Investigating the enhancement of visual cortex plasticity through non-invasive brain stimulation

by

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Author's Declaration

This thesis contains materials all of which I authored or co-authored: see Statement of Contributions included in the 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.

Statement of Contributions

Xiaoxin Chen was the sole author for Chapters 1-2, 5 and 7. These chapters were written under the supervision of Dr. Benjamin Thompson and Dr. William Bobier and have not been published for publication.

Chapters 3, 4 and 6 are experimental chapters either published or submitted for publication. These chapters have not been made possible without the contribution of all valuable collaborators.

Chapter 3

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Dr. William Bobier: reviewing drafts, funding acquisition

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Abstract

Purpose: (1) To investigate the effects of various non-invasive brain stimulation (NIBS) modalities, including high-frequency transcranial random noise stimulation (hf-tRNS), anodal transcranial direct current stimulation (a-tDCS), and repetitive transcranial magnetic stimulation (rTMS), on short-term ocular dominance plasticity in adults with normal vision; (2) To probe the neural mechanisms underlying short-term ocular dominance plasticity using NIBS techniques; (3) To explore the state-dependency of NIBS within the visual cortex; (4) To evaluate the efficacy of a novel ocular dominance test (the letter-polarity test) as a tool of measuring ocular dominance shifts following monocular deprivation (MD).

Methods: Three studies using hf-tRNS, a-tDCS and rTMS were conducted. NIBS was delivered to V1 during MD. The primary outcome was ocular dominance shift, measured through two ocular dominance tests, a traditional binocular rivalry test and the letter-polarity test, before and after the interventions. Secondary outcomes included mixed percept durations and alternation rates as provided by the binocular rivalry test. The reliability of the letter-polarity test was evaluated in comparison to the binocular rivalry test through a comprehensive set of analyses.

Results: (1) In three studies, short-term ocular dominance plasticity was observed as a shift in ocular dominance towards the deprived eye. (2) No significant effects of NIBS were observed on the primary and secondary outcome measures. (3) By comparing the effect of 120-minute MD and 30-minute MD, we observed a significantly smaller magnitude of ocular dominance shifts with 30-minute MD. (4) The reliability of the letter-polarity test was similar to that of the binocular rivalry test.

Conclusions: These experiments suggest that the neural mechanisms underlying short-term ocular dominance plasticity in adults with normal vision may be more complex than a simple reduction in cortical inhibition. It may be necessary to reconsider the cortical site responsible for this plasticity and the neuromodulatory effects of NIBS on visual cortex activity. Our null findings of NIBS effects may also be explained by a different cortical activation state induced by MD. These findings provide valuable reference points for future studies investigating the enhancement of visual cortex plasticity.

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Coming from in a rural countryside in eastern China, my parents did not receive education higher than junior middle school. Yet despite financial difficulty, they insisted on prioritizing my education, which paved the way for my academic achievements. It is their unwavering support and their hard-working attitude that made me who I am. I am extremely grateful for their belief in me, and I am proud to say that I have not let them down.

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Chapter 1
Neuroplasticity in Human Visual Cortex

1.1 Visual Pathway

Vision is one of the most crucial senses for many species in the world, including humans. While human eyes are small in size, the visual system is, in fact, a complex pathway (Daw, 2014; Tovée, 2008; Werner & Chalupa, 2013). In order to perceive an object, the retina first captures incoming light from the object. Visual information is then relayed from the retina, through the optic nerve, to the lateral geniculate nucleus (LGN) in the thalamus. Before entering the LGN, visual inputs from two hemifields are separated at the optic chiasm; inputs from the left hemifield cross to the right hemisphere, and those from the right hemifield are transmitted to the left hemisphere. These inputs are subsequently projected from LGN to the primary visual cortex (V1), also known as the striate cortex. V1 is the first cortical area that processes visual information, such as orientations and colours, from binocular inputs. Visual information is then transmitted to extrastriate visual areas for more complex processing, such as object recognition and motion detection. The collaboration of all these structures allows one to finally perceive and recognize an object.

V1 is located at Brodmann's area 17 in the occipital lobe of the human brain. Visual inputs in V1 are organized based on their origins and properties. As described above, each hemisphere accepts inputs from the contralateral hemifield. Additionally, inputs from the fovea of the retina (central vision) are represented closer to the surface of V1, while those from the periphery are represented in deeper parts of the calcarine sulcus that bisects V1 based on their eccentricity (Adams & Horton, 2009; Tootell et al., 1988; Yu et al., 2015). Evidence from other mammals also shows varying degrees of preference for left and right eye inputs across V1 cells. Based on the strength of preference for one eye, neurons can be classified into different ocular dominance categories, including entire dominance by one eye, marked or slight dominance by one eye, and no preference (Hubel, Wiesel, & LeVay, 1977; Hubel & Wiesel, 1970). Furthermore, V1 neurons demonstrate different preferences when processing orientation and spatial frequency information (Hubel, Wiesel, & Stryker, 1977; Tootell et al., 1981). Neurons processing similar properties with similar binocular preferences tend to cluster together, forming orientation columns, spatial frequency columns and ocular dominance columns (Daw, 2014; Hubel, Wiesel, & LeVay, 1977; Hubel, Wiesel, & Stryker, 1977; Tootell et al., 1981). These columns represent the first step of visual processing within the cortex, where the visual world is represented as localized regions of spatial and temporal information. This information is then further processed and integrated by higher visual areas.

Higher visual areas are responsible for processing specific types of visual information (Daw, 2014; Tovée, 2008; Werner & Chalupa, 2013). For instance, V4, located anteriorly and ventrally to V1, is primarily involved in pattern discrimination. Information from V4 appears to be further relayed to the inferior temporal (IT) area for object recognition. Meanwhile, V5 (the middle temporal area, MT), processes motion and depth information, and the parietal cortex handles spatial representation. These apparently distinct processing specializations have led to the theory that there are two different streams in the visual system: the ventral stream which involves V1, V2, V4 and anterior and posterior inferotemporal cortices (AIT and PIT), mainly responsible for the visual recognition of objects (known as the "what" pathway), and the dorsal stream which involves V1, V2, V3, V5/MT and the parietal cortex, believed to be responsible for location representation and action control (previously known as the "where" pathway, later revised as the "how" pathway) (Gallivan & Goodale, 2018; Goodale & Milner, 1992; Tovée, 2008; Werner & Chalupa, 2013). It is important to note that these pathways are interconnected (Freud et al., 2016; Werner & Chalupa, 2013). In other words, different parts of the visual system function cohesively to create a comprehensive perception of the world.

1.2 Two Types of Synaptic Plasticity

Neurons communicate with each other through structures called synapses. Within a synapse, neurotransmitters are released from the presynaptic neuron through vesicle exocytosis. These molecules traverse the synaptic cleft and then bind to receptors on the postsynaptic membrane, initiating subsequent activity in the postsynaptic neuron (Vitureira & Goda, 2013). The strength of synaptic transmission is determined by the number of neurotransmitters released and the number of postsynaptic receptors (Vitureira & Goda, 2013). Importantly, synaptic strength is not fixed and undergoes changes in response to neuronal activity, a phenomenon known as synaptic plasticity. There are two main types of synaptic plasticity: Hebbian plasticity and homeostatic plasticity.

Hebbian plasticity involves the strengthening (long-term potentiation, LTP) or weakening (long-term depression, LTD) of a synaptic connection, characterized by positive feedback (Bang et al., 2023). For example, during the critical period, when one eye experiences visual deprivation (monocular deprivation), a binocular neuron—one that receives inputs from both eyes—becomes more responsive to inputs from the non-deprived eye and less responsive to those from the deprived eye (Hubel & Wiesel, 1964, 1970; Wiesel & Hubel, 1963). This change aligns with Hebbian plasticity, where a loss of inputs can be expected to cause pruned synaptic connections (Drager, 1978; Frenkel & Bear, 2004;

Yee et al., 2017). Another example of Hebbian plasticity is perceptual learning. Perceptual learning involves a lasting change in one's perception of a visual stimulus through repeated exposure to a specific visual task (Prettyman, 2019). This change, usually an improvement in behavioural performance, is believed to involve the reinforcement of synaptic connections related to the trained visual task (Bang et al., 2023; Sumner et al., 2020). In essence, Hebbian plasticity strengthens local synaptic efficacy to adapt involved neurons to better represent an external stimulus.

On the other hand, homeostatic plasticity operates in an opposite direction to Hebbian plasticity. This type of plasticity, characterized by negative feedback, is found to downscale Hebbian changes, thereby preventing excessive synaptic strengthening or pruning and ensuring synaptic stability within individual neurons (Bang et al., 2023; Vitureira & Goda, 2013; Yee et al., 2017). Importantly, this downscaling appears to globally affect all synaptic connections across the neuronal membrane, hence preserving the relative strength differences between synapses established through Hebbian changes. (Bang et al., 2023; Keck et al., 2017; Turrigiano, 2012; Vitureira & Goda, 2013; Yee et al., 2017). Thus, homeostatic plasticity can be considered a compensatory mechanism to Hebbian plasticity. Another example of homeostatic plasticity is contrast gain control, where the visual cortex dynamically adjusts its response function based on stimulus contrast levels (Boynton, 2005; Burrone & Murthy, 2003; Gardner et al., 2005). When exposed to a low-contrast stimulus, neuronal responses to different levels of contrasts are globally upscaled, ensuring that the neuron remains most sensitive to the target contrast. Conversely, when presented with a high-contrast stimulus, neuronal responses are globally downscaled. This adaptive shift in neuronal response allows neurons to maintain their sensitivity to visual inputs despite varying contrasts (Boynton, 2005; Gardner et al., 2005). In this manner, homeostatic plasticity empowers the visual cortex to discern complex contrast changes in visual stimuli.

In summary, Hebbian plasticity and homeostatic plasticity are two types of neural plasticity that modulate the strength of synaptic connections. These types of plasticity operate through distinct neural mechanisms. Despite their opposing effects, both types of plasticity work in concert to shape the neural network, enhancing the ability of our brain to adapt to the ever-changing sensory environments encountered in the real world.

1.2.1 Critical Periods and Amblyopia

The development of the visual system relies heavily on visual experience early in life. This period of heightened sensitivity to visual experience is known as the critical period (Wiesel, 1982). Disrupted

visual experience during this critical period can lead to lifelong changes in visual development. In particular, monocular deprivation has been found to significantly alter ocular dominance columns in the developing visual cortex (Hubel & Wiesel, 1964, 1970, 1977; Wiesel & Hubel, 1963). Synaptic connections with the deprived eye are pruned and those with the non-deprived eye are expanded (Antonini & Stryker, 1993). Consequently, neurons become more responsive to the non-deprived eye input and less driven by the deprived eye. The duration of the critical period varies across species and depends on visual functions (Daw, 1998; Hensch & Quinlan, 2018). For ocular dominance, the critical period is thought to end at 1-2 months in rodents (Mitchell & Maurer, 2022), 1 year of age in kittens (Daw et al., 1992; Mitchell & Maurer, 2022), and 1 year in monkeys (Mitchell & Maurer, 2022). In humans, while there is no direct observation, indirect evidence from amblyopia seems to suggest that the critical period for ocular dominance plasticity may last up to 8 to 10 years of age (Daw, 1998; Hensch & Quinlan, 2018; Mitchell & Maurer, 2022; Vaegan & Taylor, 1979).

Amblyopia, commonly known as the "lazy eye", is a visual developmental disorder caused by abnormal visual experience early in life, such as ametropia, strabismus and congenital cataracts (Bretas & Soriano, 2016; von Noorden, 1981). While reminiscent of the monocular deprivation effect described above, amblyopia in humans may not necessarily involve a shift in ocular dominance columns (Goodyear et al., 2002; Horton & Hocking, 1996; Horton & Stryker, 1993). Nevertheless, amblyopia can lead to severely reduced vision in the affected eye, which cannot be immediately corrected through surgical and refractive treatments. Apart from visual acuity loss, other visual functions are also significantly impaired in patients with amblyopia, including contrast sensitivity, stereo vision, second-order processing, global image processing, temporal processing, and visuomotor skills (Birch, 2013; Hu et al., 2021; P.-C. Huang et al., 2012; Levi, 2006; Niechwiej-Szwedo et al., 2019), greatly affecting their quality of life. Treatment for amblyopia involves occluding or pharmaceutically penalizing the non-amblyopic eye. However, such treatment is often unsuccessful for individuals older than 10 years of age (Maconachie & Gottlob, 2015; Wu & Hunter, 2006). This evidence, along with the notion of the critical period, seems to support the idea that older children and adults may have limited cortical plasticity compared to younger children.

Nevertheless, studies have demonstrated robust plasticity in the adult visual cortex using various interventional techniques. These techniques include visual perceptual learning, dichoptic training, non-invasive brain stimulation and short-term monocular deprivation (Astle et al., 2011; Hess & Thompson, 2013, 2015; Sengpiel, 2014; Vagge & Nelson, 2016; Wong, 2012; Zhang et al., 2014). These treatments, which concentrate on reducing interocular suppression and improving binocular functions,

have demonstrated promising results, suggesting that amblyopia is fundamentally a binocular disorder (Bui Quoc et al., 2023; Chaturvedi et al., 2023; Levi et al., 2015; Lunghi, Sframeli, et al., 2019; Rodán et al., 2022; J. Zhou et al., 2019). It is conceivable that efforts to enhance these forms of visual cortex plasticity will pave the way for the development of effective treatments for amblyopia in adulthood in the future.

1.2.2 Neurotransmitters

As mentioned above, neurotransmitters are molecules that transmit synaptic signals between cells. Within the brain, there exist diverse types of active neurotransmitters, such as glutamate, gamma-aminobutyric acid (GABA), serotonin (5-HT), adrenaline and acetylcholine (ACh). Among these, glutamate and GABA emerge as particularly relevant for visual cortex plasticity (Skangiel-Kramska, 1988).

Glutamate is a notable excitatory neurotransmitter in the brain (Petroff, 2002). Among several types of glutamate receptors, N-methyl-D-aspartate (NMDA) receptors have been proposed to be instrumental in the plasticity of the developing visual cortex (Bear, 1996; Berardi et al., 2000; Daw et al., 1995; Skangiel-Kramska, 1988; Sur et al., 2013). In particular, NMDA receptors appear highly active during the critical period (Catalano et al., 1997; Kapfhammer, 1996; Tsumoto et al., 1987). The inhibition of NMDA activity obstructs the impact of monocular deprivation (Kleinschmidt et al., 1987). Moreover, the postnatal shift in NMDA receptor subunits from NR2A to NR2B (i.e., an increase in the 2A/2B ratio) coincides with the critical period and is believed to regulate its onset and/or closure (Berardi et al., 2000; Quinlan et al., 1999; Roberts & Ramoa, 1999; Yashiro & Philpot, 2008). Collectively, these studies provide compelling evidence affirming the essential role of glutamate and NMDA receptors in driving visual cortex plasticity.

GABA, on the other hand, is the primary inhibitory neurotransmitter in the visual cortex (Petroff, 2002). It is synthesized by an enzyme named glutamic acid decarboxylase (GAD) and binds predominantly to $GABA_A$ and $GABA_B$ receptors (Daw, 2014; Petroff, 2002; Skangiel-Kramska, 1988). Evidence shows that the maturation of the GABAergic system occurs subsequent to that of excitatory circuits, leading to the proposition that the gradual maturation of GABAergic inhibition might be responsible for the closure of the critical period (Bavelier et al., 2010; Berardi et al., 2000; Hensch & Quinlan, 2018). In particular, reducing GABAergic inhibition appears to reinstate closed ocular dominance plasticity in adult rodents (Harauzov et al., 2010; Vetencourt et al., 2008). On the other

hand, mice lacking GAD enzymes exhibit little ocular dominance change after monocular deprivation (Hensch et al., 1998), indicating that GABA might also be crucial for the onset of the critical period. In addition to its role in visual cortex plasticity, GABA also contributes to interocular inhibition (Sengpiel & Vorobyov, 2005). Larger differences in GABA concentrations between dominant-eye viewing and non-dominant eye viewing conditions have been reported to correlate with stronger eye dominance (Ip et al., 2021). GABA is also implicated in perceptual alternations during binocular rivalry; further details on binocular rivalry will be discussed below. Altogether, these investigations highlight the pivotal role of GABA in visual cortex plasticity and visual perception.

1.3 Short-Term Ocular Dominance Plasticity in Adults

Details regarding short-term ocular dominance plasticity in adults are extensively covered in Chapters 3, 4 and 6. As a concise introduction, a brief period of monocular deprivation (MD) temporarily modifies sensory eye dominance. In contrast to the synaptic plasticity during the critical period, where binocular neurons become more responsive to the *non-deprived* eye, a few hours of MD leads to an increased dominance of the *deprived* eye in human adults, aligning with the concept of homeostatic plasticity (Bang et al., 2023; Castaldi et al., 2020; Hess & Thompson, 2015; Lunghi et al., 2011; J. Zhou et al., 2015). This ocular dominance plasticity can be induced through different visual deprivation approaches, including light deprivation (using a light-proof eye patch) (J. Zhou, Clavagnier, et al., 2013), form deprivation (using a translucent eye patch) (Lunghi et al., 2011; Lunghi & Sale, 2015; Min et al., 2018; J. Zhou et al., 2017; J. Zhou, Clavagnier, et al., 2013) and kaleidoscopic deprivation (creating fractionated, uninformative images) (Ramamurthy & Blaser, 2018). Furthermore, this shift in ocular dominance is associated with an elevation in visual evoked potential (VEP) amplitudes (Lunghi, Berchicci, et al., 2015) and blood oxygenation level–dependent (BOLD) activity (Binda et al., 2018) measured for the deprived eye after MD. Notably, it has been documented that short-term MD reduces GABA levels in V1, suggesting that diminished interocular inhibition may be an underlying mechanism (Lunghi, Emir, et al., 2015). Hence, it is plausible that interventions targeting the reduction of GABA in the primary visual cortex may potentially enhance this ocular dominance plasticity.

1.3.1 Binocular Rivalry

When observing opposing images through two eyes, perception alternates between either exclusive image (exclusive dominance percepts) and a blend of both images (mixed percepts). This phenomenon is referred to as binocular rivalry. Binocular rivalry can serve as a tool for assessing ocular dominance (Castaldi et al., 2020), which involves comparing the durations of each exclusive dominance percept for each eye.

Interocular inhibition has been suggested as a pivotal factor responsible for perceptual alternations (Kang & Blake, 2011; Mentch et al., 2019; Pitchaimuthu et al., 2017; Robertson et al., 2016; van Loon et al., 2013; Werner & Chalupa, 2013). A double-well energy landscape (Kang & Blake, 2011; Werner & Chalupa, 2013) and subsequently an additional well serving as a transition region (Skerswetat et al., 2018) are proposed to illustrate these perceptual changes. Initially when a stimulus presented to one eye dominates, the energy well is sufficiently deep, compared to internal noise (neuronal spontaneous discharge), enabling the current dominance state to persist. As adaptation accumulates, diminishing the inhibition on the currently suppressed eye, the energy well becomes shallower, permitting internal noise of sufficient strength to trigger a shift in the perceptual state. As interocular inhibition alleviates, the perceptual state starts to enter the transition region, resulting in mixed percepts. Either *piecemeal* (partial fusion with residual rivalry within small spatial zones) or *superimposed* (complete fusion) percepts may occur. Intrinsic noise then further propels the perceptual state towards either exclusive dominance percept. In line with this energy landscape model are findings that demonstrate the essential role of GABAergic inhibition in binocular rivalry. In particular, higher GABA concentrations have been associated with longer percept durations and slower perceptual alternations (Pitchaimuthu et al., 2017; Robertson et al., 2016; van Loon et al., 2013). Similarly, by administering GABA receptor agonists, Mentch et al. (2019) observed a significant increase in the proportion of exclusive dominance percepts. Based on these findings, it is conceivable that interventions that modify GABAergic inhibition may cause changes in perceptual alternations.

