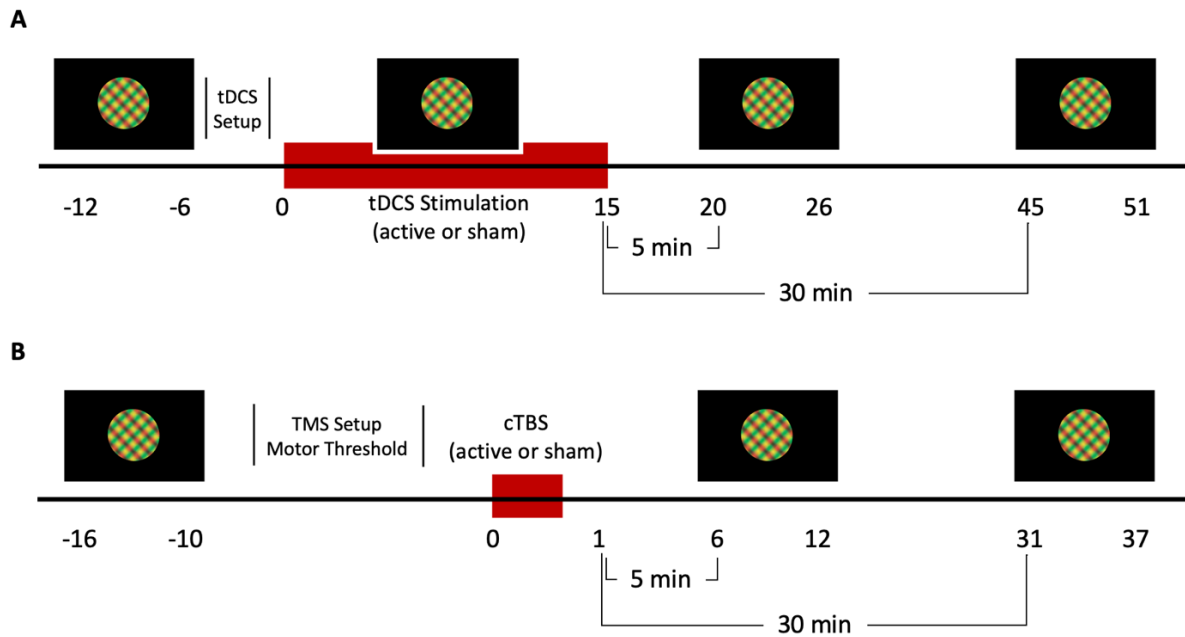


Figure 4.1: Protocol timeline for a-tDCS (A) and cTBS (B). Binocular rivalry dynamics were recorded for 6 minutes before, during, 5 minutes post and 30 minutes post tDCS. Electrodes were placed following the baseline measure. Similarly, for cTBS, binocular rivalry dynamics were recorded before, 5 minutes post and 30 minutes post stimulation. Motor thresholding was completed on the first visit following the baseline measure.

#### 4.3.4 Continuous theta burst stimulation

Stimulation was delivered using a MagVenture<sup>®</sup> MagPro X100 stimulator (MagVenture Farum, Denmark) with BrainSight frameless neuro-navigation software (Rogue Research Inc., Montreal, Canada). Active motor threshold (AMT) was used to calibrate visual cortex cTBS intensity. The procedure for determining AMT involved placing a surface electrode on the belly of the first dorsal interosseous muscle tendon (left or right based on hand dominance) and a second electrode on the lateral bone of the wrist. The electromyographic

(EMG) response was monitored using Brainsight©software as the participant was asked to steadily press their pointer finger against the arm of their chair to generate a motor evoked potential (MEP) of  $100\mu\text{V}$ . A single pulse of TMS was systematically delivered to different points of a contralateral motor cortex stimulation grid (3 by 3 cm) beginning at 40% of the maximum stimulator output (MSO) until the region hotspot—defined as the stimulation location corresponding to the maximum TMS-induced MEP amplitude—was located (Groppa et al., 2016; Tranulis et al., 2006). Using the Rossini-Rothwell algorithm for determining AMT, single pulses were then delivered to this region while increasing the intensity by 1% until a peak-to-peak amplitude of  $200\mu\text{V}$  was generated for 5 out of 10 pulses (50%) (Rothwell et al., 1999).

For visual cortex cTBS, the coil was placed over V1, identified as 2 cm above theinion, 0 cm lateral. Stimulation involved 600, 20 ms pulses delivered in 50Hz bursts for 40 seconds at 100% of the participant’s AMT. The control condition used the same protocol with a sham coil. Both the participant and experimenter were masked to the stimulation condition (active and sham condition codes were given to the experimenter by another researcher). Binocular rivalry dynamics were recorded for six 60-second trials before, 5 minutes post, and 30 minutes post stimulation (Figure 4.1B).

### 4.3.5 Analysis

Binocular rivalry dynamics analyzed included alternation rates (any change in perception), eye dominance ((time viewing dominant eye percept – time viewing nondominant eye percept)/total time excluding mixed percepts), and duration of mixed perception (in



seconds per 60 second trial). Measures of dynamics were then averaged across all six trials separately for each participant. The dominant eye was defined as the eye with the longest pre-stimulus viewing time at the initial visit.

A repeated measures ANOVA with factors of Condition (active vs. sham) and Time (a-tDCS: pre vs. during vs. 5min post vs. 30min post; cTBS: pre vs. 5min post vs. 30min post) was conducted separately for alternation rates, ocular dominance index and mixed percept duration for each stimulation type. Post-hoc testing of significant interactions was conducted using t-tests.

For one tDCS participant, the 5 minutes post stimulation data for the sham condition was irretrievably lost. For one TMS participant, baseline data and 5 minutes post stimulation data for the sham condition were irretrievably lost. The chosen imputation method for dealing with these missing values was to substitute the mean value of the other 14 participants (Kang, 2013).

## 4.4 Results

### 4.4.1 Anodal transcranial direct current stimulation

No significant effects of a-tDCS were observed for any measure of binocular rivalry dynamics ( $p > 0.05$ ). Figure 4.2 illustrates the alternation rates, ocular dominance and duration of mixed percepts for the active a-tDCS and sham conditions.

### 4.4.2 Continuous theta burst stimulation

cTBS significantly increased the duration of mixed percepts with a significant main effect of Time ( $F_{28} = 4.154$ ,  $p = 0.026$ ) and a relative increase compared with sham stimulation (significant interaction between Condition and Time,  $F_{28} = 3.528$ ,  $p = 0.043$ ; Figure 3C). Post hoc t-tests revealed a significant increase in mixed percept duration with active cTBS from pre to 5min post ( $t_{14} = -3.065$ ,  $p = 0.008$ ) and from pre to 30min post ( $t_{14} = -2.306$ ,  $p = 0.037$ ; Figure 4.3C). There were no effects of cTBS on alternation rates or on ocular dominance index (Figure 4.3A and 4.3B).

## 4.5 Discussion

The aim of this study was to investigate whether a-tDCS and cTBS alter visual cortex inhibition. Both a-tDCS and cTBS have been shown to alter GABA concentration in motor cortex studies. Specifically, studies with a-tDCS have demonstrated a reduction in GABA concentration (Antonenko et al., 2017a; Patel et al., 2017), while cTBS was found to increase GABA concentration (Stagg et al., 2009b). With this evidence of GABA modulation within the motor cortex, we hypothesized that a-tDCS and cTBS would inversely influence binocular rivalry dynamics. Perceptual dominance during binocular rivalry has been directly associated with GABA concentration in young adults through pharmacological manipulation (Mentch et al., 2019). The study found that drugs that increased GABAergic inhibition in the brain resulted in increased the proportion of time spent viewing the dominant percepts during binocular rivalry. Although no changes in dominance

duration or alternation rates were observed as hypothesized, cTBS resulted in a significant increase in the duration of mixed percept, suggesting a disruptive effect on perceptual suppression. Furthermore, a-tDCS had no effect on BR dynamics.

The unexpected increase in mixed percept duration following visual cortex cTBS may be explained by stochastic resonance, a phenomenon wherein increased noise can enhance the detection of an otherwise weak signal (McDonnell and Abbott, 2009). A recent study found that adding noise to the primary visual cortex using transcranial random noise stimulation (tRNS) resulted in a significant reduction in mixed percept duration (van der Groen et al., 2019). In other words, an increase of neural noise within the visual system increased interocular suppression and therefore reduced the time spent viewing an ambiguous percept. Complementary, our results are consistent with reduced neural noise within the visual cortex following cTBS thereby increasing the duration of mixed perception. Reducing neural noise may have weakened interocular suppression resulting in longer times spent viewing the mixed percept. There are differences in binocular rivalry dynamic calculations across studies, and subtle differences in definitions. For instance, a proportion of perceptual dominance is analyzed in one study and referred to as a measure of perceptual suppression (Mentch et al., 2019; Robertson et al., 2016), while mean dominance durations calculated as the average duration that a dominant percept lasts in seconds is used in another (van Loon et al., 2013). Our measures were designed to capture any changes in dominance and mixed percepts.

While studies have suggested that GABA concentration measured using magnetic resonance spectroscopy is correlated with BR alternation rates in young adults (Robertson et al., 2016; van Loon et al., 2013), we were unable to demonstrate an association between

BR alternation rates and non-invasive brain stimulation. There is direct evidence, however, that BR alternation rates are in fact moderated by the excitation-inhibition activity within the brain (van Loon et al., 2013), and that administering drugs that modulate GABA effects alternation rates (Mentch et al., 2019; van Loon et al., 2013). Other factors such as alcohol (Donnelly and Miller, 1995) and caffeine (George, 1936) have been shown to influence alternation rates, although changes in visual cortex GABA concentration was not hypothesized as a possible explanation within these studies. Additionally, there is growing evidence that binocular rivalry dynamics differ in patients with disorders that affect neurotransmitters, such as anxiety, depression, and autism. One study found that patients with anxiety had faster alternation rates than controls, while patients with depression had slower alternation rates (Jia et al., 2020).

Our results suggest that the effects of a-tDCS and cTBS on the visual cortex may be different as compared to the motor cortex. Consistent with this idea, cTBS, although theoretically acting to increase inhibition, has induced improvements in visual acuity (Brückner and Kammer, 2016). (Brückner and Kammer, 2016). In support of this difference in the mechanisms underlying the effects of visual and motor cortex stimulation, a recent study found that the physiological mechanism of non-invasive brain stimulation depends on the characteristics and composition of the brain region being stimulated (Castrillon et al., 2020). To our knowledge, there is no direct evidence for changes in visual cortex GABA concentration following brain stimulation.

We postulate that the change in the duration of mixed perception following visual cortex cTBS that we observed may be a result of stochastic resonance and reduced neural noise. Our results support the notion that the effect that brain stimulation may differ

across brain regions have. In particular, the lack of change in alternation rates raises the question of whether the effect of a-tDCS on the visual cortex is the same as that of the motor cortex.

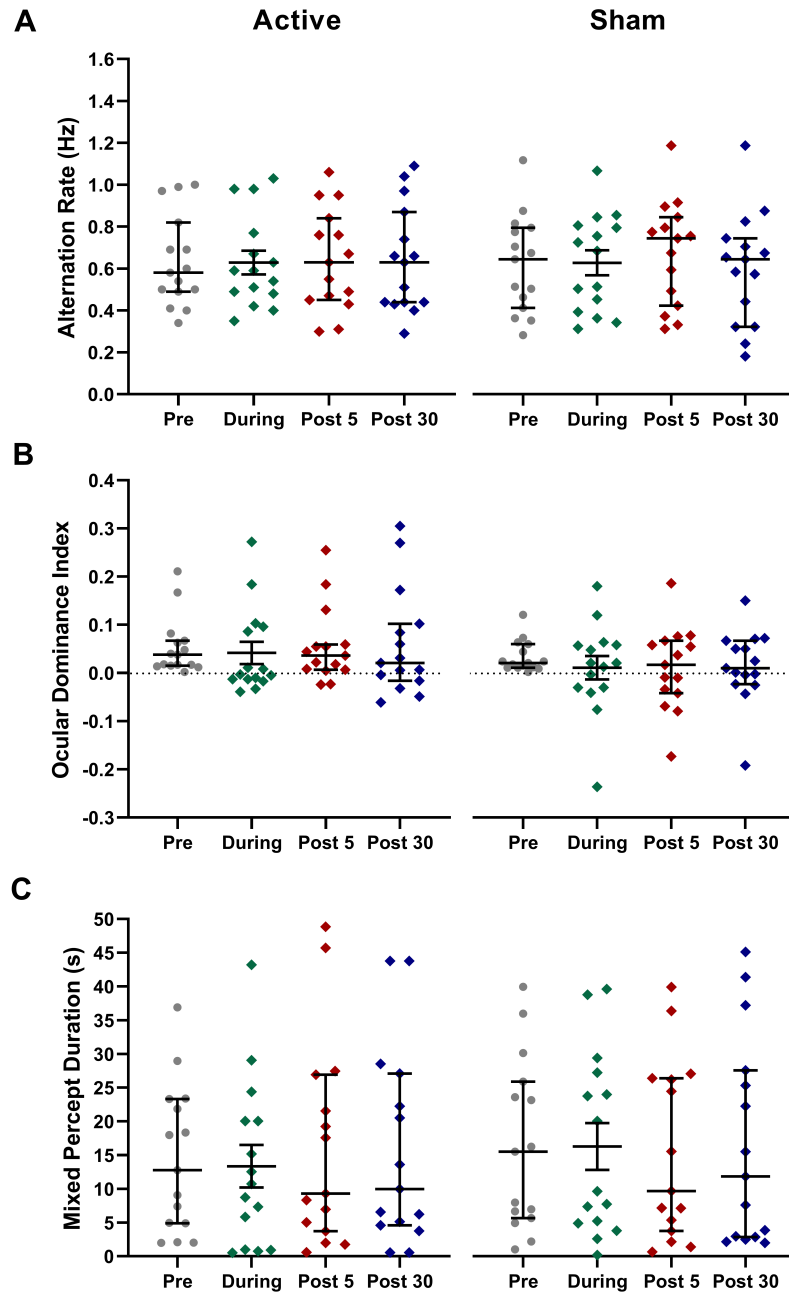


Figure 4.2: Average alternation rates (A), ocular dominance indices (B), and time spent in mixed percept (C) for 15 participants before, during, 5 minutes and 30 minutes post a-tDCS. Error bars = SEM. Differences are not significant (repeated measures ANOVAs  $p > 0.05$ ).