1.4 Effects of Physical Exercise

Physical exercise is shown to enhance a diverse array of cognitive functions, including executive functions, attentional control, learning and memory (Cassilhas et al., 2016; Hötting & Röder, 2013; Kirk-Sanchez & McGough, 2013). It has also been identified as a potential enhancer of visual cortex plasticity, especially in animals. For example, research has demonstrated that physical exercise can

restore juvenile-like ocular dominance plasticity in adult mice (Kalogeraki et al., 2014) and induce the recovery of depth perception and visual acuity in adult amblyopic rats (Baroncelli et al., 2012; Sansevero et al., 2020). Notably, locomotion and motor enrichment have been found to decrease GABAergic inhibition in the rat visual cortex (Baroncelli et al., 2012; Fu et al., 2014), suggesting that the diminution of cortical inhibition may underlie exercise-induced visual cortex plasticity in adulthood.

However, the effects of physical exercise on visual cortex plasticity in human adults appear heterogeneous. Some studies indicate positive influence of exercise within the visual cortex. For instance, cycling facilitated the effect of perceptual learning on an orientation discrimination task, which, according to the authors, may be attributed to the release of brain-derived neurotrophic factor (BDNF) during physical activity (Perini et al., 2016). In addition, cycling has also been shown to amplify ocular dominance shifts following short-term MD, as measured through binocular rivalry, perhaps involving a shift in the excitation/inhibition balance within the visual cortex (Lunghi & Sale, 2015). Nevertheless, other studies failed to report similar enhancement on visual perceptual learning (Campana et al., 2020; Connell et al., 2018) or short-term ocular dominance plasticity, whether measured through binocular combination (J. Zhou et al., 2017) or binocular rivalry (Finn et al., 2019; Virathone et al., 2021). The exact reasons for the inconsistency on the effects of physical exercise across studies are unclear. Differences in exercise intensities, dosage, timing and the measurement tasks employed across studies may contribute to the discrepancies in outcomes (Abuleil et al., 2022). In summary, the current body of evidence regarding the modulatory effects of physical exercise remains inconclusive. More comprehensive research is warranted to systemically investigate the impact of physical exercise on visual cortex plasticity.

1.5 Chapter Summary

The visual system is a complex pathway projecting visual information from the retina to early and higher visual cortices. Different parts of this intricate pathway collaborate cohesively to construct the perception of the external visual world. Two types of synaptic plasticity exist within the brain. Hebbian plasticity reinforces synaptic changes brought by external stimuli, and homeostatic plasticity acts to downscale Hebbian changes and maintain the sensitivity of neurons to external stimuli. Both types of plasticity work in concert to refine synaptic connections between neurons, enabling the brain to adapt to changes in visual environments.

Early in life, there is a period of heightened sensitivity for visual development, known as the critical period. Abnormal visual experience during the critical period can lead to amblyopia, characterized by reduced vision in the affected eye. Amblyopia can be treated by occluding or penalizing the non-amblyopic eye in childhood. However, such treatment is often ineffective for older children and adults, suggesting limited cortical plasticity compared to younger individuals. Glutamate and GABA are two neurotransmitters that are crucial in governing visual cortex plasticity during the critical period. GABA also plays a pivotal role in interocular inhibition, which is relevant to ocular dominance and binocular rivalry.

Recent advancements reveal robust plasticity in the adult visual cortex. Short-term ocular dominance plasticity is a type of homeostatic plasticity characterized by a shift in ocular dominance following MD in favour of the deprived eye. This plasticity can be induced in human adults through various deprivation approaches and is believed to be associated with a reduction in GABAergic inhibition in V1. This raises the intriguing question of whether interventions targeted at reducing GABA levels can potentially enhance ocular dominance plasticity. Ocular dominance can be measured by various behavioural tasks, including a binocular rivalry task. The role of interocular inhibition underlying perceptual alternations in binocular rivalry can be depicted by a double-well energy landscape model with a transition region. On the other hand, although physical exercise has been shown to augment various cognitive functions and improve visual performance in animal models, its effects on visual cortex plasticity in human adults remain inconclusive. Therefore, further research is needed to fully comprehend the enhancement of visual cortex plasticity in adulthood. This thesis aims to contribute to the existing body of literature by examining the efficacy of enhancing short-term ocular dominance plasticity through non-invasive brain stimulation techniques, introduced in Chapter 2.

Chapter 2
Non-Invasive Brain Stimulation (NIBS)

2.1 Overview

In the nervous system, neural signals are transmitted in the form of electric current. At a resting state, the nerve membrane maintains a polarized resting potential through sodium-potassium exchange (Matthews, 2002; Newman, 1980). The inside of the membrane remains negative compared to the outside, creating a voltage difference at approximately -70 millivolts (mV) (Figure 2-1). Stimulation by an external signal opens sodium channels on the nerve membrane. As a result, the strong electrochemical force created by the resting potential propels sodium ions (Na^+) from the outside to the inside. The membrane potential begins to increase, a process known as depolarization. Upon reaching a certain voltage threshold, sodium channels are further opened, resulting in a huge influx of Na^+. This rapid depolarization triggers an action potential, shifting the membrane potential to positivity. This action potential is then propagated to the neuron's soma and axon, subsequently transmitted to its downstream neurons through synapses, triggering further alterations in the downstream network. Simultaneously, as the membrane potential becomes positive, potassium channels are activated, rapidly moving potassium ions (K^+) from the inside to the outside, leading to the repolarization of the membrane potential. Excess efflux of K^+ briefly causes hyperpolarization, after which the membrane potential gradually returns to its resting state, prepared for the next stimulus. It is noteworthy that an influx of calcium ions (Ca^{2+}) can also lead to an action potential. In fact, elevated intracellular concentration of Ca^{2+} carries other functional implications, including triggering the opening of potassium channels, the release of neurotransmitters, and the contraction of muscle fibres (Matthews, 2002). Therefore, neuronal activity essentially involves the opening of ion channels and alterations in the membrane potential, triggering internal changes such as neurotransmitter release and subsequently leading to downstream modifications through synaptic connections.

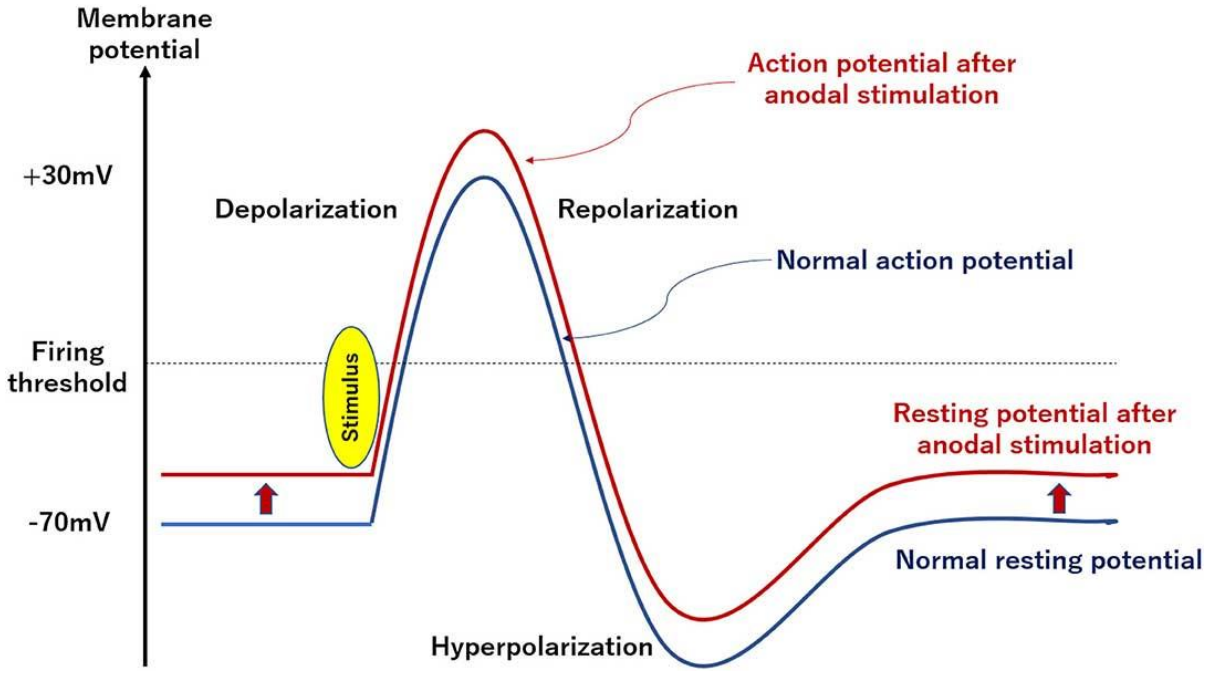

Figure 2-1. Illustration of an action potential (blue curve) and the influence of anodal transcranial direct current stimulation (a-tDCS) (red curve). Normally when stimulated by an external signal (blue curve), the nerve membrane undergoes depolarization, with the membrane potential shifting towards positivity. Upon reaching the firing threshold, an action potential occurs, after which the membrane repolarizes until hyperpolarization. Eventually, the membrane gradually returns to its resting potential. When a-tDCS is applied (red curve), the resting membrane potential is elevated, closer to the firing threshold. The action potential is also higher than normal. a-tDCS is a type of electrical stimulation. A detailed explanation of a-tDCS is provided below in Section 2.2.1. (Reprinted from "Neurobiological Mechanisms of Transcranial Direct Current Stimulation for Psychiatric Disorders; Neurophysiological, Chemical, and Anatomical Considerations," by Yamada, Y., & Sumiyoshi, T., 2021, *Frontiers in Human Neuroscience, 15*, p. 3. Copyright © 2021 Yamada and Sumiyoshi under the Creative Commons CC-BY license.)

The membrane potential can be experimentally manipulated. For instance, physiologically increasing K^+ concentration in the extracellular fluid significantly lowers the resting potential, hindering the firing of an action potential (Huxley & Stämpfli, 1951), which renders a neuron less excitable. Similar alterations can be achieved through non-invasive brain stimulation (NIBS) (Newton et al., 1999; Paulus, 2011; Siebner et al., 2022). By exerting a change in current flow, NIBS is capable of modulating the

functional states of the stimulated neurons and their downstream networks, eventually leading to a measurable change at a behavioural level. Indeed, research has shown that NIBS is able to modulate various brain functions including mood, perception, attention, working memory, motor functions and more (Antal et al., 2022; Bradley et al., 2022). More importantly, NIBS effects are not limited to the duration of stimulation, but are enduring, lasting from hours to even months (Hess & Thompson, 2015; Oberman, 2014; Perin et al., 2020). These long-lasting "offline" effects (effects that persist after cessation of stimulation) are believed to have different mechanisms from "online" modulation (modulatory effects during the stimulation) on membrane potential and appears to involve synaptic alterations including long-term potentiation (LTP) and long-term depression (LDP) (Antal et al., 2022; Sabel et al., 2020; Sudbrack-Oliveira et al., 2021). These enduring aftereffects open the possibility of visual rehabilitation using NIBS techniques (Clavagnier et al., 2013; Hess & Thompson, 2015; Perin et al., 2020; Sabel et al., 2020).

In the past few decades, various types of NIBS have emerged, such as transcranial electrical stimulation (tES), transcranial magnetic stimulation (TMS) and transcranial ultrasound stimulation (TUS) (Darmani et al., 2022; Rotenberg et al., 2014; Sabel et al., 2020; Wagner et al., 2007). These techniques involve different neural mechanisms. This chapter will focus on the neuromodulatory effects of tES and TMS.

2.2 Transcranial Electrical Stimulation (tES)

Transcranial electrical stimulation (tES) involves the delivery of low-intensity electrical current, typically 0.5-2 milliamperes (mA), to the brain (Bradley et al., 2022; Thair et al., 2017). Electrical current is generated by a stimulator and flows to and back from the brain through electrodes placed on the scalp (Figure 2-2). The number of electrodes used and their placement depend on the purpose and design of each study (Thair et al., 2017). At least one anode (through which current flows into the brain) and one cathode (through which current flows back to the stimulator) are required. The current amplitude and electrode sizes determine current density, which can be crucial for electrical stimulation (Nitsche et al., 2007; Thair et al., 2017). With the same amplitude, a larger electrode results in smaller density, whereas a smaller electrode increases the density and focality of stimulation. A density of at least 0.017 mA/cm^2 is recommended for modifying cortical excitability in the human motor cortex (Nitsche & Paulus, 2000; Thair et al., 2017), although a minimum density is not yet established for the visual cortex. Besides current density, it should be noted that individual anatomical differences (such

as skull and cerebrospinal fluid thickness and the folding patterns of gyri) may also have a critical impact on tES effects (Opitz et al., 2015). These variations may partially explain why tES shows an effect in some studies but not in others (Bello et al., 2023).

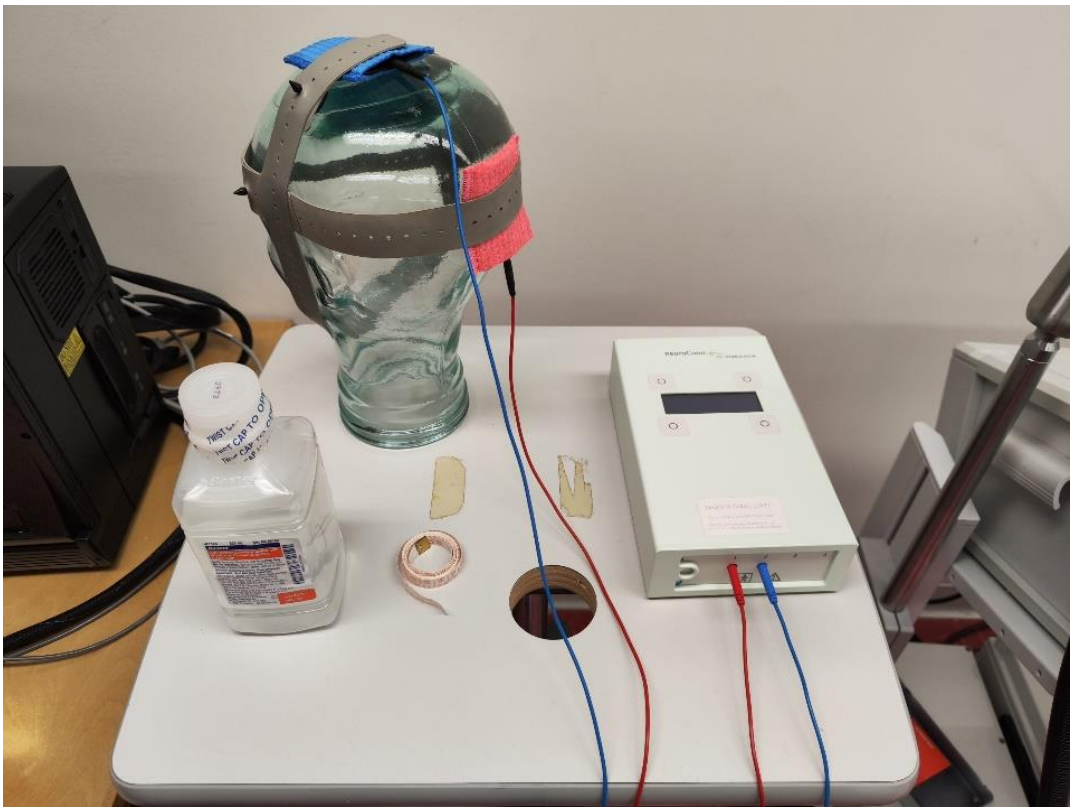

Figure 2-2. tES setup. From left to right: saline solution, two electrodes placed in sponge pads soaked with saline and fastened by elastic straps, a measuring tape and an electrical stimulator (DC Stimulus Plus, neuroConn GmbH, Ilmenau, Germany).

Based on the specific type of electrical current delivered, tES encompasses a range of stimulation modalities. The following sections will discuss two types of tES, namely transcranial direct current stimulation (tDCS) and transcranial random noise stimulation (tRNS).

2.2.1 Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation employs a constant, direct current to stimulate the brain. It involves placing a stimulation electrode on the target cortical area and a reference electrode on a reference area (such as the vertex). Depending on which electrode acts as the stimulation electrode, there are two types of tDCS: anodal (a-)tDCS and cathodal (c-)tDCS. Research shows that a-tDCS produces facilitatory effects on the stimulated area whereas c-tDCS appears to inhibit cortical excitability (Antal et al., 2003, 2004; Nitsche & Paulus, 2000; Reinhart et al., 2016; Sabel et al., 2020). As a result, studies have been employing mainly a-tDCS to investigate the enhancement of visual cortex plasticity. Details regarding this are provided in Chapter 4.

In terms of neural mechanisms, it is believed that low-intensity a-tDCS does not directly induce neuronal firing, but rather shifts the resting membrane potential closer to the firing threshold by activating sodium and calcium channels (Figure 2-1) (Korai et al., 2021; Stagg et al., 2018; Yamada & Sumiyoshi, 2021). In particular, underneath the anodal electrode, negative potential accumulates around proximal dendrites, while positive potential accumulates around the distal soma and axon (Reinhart et al., 2017). This increase in positive potential depolarizes the soma and axon, elevating the probability of an external signal triggering an action potential (Yamada & Sumiyoshi, 2021). Online modulation by a-tDCS may further activate a cascade of signalling transduction within the neuron, trigger a downregulation in GABAergic activity, as shown in the human motor cortex (Stagg et al., 2009, 2011) and the cat visual cortex (Zhao et al., 2020), and modify the strength of its synaptic connections with post-synaptic neurons, resulting in LTP-like alterations in participants' behaviour (Korai et al., 2021; Stagg et al., 2018; Yamada & Sumiyoshi, 2021). With these long-term mechanisms, a-tDCS remains a powerful tool for neuromodulation and has promising application in visual rehabilitation.

2.2.2 Transcranial Random Noise Stimulation (tRNS)

As a form of alternating current stimulation, tRNS is a relatively recent technique, initially introduced by Terney et al. (2008). Electrical current flows between two electrodes, the amplitude and direction of which randomly changes while conforming to a Gaussian distribution (Antal & Herrmann, 2016; Potok et al., 2022). The frequency of the alternating current also fluctuates randomly within a specific range. Frequencies ranging from 0.1 Hz to 100 Hz are categorized as low frequency, while those between 100 Hz and 640 Hz are classified as high frequency. Notably, high-frequency tRNS (hf-tRNS) has

demonstrated greater efficacy within the visual cortex (Terney et al., 2008). Therefore, the majority of studies have employed the high-frequency band for investigations into visual cortex plasticity.

Evidence of hf-tRNS enhancing visual performance is reviewed in detail in Chapter 3. Examples of such enhancement include reduced phosphene thresholds indicating increased cortical excitability (Herpich et al., 2018), heightened orientation discrimination performance (Fertonani et al., 2011), improved visual acuity (Donkor et al., 2021) and faster and more pronounced effects of perceptual learning (Camilleri et al., 2014, 2016; Contemori et al., 2019; Herpich et al., 2019; Moret et al., 2018). Similar to tDCS, hf-tRNS is believed to activate sodium channels on neuronal membranes, inducing an influx of sodium ions, thereby heightening cortical excitability (Chaieb et al., 2015; Perin et al., 2020; Terney et al., 2008; van der Groen et al., 2019). Additionally, hf-tRNS appears to operate in a stochastic resonance manner, a phenomenon where an optimal level of noise enhances the neuronal representation of a subthreshold signal (Figure 2-3) (Miniussi et al., 2013; Potok et al., 2022). In line with this model, studies comparing various intensities of hf-tRNS have shown that 1-1.5 mA stimulation yields the most notable enhancement in visual task performance, surpassing both higher and lower intensities (Pavan et al., 2019; van der Groen & Wenderoth, 2016). Still, these mechanisms accounting for the online effects of hf-tRNS do not fully explain the enduring enhancement in visual performance observed for up to 6 months (Campana et al., 2014; Donkor et al., 2021; Herpich et al., 2019). Recent findings suggest that tRNS effects may be reliant on the GABAergic system in the human motor cortex (Chaieb et al., 2015), and tRNS seems to decrease GABA levels in the mouse prefrontal cortex (Sánchez-León et al., 2021). Although such evidence is yet to be found in the visual cortex, it remains a plausible hypothesis that hf-tRNS may enhance visual cortex plasticity by decreasing GABAergic inhibition, thereby leading to long-term improvements in visual performance.