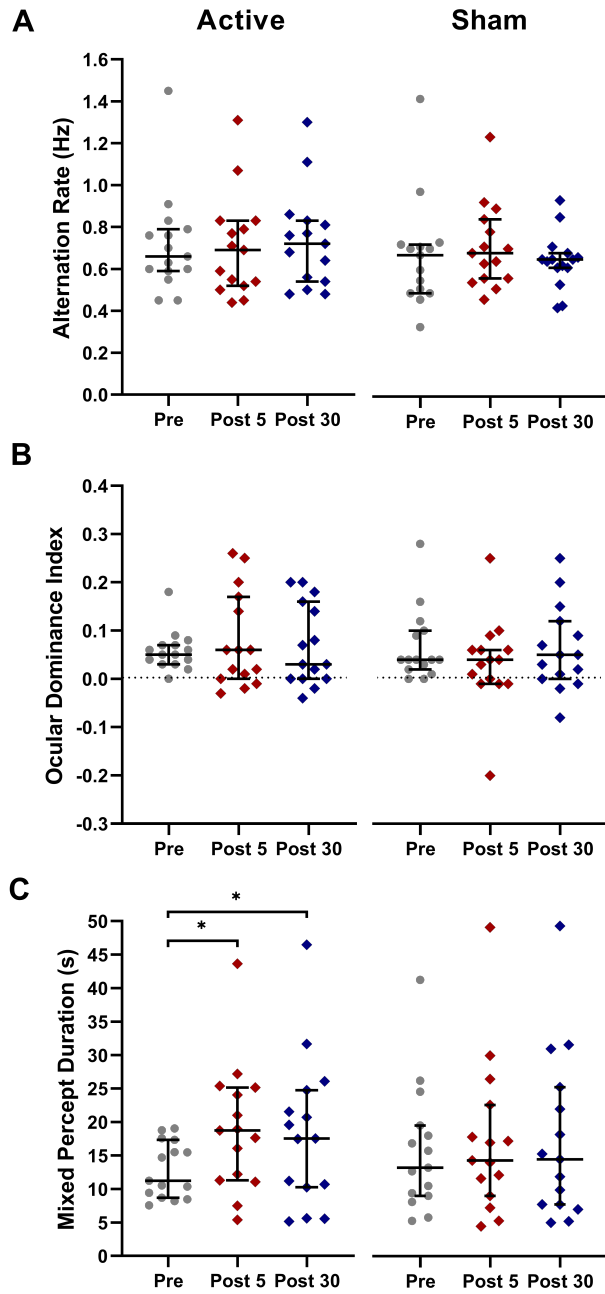


Figure 4.3: Average alternation rates (A), ocular dominance indices (B), and time spent in mixed percept (C) for 15 participants before, 5 minutes and 30 minutes post cTBS. Error bars = SEM. \*  $p < 0.05$ .

## 4.6 Summary

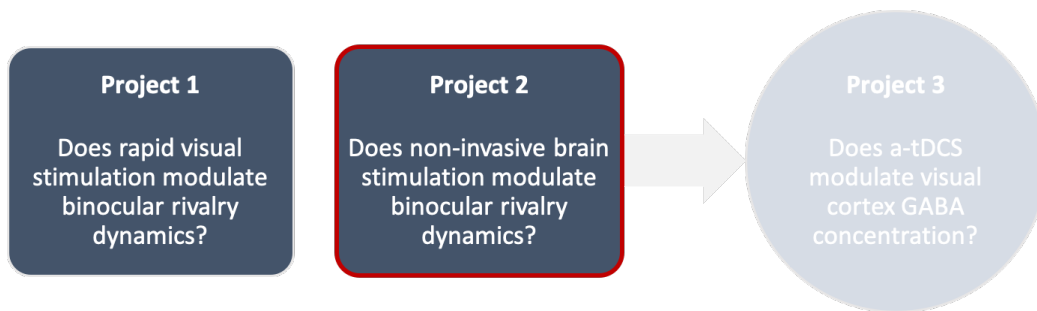


Figure 4.4: Project 2 diagram and rationale.

The aim of Project 2 was to investigate the effects of non-invasive brain stimulation on binocular rivalry dynamics. Since non-invasive brain stimulation modulates the primary inhibitory neurotransmitter GABA as seen in the motor cortex (Heise et al., 2014; Stagg et al., 2009a), and GABA is associated with binocular rivalry dynamics both directly (Mentch et al., 2019) and indirectly (Robertson et al., 2016; van Loon et al., 2013), we hypothesized that non-invasive brain stimulation would modulate binocular rivalry dynamics. Specifically, we tested the hypothesis that a-tDCS, thought to reduce cortical GABA concentration, would increase binocular rivalry alternation rates, while cTBS, thought to increase GABA concentration, would have the opposite effect. Alternation rates were unchanged following both a-tDCS and cTBS; however, unexpectedly, we found a significant increase in mixed percept duration following cTBS. It is possible that increasing GABA concentration reduced the neural noise in the visual system thereby increasing the duration of mixed perception. A recent study showed the opposite effect, where increasing neural noise resulted in reduced mixed percept duration (van der Groen et al., 2019). The results



of Project 1 and Project 2 together led us to Project 3, which was to directly investigate the effects of a-tDCS on visual cortex GABA concentration.

# Chapter 5

## The effect of occipital a-tDCS on primary visual cortex GABA and glutamate concentration

### 5.1 Overview

Anodal transcranial direct current stimulation (a-tDCS) is a non-invasive brain stimulation technique that can enhance neuroplasticity within targeted areas of the human cerebrum including the motor cortex and the primary visual cortex. For motor cortex, enhanced neuroplasticity following a-tDCS has been linked to a reduction in concentration of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. Currently it is unclear whether a-tDCS has a similar effect when applied to the primary visual cortex. To

address this question, we used magnetic resonance spectroscopy to measure concentrations of GABA and glutamate (an excitatory neurotransmitter) within primary visual cortex before and after real and sham visual cortex a-tDCS (within-subjects design,  $n = 14$ ). We also measured alternation rates for binocular rivalry, which may be positively correlated with visual cortex GABA concentration. We found no effect of a-tDCS on visual cortex GABA concentration and baseline GABA concentration was not correlated with binocular rivalry alternation rates. However, although we observed no significant interaction between Stimulation (active vs. sham) and Time (pre vs. post stimulation) for visual cortex glutamate concentration, planned comparisons revealed a significant increase in visual cortex glutamate concentration following active but not sham stimulation. These results suggest that the pattern of neurochemical changes induced by a-tDCS depend on the region being stimulated. Although only evident in post-hoc testing, our results also suggest that a-tDCS induced changes in visual cortex function may be associated with an increased concentration of glutamate concentration rather than a decreased concentration of GABA.

## 5.2 Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive method for modulating human behaviour by inducing changes in neural activity and metabolite concentration within the brain (Fertonani and Miniussi, 2016; Nitsche et al., 2008; Nitsche and Paulus, 2000; Reed and Kadosh, 2018). Animal research has demonstrated the potential for direct current stimulation to induce synaptic plasticity in several regions of the brain, including the motor cortex (Fritsch et al., 2010), hippocampus (Ranieri et al., 2012) and visual cortex

(Cambiaghi et al., 2011; Castaldi et al., 2020).

In humans, changes in gamma-amino butyric acid (GABA), the primary inhibitory neurotransmitter in the brain, have been reported following anodal-tDCS (a-tDCS) of motor cortex (Antonenko et al., 2017b; Bachtiar et al., 2015; Kim et al., 2014; Patel et al., 2017). Specifically, magnetic resonance spectroscopy (MRS) studies have indicated that a-tDCS increases cortical excitability by decreasing GABA concentration (Antonenko et al., 2017a; Patel et al., 2019; Stagg et al., 2009a), while cathodal tDCS (c-tDCS) has the opposite effect (Stagg et al., 2009a). (Stagg et al., 2009). GABA is thought to play a critical role in human neuroplasticity and a-tDCS modulation of motor cortex GABA has been associated with increased neural plasticity (Bachtiar et al., 2015; Griffen, 2014; Heise et al., 2014; Kim et al., 2014; Patel et al., 2017; Sale, 2010). For example, the degree of motor learning is positively correlated with the magnitude of GABA reduction measured using magnetic resonance spectroscopy (Stagg et al., 2011a), suggesting that a-tDCS may in fact modulate neural plasticity.

Although reduced motor cortex GABA concentration following a-tDCS is the most replicated combined a-tDCS and MRS result, the effect of tDCS on concentration of the excitatory neurotransmitter glutamate within the motor cortex has also been assessed. Results have been inconsistent. Glutamate concentration has been found to either decrease with c-tDCS (Roche et al., 2015; Stagg et al., 2009a), remain the same following a-tDCS or c-tDCS (Kim et al., 2014; Roche et al., 2015), or is not reported, but rather the reduction of GABA is implicated as the gate to glutamatergic plasticity (Patel et al., 2019). GABA and glutamate are related through the enzyme glutamic acid decarboxylase (GAD) which converts glutamate into GABA (Siegel et al., 2006). It has been shown that

hormonal fluctuations in females influence neurotransmitters within the brain, including GABA concentration (Akk et al., 2005; Smith et al., 1987; Smith et al., 1988), a result that may explain, in part, the differences in results across studies. Some studies look at male only populations to avoid the changes that may occur across the hormonal (or menstrual) cycle, although a recent study demonstrated that while these effects may exist, they may not translate behaviourally (Sy et al., 2016).

The behavioural effects of a-tDCS applied to non-motor areas of the human brain such as the visual cortex have also been investigated. Visual cortex a-tDCS modulates visual evoked potential (VEP) amplitude (Antal et al., 2004a; Reinhart et al., 2016) and improves visual acuity (Reinhart et al., 2016), contrast sensitivity (Antal et al., 2001; Behrens et al., 2017), perception of faces and objects (Barbieri et al., 2016), colour discrimination (Costa et al., 2012), as well as motion perception (Antal et al., 2004b; Battaglini et al., 2017) in humans with normal vision. When applied to patients with amblyopia, visual cortex a-tDCS induces a significant improvement in visual acuity (Bocci et al., 2018), contrast sensitivity (Ding et al., 2016; Spiegel et al., 2013a), and stereopsis (Spiegel et al., 2013b). These effects are hypothesized to be associated with a reduction in GABA concentration because GABA is linked to interocular suppression (Sengpiel, 2014) a key feature of amblyopia, and plays a critical role in visual cortex plasticity. Furthermore, a-tDCS reduces surround suppression and lateral inhibition in normal vision (Raveendran et al., 2020; Spiegel et al., 2012), results that are consistent with reduced GABA-mediated inhibition following visual cortex a-tDCS. However, direct measurements of visual cortex a-tDCS effects on neurotransmitter concentrations in the human brain using MRS have not previously been performed.

Moreover, visual cortex GABA concentration has been associated with binocular rivalry, the stochastic change in percept that occurs when different images are shown to each eye (Mentch et al., 2019; Robertson et al., 2013; van Loon et al., 2013). Most recently, a direct manipulation using clobazam and arbaclofen, drugs that agonise GABAA and GABAB receptors respectively, found that increased GABA-mediated inhibition resulted in increased perceptual suppression during binocular rivalry; that is, participants spent more time viewing dominant percepts (one-eye only) as compared to mixed percepts (Mentch et al., 2019). More indirectly, higher visual cortex GABA concentration has been correlated with slower alternation rates during binocular rivalry (Pitchaimuthu et al., 2017; Robertson et al., 2016; van Loon et al., 2013), albeit a modest correlation (van Loon et al., 2013).

In summary, while a-tDCS can modulate visual function, the mechanism is unknown. We used MRS to directly measure changes in primary visual cortex GABA and glutamate concentration following 20 minutes of a-tDCS. Based on the effects seen in the motor cortex, we hypothesized that a-tDCS would decrease visual cortex GABA concentration. As a secondary measurement, we aimed to investigate the correlation between visual cortex GABA concentration and binocular rivalry dynamics.

## 5.3 Materials and Methods

### 5.3.1 Participants

Fourteen participants (mean age 27; range 20-39; 9 female) with normal or corrected-to-normal vision (0.1 logMAR or better in each eye) and normal or corrected-to-normal

binocular vision based on a stereoacuity  $\leq 40$  arc sec using The Fly Stereo Acuity Test<sup>®</sup> Vision Assessment Corporation took part in the study. Participants were screened for MRI and brain stimulation safety and eligibility. Exclusion criteria included neurological conditions and psychoactive drugs. All participants were informed of the nature of the study before participation. Written consent was required prior to any data collection. The study was approved by the University of Waterloo and York University Office of Research Ethics.

### **5.3.2 Study design**

A within-subjects study design was adopted. Participants took part in two visits: active stimulation and sham, the order of which was randomised. During the first visit, written informed consent was provided and screening was performed. Each visit consisted of a short binocular rivalry psychophysical computer-based task, a 45-minute scanning session, 20-minutes of stimulation (active or sham), and finally another 45-minute scanning session (Figure 5.1). Stimulation was performed outside the scanner. Visits were booked a minimum of 48 hours apart to ensure any effects of stimulation were diminished.

### **5.3.3 Binocular rivalry**

The binocular rivalry task conducted at the start of each visit was based on a previous study (Abuleil et al., 2020). A CRT monitor displayed two orthogonally oriented ( $45/135^\circ$ ) black and white gratings with a spatial frequency of 0.5 cpd and a circular field subtending  $6.1^\circ$  of visual angle presented on a luminance-matched grey background. Participants

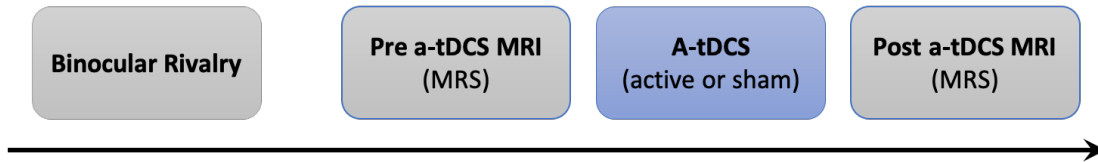


Figure 5.1: Experiment protocol. Participants took part in two visits, both identical except for the delivery of active or sham a-tDCS. A 6-minute task of binocular rivalry dynamics was performed immediately before prepping the participant for the MRI. Pre and post scans lasted approximately 45 minutes each, with 20 minutes of either active or sham stimulation between each scan delivered outside the scanner room. Participants closed their eyes from the beginning of the pre scanning session until the end of the experimental session.

viewed the gratings dichoptically through a mirror stereoscope while sitting 75cm away from the monitor. Participants reported their perception ( $45^\circ$ ,  $135^\circ$ , or mixed percept) by pressing designated keys on a keyboard and changing when their percept changed. The total duration of each percept, as well as the rate of alternations from one percept to another, were analyzed.

### 5.3.4 Transcranial direct current stimulation

Active anodal transcranial direct current stimulation (a-tDCS) or sham stimulation was performed in the within-subjects study design using a DC Stimulator (NeuroConn DC-Stimulator MC-8). Participants received either active a-tDCS or the sham equivalent upon their first visit in a randomised manner. The remaining protocol was performed upon the second visit.

The International 10-20 system was used for electrode placement. The 5x7 cm electrodes were covered in a saline-soaked sponge and secured on the scalp with a head mount.



Both conditions (active and sham) involved placing the centre of the anodal electrode over Oz (approximately 2 cm above theinion) and the centre of the cathodal electrode over Cz. In the active condition, participants received 20 minutes of 2mA stimulation in addition to a 30-second ramp up and 30-second ramp down period. The sham condition consisted only of the 30-second ramp up and 30-second ramp down periods.