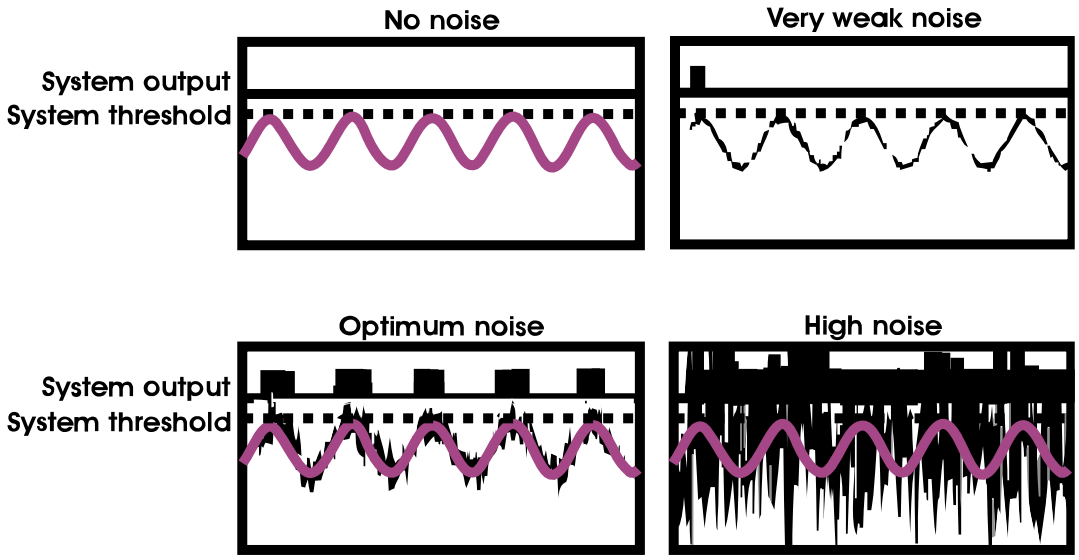

Figure 2-3. Illustration of the stochastic resonance phenomenon. In each panel, the sinusoidal curve represents a subthreshold signal; the dotted line indicates the firing threshold; and the solid line depicts the baseline state of no response. When weak random noise is added to the signal (B), the subthreshold signal rarely reaches the threshold, resulting in minimal system output. With an optimal amount of noise (C), the system is able to represent the signal correctly. Excessive noise (D), however, leads to false positive responses that fail to accurately represent the signal. (Reprinted from "Modelling non-invasive brain stimulation in cognitive neuroscience," by Miniussi, C., Harris, J. A., & Ruzzoli, M., 2013, *Neuroscience & Biobehavioral Reviews, 37(8)*, p. 1706. Copyright © 2013 The Authors under the Creative Commons CC-BY license.)

2.3 Transcranial Magnetic Stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a different type of non-invasive brain stimulation technique, first proposed by Barker et al. (1985). It involves the use of a TMS coil (Figure 2-4) to generate a changing magnetic field. When the coil is placed over a brain area, this changing magnetic field induces electric current in the underlying cortex through a phenomenon known as electromagnetic induction (Rotenberg et al., 2014; Siebner et al., 2022). This induced current is thought to cause an influx of calcium ions and depolarize the neuronal membrane, allowing external suprathreshold signals to reach the firing threshold (Wagner et al., 2007). The influx of calcium ions subsequently activates calcium-dependent potassium channels, resulting in hyperpolarization (Kamitani et al., 2001; Wagner

et al., 2007). This proposed mechanism aligns with the observation that TMS pulses lead to a burst of neural firing, which is then followed by a brief period of suppressed electromyography (EMG) activity, i.e., the cortical silent period, believed to involve inhibitory mechanisms mediated by $GABA_B$ receptors (Fitzgerald et al., 2006; Valero-Cabré et al., 2017; Werhahn et al., 1999). In essence, TMS serves as a potent technique for brain stimulation and can be utilized to explore and modulate neural processing.

Figure 2-4. TMS apparatus, featuring a figure-of-eight coil (MCF-B65, MagVenture, Denmark). For a detailed description of TMS apparatus, please refer to the caption for Figure 6-1 in Chapter 6.

Various designs of TMS coils have been developed (Burke et al., 2019; Rotenberg et al., 2014; Valero-Cabré et al., 2017). Early coils were designed in a simple circular shape, which exhibit poor focality. Figure-of-eight coils were later developed, significantly improving TMS focality and enabling the selective stimulation of specific brain areas. The above coils, however, are only able to target superficial cortices (Burke et al., 2019; Siebner et al., 2022). H-shape coils have recently been developed for deeper stimulation, although with reduced focality compared to figure-of-eight coils

(Burke et al., 2019). Thus, the choice of a coil type can significantly impact the effects of brain stimulation (Brückner & Kammer, 2016). At present, figure-of-eight coils are the most widely used worldwide. Some coil models have also integrated cooling systems to prevent overheating. These coils can be used for longer and more intense stimulation (Valero-Cabré et al., 2017). In short, various types of TMS coils are available, and each study may choose one or more that best suits their research purpose.

TMS can be administered in the form of single pulses or repeated pulses (Valero-Cabré et al., 2017). The intensity of stimulation is quantified as a percentage of the maximum stimulator output (MSO) (e.g., an intensity of 45% MSO). Single-pulse TMS involves delivering single pulses separated by at least 3 seconds. It is commonly used to disrupt neuronal activity (thus inducing "virtual lesions") as well as to evoke neuronal responses (such as muscle twitches and phosphene perception) (Leitão et al., 2017; Rotenberg et al., 2014). On the other hand, repetitive TMS (rTMS) consists of three or more pulses delivered at a higher frequency (more than 1 pulse per 2 seconds). It is typically employed for therapeutic purposes and in interventional research (Sabel et al., 2020). TMS-induced phosphenes and the effects of rTMS are discussed below in detail.

2.3.1 Phosphenes and Phosphene Thresholds

By directly stimulating a visual area, TMS is able to elicit the perception of a faint flash of light, known as a phosphene. Phosphenes can be generated within multiple visual areas, including V1, V2 and V3, although those originating from V1 have been found to be the brightest (Salminen-Vaparanta et al., 2014; Schaeffner & Welchman, 2017). The perceived phosphenes exhibit significant variability in their properties, including shapes, colours and sizes, across individuals (Dugué et al., 2016; Marg & Rudiak, 1994; Salminen-Vaparanta et al., 2014). Nevertheless, higher-intensity TMS is found likely to generate more noticeable phosphenes (Lou et al., 2011).

An intensity that leads to a 50% chance of perceiving phosphenes (e.g., in 5 out of 10 trials) is commonly referred to as a phosphene threshold (PT). Typical procedures for measuring PTs include the following steps: 1) performing dark adaptation or preparing a dimly lit room, 2) applying single-pulse TMS to locate the phosphene "hotspot" (the most reliable cortical spot to induce phosphene perception), 3) applying single-pulse TMS at various intensities to determine the PT (Abrahamyan et al., 2015; Clavagnier et al., 2013; de Graaf et al., 2017; Deblieck et al., 2008; Rahnev et al., 2013; Silvanto & Cattaneo, 2021; Stoby et al., 2022; Thompson et al., 2008, 2009, 2016). It should be noted,

however, that different studies may employ various procedures to measure PTs. For instance, some studies may use double- or triple-pulse TMS (Lou et al., 2011; Silva et al., 2021; Tashiro et al., 2007). A simple binary search is commonly employed (Deblieck et al., 2008; Pearson et al., 2007; Silva et al., 2021; Silvanto & Cattaneo, 2021; Stoby et al., 2022; Thompson et al., 2016), although more complicated methods, such as a Bayesian staircase (Abrahamyan et al., 2015; de Graaf et al., 2017) or the method of constant stimuli (Brückner & Kammer, 2014, 2016; Kammer et al., 2001; Zazio et al., 2019), have been adopted by some researchers to determine the threshold. Some studies may define a PT differently (Pearson et al., 2007; Pitskel et al., 2007; Silva et al., 2021; Tashiro et al., 2007; Tuna et al., 2020). Some may perform the procedures under normal lighting instead of a dark or dimly lit room (Brückner & Kammer, 2016). Interestingly, even when blindfolded, whether the eyes are open or closed has been reported to significantly affect PT results (de Graaf et al., 2017). Such substantial variability in PT measurement methodology makes it challenging to compare results across studies.

PTs have been widely employed as a measure of visual cortex excitability (Boroojerdi et al., 2000; Franca et al., 2006; Gerwig et al., 2003; Valero-Cabré et al., 2017). A lower PT indicates a higher level of excitability in the cortex, while a higher PT indicates reduced excitability. Given the considerable variability in individual cortical excitability and anatomical factors (such as coil-to-cortex distance), PTs have been commonly used to guide normalized and individualized TMS intensities by studies that target the visual cortex (Siebner et al., 2022; Valero-Cabré et al., 2017). As a result, within each study, this normalization approach enables the comparison of results across different participants.

Taken together, these studies demonstrate that phosphenes induced by TMS to the visual cortex serve as a valuable tool for normalizing TMS intensities across individuals, which facilitates the interpretation of TMS effects. Nonetheless, it is important to note that comparing findings between studies remains challenging due to the variations in the methodologies employed.

2.3.2 Repetitive Transcranial Magnetic Stimulation (rTMS)

Repetitive TMS (rTMS) refers to the delivery of repeated TMS pulses with an inter-pulse interval of less than 2 seconds (Burke et al., 2019; Klomjai et al., 2015; Rossini et al., 2015; Valero-Cabré et al., 2017). Depending on the frequency of TMS pulses used, there are different forms of rTMS. Traditional forms include low frequency (≤ 1 Hz) and high frequency (> 1 Hz) rTMS. Low-frequency rTMS is generally delivered continuously. For instance, in 1-Hz rTMS, one TMS pulse is delivered each second. High-frequency rTMS, on the other hand, is usually applied in the form of high-frequency trains that

last a few seconds. These trains may be interleaved with an inter-train interval that lasts dozens of seconds (Rotenberg et al., 2014). Other newer forms of rTMS protocols include theta-burst stimulation (TBS), paired-pulse stimulation and rhythmic TMS (Cirillo et al., 2017; Sabel et al., 2020). These newer rTMS protocols, however, are out of the scope of this thesis and therefore not discussed in detail.

The effects of rTMS on brain activity display a frequency-dependent pattern. Studies, especially those targeting the motor cortex, have demonstrated that low-frequency rTMS reduces neuronal activity while high-frequency rTMS exhibits a facilitatory effect (Casula et al., 2014; Fitzgerald et al., 2006; Sabel et al., 2020; Valero-Cabré et al., 2017). This finding is supported by metabolic measurements in the cat visuo-parietal cortex, which revealed diminished and heightened brain activity following low- and high-frequency rTMS, respectively (Valero-Cabré et al., 2007). It is suggested that rTMS can influence Ca^{2+} signalling (Cirillo et al., 2017; Moretti & Rodger, 2022), which may lead to alterations in gene expression, the release of neurotransmitters (such as GABA, glutamate and serotonin) and synaptic plasticity (Brown et al., 2022; Cirillo et al., 2017; Lin et al., 2023; Moretti & Rodger, 2022; Siebner et al., 2022), thereby resulting in long-term modifications of brain activity. Overall, these studies highlight rTMS as a potent tool for modulating neural plasticity.

On the other hand, investigations into the effects of traditional rTMS of the visual cortex remain limited (Sabel et al., 2020). Some studies have reported inhibitory effects of low-frequency rTMS in line with the dichotomy observed in the motor cortex (Bocci et al., 2011; Hirose et al., 2007; Tashiro et al., 2007). There are, however, also studies suggesting a facilitatory effect (Fierro et al., 2005) and no significant effect (Brückner & Kammer, 2014). Studies on high-frequency rTMS effects in the visual cortex are even scarcer, although facilitatory effects have been reported in cats (Kozyrev et al., 2018) and in patients with amblyopia (Thompson et al., 2008). In addition, a more recent study shows that a single session of rTMS may not significantly affect neurotransmitters in the visual cortex, while repeated sessions may yield more profound effects (Rafique & Steeves, 2020). Given the limited and occasionally inconsistent evidence, further research is necessary to fully elucidate the effects of rTMS at different frequencies on the visual system.

2.4 The State-Dependency of NIBS

Although initially surprising, the observation that the same stimulation protocol applied to the same cortical area does not always yield the same effects is not uncommon. Indeed, NIBS effects, particularly the modulatory effects of TMS, are found to depend on the activation state of the cortical area prior to

brain stimulation, a phenomenon known as the state-dependency of NIBS (Rotenberg et al., 2014; Silvanto & Pascual-Leone, 2008). This phenomenon has been observed with TMS in multiple brain areas, including the prefrontal cortex (Borgomaneri et al., 2020), the motor cortex (Bergmann et al., 2012; Schaworonkow et al., 2019; Siebner et al., 2004; Zrenner et al., 2018) and visual areas (Cattaneo & Silvanto, 2008b, 2008a; Schwarzkopf et al., 2011; Silvanto et al., 2007, 2008). For instance, while both single-pulse TMS and 1-Hz rTMS impaired motion detection performance, single-pulse TMS delivered after 1-Hz rTMS, instead, resulted in a facilitatory effect on task performance (Silvanto et al., 2008). Another example with regard to visual areas involves visual adaptation. Prolonged presentation of the same stimulus (i.e., visual adaptation) is known to result in decreased neuronal response to the adapted attribute (e.g., motion direction). TMS applied after adaptation, however, reversed such effects of adaptation and selectively facilitated the neural processing of the adapted attribute (Cattaneo et al., 2008; Cattaneo & Silvanto, 2008a, 2008b; Silvanto et al., 2007; Silvanto & Muggleton, 2008). Therefore, TMS may be more likely to activate less active neurons that have been affected by adaptation than non-adapted neurons (Cattaneo et al., 2008; Cattaneo & Silvanto, 2008a; Silvanto et al., 2007; Silvanto & Muggleton, 2008). Collectively, these studies demonstrate that the cortical activation state has a significant impact on the direction of TMS effects. For tES, research on this topic is sparse, although there are some reports of state-dependency when stimulating the parietal or prefrontal cortex (Hsu et al., 2016; J. Nguyen et al., 2018; Schutter et al., 2023; Vergallito et al., 2023). More research on the state-dependency of tES is needed, especially regarding tES to the visual cortex.

The effects of TMS can also depend on the delivered intensity. It has been shown that low-intensity TMS tends to produce a facilitatory effect, while high-intensity TMS appears to be inhibitory (Schwarzkopf et al., 2011). Silvanto & Cattaneo (2017) proposed a facilitatory/suppressive range model to characterize the varying effects observed with low- and high-intensity TMS. Importantly, Silvanto et al. demonstrated that the same TMS intensity can produce different effects on primed and non-primed visual stimuli (Silvanto et al., 2017; Silvanto & Cattaneo, 2021). The authors propose that the facilitatory/suppressive range may shift under different cortical states (Silvanto et al., 2017; Silvanto & Cattaneo, 2021). This shift in the facilitatory/suppressive range may, at least in part, explain the state-dependency of TMS.

Another explanation for the state-dependency of TMS involves neural oscillations. Research conducted in the motor cortex demonstrate that a same brain stimulation protocol produces varying effects depending on whether it is delivered during the positive or peak of specific oscillations (Fakche et al., 2022; Granö et al., 2022; Zrenner et al., 2018). For instance, the phase of μ-oscillation, which is

the most important rhythm in the sensorimotor cortex, impacts motor cortex excitability (Zrenner et al., 2018). Higher motor evoked potentials were associated with the negative peak of μ-oscillation, indicating higher cortical excitability (Zrenner et al., 2018). For the visual cortex, it is plausible that oscillation phases may similarly modulate the excitability of target neurons, thereby leading to state-dependent TMS effects.

In summary, the initial state of the brain plays a crucial role in NIBS effects, particularly those of TMS. This state-dependency may involve a shift in the facilitatory/suppressive range for TMS and can be dependent on the phases of neuronal oscillations. It is essential to consider this state-dependency when interpreting NIBS effects. It is worth noting that the majority of these studies investigated the state-dependency of single-pulse TMS. Further research is warranted to comprehensively explore the mechanisms underlying this state-dependency in the visual cortex for various NIBS techniques, including rTMS and tES.

2.5 Chapter Summary

Neural signals are transmitted through electric current. Techniques that alter membrane potentials, such as NIBS, can influence the firing of action potentials and therefore modulate the excitability of stimulated neurons. Different modalities of NIBS, including tES and TMS, operate through different mechanisms. More importantly, in addition to online effects (during stimulation), both tES and rTMS can induce long-lasting changes in behavioural performance after stimulation. These enduring offline effects hold significant relevance for clinical treatments. The excitatory effects of tES have been associated with a reduction in GABA levels, whereas the effects of rTMS in the visual cortex are less clear and may depend on the activation state of the stimulated cortex. Other factors can also influence the outcomes of NIBS, including both the NIBS protocols employed and the individual variability in cortical excitability and cranial anatomy. The utilization of customized TMS intensities based on PTs is likely to mitigate individual variability and facilitate across-participant comparisons.

This thesis investigates whether NIBS techniques, including hf-tRNS, a-tDCS and rTMS enhances short-term ocular dominance plasticity in adults with normal vision. Details on these experiments are explained in Chapters 3, 4 and 6. In addition to binocular rivalry, we adopted a novel ocular dominance test proposed by Bossi et al. (2018), referred to as the letter-polarity test. Given the involvement of rivalrous images in both tests, we refer to the binocular rivalry test as “grating rivalry” to avoid

confusion. A comprehensive evaluation of the reliability of both tests is provided in Chapter 5. Finally, we provide possible explanations in Chapter 7 for interpreting our experimental findings.

The objectives of this thesis are as follows:

Objective 1: To investigate the effects of various NIBS modalities on short-term ocular dominance plasticity in adults with normal vision.

Objective 2: To deepen the understanding of the neural mechanisms underlying short-term ocular dominance plasticity.

Objective 3: To contribute further insights into the state-dependency of NIBS within the visual cortex.

Objective 4: To evaluate the efficacy of the letter-polarity test as a tool of measuring ocular dominance shifts following MD.

Chapter 3
The Effect of Transcranial Random Noise Stimulation and Physical Exercise on Ocular Dominance Plasticity in Adults with Normal Vision

This chapter was published in Journal of Vision in 2022 (doi: 10.1167/jov.22.10.14). Individual author contributions can be found in the Summary of Contributions section above. This work was supported by grants from the Natural Sciences and Engineering Research Council of Canada (NSERC; RGPIN-04404 to WB and RGPIN-05394 and RGPAS-477166 to BT) and the Canadian Foundation for Innovation (34095 to BT), as well as a Midwestern University Faculty Start-Up Seed Grant to AC. BT was also supported by the Hong Kong Special Administrative Region Government and InnoHK. None of the authors have any conflicts of interest to declare.

3.1 Overview

Short-term deprivation of one eye by monocular patching causes a temporary increase in the contribution of that eye to binocular vision when the eye patch is removed. This effect, known as ocular dominance plasticity, provides a model of neuroplasticity within the human binocular visual system. We investigated whether physical exercise and the non-invasive brain stimulation technique transcranial random noise stimulation (tRNS), two interventions that may increase visual cortex neuroplasticity, enhance ocular dominance plasticity when delivered individually or in combination. Ocular dominance was measured using a grating rivalry test and a dichoptic letter contrast polarity judgement test. We observed robust ocular dominance changes for both outcome measures following 2-hour monocular deprivation; however, the magnitude of the effect was not influenced by exercise or tRNS. Ocular dominance plasticity may already be maximal after 2 hours of monocular deprivation in those with normal vision and therefore cannot be augmented by interventions designed to enhance neuroplasticity.