### 5.3.5 MRI acquisition

A 3T Siemens Magnetom<sup>®</sup> Tim Trio magnetic resonance scanner with a 32-channel high-resolution brain array coil was used to acquire anatomical, spectroscopy, and resting-state fMRI data from each participant. Soft padding was placed around the participant's head to minimize movement. Imaging was acquired at rest and participants were instructed to keep their eyes closed throughout the scan.

First, a three dimensional T1 magnetization-prepared rapid gradient echo imaging (MPRAGE) sequence was used to acquire anatomical images at the start of each scan (number of slices = 192; slice thickness = 1.0 mm; in-plane resolution = 1mm<sup>2</sup>; TR = 2300 ms; TE = 2.26 ms; flip angle = 8°; FoV = 256 mm; acquisition time = 1365 ms). This image was used to place a 25 x 25 x 25 mm voxel-of-interest (VOI) over V1. The VOI was centered on the calcarine sulcus and positioned far back in the occipital lobe to avoid non-brain tissue such as cerebrospinal fluid and the sagittal sinus (Figure 5.2). Next either magnetic resonance spectroscopy (MRS) or resting-state data was collected in a randomized, within-subjects, counter-balanced manner to accommodate data collection for a separate study. The resting-state data do not form part of this thesis.



Figure 5.2: Representative visual cortex voxel of interest (25 x 25 x 25 mm) for axial, sagittal, and coronal T1-weighted MRI images of one subject.

For MRS, the Mescher-Garwood point-resolved spectroscopy (MEGA-PRESS) technique (Mescher et al., 1998) was used to record  $^1\text{H}$  MR GABA-edited spectra (TR = 3000 ms; TE = 68 ms; spectral bandwidth = 1500 Hz; 2048 data points with water suppression yielding 32 averages; acquisition time = 3:37; this acquisition was repeated 4 times for a total of 128 averages). Siemens standard and manual shimming were performed for each acquisition. The acquisition of ON and OFF edited spectra results in peaks affected by the editing pulses with GABA at approximately 3.02 ppm and Glx (glutamate and glutamine) at 3.80 ppm. This allows for the separation of GABA from creatine (Cr), an organic compound that peaks at 3.0 ppm. A water reference was acquired (1 average; acquisition time = 0:30).

### 5.3.6 MRI analysis

The Matlab-based tool Gannet was used for analysis (v3.0; Edden et al., 2014). Standard processing was performed for each acquisition, including frequency and phase correction, fast Fourier transformation and Gaussian model fitting of the GABA and Glx peaks

to improve SNR and limit the spectra by applying digital filters. The total concentration of GABA and Glx was estimated as the area under the curve for GABA, Glx and Cr using the GannetFit function. GannetCoRegister registered the chosen VOI to the anatomical image, using the program SPM8 (Statistical Parametric Mapping, Wellcome Centre for Human Neuroimaging, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>). GannetSegment performed segmentation of the anatomical images, and determined the relative amounts of grey matter, white matter, and CSF within the voxel, which allowed for the estimation of a CSF-corrected GABA and Glx concentration using SPM8. Lastly, GannetQuantify provided a tissue-corrected (relaxation- and alpha-corrected, voxel-average normalized) estimate of GABA and Glx concentrations. All concentrations were provided in institution units (i.u.) relative to water. The standard deviation of the residual was used to determine the fit error of the model for each spectrum. All fit errors were <10%.

### **5.3.7 Statistical analysis**

#### **5.3.7.1 Effect of a-tDCS on GABA and Glx concentration**

A repeated measures ANOVA was performed separately for GABA and Glx concentrations with factors of Condition (active vs. sham) and Time (pre vs. post). Planned post-hoc comparisons compared pre and post stimulation concentrations for each condition using within subject t-tests.

### **5.3.7.2 Association of binocular rivalry dynamics and concentrations of GABA and Glx**

Pearson's linear correlations were performed to investigate the relationships between pre stimulation GABA and Glx concentrations and binocular rivalry dynamics; specifically, alternation rates and mixed percept duration. Correlations were calculated separately for session 1 and session 2.

### **5.3.7.3 Comparisons between male and female participants**

A repeated measures ANOVA was performed separately for GABA and Glx concentration for males (n=5) and females (n=8) with factors of Condition (active vs. sham) and Time (pre vs. post). Planned post-hoc comparisons compared pre and post stimulation concentration for each condition using within subject t-tests. Pearson's linear correlations were performed to investigate the relationships between pre stimulation and GABA and Glx concentrations and binocular rivalry dynamics for males and females separately.

## **5.4 Results**

Fourteen participants completed the study. One participant's MRS data could not be processed—likely a consequence of too much movement during the scans which resulted in a low signal-to-noise ratio. The participant was not included in the analysis.

### 5.4.1 Effect of a-tDCS on GABA and Glx concentration

Mean GABA and Glx concentrations and the standard deviations are shown in Table 5.1. There was no significant interaction between treatment Condition (active vs. sham) and Time (pre vs. post treatment) for either GABA or Glx ( $p > 0.05$ ; Figure 5.3). However, there was a main effect of treatment Condition for Glx ( $F_{1,12} = 5.732$   $p = 0.034$ ) with lower Glx concentration overall in the active condition. A post-hoc t-test showed that Glx increased significantly post treatment in the active condition ( $t_{12} = -2.239$ ,  $p = 0.045$ ) but not the sham condition ( $t_{12} = -0.330$ ,  $p = 0.747$ ).

Table 5.1: GABA and Glx concentrations<sup>a</sup> in primary visual cortex.

(n=13)	GABA (mean $\pm$ SD)		Glx (mean $\pm$ SD)	
	Pre	Post	Pre	Post
Active <sup>b</sup>	3.5 $\pm$ 0.18	3.6 $\pm$ 0.12	7.9 $\pm$ 0.12	8.5 $\pm$ 0.18
Sham	3.7 $\pm$ 0.12	3.7 $\pm$ 0.14	8.7 $\pm$ 0.25	8.8 $\pm$ 0.31

<sup>a</sup>All concentrations are in internal units i.u. relative to water (see text for detail).

<sup>b</sup>Active treatment was a-tDCS centered at Oz at 2 mA for 20 min.

### 5.4.2 Association of binocular rivalry dynamics and concentrations of GABA and Glx

Binocular rivalry alternation rates for the first and second session were  $0.43 \pm 0.18$  and  $0.44 \pm 0.22$  alternations per second (mean  $\pm$  SD), respectively. Mixed percept durations for the first and second session were  $16.7 \pm 7.5$  and  $16.6 \pm 5.6$  seconds (mean  $\pm$  SD), respectively. Neither session 1 nor session 2 binocular rivalry alternation rates were

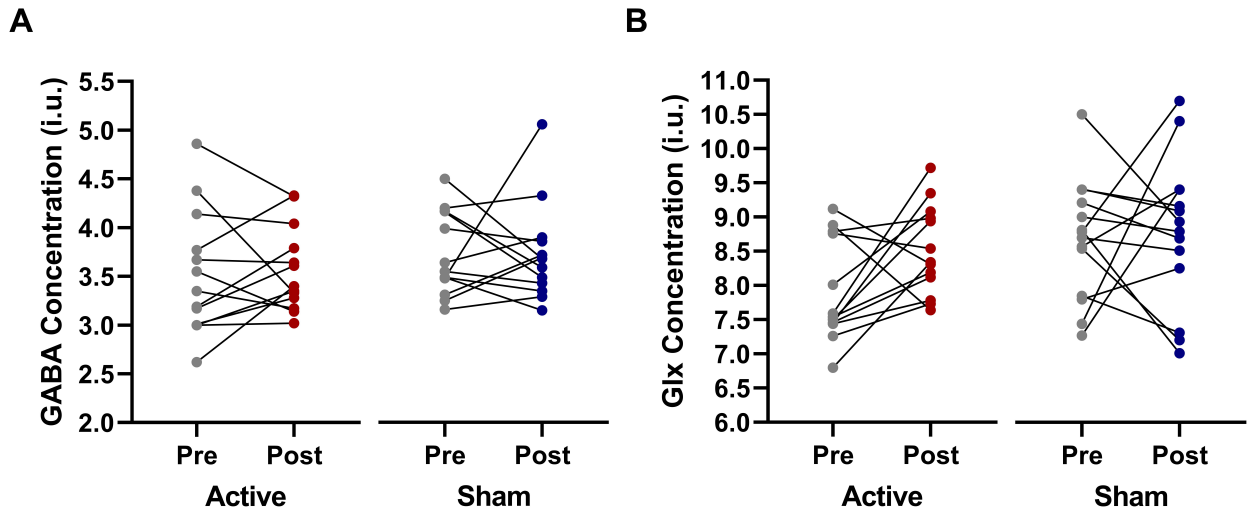


Figure 5.3: Pre and post GABA (A) and Glx (B) concentrations for both active and sham conditions.