3.2 Introduction

Patching one eye (monocular deprivation, MD) for a short period of time alters eye dominance in human adults. Lunghi et al. (2011) were the first to demonstrate this effect, now referred to as ocular dominance

plasticity, by measuring binocular rivalry dynamics using dichoptic gratings (grating rivalry) before and after 2.5 hours of MD. They found that, after MD, the deprived eye exhibited increased dominance during grating rivalry. This effect has been independently replicated in individuals with normal vision and those with amblyopia using grating rivalry tasks (Finn et al., 2019; Lunghi et al., 2011, 2013; Lunghi & Sale, 2015; Sheynin, Chamoun, et al., 2019), global motion coherence tasks (J. Zhou, Clavagnier, et al., 2013), binocular phase combination tasks (Bai et al., 2017; X. Chen et al., 2020; Min et al., 2018; Sheynin, Chamoun, et al., 2019; J. Zhou et al., 2017; J. Zhou, Clavagnier, et al., 2013; J. Zhou, Thompson, et al., 2013), binocular orientation combination tasks (Spiegel et al., 2017; Y. Wang et al., 2019) and electrophysiological recordings (Chadnova et al., 2017; Lunghi, Berchicci, et al., 2015; J. Zhou et al., 2015). In these studies, MD duration ranged from 30 minutes to 5 hours and the ocular dominance plasticity effect lasted from approximately 30 minutes to 1 hour. Together, the results of ocular dominance plasticity studies indicate that MD modifies a fundamental component of binocular vision.

Increased neural activity in response to visual stimulation of the deprived eye has been observed using both functional magnetic resonance imaging (fMRI) (Binda et al., 2018) and steady-state visual evoked potentials (SSVEPs) (J. Zhou et al., 2015). Along with psychophysical observations (Baldwin & Hess, 2018; Sauvan et al., 2019; J. Zhou, Clavagnier, et al., 2013), these findings suggest that ocular dominance plasticity arises from an upregulation of contrast gain for deprived eye inputs to the visual cortex. The observation that MD causes a reduction in gamma-aminobutyric acid (GABA) levels in the primary visual cortex (Lunghi, Emir, et al., 2015) suggests that reduced cortical inhibition may enable the associated contrast gain changes.

Several interventions have been identified that may enhance neuroplasticity within the visual cortex. These include systemic drugs (Gratton et al., 2017; Silver et al., 2008), exercise (Cassilhas et al., 2016; Hötting & Röder, 2013), video games (Bediou et al., 2018; Föcker et al., 2018) and non-invasive brain stimulation techniques (such as transcranial random noise stimulation, tRNS) (Fertonani et al., 2011; Sabel et al., 2020; for a review, see Thompson, 2021). Studies involving some of these interventions have used ocular dominance plasticity as a neuroplasticity index. For example, Sheynin et al. (2019b) investigated the effect of cholinergic potentiation, which counteracts GABAergic inhibition, on ocular dominance plasticity, hypothesizing that it might enhance the effect of MD. Contrary to their hypothesis, they found that donepezil, a cholinesterase inhibitor, reduced ocular dominance plasticity in adults with normal vision. In another study, participants played different genres of video games during monocular deprivation to test the hypothesis that attentionally demanding games would enhance

ocular dominance plasticity (X. Chen et al., 2020). No effect of video game play was observed. However, in a different study where participants either completed an attentive jigsaw task or passively stared at a plain curtain, Wang and colleagues found greater ocular dominance plasticity following the attentive task, suggesting that attention may still play a role in the effect of MD (M. Wang et al., 2021). Moreover, inspired by evidence from animal studies that physical exercise enhances neuroplasticity by reducing GABAergic inhibition (Baroncelli et al., 2012; Kaneko & Stryker, 2014), several groups have explored the effect of exercise on ocular dominance plasticity. The results have been mixed. Lunghi and Sale (2015) demonstrated that cycling increased the magnitude of the ocular dominance plasticity. Other groups, however, failed to replicate this effect (Finn et al., 2019; J. Zhou et al., 2017). Thus, despite these attempts, an effective protocol for enhancing human neuroplasticity indexed by increased ocular dominance plasticity has not yet been identified.

tRNS, which involves the delivery of an alternating current with randomly varying amplitudes and frequencies to targeted brain areas via head mounted electrodes (Terney et al., 2008), has the potential to enhance visual cortex neuroplasticity and enhance ocular dominance plasticity. Cortical excitability can be modulated using tRNS (Herpich et al., 2018), and several studies have reported that high-frequency tRNS (hf-tRNS; frequency range 100–640 Hz) to the visual cortex improves vision task performance. To illustrate, delivering hf-tRNS to the visual cortex for 22 minutes resulted in significantly better performance in an orientation discrimination task compared with sham stimulation (Fertonani et al., 2011). In addition, visual cortex hf-tRNS increased the rate and magnitude of visual perceptual learning for a global motion detection task in both healthy participants and patients with cortical blindness (Herpich et al., 2019). In patients with amblyopia, hf-tRNS to the visual cortex coupled with 2 weeks of perceptual learning significantly improved the visual acuity of both trained and untrained eyes (Campana et al., 2014; Moret et al., 2018). Possible mechanisms for tRNS effects include modulation of voltage-gated sodium channels leading to faster depolarization and the induction of stochastic resonance by adding noise to stimulated neural areas which results in a higher signal-to-noise ratio, a higher probability of positive response, and thus an improvement in signal detection (Moret et al., 2019; Pavan et al., 2019; van der Groen et al., 2019; van der Groen & Wenderoth, 2016). There is also evidence that tRNS induced a reduction in GABAergic inhibition when applied to the motor cortex (Chaieb et al., 2015) or the prefrontal cortex (Sánchez-León et al., 2021). Therefore, it is possible that tRNS may interact with MD to enhance deprived eye contrast gain and augment ocular dominance plasticity.

Based on their potential to modulate neural excitability and GABA-mediated inhibition within the human visual cortex, we explored the effects of physical exercise and occipital hf-tRNS on ocular dominance plasticity in adults with normal vision. We further explored whether any effects of these two interventions were additive. Because ocular dominance plasticity may arise from reduced visual cortex inhibition, we hypothesized that hf-tRNS and exercise would each enhance the magnitude of eye dominance changes compared with monocular deprivation alone. We also predicted larger increases in ocular dominance plasticity when both interventions were combined. Deprived eye dominance was measured using two binocular rivalry tests – one that was a traditional rivalry test involving dichoptic gratings (hereafter referred to as the grating rivalry test) to measure periods of dominance of the component grating percept of each eye (Finn et al., 2019; Lunghi & Sale, 2015; Sheynin, Chamoun, et al., 2019; Sheynin, Proulx, et al., 2019) and the other involving dichoptic letters with opposite contrast polarities (hereafter referred to as the letter-polarity test). The letter-polarity test was recently proposed by Bossi et al. (2018). Compared with other psychophysical eye dominance tests, the letter-polarity test is a relatively easy task for participants to perform and has the potential to be used in clinical settings; therefore, we wanted to assess whether this test can measure eye dominance changes. Our secondary outcome was the duration of grating rivalry mixed percepts. An increase in mixed percept durations (perceiving the images of both eyes during grating rivalry) indicates a reduction of interocular inhibition (Kang & Blake, 2011). Because any changes in visual cortex inhibition induced by tRNS and/or exercise would be general (i.e., not specific to one eye), we anticipated that mixed percept durations might increase following these interventions.

3.3 Methods

3.3.1 Participants

Inclusion criteria were best corrected visual acuity ≤ 0.0 logMAR in each eye. Exclusion criteria were (a) inability to fuse dichoptic images; (b) high baseline eye dominance (ED > 0.7), as determined by our computerized eye dominance tests described below; and (c) common safety considerations for transcranial electrical stimulation, including a history of epilepsy or seizures, pacemakers or metal implants within the skull, pregnancy, mental illness or psychiatric conditions, and psychoactive medication. Participants were asked to avoid any recreational drugs within 24 hours before their visits. This study conformed with the tenets of the Declaration of Helsinki and was approved by the Ethics

Committee of Midwestern University (Downers Grove, IL). Written informed consent was obtained from all participants prior to their participation.

3.3.2 Eye dominance tests

Eye dominance was measured using two tests: the grating rivalry test and the letter-polarity test. Visual stimuli for both tests were presented on a light-emitting diode monitor (ROG PG278QR, ASUSTeK Computer Inc., Taipei, Taiwan) against a grey background (48 cd/m^2). The refresh rate of the monitor was 60Hz, and the resolution was 1920×1080 pixels. The stimuli for the grating rivalry test were generated on a Windows computer (Intel Core i7-8700K, 16GB RAM) using MATLAB R2019a (MathWorks, Natick, MA) with Psychtoolbox 3.0.15 extensions. The stimuli for the letter-polarity test were generated on the same computer via the PsychoPy module in Python 3.6.6. Participants viewed left and right stimuli dichoptically through a mirror stereoscope. The viewing distance was 108 cm. A chinrest was used to stabilize participants' head position.

In the grating rivalry test (Figure 3-1), two stationary, orthogonally oriented (+45° and -45°) circular gratings (2° diameter, 2 cycles per degree (cpd), 100% Michelson contrast) were dichoptically presented. Participants continuously reported their perception using a keyboard while fixating a central cross. Specifically, participants were instructed to press one of four keys to indicate exclusive perception of the -45°grating, exclusive perception of the +45° grating, perception of a uniform plaid pattern ("superimposition"), or perception of patches of the orthogonal gratings ("piecemeal"). Six 1-minute trials were presented. Percept durations were summed and averaged across trials. We subsequently added superimposition and piecemeal durations together to calculate the duration of total "mixed" percepts (d_M). Half of the mixed percept duration was added to each exclusive percept (deprived, d_D; non-deprived, d_{ND}) to calculate eye dominance. This was done to include the contribution of each eye to mixed percepts within the equation. Thus, deprived eye dominance was $ED_{rivalry} = \frac{d_D + \frac{1}{2} * d_M}{d_D + d_{ND} + d_M}$. Eye dominance results ranged from 0 to 1, with a larger value indicating more dominance by the deprived eye. This calculation is mathematically equivalent to the ocular dominance index ($ODI = \frac{d_D - d_{ND}}{d_D + d_{ND} + d_M}$) used in Min et al., 2021 (i.e., $ED_{rivalry} = \frac{1}{2} * ODI + \frac{1}{2}$). The rate of perceptual alternations (i.e., the alternation rate) was calculated as the average number of alternations per second.

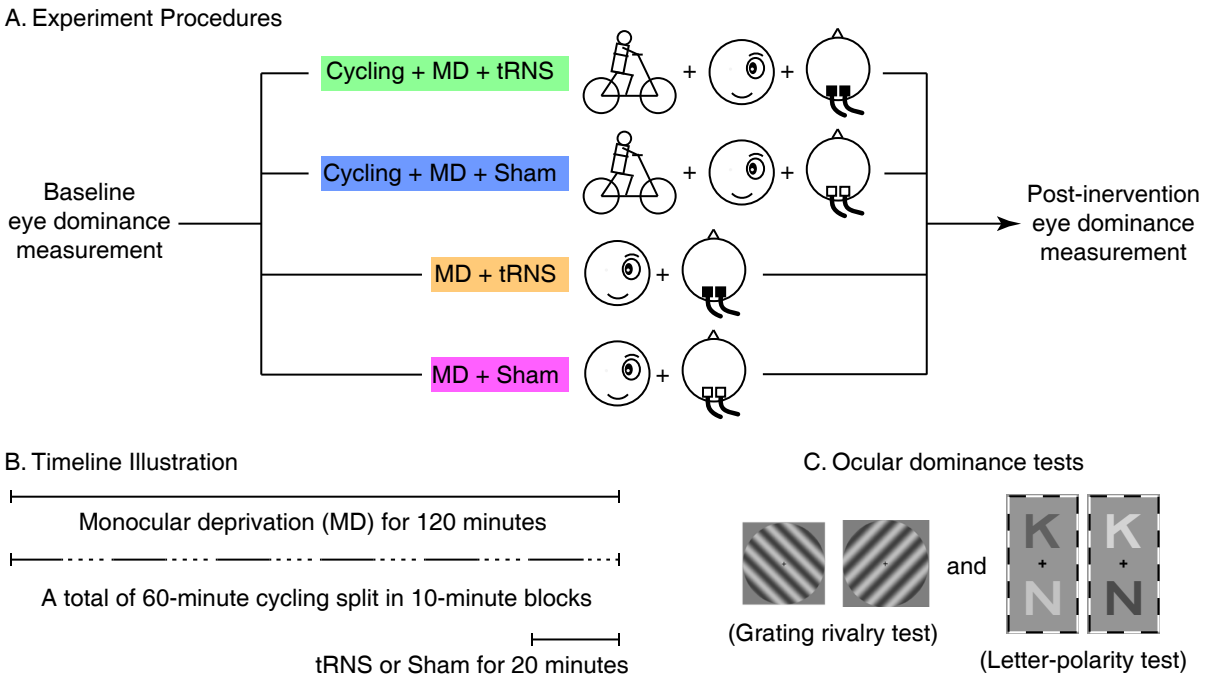

Figure 3-1. tRNS experimental design. (A) Procedures in the experiment. (B) Timeline of interventions during MD. In all conditions, participants received MD of their dominant eye for 2 hours. During the final 20 minutes of MD, participants received either tRNS or sham stimulation. In two conditions, participants performed a cycling task for a total of 60 minutes (10-minute blocks of cycling separated by 10-minute rests). Participants wore a heart rate sensor while cycling and were asked to maintain 60% of their maximum heart rate. Eye dominance was measured before and after MD using two computerized tests (C). Please refer to the main text for further details.

The letter-polarity eye dominance test was originally described by Bossi et al. (2018). Briefly, two pairs of inverse polarity letters were presented dichoptically (Figure 3-1). Each pair in the top and bottom rows contained a dark letter (with a negative contrast coded as a minus value) and a bright letter (with a positive contrast coded as a positive value). The contrasts of the two letters presented to each eye always summed to zero. Participants fused the fixation cross and the fusion-lock boarder of the stimuli to superimpose the positive and negative contrast versions of the same letter. Participants reported whether the top or bottom letter was whiter. When rivalry was experienced, participants were asked to compare the whiteness of the positive contrast upper and lower letters. To measure the "balance point" of the interocular contrast difference at which the left eye and right eye letters had an equal probability of dominance, we implemented the method of constant stimuli. Twenty repeats of nine letter

contrasts (from 0.3 to 0.7, in steps of 0.05, producing interocular differences ranging from 0 to 0.4) were tested in a random order for a total of 180 trials. With a given contrast value *c*, the contrasts in each vertical letter pair were either *c* and -(1-*c*) or -*c* and (1-*c*). These two pairs of contrasts were randomly assigned to the top or bottom row of the stimulus. For full details of the manipulation of letter contrasts, please refer to Bossi et al. (2017) and Bossi et al. (2018). We subsequently used a Logistic function to fit these data and calculated the point of subjective equality (PSE) as the balance point. This balance point was used to indicate deprived eye dominance (ED_{letter}). A value greater than 0.5 indicated greater dominance by the deprived eye; a value smaller than 0.5 indicated greater dominance by the non-deprived eye.

3.3.3 Cycling

In two visits, participants completed six 10-minute blocks of cycling on a stationary bike separated by 10 minute rest blocks (Finn et al., 2019; Lunghi & Sale, 2015) during the 2-hour monocular deprivation period (Figure 3-1). Participants wore a Polar H10 heart rate sensor (Polar Electro, Helsinki, Finland) to monitor their heart rate, and they were able to read their heart rate from a mobile app. While cycling, participants were asked to maintain their heart rate at 60% maximal heart rate. This maximal heart rate was calculated based on the Tanaka formula ($HR_{max} = 208 – 0.7 \times age$) (Tanaka et al., 2001). A 1-mile walk test was used to estimate participants' maximal oxygen consumption (VO_{2max}) (Kline et al., 1987). VO_{2max} was used to ensure that participants were of average cardiovascular fitness for their age so that the heart rate estimation was valid.

3.3.4 Transcranial random noise stimulation (tRNS)

During the final 20 minutes of the 2-hour monocular deprivation period, hf-tRNS (100–640 Hz) was delivered to the visual cortex using a battery-driven stimulator (DC-Stimulator Plus; neuroConn GmbH, Ilmenau, Germany). Two electrodes were placed over O_1 and O_2 as identified using the international 10/20 electrode positioning system. These sponge electrodes (35 cm^2) were soaked in saline to reduce impedance. The electrodes were kept in place with elastic bands. A 1-mA current was applied to the visual cortex for 20 minutes. The current ramped up to 1 mA for 20 seconds at the beginning and ramped down for 20 seconds at the end. For sham stimulation, the electrodes were placed over the same cortical areas. The current ramped up for 20 seconds, and then ramped down for 20 seconds. The

stimulator was kept behind participants with its screen covered so that participants would not see it. The experimenter occasionally checked the screen as if real stimulation were being delivered.

3.3.5 Procedures

This study employed a within-subjects design and involved four laboratory visits (Figure 3-1). During each visit, participants first completed both eye dominance tests to measure their baseline eye dominance and then wore a translucent eye patch over their dominant eye as determined by the grating rivalry test (MD) for 2 hours. The eye patch allowed only diffuse light transmission. Participants were asked to keep their deprived eye open while using their other eye to watch a movie randomly picked from the *Harry Potter* franchise.

During the final 20 minutes of monocular deprivation, participants received either tRNS or sham stimulation of their visual cortex. In two of the four visits, participants were also asked to perform a cycling task while one eye being deprived. Thus, the combinations of interventions were (a) cycling + MD + tRNS; (b) cycling + MD + sham; (c) MD + tRNS; (d) MD + sham (Figure 3-1). The sequence of these four conditions was randomized. Immediately after MD, eye dominance was measured again. Because the grating rivalry test was our primary measure of eye dominance, participants always completed this test before the letter-polarity test.

3.3.6 Data analysis

Data were analysed using JASP. A p value < 0.05 was considered statistically significant. Normality of data was assessed using Shapiro-Wilk tests. Mauchly's sphericity tests were used to confirm the sphericity of data. Non-spherical data were corrected using the Greenhouse-Geisser method. Outcome changes across conditions were compared using a two-way repeated measures analysis of variance (ANOVA) with a within-subjects factor of condition (four conditions as described above) and a within-subjects factor of time (pre- vs post-intervention). Deprived eye dominance from each test, mixed percept durations, and alternation rates were analysed separately. A one-way repeated measures ANOVA was also performed on the differences from baseline scores for deprived eye dominance. Effect sizes were reported using omega squared (ω^2).

3.4 Results

A total of 20 healthy adult participants (12 females) were recruited. Three participants were excluded due to high baseline eye dominance (ED > 0.7). Seven participants withdrew due to personal reasons. Hence, 10 participants (age: 22-30 years, median 25 years; 9 females) completed the study. All participants except two were naïve to this study. To ensure grating rivalry dynamics were correctly recorded, we removed any blocks with a total response duration < 50 seconds, indicating a failure to hold down a response button or the use of two button simultaneously. As a result, six trials out of the total 480 trials were removed from the analysis. As expected for participants with weak eye dominance, baseline eye dominance varied across sessions and across the two eye dominance tests (Li et al., 2010) (see Supplementary Table 1 in Appendix A).

3.4.1 Primary outcome: deprived eye dominance shift

Figure 3-2 (A & B) shows deprived eye dominance changes (ocular dominance plasticity) as measured by the grating rivalry test. There was a significant increase in deprived eye dominance after intervention, with a significant main effect of time: $F(1, 9) = 13.56$, $p = 0.005$, $\omega^2 = 0.254$. However, there were no significant differences across conditions, with no main effect of condition: $F(3, 27) = 0.113$, $p = 0.952$, $\omega^2 < 0.001$, and no interaction between these two factors, $F(3, 27) = 0.081$, $p = 0.970$, $\omega^2 < 0.001$.