correlated with baseline GABA (session 1:  $r = -0.132$ ,  $p = 0.666$ ; session 2:  $r = 0.324$ ,  $p = 0.280$ ) or Glx levels (session 1:  $r = 0.155$ ,  $p = 0.613$ ; session 2:  $r = -0.357$ ,  $p = 0.231$ ) recorded immediately after psychophysical testing. Similarly, mixed percept durations were not correlated with baseline GABA (session 1:  $r = 0.004$ ,  $p = 0.990$ ; session 2:  $r = 0.316$ ,  $p = 0.292$ ) or Glx levels (session 1:  $r = 0.057$ ,  $p = 0.853$ ; session 2:  $r = 0.357$ ,  $p = 0.230$ ).

### 5.4.3 Comparisons between male and female participants

Mean GABA and Glx concentrations for each sex separately are shown in Table 5.2. For both males and females, here was no significant interaction between treatment Condition

(active vs. sham) and Time (pre vs. post) for either GABA or Glx ( $p > 0.05$ ; Figure 5.4). However, for the males, there was a main effect of both Condition ( $F_{1,4} = 12.671$ ,  $p = 0.024$ ) and Time ( $F_{1,4} = 9.545$ ,  $p = 0.037$ ) for Glx, with lower Glx concentrations overall in the active condition, similar to the pooled results. Post-hoc t-tests showed a significant increase in Glx concentration post treatment in the active condition ( $t_4 = -2.923$ ,  $p = 0.043$ ) but not the sham condition ( $t_4 = -1.095$ ,  $p = 0.335$ ).

Binocular rivalry dynamics were not correlated with GABA concentrations for neither males nor females. For males, neither session 1 nor session 2 binocular rivalry alternation rates were correlated with GABA (session 1:  $r = 0.325$ ,  $p = 0.594$ ; session 2:  $r = 0.175$ ,  $p = 0.778$ ) or Glx levels (session 1:  $r = -0.025$ ,  $p = 0.968$ ; session 2:  $r = -0.631$ ,  $p = 0.254$ ). Similarly, mixed percept durations were not correlated with GABA (session 1:  $r = 0.323$ ,  $p = 0.597$ ; session 2:  $r = 0.471$ ,  $p = 0.423$ ) or Glx levels (session 1:  $r = 0.058$ ,  $p = 0.926$ ; session 2:  $r = 0.061$ ,  $p = 0.922$ ). For females, neither session 1 nor session 2 binocular rivalry alternation rates were correlated with GABA (session 1:  $r = -0.302$ ,  $p = 0.468$ ; session 2:  $r = 0.370$ ,  $p = 0.367$ ) or Glx levels (session 1:  $r = 0.127$ ,  $p = 0.764$ ; session 2:  $r = -0.283$ ,  $p = 0.497$ ). Mixed percept durations were also not correlated with GABA (session 1:  $r = -0.157$ ,  $p = 0.711$ ; session 2:  $r = 0.264$ ,  $p = 0.528$ ) or Glx (session 1:  $r = 0.029$ ,  $p = 0.945$ ; session 2:  $r = 0.521$ ,  $p = 0.185$ ).

## 5.5 Discussion

The primary aim of our study was to investigate the effects of a-tDCS on visual cortex GABA and glutamate concentration. A-tDCS has been consistently shown to modulate

Table 5.2: GABA and Glx concentrations in primary visual cortex for males and females separately

		GABA (mean $\pm$ SD)		Glx (mean $\pm$ SD)	
		Pre	Post	Pre	Post
Female	Active	3.6 $\pm$ 0.74	3.6 $\pm$ 0.48	8.0 $\pm$ 0.82	8.5 $\pm$ 0.68)
	Sham	3.9 $\pm$ 0.42	3.7 $\pm$ 0.31	8.8 $\pm$ 0.97	8.6 $\pm$ 1.29)
Male	Active	3.4 $\pm$ 0.49	3.6 $\pm$ 0.41	7.7 $\pm$ 0.62	8.6 $\pm$ 0.67)
	Sham	3.4 $\pm$ 0.20	3.8 $\pm$ 0.76	8.5 $\pm$ 0.86	9.2 $\pm$ 0.81)

GABA concentration and cortical excitability in the motor cortex (Antonenko et al., 2017b; Heise et al., 2014; Nitsche and Paulus, 2000; Patel et al., 2017; Stagg et al., 2009a). We examined the visual cortex and found no significant change in GABA concentration after 20 minutes of a-tDCS; however, an increase in glutamate concentration was seen pre to post in the active condition with a post hoc paired comparison. This result was not evident in the general linear model that included the sham condition, likely due to our small sample size and low power. Therefore, it appears that the motor and visual cortices respond differently to similar a-tDCS protocols. The mechanisms of non-invasive brain stimulation across different brain regions is not fully understood, and there is evidence to suggest brain stimulation effects may depend on cortical composition of inhibitory and excitatory neurons (Castrillon et al., 2020) that differ between motor and visual cortices. In agreement with the idea that the effects of a-tDCS on GABA concentration may differ across brain areas, a recent study of both monocularly deprived and normal rats found an increase in labelling of parvalbumin positive GABAergic neurons in visual areas in both groups following 8 sessions of a-tDCS (Castaño-Castaño et al., 2019b). The authors propose that a-tDCS may have increased glutamate release that subsequently caused an





Kraft et al., 2010; Spiegel et al., 2013a; Spiegel et al., 2013b). These results indicate that the mechanisms underlying the neuromodulatory effects of visual cortex a-tDCS extend beyond a direct reduction in GABA mediated inhibition.

We observed that Glx values increased post stimulation in the active as well as the sham condition, a possible result of participants having closed their eyes for the duration of the experiment leading to increased visual cortex excitability. Recent evidence has shown that visual cortex metabolite concentrations may differ based on whether participants have their eyes closed or open; specifically, GABA concentrations were highest and Glx concentrations lowest when the eyes were closed compared to eyes open in the dark and eyes open with visual stimulation (Kurcyus et al., 2018). Additionally, it has been shown that visual deprivation results in an increase in glutamate release (Yashiro et al., 2005). It is possible that eye closure throughout the duration of the experiment for both a-tDCS and sham conditions may have diluted the effect of a-tDCS in the active condition.

As a secondary measure, we investigated the correlation between binocular rivalry alternation rates and GABA concentration in young adults. Pharmacological manipulation of GABA concentration has been recently shown to effect perceptual suppression during binocular rivalry, whereby increasing GABA concentration reduced the duration of mixed percepts and increased perceptual dominance (Mentch et al., 2019). Additionally, higher visual cortex GABA concentrations have been correlated with slower perceptual alternation rates and stronger periods of full suppression (Robertson et al., 2016; van Loon et al., 2013). We were unable to replicate these results with our sample of 14 young, healthy adults. Our results show no correlation with visual cortex GABA or Glx concentration for either alternation rate or mixed percept duration, the calculated dynamics of binocular

rivalry. This suggests that the correlation may not be reliably representative of the greater population, as the original study's correlation was modest ( $Rho = 0.506$ ) (van Loon et al., 2013). Additionally, we observed higher variability in the levels of GABA and glutamate in the pre scans as compared to the post treatment scans, which may suggest participants became familiar with the procedure during the second scan and possibly show reduced artifact or noise. However, active and sham sessions were randomized so half of the participants at each pre-testing session had experienced previous scanning procedures.

It is important to note that the original study to report this correlation tested a sample of 18 typical young male participants (van Loon et al., 2013) while the majority of our participants were female. Binocular rivalry dynamics for male participants may differ from females where hormonal fluctuations may have a complex relationship with GABA-mediated inhibition and therefore influence rivalry ((Sy et al., 2016). Additionally, differences in the response to a-tDCS may exist between males and females (Chaieb et al., 2008). Robertson and colleagues examined patients with autism and aged-matched controls and found a strong correlation between GABA concentration and perceptual suppression, although the sex of the participants was not reported (Robertson et al., 2016). Another study looked at a sample of young and older adults—both male and female—and found GABA concentration was correlated with the mean percept duration only when both populations were pooled together (Pitchaimuthu et al., 2017). In exploring our results further by separating males and female, it is possible that the neurochemical changes of a-tDCS affect each sex differently. The data we collected from females is substantially more variable than that of males, so it is possible that the effect of glutamate, which is visible in the paired t-test in the male sample ( $n=5$ ) was diluted by the female response to stimulation.

Although we present a relatively small sample size, we propose that the neurotransmitter glutamate may underlie the modulation of visual cortex excitability, as opposed to GABA modulation in the motor cortex. Analysis of the resting state data may provide insight into the possible changes in cortical connectivity following stimulation. Additionally, a larger sample size with sufficient power may confirm our speculations that the effect of stimulation on the visual cortex is potentially different than that of the motor cortex. Overall, our results suggest an effect of visual cortex a-tDCS on glutamate and not GABA concentration and therefore indicate distinct mechanisms for the behavioral effects of visual cortex a-tDCS.

## 5.6 Summary

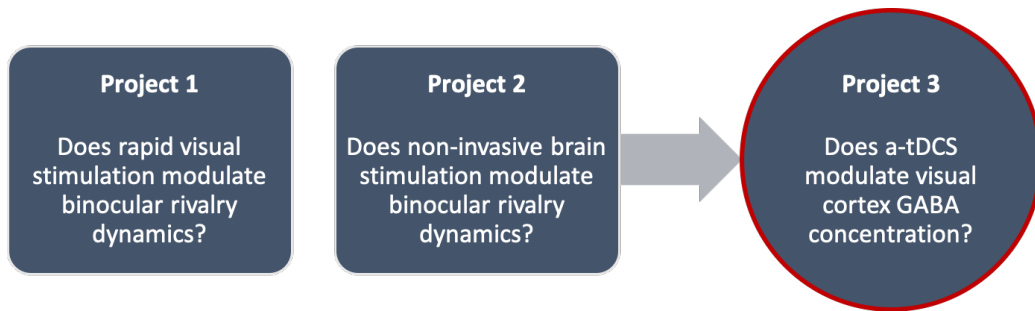


Figure 5.5: Project 3 diagram and rationale.

The primary aim of Project 3 was to directly investigate the effects of a-tDCS on visual cortex neurotransmitter concentration. There are many studies that show a significant reduction in motor cortex GABA concentration following a-tDCS (Heise et al., 2014; Patel et al., 2017; Stagg et al., 2009a). To our knowledge, there are no direct reports of the effects of a-tDCS on the visual cortex. Unexpectedly, we found no significant change in visual cortex GABA concentration following 20 minutes of a-tDCS; however, our results hint at an increase in Glx concentration following active stimulation. It is possible that an increase in cortical excitability is achieved through a different mechanism in the visual cortex as compared to the motor cortex; specifically, an increase in glutamate rather than a decrease in GABA concentration. Additionally, we were unable to replicate the correlation between binocular rivalry dynamics and GABA concentration as previous studies have reported (Mentch et al., 2019; Robertson et al., 2016; van Loon et al., 2013). While this may be a result of our small size, our results support the possibility that different a-tDCS acts on different mechanisms based on the characteristics of the cortical region being stimulated

(Castrillon et al., [2020](#)), and demonstrate that the established effect of a-tDCS on motor cortex GABA concentration may not apply to the visual cortex.

# Chapter 6

## Overview and Future Work

### 6.1 General Discussion

Neuroplasticity has been a widely researched phenomenon in the past few decades. The modulation of existing neural connections and the formation of new connections in the adult human brain can have extensive implications for recovery and rehabilitation from neurodevelopmental disorders as well as from loss of function due to brain injuries. Neural modulation techniques, such as inducing long-term potentiation (LTP) and delivering non-invasive brain stimulation, are used to induce and investigate the mechanisms underlying neuroplasticity. We investigated whether these techniques modulate the visual cortex both behaviourally using binocular rivalry as an indirect measure of neural changes in visual cortex inhibition, and directly by quantifying neurochemical changes within the brain using magnetic resonance spectroscopy.

### 6.1.1 Does rapid visual stimulation modulate binocular rivalry dynamics?

LTP, a fundamental mechanism of neuroplasticity, has been studied in both animal models and humans and used to modulate learning and memory formation within the brain (Teyler and DiScenna, 1987). Rapid visual stimulation has been found to be an alternative, non-invasive technique for inducing LTP-like effects in humans as a result of repeated synaptic activation (Clapp et al., 2006b; Kirk et al., 2010; Norman et al., 2007; Ross et al., 2008; Teyler et al., 2005). We hypothesized that monocular rapid visual stimulation would increase the dominance of the stimulated eye during binocular rivalry. Unexpectedly, we found a significant reduction in dominance of the stimulated eye which could not be explained by adaptation.

While most studies report LTP-like effects following rapid visual stimulation, measured by an increase in amplitude of visual evoked potentials (Norman et al., 2007; Teyler et al., 2005), it is possible that our study resulted in long-term depression-like effects (LTD-like). Visual stimulation results are inconsistent since optimal stimulus features to induce LTP-rather than LTD-like effects are still unknown (Sanders et al., 2018). Our results may also be explained by activation of a homeostatic interocular gain control mechanism. Following short-term monocular occlusion, the deprived eye is strengthened during a binocular rivalry task relative to the non-deprived eye (Lunghi et al., 2015a; Lunghi et al., 2011; Lunghi et al., 2013; Lunghi et al., 2016). This effect is also seen for deprivation without occlusion, where lower contrast images presented to one eye result in a subsequent increase in that eye's dominance during binocular rivalry (Kim et al., 2017). Other studies support



this hypothesis, demonstrating that the eye that is more visually stimulated is reduced in dominance (Ramamurthy and Blaser, 2018; Zhou et al., 2014). While rapid visual stimulation had no effect on binocular rivalry alternation rates or mixed percept duration, the unexpected effect on ocular dominance supports previous work and suggests a homeostatic balance of visual input following stimulation. Further investigation is needed to understand the extent of this effect and how rapid visual stimulation may be used as a method of modulating dominance in normal, as well as in patient populations.