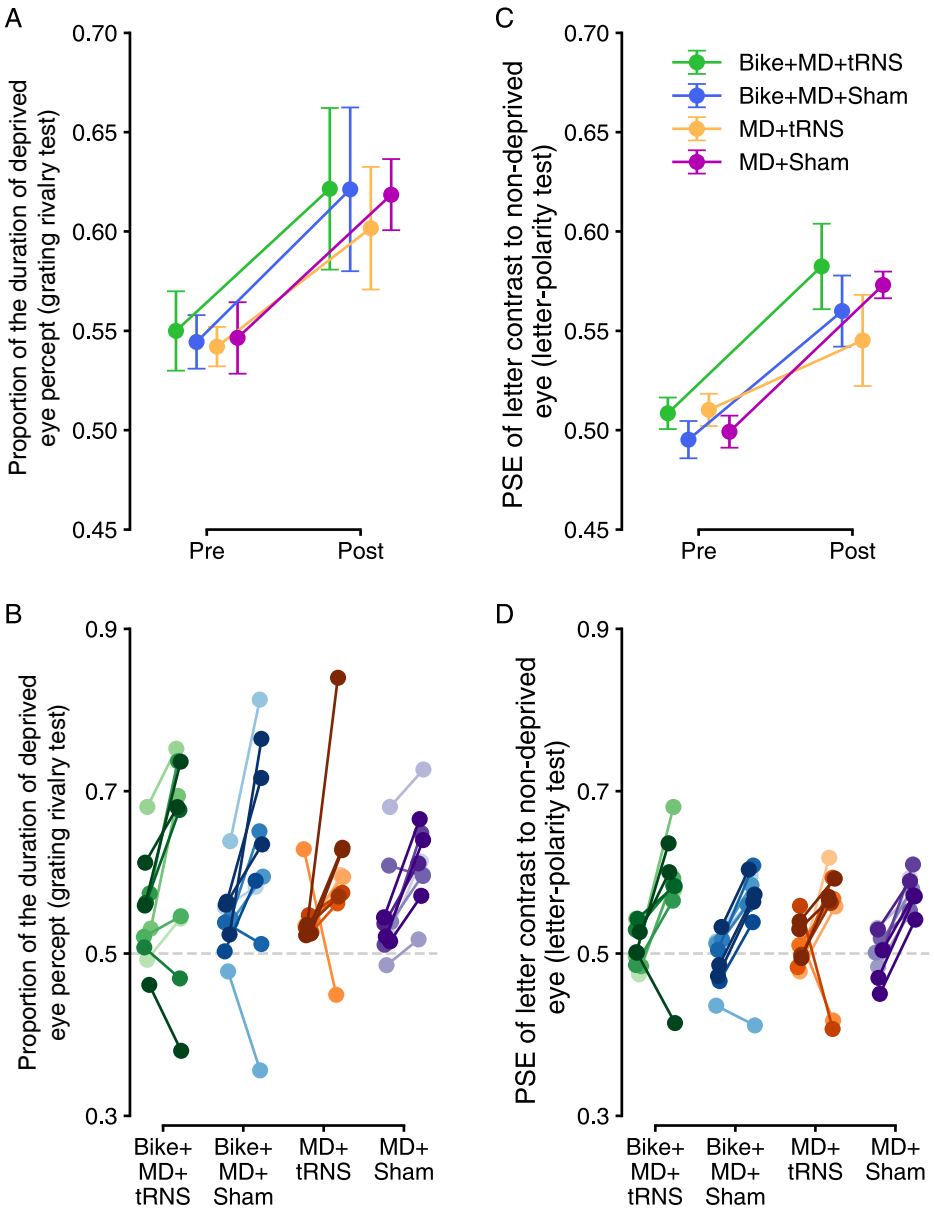

Figure 3-2. Deprived eye dominance data for the grating rivalry (A & B) and letter-polarity (C & D) tests in Experiment 1. The top row shows group mean data before (pre-) and after (post-) intervention. Error bars denote standard errors of the mean. The bottom row shows individual pre and post data within each condition. In the grating rivalry test (A & B), the proportion of deprived eye percept duration was calculated to indicate deprived eye dominance. In the letter-polarity test (C & D), the letter contrast presented to the non-deprived eye at the PSE was calculated to indicate deprived eye dominance. Dashed grey lines represent an eye dominance of 0.5 (i.e., two eyes are perfectly balanced). A value above the dashed lines indicates greater dominance by the deprived eye. On four occasions

there was an eye dominance assignment error for participants with weak eye dominance. Therefore, there are four baseline data points slightly below the 0.5 line in Panel B. Because the grating rivalry test (A & B) was used to assign the dominant (deprived) eye, there are many baseline datapoints below the 0.5 line as anticipated for the letter-polarity test (C & D).

Figure 3-2 (C & D) shows deprived eye dominance changes as measured by the letter-polarity test. There was a significant increase in deprived eye dominance after intervention, $F(1, 9) = 64.36$, $p < 0.001$, $\omega^2 = 0.657$. However, there were no significant differences across conditions, $F(3, 27) = 0.708$, $p = 0.556$, $\omega^2 < 0.001$, and no interaction, $F(1.851, 16.661) = 0.811$, $p = 0.452$, $\omega^2 < 0.001$.

We also baseline normalized the data for each session for each participant using subtraction and performed a one-way repeated measures ANOVA for each eye dominance test to check for any differences between conditions. The results remained unchanged: grating rivalry test $F(3, 27) = 0.081$, $p = 0.970$, $\omega^2 < 0.001$; letter-polarity test $F(1.851, 16.661) = 0.811$, $p = 0.452$, $\omega^2 < 0.001$.

3.4.2 Secondary outcomes: mixed percept durations & alternation rates

We designed our button press options in the grating rivalry test to distinguish superimposition and piecemeal percepts, as it was reported that these two percepts could be influenced differently by monocular deprivation (Sheynin, Proulx, et al., 2019). However, superimposition was reported only by four participants for an average of 11.6 ± 8.5 seconds. Therefore, we combined the superimposition and piecemeal percept responses to assess mixed percept durations.

Figure 3-3 (A & B) shows mixed percept durations changes as measured by the grating rivalry test. There were no main effects of time, $F(1, 9) = 0.021$, $p = 0.889$, $\omega^2 < 0.001$, or condition, $F(3, 27) = 0.336$, $p = 0.800$, $\omega^2 < 0.001$, and no interaction, $F(3, 27) = 0.740$, $p = 0.538$, $\omega^2 < 0.001$.

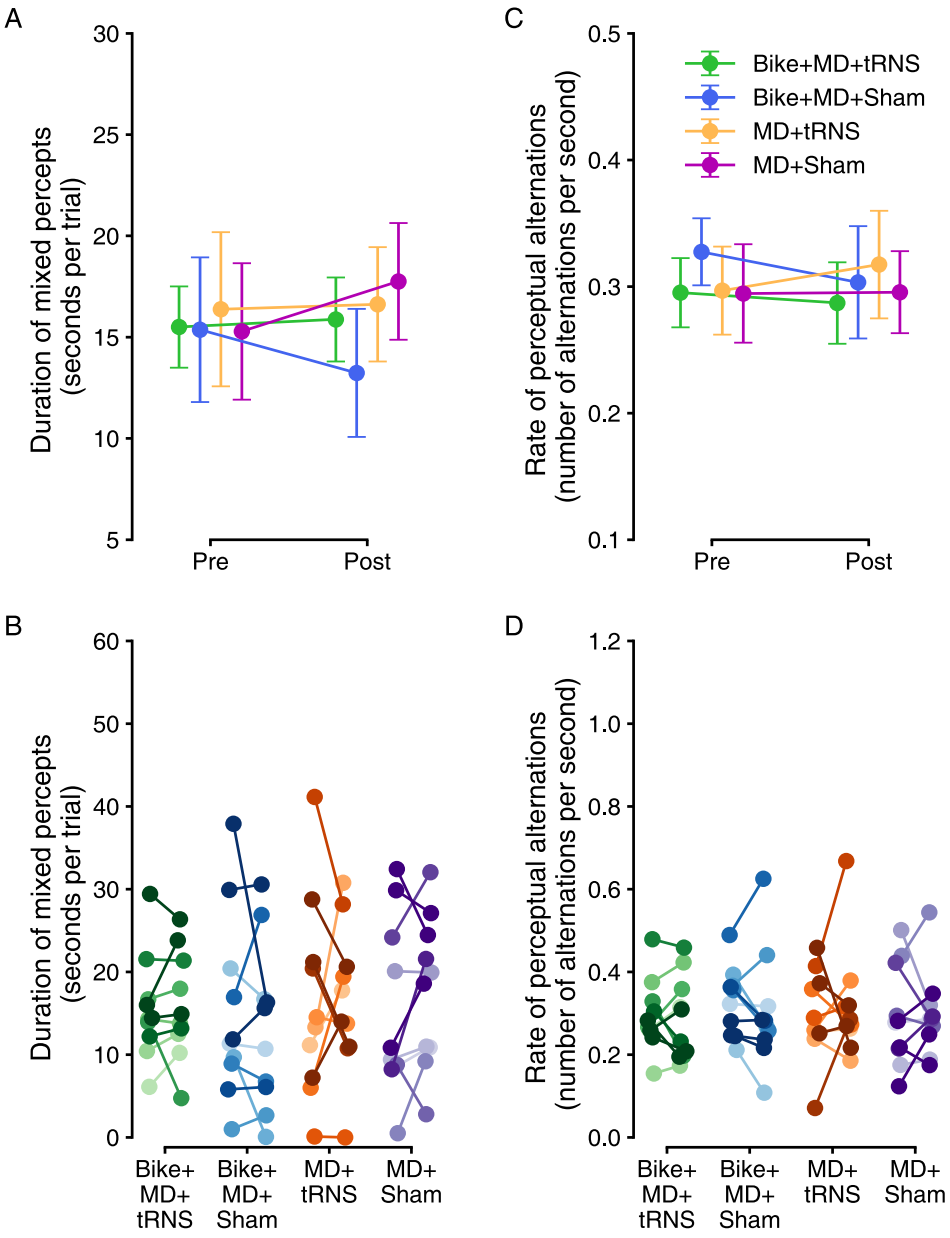

Figure 3-3. Durations of mixed percepts (A & B) and alternation rates (C & D) measured by the grating rivalry test in Experiment 1. The top row shows group mean data before (pre-) and after (post-) intervention. Error bars denote standard errors of the mean. The bottom row shows individual pre and post data within each condition. Both the durations of mixed percepts and alternation rates were averaged over six 1-minute trials.

Figure 3-3 (C & D) shows alternation rate changes as measured by the grating rivalry test. There were no significant differences between pre- and post-intervention, $F(1, 9) = 0.039$, $p = 0.848$, $\omega^2 < 0.001$, or across conditions $F(3, 27) = 0.406$, $p = 0.750$, $\omega^2 < 0.001$, and no interaction $F(3, 27) = 0.286$, $p = 0.835$, $\omega^2 < 0.001$.

3.5 Discussion

We replicated previous reports of ocular dominance plasticity following MD using both a grating rivalry test and a dichoptic letter-polarity test. Eye dominance shifted significantly in favour of the deprived eye after MD. This shift was not influenced by physical exercise, tRNS, or their combination. We also observed that neither mixed percept durations nor alternation rates during grating rivalry were significantly altered by tRNS, physical exercise, or MD.

We expected physical exercise to increase the magnitude of ocular dominance plasticity. Our hypothesis was mainly predicated on findings indicating that physical activity promotes visual cortex neuroplasticity and enables recovery of vision following early monocular deprivation (Baroncelli et al., 2012; Kaneko & Stryker, 2014) or stroke (Kalogeraki et al., 2016) in adult rats. In human adults, there has been evidence that physical exercise enhances neuroplasticity, resulting in cognitive function improvement (Cassilhas et al., 2016; Hötting & Röder, 2013). Furthermore, Lunghi and Sale (2015) observed that physical exercise enhanced ocular dominance plasticity. Finn et al. (2019) reanalysed Lunghi and Sale's data and found that the effect of exercise on ocular dominance plasticity was present when grating rivalry data were analysed using mean dominance durations but not when using median durations, indicating high variation across subjects. Within their own data, Finn et al. (2019), along with Zhou et al. (2017), did not observe any effect of exercise on ocular dominance plasticity. Moreover, studies using different experimental paradigms to explore exercise-induced neuroplasticity did not observe any effect of exercise on visual perceptual learning (Campana et al., 2020; Connell et al., 2018). Interestingly, Connell et al.'s (2018) work showed that exercise prior to perceptual learning blocked the learning effect. Here we observed that exercise did not modulate ocular dominance plasticity. It remains unclear why exercise had an effect in Lunghi and Sale (2015) but not in other studies.

High-frequency tRNS is a promising non-invasive brain stimulation technique that can modulate cortical excitability. hf-tRNS for as little as 20 minutes is able to reduce phosphene thresholds (increase visual cortex excitability) for up to 1 hour (Herpich et al., 2018). hf-tRNS also strengthens perceptual

learning for a variety of visual tasks (Campana et al., 2014; Contemori et al., 2019; Fertonani et al., 2011; Herpich et al., 2019; Moret et al., 2018). In patients with amblyopia, full-frequency tRNS leads to acute improvements in monocular contrast sensitivity and visual acuity (Donkor et al., 2021). Our results did not reveal an effect of hf-tRNS on ocular dominance plasticity.

Our finding that exercise, tRNS and their combination did not influence ocular dominance plasticity may simply indicate that these interventions have no effect on the homeostatic plasticity processes that are thought to underlie the effects of short-term MD. Another possibility is that there may be a ceiling effect for ocular dominance plasticity in visually-normal adults. In fact, as described in the introduction, several groups have tried to augment ocular dominance plasticity by combining MD with different interventions (X. Chen et al., 2020; Finn et al., 2019; Lunghi & Sale, 2015; Sheynin, Chamoun, et al., 2019; M. Wang et al., 2021; J. Zhou et al., 2017). Min et al. (2019) also examined whether there was any cumulative effect of multiple sessions of monocular deprivation on ocular dominance plasticity. Most of these studies did not observe an increase in ocular dominance plasticity, in agreement with our results. On the other hand, there is initial evidence that interventions such as exercise and tRNS may increase ocular dominance plasticity and improve vision in visually-impaired populations such as adults with amblyopia (Hess & Thompson, 2013; Lunghi, Sframeli, et al., 2019; Perin et al., 2020; Sabel et al., 2020; Tuna et al., 2020). Future studies should further explore the use of such interventions in these populations.

Most ocular dominance plasticity studies have adopted 2 to 2.5 hours of MD (Chadnova et al., 2017; X. Chen et al., 2020; Lunghi & Sale, 2015; Sheynin, Chamoun, et al., 2019; J. Zhou et al., 2017). Min et al. (2018) assessed whether varying the duration of MD from 30 minutes to 5 hours would influence the MD effect. They reported no statistically significant effect of duration; however, there did appear to be a trend for longer MD producing larger effects. In a neuromodulation study, Sheynin, Chamoun, et al. (2019) performed both 2-hour and 1-hour MD. Although the authors did not compare these two deprivation durations, it seems, from their data, that 2-hour MD produced ocular dominance plasticity that was two times the magnitude of that induced by 1-hour MD. Given such evidence, we suspect that shorter MD durations (i.e., less than 2 hours) may remove the ocular dominance plasticity ceiling effect in adults with normal vision and reveal enhanced plasticity following interventions such as exercise and tRNS.

We also examined the differential influence of MD, tRNS and exercise on mixed percept durations. This type of percept is believed to happen when interocular inhibition is relatively low, allowing for a temporary combination of left and right eye images (Kang & Blake, 2011). There are two subtypes of

mixed percepts: superimposition, which involves binocular combination of both images, and piecemeal, where rivalry still exists in some parts of the stimuli (Alais & Melcher, 2007; Sheynin, Proulx, et al., 2019; Skerswetat et al., 2018). The prominence of mixed percepts during rivalry has been linked to GABA-mediated inhibition within the visual cortex. Increased GABA-mediated inhibition reduces mixed percept durations (Mentch et al., 2019), whereas MD has been found to increase mixed percept durations (Sheynin, Proulx, et al., 2019), presumably due to reduced visual cortex inhibition (Lunghi, Emir, et al., 2015). However, not all results are consistent with this model. For example, Abuleil et al. (2021) observed prolonged mixed percept durations following continuous theta burst stimulation (cTBS) to the visual cortex, an intervention that increases inhibition (Franca et al., 2006; Sabel et al., 2020). In the same study, no change in mixed percept durations was observed following excitatory anodal tDCS of the visual cortex (Abuleil et al., 2021). A recent study (B. N. Nguyen et al., 2023) also observed no effect of MD on mixed percepts, contrary to Sheynin, Proulx, et al.'s observation (2019) but similar to ours.

One possible explanation for the absence of an effect of MD on mixed percept durations may be related to the size and spatial frequency of our grating rivalry stimuli. It has been demonstrated that these parameters influence grating rivalry dynamics whereby large and high spatial frequency stimuli tend to produce longer mixed percepts (Kang, 2009; O'Shea et al., 1997; Skerswetat et al., 2016). Previous studies on mixed percept durations have used various stimulus parameters for their grating rivalry tests, with sizes ranging from 1 to 6.1 degrees of visual angle and spatial frequencies ranging from 0.5 to 4 cpd (Abuleil et al., 2021; Bai et al., 2017; Lunghi et al., 2011, 2016; Lunghi, Galli-Resta, et al., 2019; Lunghi, Sframeli, et al., 2019; Lunghi & Sale, 2015; Min et al., 2021; Sheynin, Proulx, et al., 2019). We chose stimuli with a size of 2 degrees and a spatial frequency of 2 cpd because it was the most common combination used by Lunghi et al. in their MD studies (Lunghi et al., 2016; Lunghi, Daniele, et al., 2019; Lunghi, Galli-Resta, et al., 2019; Lunghi, Sframeli, et al., 2019; Lunghi & Sale, 2015). It is worth noting that, as O'Shea et al. (1997) demonstrated, the combination of 2 cpd and 2° seems to produce nearly maximum exclusive percepts (thus minimum mixed percepts) compared with other combinations. It is possible that the few reports of superimposition from our participants and our findings of null effect on mixed percept durations may be a result of our combination of stimulus parameters.

Finally, we tested whether ocular dominance plasticity can be measured using the letter-polarity test proposed by Bossi et al. (2018). In their study, the authors compared eight different tests for eye dominance measurement. Their data demonstrated that the letter-polarity test was the most reliable one

among those tests. With the use of two-alternative forced choice, this test is likely to be straightforward for participants and therefore achieve good compliance and accurate results (Bossi et al., 2018). Here, with consistent findings from two eye dominance tests, we demonstrate that the letter-polarity test is sensitive to eye dominance changes in adults with normal vision. To our knowledge, this test has not yet been evaluated in visually-impaired populations such as adults with amblyopia. Future studies could examine whether this test is also accurate and sensitive for eye dominance measurement in these populations.

3.6 Conclusion

Our study demonstrates that neither tRNS, exercise nor their combination affected ocular dominance plasticity after 2 hours of monocular deprivation in adults with normal vision. Our null findings could result from a ceiling effect in our participants. These interventions also do not appear to modulate mixed percepts and alternation rates. We also show that the letter-polarity test is sensitive to eye dominance changes following MD in adults with normal vision. Future studies may examine whether exercise and hf-tRNS would affect ocular dominance plasticity with shorter deprivation durations and whether these interventions would enhance ocular dominance plasticity in visually-impaired populations.