### **6.1.2 Do a-tDCS and cTBS modulate binocular rivalry dynamics?**

Binocular rivalry has been shown to be correlated with visual cortex GABA concentration in young, healthy adults, with slower alternation rates and higher perceptual dominance being associated with higher levels of the inhibitory neurotransmitter (Robertson et al., 2016; van Loon et al., 2013). More recently, a study demonstrated a direct relationship between GABA and binocular rivalry dynamics, reporting a significant increase in perceptual dominance following the administration of a GABA-modulating drug which reduces GABA concentration (Mentch et al., 2019). We hypothesized that if visual cortex GABA concentration indeed plays a role in binocular rivalry dynamics, non-invasive brain stimulation techniques, such as a-tDCS and cTBS, which have been shown to modulate GABA concentration in the human motor cortex, should have an effect on dominant percept duration and alternation rates. A-tDCS, thought to increase excitability by decreasing GABA concentration, had no effect on binocular rivalry dynamics. On the other hand,

cTBS, thought to decrease excitability by increasing GABA concentration, resulted in a significant increase in mixed percept duration.

Our results suggest several explanations. First, it may be that non-invasive brain stimulation acts differently on different regions of the brain. A recent study demonstrated that brain region composition and tissue characteristics differ in ways that influence the mechanistic effect of brain stimulation (Castrillon et al., 2020). Identical stimulation to both the frontal and occipital cortex had the opposite effect, where repetitive TMS decreased frontal cortex inhibition but increased occipital cortex inhibition. The authors attributed these differences to the distinct functional connectivity that each region has with other areas of the brain. With this evidence, although many studies show that a-tDCS and cTBS modulate motor cortex GABA concentration (Bachtiar et al., 2015; Heise et al., 2014; Patel et al., 2017; Stagg et al., 2009a; Stagg and Nitsche, 2011), we are unable to assume that the neurochemical response of the visual cortex would be the same as the motor cortex. To our knowledge, neurotransmitter concentration has not been directly measured in the visual cortex following non-invasive brain stimulation.

Secondly, assuming that a-tDCS and cTBS influence the visual cortex similarly to the motor cortex, the change in GABA concentration that results may not be substantial enough to translate to changes in a behavioural measure such as binocular rivalry. Finally, seeing an increase in mixed percept duration only following cTBS may be explained by the relative changes in neural noise that result from the increase in inhibition. A recent study demonstrated changes in binocular rivalry alternation rates following transcranial random noise stimulation (van der Groen et al., 2019). Specifically, adding noise to the visual cortex resulted in a significant reduction in mixed percept duration. On the other hand, cTBS

is thought to increase inhibition by increasing GABA concentration, and consequently, we found a significant increase in mixed percept duration following cTBS. It is possible that an increase in inhibition may have reduced neural noise, thereby increasing time spent viewing the mixed percept.

### **6.1.3 Are binocular rivalry dynamics correlated with visual cortex GABA concentration?**

Binocular rivalry alternation rates have been previously correlated with visual cortex GABA concentrations (Robertson et al., 2016; van Loon et al., 2013); albeit a modest correlation. Specifically, higher levels of visual cortex GABA concentration are correlated with slower alternation rates or higher dominant percept duration in young adults (Robertson et al., 2016; van Loon et al., 2013). Another group was only able to replicate this result when both young and older adults were combined together (Pitchaimuthu et al., 2017). It is also possible that normal dominance during binocular rivalry could be explained by a balance of inhibition and excitation in the primary visual cortex (Ip et al., 2019). We did not find a significant correlation of visual cortex GABA concentration with binocular rivalry alternation rates or with perceptual suppression in our sample of young adults.

A relationship between binocular rivalry and GABA concentration could provide an indirect estimate of visual cortex inhibition; however, there are many factors that influence each measure. For instance, differences in binocular rivalry alternation rates across individuals have been attributed, in part, to genetic variation (Miller et al., 2010). Increased time in mixed perception may be influenced by hormonal fluctuations (Sy et al., 2016)

or alcohol intake (Cao et al., 2016). It is also possible that different stimulus parameters may affect the correlations, as stimulus size, grating orientation and spatial frequency vary across studies (Fahle, 1982; Kang, 2009). It is also likely that not only GABA modulates rivalry, but rather several mechanisms play a role in a more integrated and complex method. Acetylcholine, an excitatory neurotransmitter modulated binocular rivalry mixed percept durations, where cholinergic agonists increase the time spent in mixed perception (Sheynin et al., 2020). These external influences on binocular rivalry dynamics and complex neural systems may weaken the correlation and make it difficult to detect one if it does indeed exist.

## **6.2 Does a-tDCS modulate visual cortex GABA concentration?**

To directly assess the effects of a-tDCS on visual cortex GABA concentration, we used magnetic resonance spectroscopy (MRS) to quantify GABA and glutamate in the primary visual cortex before and after 20 minutes of a-tDCS. Motor cortex studies have consistently found that a-tDCS reduces GABA concentration (Bachtiar et al., 2015; Heise et al., 2014; Patel et al., 2017; Stagg et al., 2009a) and have also shown associations of -tDCS with improved motor function and rehabilitation (Kim et al., 2014; Yamaguchi et al., 2020). While visual cortex stimulation with a-tDCS has been shown to improve contrast sensitivity (Ding et al., 2016; Spiegel et al., 2013a) and stereopsis (Spiegel et al., 2013b) in patients with amblyopia, a direct measure of how a-tDCS influences GABA in the visual cortex

has not been reported. Contrary to our hypothesis and to motor cortex studies, we found no significant change in GABA concentration following a-tDCS. Unexpectedly, we found a marginal increase in glutamate concentration, the primary excitatory neurotransmitter in the brain. While most a-tDCS studies report a decrease in GABA concentration and find no change in glutamate if it is reported, our results suggest that a-tDCS of the visual cortex may act by a different mechanism (Castrillon et al., 2020), namely increasing excitation by increasing glutamate, rather than increasing excitation by decreasing GABA. With a larger sample size, this result may be stronger, or may disappear; however, it is important to recognize that the effect a-tDCS on the motor cortex cannot be translated to the visual cortex without further investigation of whether or not the same effect exists.

### 6.3 Strengths and Limitations

Our studies shed light on the application and efficacy of visual cortex modulation via LTP and non-invasive brain stimulation. We demonstrate a potential for modulating ocular dominance with rapid visual stimulation and reveal intriguing changes in the visual cortex following a-tDCS, suggesting stimulation may act via a distinct mechanism as compared to the motor cortex. One limitation of our studies was the relatively small sample sizes, particularly in our spectroscopy study (see Chapter 5). A larger-scale experiment may increase the power of the study and better reveal patterns of changes in neurochemical concentrations. To support our results however, recent evidence suggests that brain stimulation may act differently on different regions of the brain based on that regions' characteristics and composition (Castrillon et al., 2020).

## 6.4 Conclusions and Future Directions

Evidently, there are complex mechanisms in the brain that take part in responding to external modulation in an intricate and multifaceted manner. Our results provide insight into modulation of the visual cortex and suggest the possibility that different mechanisms play a role in modulating visual cortex plasticity as compared to those in the motor cortex. Further research on the effect of non-invasive brain stimulation on the visual cortex is important to understand whether these techniques can effectively be used for clinical purposes, or how modulation can affect psychophysical outcomes. Understanding the mechanisms underlying neuroplasticity in the human brain and the techniques to modulate neuroplasticity may provide new treatments for adults with neurodevelopmental disorders or brain damage and may have implications for the extent of recovery and rehabilitation of vision as well as other neural functions.

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Abbreviations included in the figure:

**ppm:** parts per million

**Cr:** creatine

**Myo:** myo-inositol

**Cho:** choline

**NAA:** N-acetyl aspartate

**Glu:** glutamate

**Gln:** glutamine

**GABA:** gamma aminobutyric acid

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