Chapter 4
The Effect of Transcranial Direct Current Stimulation on Ocular Dominance Plasticity in Adults with Normal Vision

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4.1 Overview

Transcranial direct current stimulation (tDCS) of the occipital lobe may modulate visual cortex neuroplasticity. We assessed the acute effect of visual cortex anodal (a)-tDCS on ocular dominance plasticity induced by short-term monocular deprivation (MD), a well-established technique for inducing homeostatic plasticity in the visual system. In Experiment 2a, active or sham visual cortex tDCS was applied during the last 20 minutes of 2-hour MD following a within-subjects design (n = 17). Ocular dominance was measured using two computerized tests. The magnitude of ocular dominance plasticity was unaffected by a-tDCS. In Experiment 2b (n = 9), we investigated whether a ceiling effect of MD was masking the effect of active tDCS. We replicated Experiment 2a but used only 30 minutes of MD. The magnitude of ocular dominance plasticity was decreased with the shorter intervention, but there was still no effect of active a-tDCS. Within the constraints of our experimental design and a-tDCS parameters, visual cortex a-tDCS did not modulate the homeostatic mechanisms that drive ocular dominance plasticity in participants with normal binocular vision.

4.2 Introduction

Transcranial direct current stimulation (tDCS) involves the delivery of a weak direct electrical current to targeted cortical sites via electrodes placed on the scalp. tDCS modulates neural excitability of the stimulated brain area in a polarity-dependent manner (Nitsche et al., 2008; Sabel et al., 2020). In the

motor cortex, anodal tDCS (a-tDCS) elevates motor evoked potential (MEP) amplitude, indicating increased cortical excitability, whereas cathodal tDCS (c-tDCS) has the opposite effect (Nitsche & Paulus, 2000). tDCS may alter neural membrane potentials and increase or decrease the activity of sodium and calcium channels, therefore altering the probability of action potentials (Kenney-Jung et al., 2019; Yamada & Sumiyoshi, 2021). In addition, a-tDCS may modulate neurotransmission by facilitating serotonin, dopamine and glutamate signalling and attenuating the inhibitory GABAergic system, thus producing after effects on neural activity that outlast the stimulation itself (Antal et al., 2006; Reinhart et al., 2017; Stagg et al., 2009, 2011; Yamada & Sumiyoshi, 2021; Zhao et al., 2020).

When applied to the visual cortex, a-tDCS has effects that are consistent with reduced cortical inhibition. For instance, visual cortex a-tDCS enhanced visually evoked potential (VEP) amplitude in adults with normal vision for up to 50 minutes post stimulation, indicating increased cortical excitability, perhaps due to reduced inhibition (Frase et al., 2021). Visual cortex a-tDCS also improves vernier acuity, Snellen acuity, contrast sensitivity for high spatial frequencies (Reinhart et al., 2016), crowding in peripheral vision (G. Chen et al., 2021) and can augment the effect of visual perceptual learning (VPL) (X.-Y. Yang et al., 2022). In addition, a-tDCS effects have been examined among patients with amblyopia, a neurodevelopmental vision disorder characterised by chronic suppression of one eye. Spiegel et al. observed that visual cortex a-tDCS improved contrast sensitivity in some adults with amblyopia (Spiegel, Byblow, et al., 2013) and enhanced the effect of videogame-based dichoptic therapy on stereoacuity (Spiegel, Li, et al., 2013). Ding et al. (2016) demonstrated that a-tDCS increased VEP amplitude and improved contrast sensitivity in both adults with normal vision and adults with amblyopia. These studies indicate that a-tDCS can modulate visual cortex function and enhance visual cortex neuroplasticity.

To further examine the short-term effect of a-tDCS on visual cortex plasticity, we tested the hypothesis that a single session of visual cortex a-tDCS would enhance ocular dominance plasticity induced by short term monocular deprivation (MD). This is a well-established paradigm for producing homeostatic neuroplasticity within the human binocular visual system that causes a transient increase in deprived eye dominance (Chadnova et al., 2017; Lunghi et al., 2011; Min et al., 2018; J. Zhou, Clavagnier, et al., 2013). Ocular dominance plasticity involves mechanisms that may be modulated by a-tDCS. These include reduced GABAergic inhibition within the visual cortex and a transient increase in contrast gain for the deprived eye (Chadnova et al., 2017; Lunghi, Emir, et al., 2015; J. Zhou, Clavagnier, et al., 2013).

In our first experiment (2a), participants received MD for two hours and anodal, cathodal or sham tDCS was applied to the visual cortex during the final 20 minutes of MD. We assessed whether ocular dominance changes were augmented by a-tDCS. Cathodal tDCS (c-tDCS) was included as an active control condition. In Experiment 2b, we reduced the deprivation time to 30 minutes to test for ceiling effects in the magnitude of ocular dominance plasticity.

4.3 Methods

4.3.1 Participants

All participants had normal vision as defined by aided visual acuity $\leqslant$ 0.0 logMAR in each eye and stereoacuity $\geqslant$ 40 seconds of arc. Visual acuity was measured by an ETDRS chart (Precision Vision, Woodstock, IL). Stereoacuity was measured by the Titmus circle test (Stereo Optical Company, Inc., Chicago, IL). We excluded participants who were unable to fuse dichoptic images reliably or had an ocular dominance > 0.7 (one eye significantly more dominant than the other) as measured by either of our ocular dominance tests described below. Additionally, in line with guidelines in the tDCS literature, we excluded participants with a history or immediate family history of epilepsy or seizures, an implanted medication pump, a pacemaker, a defibrillator, metal implants in the head, heart disease, skin conditions at the electrode sites, pregnancy, hearing loss, recurring headaches, head injury, psychiatric conditions or psychoactive medication. Participants were instructed to avoid alcohol (more than one standard drink per hour) within 24 hours of testing, avoid caffeinated beverages within 3 hours of testing and ensure at least 5 hours of sleep before each visit. All participants provided written informed consent prior to participation. This study was reviewed and approved by the University of Waterloo Research Ethics Board and adhered to the tenets of the Declaration of Helsinki.

4.3.2 Visual stimuli for ocular dominance measurement

We employed two measures of ocular dominance, a grating rivalry test and a letter-polarity test (Figure 4-1). For both tests, visual stimuli were presented on a Windows computer (Lenovo M710s, Intel i7-7700, 8GB RAM) with an Asus VG279 monitor (refresh rate: 60Hz; resolution: 1920×1080 pixels). The grating rivalry test stimuli were generated using MATLAB R2018a (MathWorks, Natick, MA) with Psychtoolbox 3.0.18 extensions. The letter-polarity test stimuli were prepared using the PsychoPy

module in Python 3.6.6. Stimuli were dichoptically presented through a mirror stereoscope. Participants rested their head on a chinrest and viewed the stimuli at a distance of 86 cm.

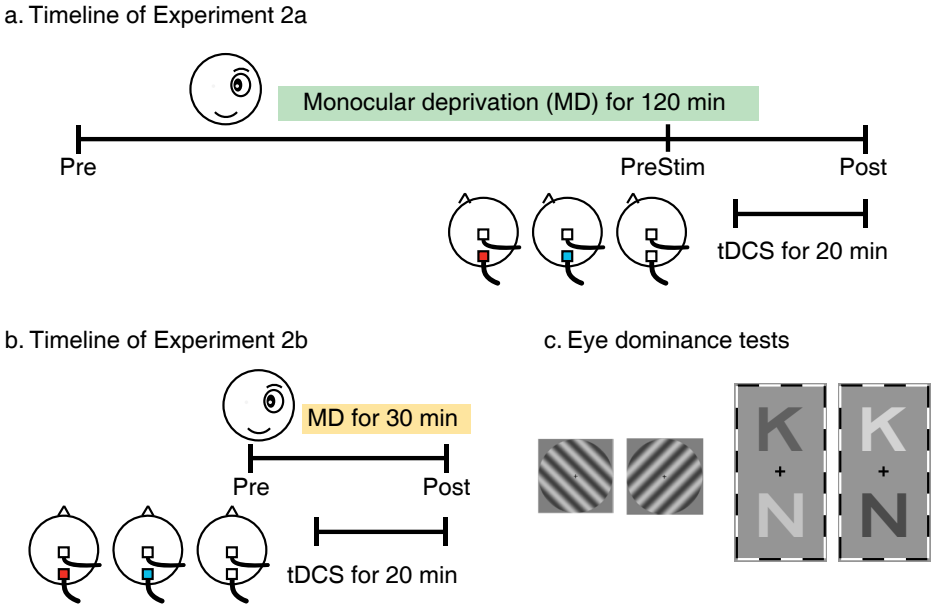

Figure 4-1. tDCS experimental design. (a) The timeline in Experiment 2a. Ocular dominance was measured at baseline (Pre), before tDCS at the 90th minute of MD (PreStim) and immediately after 120 minutes of MD (Post). (b) Illustration of the timeline for Experiment 2b. Ocular dominance was measured at baseline (Pre) and immediately after 30 minutes of MD (Post). In both experiments, a-tDCS, c-tDCS or sham stimulation was delivered to the visual cortex during the final 20 minutes of MD. (c) Examples of the two ocular dominance tests. Participants viewed the stimuli dichoptically. In the grating rivalry test, participants continuously pressed one of four buttons to indicate their perception. In the letter-polarity test, participants pressed the up or down arrow key to indicate the letter that they perceived as brighter than the other.

4.3.3 Ocular dominance tests

The same two ocular dominance tests used in Chapter 3, i.e., the grating rivalry test and the letter-polarity test, were used to measure participants' ocular dominance. For detailed descriptions of these two tests, please refer to Section 3.3.2. Stimuli were generated in Python 3.6.6 with PsychoPy and presented on an Asus VG279 monitor (60 Hz refresh rate, 1920×1080 resolution). A chin rest was

provided to maintain a viewing distance of 86 cm. Grating rivalry data were analysed in the same manner, whereby trials with less than 50 seconds of button press responses were excluded. As a result, 9 trials were removed from a total of 612 trials in Experiment 2a; none were removed in Experiment 2b.

4.3.4 Transcranial direct current stimulation (tDCS)

In both Experiment 2a (120-minute MD) and Experiment 2b (30-minute MD), tDCS was delivered using a battery-driven stimulator (DC-Stimulator Plus; neuroConn GmbH, Ilmenau, Germany) (Figure 2-2). Towards the end of Experiment 2b, we switched to a different stimulator (DC-Stimulator MC; neuroConn GmbH, Ilmenau, Germany) while using the same stimulation protocol. This switch only affected three visits. Two 5×7 cm^2 electrodes were used, soaked in saline sponges. The target electrode was placed at Oz, and the reference electrode was placed at Cz, as defined by the international 10/20 electrode positioning system. Direct current at 2 mA was delivered for 20 minutes. The current ramped up to 2 mA for 20 seconds at the beginning and ramped down for 20 seconds at the end. During sham stimulation, the current ramped up, stimulated for 40 seconds, and then ramped down. Anodal, cathodal and sham stimulation sessions occurred on different days with an interval of at least 48 hours. The stimulation sequence was counterbalanced. Participants were not informed of the type of stimulation being delivered each day.

4.3.5 Procedures

Each participant had three visits. On each visit, baseline ocular dominance was measured using both the grating rivalry test and the letter-polarity test. The sequence of these two tests was counterbalanced across participants. The Miles eye dominance test was also performed. Participants extended their arms before them, formed a triangular aperture with their hands and viewed a distant object through the aperture. The dominant eye retained the image of the object when each eye viewed monocularly. This sighting test allowed a dominant eye to be determined if dominance measures were not consistent between the grating rivalry test and letter-polarity test. The dominant eye was subsequently deprived with a translucent eye patch (MD) for 120 minutes (Experiment 2a) or 30 minutes (Experiment 2b) (Figure 4-1). Participants were instructed to keep both eyes open and watched a common sequence of comedy videos during this time. tDCS (anodal, cathodal, or sham stimulation) was delivered during the

final 20 minutes of MD. Both computerized ocular dominance tests were repeated immediately after patching. Additionally, in Experiment 2a, the letter-polarity test was repeated after 90 minutes of MD (i.e., 10 minutes before tDCS started). We chose this test during patching to minimize disruption to the MD effect as it was shorter than the grating rivalry test (letter test mean 3.34 ± SD 1.47 min vs grating test 6 min). A questionnaire was provided at the end of each session to document any possible side effects of brain stimulation. Reported adverse effects of tDCS are listed in Supplementary Table 2 in Appendix A.

4.3.6 Data analysis

Data were analysed using JASP. Normality of the data was examined using Shapiro-Wilk tests. Mauchly's sphericity tests were used to confirm the sphericity of data. Non-spherical data were corrected using the Greenhouse-Geisser method. For normally distributed data, two-way repeated measures ANOVAs were used to assess the effect of condition (a-tDCS, c-tDCS and Sham) and time (Pre, PreStim and Post). Effect sizes (omega squared, ω^2) were reported for these analyses. For nonparametric data, Friedman tests were used in place of repeated measures ANOVAs. Effect sizes were illustrated using Kendall's *W*. Pairwise comparisons (independent samples *t* tests or Mann-Whitney *U* tests) were used to compare outcomes between the two experiments.

4.4 Results

4.4.1 Experiment 2a: 120-minute MD

Twenty participants were screened. Two were excluded due to vision not reaching 0.0 logMAR in one eye and one was excluded due to unstable fusion. Therefore, a total of 17 participants (age: 21-28, mean 24.41 years; 10 females) completed the experiment.

4.4.1.1 Primary outcome: deprived eye dominance

Changes in deprived eye dominance are shown in Figure 4-2. For the grating rivalry test (Figure 4-2, panels A & B), deprived eye dominance significantly increased after MD, with a significant main effect of time: $\chi^2 = 22.4$, $p < 0.001$, $W = 0.563$. There was no significant main effect of condition: $\chi^2 = 0.40$, $p = 0.819$, $W = 0.019$. For the letter-polarity test (Figure 4-2, panels C & D), deprived eye dominance

significantly increased after MD, with a significant main effect of time: $F(2, 32) = 166.0$, $p < 0.001$, $\omega^2 = 0.575$. Post hoc tests showed that eye dominance increased significantly at the pre-stim timepoint (90 minutes of MD immediately before tDCS), then remained stable after tDCS (Pre vs PreStim $p < 0.001$, Pre vs Post $p < 0.001$, PreStim vs Post $p = 0.068$). There was no significant main effect of condition: $F(2, 32) = 0.297$, $p = 0.745$, $\omega^2 < 0.001$, and no interaction, $F(2.055, 32.879) = 0.361$, $p = 0.705$, $\omega^2 < 0.001$.

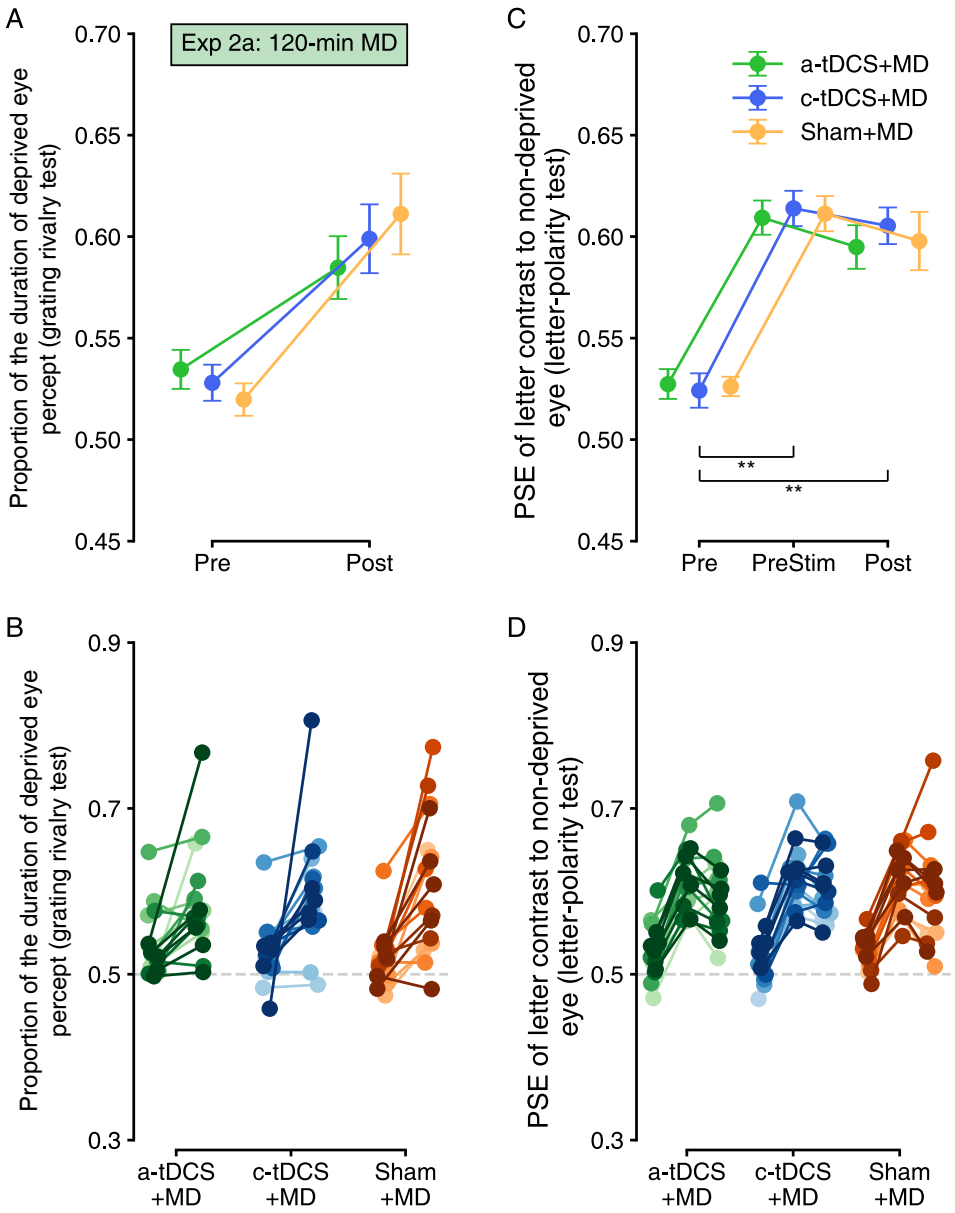

Figure 4-2. Deprived eye dominance data for the grating rivalry (A & B) and letter-polarity (C & D) tests in Experiment 2a. In the grating rivalry test (A & B), deprived eye dominance was indicated by the proportion of deprived eye percept duration. Ocular dominance was measured at baseline (Pre) and immediately after MD (Post). In the letter-polarity test (C & D), deprived eye dominance was indicated by the non-deprived eye letter contrast at the PSE. Ocular dominance was measured at baseline (Pre), 90 minutes after MD started (PreStim), and immediately after MD (Post). The top row shows group mean data. Error bars represent standard errors of the mean. **Post hoc *t* tests $p < 0.001$. The bottom row shows individual data within each condition. Dashed grey lines represent an eye dominance of 0.5 (i.e., two eyes are perfectly balanced). A value above the dashed lines indicates greater dominance by the deprived eye.

4.4.1.2 Secondary outcomes: mixed percepts & alternation rates

In the grating rivalry test, participants used two buttons to indicate their superimposition and piecemeal percepts. The durations of these two percepts were summed to give the overall duration of mixed percepts. Figure 4-3 shows the changes in these percepts. Only overall mixed percept data were normally distributed. Superimposition, piecemeal and overall mixed percept durations did not change significantly after MD, with no significant main effects of time (superimposition: $\chi^2 = 0.579$, $p = 0.447$, $W = 0.026$; piecemeal: $\chi^2 = 1.386$, $p = 0.239$, $W = 0.009$; overall mixed: $F(1, 16) = 1.820$, $p = 0.196$, $\omega^2 = 0.003$). In addition, tDCS did not modulate any of these percepts, with no significant main effects of condition (superimposition: $\chi^2 = 1.557$, $p = 0.459$, $W = 0.025$; piecemeal: $\chi^2 = 1.933$, $p = 0.380$, $W = 0.023$; overall mixed: $F(2, 32) = 0.088$, $p = 0.916$, $\omega^2 < 0.001$). No interaction was found between time and condition for overall mixed percepts, $F(1.419, 22.710) = 0.305$, $p = 0.665$, $\omega^2 < 0.001$.

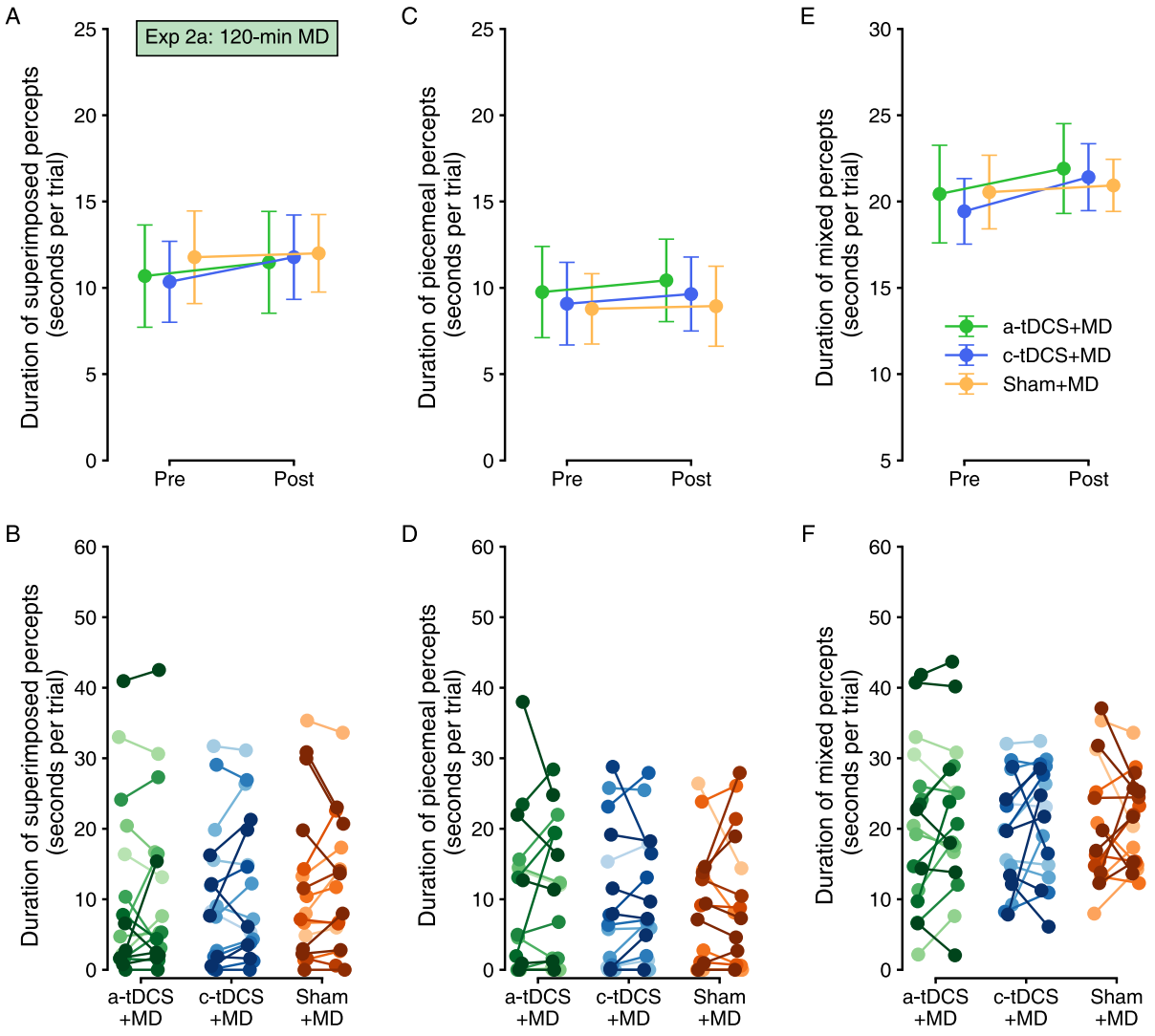

Figure 4-3. Durations of superimposed (A & B), piecemeal (C & D) and overall mixed (E & F) percepts measured by the grating rivalry test in Experiment 2a. The top row shows group mean data before (pre-) and after (post-) intervention. Error bars denote standard errors of the mean. The bottom row shows individual pre and post data within each condition. These durations were averaged over six 1-minute trials.

Figure 4-4 shows changes in alternation rates as measured by the grating rivalry test. Alternation rates did not change significantly after MD (time: $F(1,16) = 1.877$, $p = 0.190$, $\omega^2 = 0.003$). tDCS had no effect on alternation rates (condition: $F(2,32) = 3.552$, $p = 0.040$, $\omega^2 = 0.021$). There was no interaction between time and condition, $F(2,32) = 1.943$, $p = 0.160$, $\omega^2 = 0.002$.

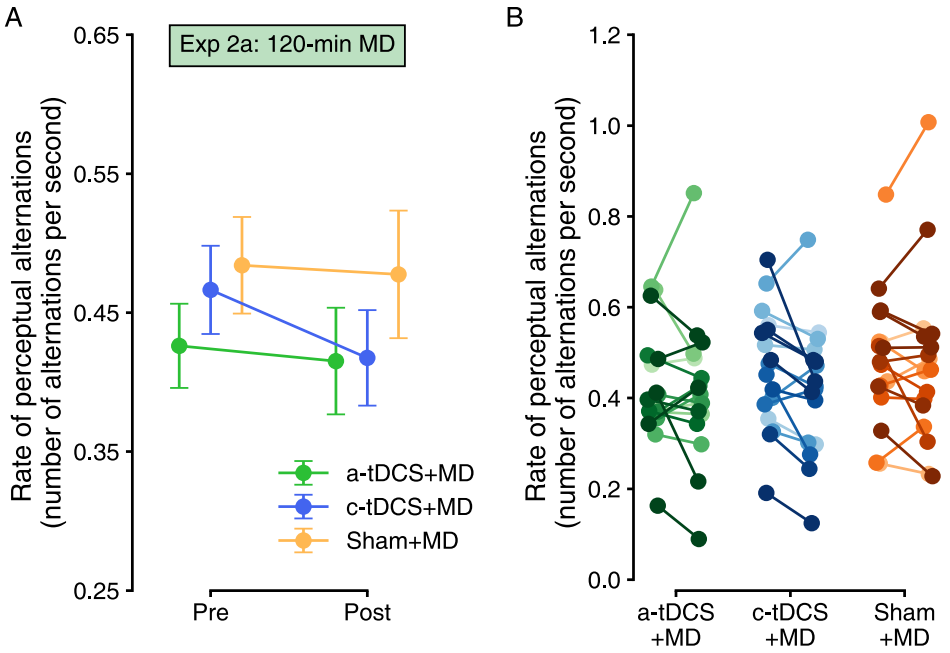

Figure 4-4. Alternation rates measured by the grating rivalry test in Experiment 2a. (A) Group data before (pre-) and after (post-) intervention. Error bars denote standard errors of the mean. (B) Individual pre and post data within each condition. Alternation rates were averaged over six 1-minute trials.

4.4.2 Experiment 2b: 30-minute MD

19 healthy adults were screened. Four were excluded due to vision not reaching 0/0 logMAR in one eye, and one due to stereo acuity not reaching 40 arcseconds. Three participants were excluded due to ocular dominance > 0.7. One participant withdrew due to "itchiness" following tDCS, though rated as mild at the end of their visit, and one participant withdrew due to personal reasons. Therefore, a total of 9 participants (age: 20-28, mean 23.44 years; 8 females) completed the experiment.

4.4.2.1 Primary outcome: deprived eye dominance

Changes in deprived eye dominance are shown in Figure 4-5. For the grating rivalry test (Figure 4-5, panels A & B), deprived eye dominance significantly increased after MD, with a significant main effect of time: $F(1, 8) = 14.37$, $p = 0.005$, $\omega^2 = 0.307$. There was no significant main effect of condition:

$F(2,16) = 2.012$, $p = 0.166$, $\omega^2 = 0.031$, and no interaction, $F(2,16) = 0.526$, $p = 0.601$, $\omega^2 < 0.001$. For the letter-polarity test (Figure 4-5, panels C & D), deprived eye dominance significantly changed after MD, with a significant main effect of time: $F(1,8) = 95.22$, $p < 0.001$, $\omega^2 = 0.564$. There was no significant main effect of condition: $F(2,16) = 0.034$, $p = 0.967$, $\omega^2 < 0.001$, and no interaction, $F(2,16) = 0.215$, $p = 0.809$, $\omega^2 < 0.001$.

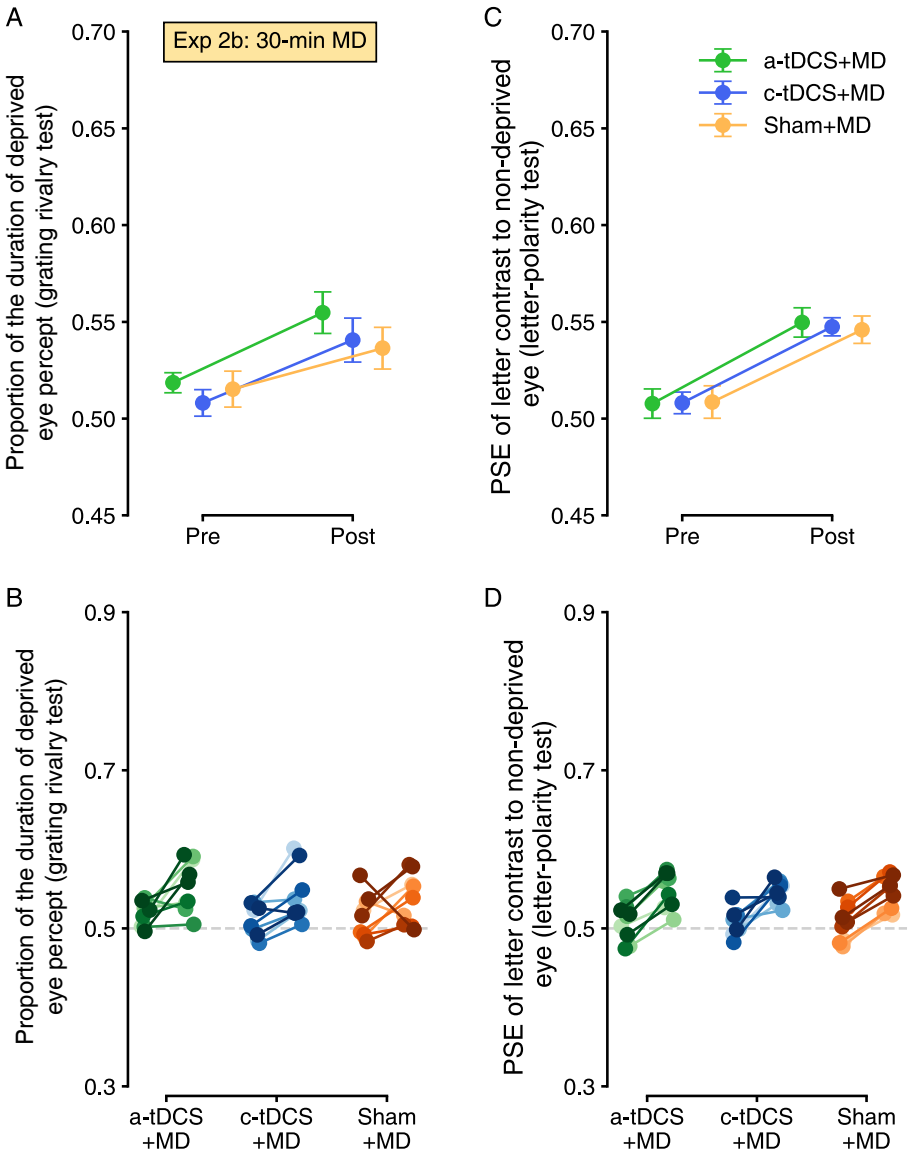

Figure 4-5. Deprived eye dominance data for the grating rivalry (A & B) and letter-polarity (C & D) tests in Experiment 2b. Ocular dominance was measured at baseline (Pre) and immediately after MD (Post). The top row shows group mean data. Error bars represent standard errors of the mean. The

bottom row shows individual data within each condition. Dashed grey lines represent an eye dominance of 0.5 (i.e., two eyes are perfectly balanced). A value above the dashed lines indicates greater dominance by the deprived eye. Note that these plots share the same y-axis scales as Figure 4-2 to facilitate comparison.

4.4.2.2 Secondary outcomes: mixed percepts & alternation rates

Figure 4-6 shows the changes in the durations of superimposition, piecemeal and overall mixed percepts. As in Experiment 2a, none of these percepts changed significantly after MD, with no significant main effects of time (superimposition: $\chi^2 = 1.146$, $p = 0.284$, $W = 0.034$; piecemeal: $F(1, 8) = 1.939$, $p = 0.201$, $\omega^2 = 0.004$; overall mixed: $F(1, 8) = 4.107$, $p = 0.077$, $\omega^2 = 0.020$). In addition, tDCS did not modulate any of these percepts, with no significant main effects of condition (superimposition: $\chi^2 = 1.244$, $p = 0.537$, $W = 0.040$; piecemeal: $F(2, 16) = 0.554$, $p = 0.585$, $\omega^2 < 0.001$; overall mixed: $F(2, 16) = 0.704$, $p = 0.509$, $\omega^2 < 0.001$). No interaction was found between time and condition for piecemeal, $F(2, 16) = 0.397$, $p = 0.679$, $\omega^2 < 0.001$, or for overall mixed percepts, $F(2, 16) = 0.480$, $p = 0.628$, $\omega^2 < 0.001$.

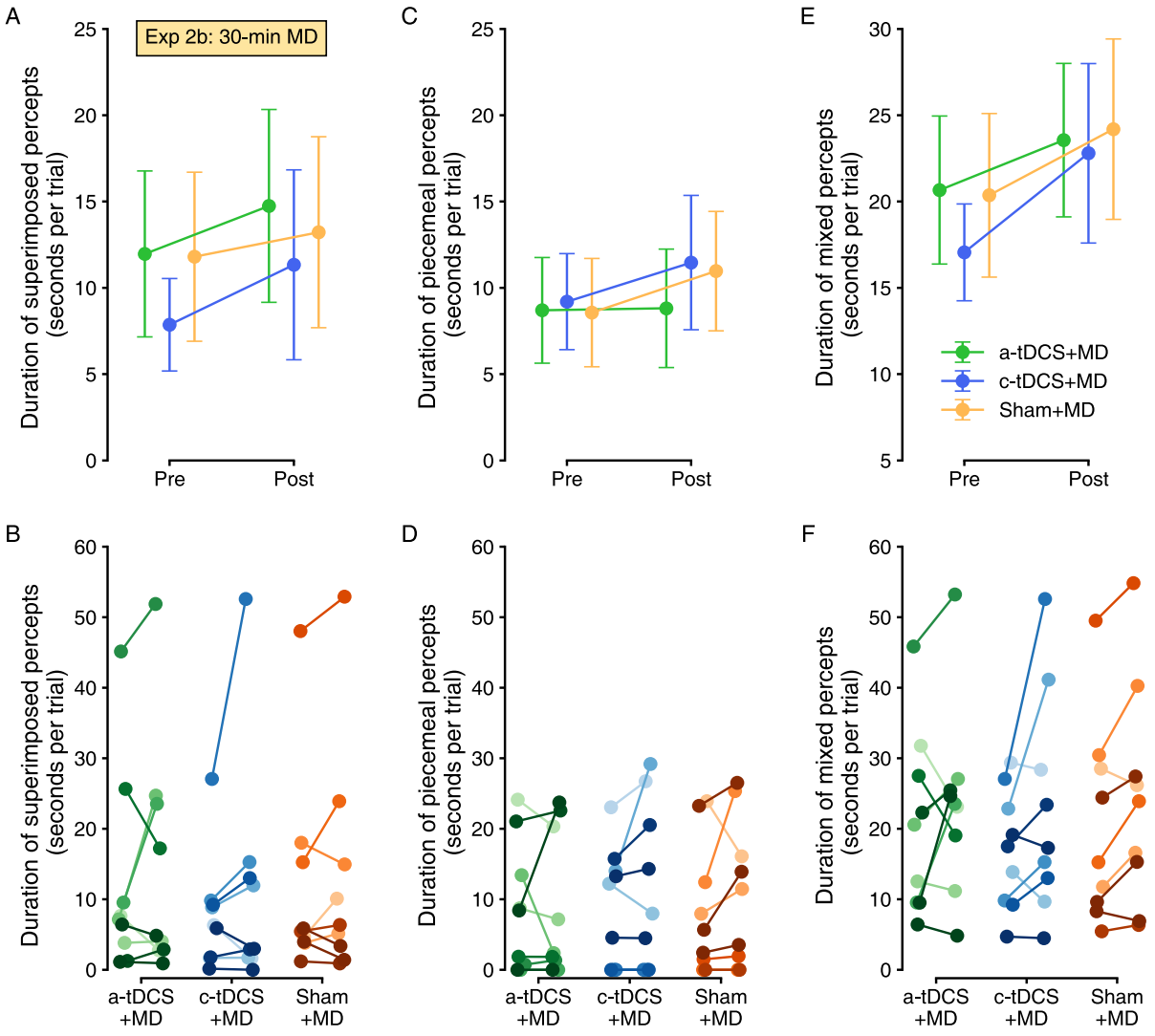

Figure 4-6. Durations of superimposed (A & B), piecemeal (C & D) and overall mixed (E & F) percepts measured by the grating rivalry test in Experiment 2b. The top row shows group mean data before (pre-) and after (post-) intervention. Error bars denote standard errors of the mean. The bottom row shows individual pre and post data within each condition. These durations were averaged over six 1-minute trials.

Figure 4-7 shows changes in alternation rates as measured by the grating rivalry test. Alternation rates did not change significantly after MD (time: $F(1, 8) = 0.562$, $p = 0.475$, $\omega^2 < 0.001$). tDCS had no effect on alternation rates (condition: $F(2, 16) = 0.869$, $p = 0.438$, $\omega^2 < 0.001$). There was no interaction between time and condition, $F(2, 16) = 0.718$, $p = 0.503$, $\omega^2 < 0.001$.

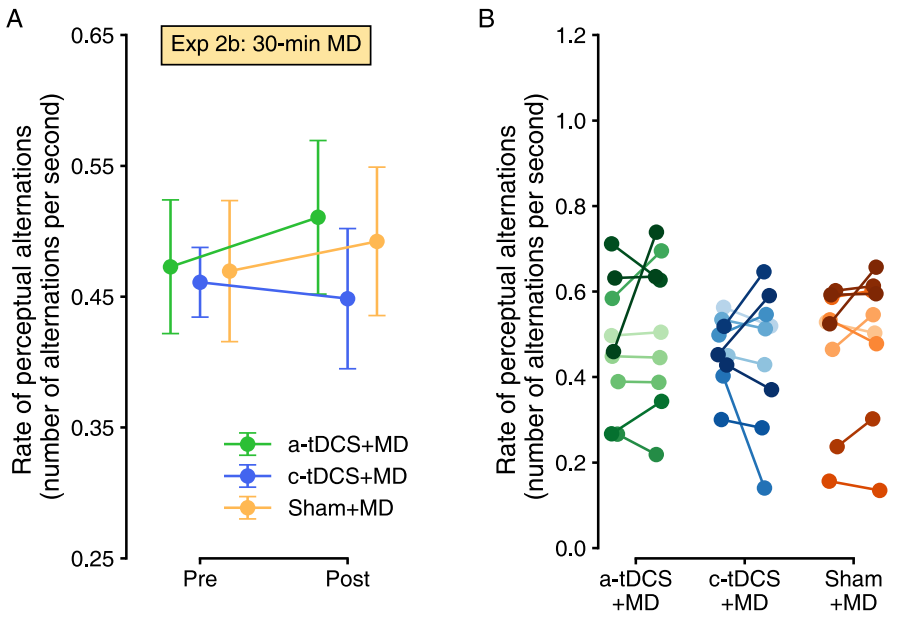

Figure 4-7. Alternation rates measured by the grating rivalry test in Experiment 2b. (A) Group data before (pre-) and after (post-) intervention. Error bars denote standard errors of the mean. (B) Individual pre and post data within each condition. Alternation rates were averaged over six 1-minute trials.

4.4.3 Comparison between Experiments 2a and 2b: an effect of MD duration

Because we did not observe any effect of tDCS, we calculated a mean ocular dominance change for each participant across the three tDCS conditions and compared these means between Experiment 2a (120-minute MD) and Experiment 2b (30-minute MD). For the grating rivalry test, the ocular dominance changes in Experiment 2a (Figure 4-2 A & B, mean 0.071 ± SE 0.014) were significantly larger than those changes in Experiment 2b (Figure 4-5 A & B, 0.030 ± 0.008) ($U = 117.0$, $p = 0.029$). For the letter-polarity test, ocular dominance changes were also significantly larger in Experiment 2a (Figure 4-2 C & D, 0.073 ± 0.006) than in Experiment 2b (Figure 4-5 C & D, 0.040 ± 0.004) ($t = 4.113$, $p < 0.001$).

4.5 Discussion

We first tested whether anodal, cathodal or sham tDCS had an effect on short-term ocular dominance plasticity induced by 120 minutes of MD. As anodal tDCS has been reported to reduce GABA inhibition (Antal et al., 2006; Reinhart et al., 2017; Stagg et al., 2009; Yamada & Sumiyoshi, 2021), we hypothesized that the reduced inhibition would augment ocular dominance changes following MD. While the MD effect was significant, we did not observe an effect of a-tDCS. In a second experiment, we investigated whether there was a ceiling effect for ocular dominance plasticity induced by 120 minutes of MD by reducing the MD duration to 30 minutes. This second experiment demonstrated that the MD effect was significantly smaller after 30 minutes of MD. However, again we did not observe any effect of a-tDCS. In both experiments we did not observe any significant effects of a-tDCS on binocular rivalry mixed percepts or alternation rates.

Using a similar experimental design (where ocular dominance plasticity was induced by MD), we previously observed no effect of transcranial random noise stimulation (tRNS) on ocular dominance plasticity (X. Chen et al., 2022). tRNS may augment subthreshold signals via stochastic resonance (Potok et al., 2022) and by reducing GABAergic inhibition in the stimulated cortex (Chaieb et al., 2015; Sánchez-León et al., 2021), thereby leading to improved resolution of visual stimuli. We concluded that there were at least two possible explanations for our null results, either that tRNS does not modulate the ocular dominance changes induced by MD or that two hours of MD produces the maximum possible amount of ocular dominance plasticity (a ceiling effect). The neuromodulatory effects of tDCS may differ from those of tRNS. The induction of a constant electric current influences the activity of sodium and calcium channels on neuron membranes (Kenney-Jung et al., 2019; Yamada & Sumiyoshi, 2021). Specifically, the anodal electrode increases the probability of channels opening on the soma (i.e., cell body) membrane of stimulated neurons, resulting in an influx of sodium and calcium ions and a higher resting membrane potential. Neurons are then more likely to fire an action potential when presented with a visual stimulus. Modulation of the GABAergic system may also be an important mechanism for enhanced neuroplasticity (Stryker & Löwel, 2018). Taken together, our two studies suggest that even with potentially differing mechanisms, stimulation of the visual cortex using either tRNS or tDCS does not alter ocular dominance plasticity resulting from MD.

Although many studies have reported a-tDCS effects on visual cortex function and plasticity (G. Chen et al., 2021; Z. Ding et al., 2016; Frase et al., 2021; Reinhart et al., 2016; Spiegel, Byblow, et al., 2013; Spiegel, Li, et al., 2013; X.-Y. Yang et al., 2022), our study is not the first to observe no effect. For instance, while Ding et al. (2016) and Frase et al. (2021) demonstrated a modulation of VEP

amplitudes using a-tDCS, other studies (Dawood et al., 2022; Lau et al., 2021) did not observe such an effect. Abuleil et al. (2021) observed that tDCS did not modulate binocular rivalry dynamics, while a type of repetitive transcranial magnetic stimulation, namely continuous theta burst stimulation (cTBS), had an effect. Lau et al. (2021) pointed out that tDCS effects on vision tasks can differ depending on whether tasks are performed during ("online") or after ("offline") tDCS. Our study used an offline design (i.e., measurements taken after tDCS), as did most studies mentioned above that observed modulatory effects of tDCS. Prior tDCS studies have investigated various types of visual cortex plasticity, including Hebbian plasticity (e.g., perceptual learning) and homeostatic plasticity (e.g., ocular dominance plasticity). The distinct mechanisms underlying these different types of plasticity (Bang et al., 2023) may explain why tDCS had effects on some types of plasticity but not on ocular dominance plasticity.

Our hypothesis for an a-tDCS effect on ocular dominance plasticity was based on studies in the human motor cortex that showed reduced GABAergic inhibition following stimulation (Antal et al., 2006; Reinhart et al., 2017; Yamada & Sumiyoshi, 2021). However, it remains an open question whether a-tDCS exerts the same effect on GABA concentration when applied to the visual cortex. In cats, a-tDCS was found to increase the neuronal response to a light stimulus whereas c-tDCS reduced the response (Creutzfeldt et al., 1962). It has also been shown that a-tDCS reduces GABA concentration while c-tDCS reduces glutamate concentration in the cat visual cortex (Zhao et al., 2020). In humans, visual cortex a-tDCS increases gamma oscillations measured using MEG, an indirect measure of reduced GABA concentration (Wilson et al., 2018). However, other studies using indirect behavioural measures linked to visual cortex GABA concentration have observed no effect of a-tDCS (Abuleil et al., 2021). A differential effect of a-tDCS on the motor versus visual cortex GABA concentration might explain the null effect of a-tDCS observed in our study.

Various factors can influence the effect of tDCS including the polarity of the electrodes placed above targeted cortical areas (anode vs cathode), the relative locations of the stimulation and reference electrodes, electrode sizes, the current intensity, and the duration of stimulation (Thair et al., 2017). Individual differences in cortical and cranial anatomy may also influence tDCS effects (Parazzini et al., 2015). The tDCS parameters used in this experiment (i.e., the stimulation electrode positioned at Oz and the reference electrode at Cz, a 5×7 cm^2 electrode size, 2-mA current and 20-minute stimulation) have been used in previous studies, some of which reported stimulation effects (G. Chen et al., 2021; Z. Ding et al., 2016; Spiegel, Byblow, et al., 2013; Spiegel, Li, et al., 2013; X.-Y. Yang et al., 2022) while others did not (Abuleil et al., 2021; Dawood et al., 2022; Lau et al., 2021). However, a wide

variety of alternative parameters could have been used and we did not attempt to model and account for anatomical differences between subjects. Therefore, our null results should be interpreted within the context of the specific tDCS parameters used and the age and sex characteristics of our sample.

The timing of tDCS in relation to MD may also matter. Some studies show that tDCS enhances motor training to a larger extent when applied concurrently than applied before training (Jin et al., 2019; Sriraman et al., 2014), while other studies report that it is more beneficial to apply tDCS prior to motor training than concurrently with training (Buchwald et al., 2019; Jo et al., 2021; Liao et al., 2020). To our knowledge, the effect of tDCS timing has not yet been investigated in the visual cortex. While we observed that a-tDCS applied at the end of MD did not modulate ocular dominance plasticity, it is possible that a-tDCS delivered prior to or at the beginning of MD could influence ocular dominance changes.

Based on our null findings from both the tRNS study (Chapter 3) and Experiment 2a in this tDCS study, we hypothesized that 120 minutes of MD may induce a ceiling effect for ocular dominance plasticity. Our second experiment showed that shorter MD does result in a smaller ocular dominance shift whereby the ocular dominance change after 120 minutes of MD was approximately two times the change after 30 minutes of MD. Nevertheless, we still did not observe an effect of a-tDCS applied at the end of 30 minutes of MD. This makes an explanation for our null results based on a ceiling effect less likely. However, we cannot rule out yet that an even shorter duration of MD might reveal an a-tDCS effect.

We did not observe an effect of a-tDCS on ocular dominance plasticity in adults with normal vision. However, the mechanisms underlying homeostatic plasticity may be different from those that underpin plasticity associated with vision rehabilitation. Whether tDCS enhances ocular dominance plasticity for patients with binocular visual impairments such as amblyopia is currently unknown.

4.6 Conclusions

This study investigated the effects of tDCS and the duration of MD on ocular dominance plasticity. Shorter MD induced smaller ocular dominance changes. With both longer MD and shorter MD, however, we did not observe any difference between anodal, cathodal or sham tDCS conditions. It remains possible that tDCS applied prior to or at the beginning of MD could influence ocular dominance changes. Future studies could investigate the effect of tDCS timing when applied to the visual cortex, and whether tDCS influences ocular dominance plasticity in patients with visual impairment.

Chapter 5
Reliability of Ocular Dominance Tests

5.1 Overview

Ocular dominance illustrates the degree to which one prefers inputs from one eye when integrating binocular inputs. Most individuals with normal vision exhibit no or weak ocular dominance, although some may exhibit stronger dominance (Li et al., 2010; E. Yang et al., 2010). Ocular dominance can be measured by a variety of tests. Examples include the hole-in-the-card test (Barbeito, 1981), dichoptic motion coherence threshold test (Li et al., 2010; Mansouri et al., 2008), binocular phase combination (J. Ding & Sperling, 2006; C. B. Huang et al., 2009; J. Zhou, Clavagnier, et al., 2013), binocular orientation combination (Spiegel et al., 2017; Y. Wang et al., 2019), and binocular rivalry (Lunghi et al., 2011; Tong et al., 2006). The precision of different ocular dominance tests varies (Bossi et al., 2018; Min et al., 2021). Recently a novel ocular dominance test has been proposed that involves the presentation of letters with opposite contrast polarities (Bossi et al., 2017, 2018). Through comparison with other tests, the authors concluded that this new ocular dominance test demonstrated the best reliability. Our experiments in Chapters 3 and 4 have employed both this new letter-polarity test and the traditional binocular rivalry test, which involves the dichoptic presentation of gratings of opposite directions. We refer to the binocular rivalry test as "grating rivalry" to avoid confusion since the letter-polarity test also involves rivalrous images. This chapter intends to analyse the reliability of these two tests and determine the selection of one test for our next experiment which requires rapid assessment of ocular dominance at multiple timepoints within each experimental session.

5.2 Methods

Ocular dominance data were assembled from the baseline data in Chapters 3 and 4. Data from participants who withdrew or were excluded were also included. This resulted in total datasets of 46 participants, all of which were independent. The complete datasets have been included in Supplementary Table 1 in Appendix A. It should be noted that data in this chapter were presented in their raw form (i.e., > 0.5 indicating right eye dominance, < 0.5 indicating left eye dominance), as opposed to being reported in terms of the deprived/non-deprived eye.

Within-test repeatability analyses were conducted on data where three baseline measurements were available (n = 39). Note that these baseline measurements were taken on separate days, at least two

days apart, with each test performed once on each day. Intraclass correlation coefficient (ICC) estimates and their 95% confident intervals were computed based on a single-rating (k=1), absolute-agreement, 2-way mixed-effects model (Koo & Li, 2016; McGraw & Wong, 1996). The criteria for interpreting ICC results are listed in Table 5-1. Additionally, standard deviations were calculated for each individual to depict the variability of each test. Tests of normality were performed with a Shapiro-Wilk test. Standard deviations were compared using a paired-samples *t* test or, in the case of deviation from a normal distribution, a Wilcoxon signed-rank test.

Table 5-1. ICC interpretation as recommended by Loo & Li (2016).

ICC Value	**< 0.50**	**0.50 - 0.75**	**0.75 - 0.90**	**> 0.90**
Reliability	Poor	Moderate	Good	Excellent

Between-test agreement was examined using the first visit data from all datasets ($n = 46$). A Bland-Altman test was employed to illustrate the spread of the datasets (Bland & Altman, 2010). The Bland-Altman Limits of Agreement (LoA) were determined as $\bar{d} \pm 1.96s$, where $\bar{d}$ was the mean difference (letter-polarity minus grating rivalry) and s was the standard deviation of the differences. The LoA provides an estimate of the range within which 95% of population differences are expected to fall (Bland & Altman, 2010; Gerke, 2020). Considering that the average post-pre differences in Chapters 3 and 4 were approximately 0.06 (letter-polarity: 0.062, grating rivalry: 0.060), an acceptable limit for between-test differences was set arbitrarily to 0.06. A linear regression was applied to investigate whether there was a proportional bias (Ludbrook, 2010); outliers were identified using the interquartile range (IQR) method (values more than 1.5 × IQR outside the IQR) and were removed from this regression analysis. An ICC analysis employing the same settings mentioned above was also used to illustrate the between-test agreement. Finally, an agreement in ocular dominance directions between tests was assessed. To exclude instances of very weak ocular dominance, where the ocular dominance result could fall randomly in either direction, a criterion of inter-test difference was set at 0.04 (0.02 on either side). Opposite directions with a between-test difference > 0.04 were considered disagreement in ocular dominance directions.

ICC was calculated in SPSS (IBM Corp., Armonk, NY). All other statistical analyses were completed in JASP.

5.3 Within-Test Repeatability

Repeatability within each ocular dominance test was assessed using ICC. The 95% confidence interval of the ICC estimate (Table 5-2) indicates that the level of repeatability was "moderate to good" for both the letter-polarity test (0.730-0.899) and the grating rivalry test (0.674-0.875).

Table 5-2. ICC for within-test repeatability.

		95% Confidence Interval	
	ICC Estimate	**Lower Boundary**	**Upper Boundary**
Letter-polarity	0.829	0.730	0.899
Grating rivalry	0.790	0.674	0.875

Individual standard deviations from each test (Table 5-3) were also calculated to depict their variability. The data were not normally distributed ($W = 0.908$, $p = 0.004$). Comparison indicated that the letter-polarity test had significantly lower standard deviations than the grating rivalry test ($Z = 2.414$, $p = 0.015$).

Table 5-3. Summary of individual standard deviations from each test.

	Letter-polarity	**Grating rivalry**
Median	0.015	0.023
Quartiles	0.009 – 0.019	0.012 – 0.034
Range	0.001 - 0.045	0.003 - 0.088

Collectively, these two analyses demonstrate that both ocular dominance tests had moderate to good repeatability; however, the letter-polarity test did exhibit less variability than the grating rivalry test.

5.4 Between-Test Agreement

The difference between both tests was first illustrated through a Bland-Altman analysis (Figure 5-1A). As recommended by Ludbrook J. (2010), we performed a linear regression analysis to examine any

proportional bias. Assumptions of this analysis were initially violated with the entire dataset (n = 46); after the removal of 5 outliers (n = 41), the linear regression model was fitted as $\hat{y} = 0.034 - 0.085 \cdot x$ (Figure 5-1A). The slope did not significantly deviate from zero (t = -0.478, p = 0.635), indicating no proportional bias[1]. Hence, the classical determination of LoA was adopted (i.e., $\bar{d} \pm 1.96s$). The mean difference between tests was -0.009, suggesting that, on average, there was only a negligible difference between tests. 95% of the population differences, indicated by the LoA, was estimated to fall between -0.115 and 0.097. This range was larger than the pre-established acceptable limit of ±0.06 (i.e., -0.069 to 0.051), suggesting that, overall, the two tests did not completely agree. Nevertheless, it is important to note that the majority of the data points (37 out of 46, 80.43%) fell within this acceptable range, with only 9 outstanding datasets out of 46 (19.57%).

[1] An additional linear regression analysis including the outliers still indicated no proportional bias between both tests (slope = -0.191, t = -1.586, p = 0.120).

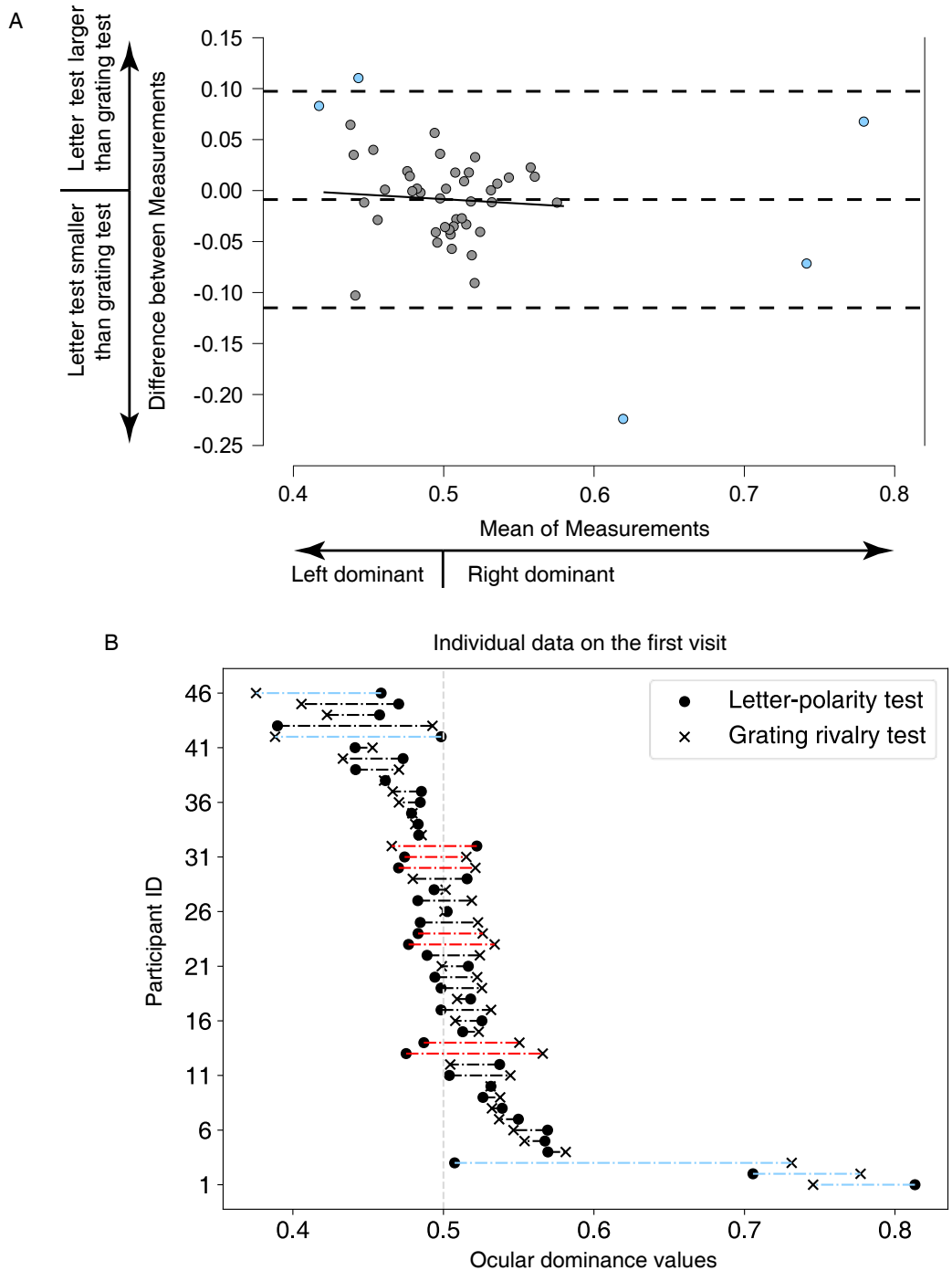

Figure 5-1. Individual data from the first visit. (A) A Bland-Altman plot. The abscissa (*x* axis) shows the mean of both tests. A value of $x = 0.5$ indicates balanced ocular dominance, > 0.5 indicates right eye dominance, and < 0.5 indicates left eye dominance. The ordinate (*y* axis) shows the difference between two tests. A positive y value indicates that the letter-polarity value was greater than that of the

grating rivalry test, and vice versa. The dashed lines denote the mean of differences and the upper and lower boundaries of the LoA. The solid curve represents a regression fitted to the mean of both tests and their differences, with outliers (depicted as blue data points) removed. (B) Ocular dominance data from each individual as measured by both tests. Data were ordered from top to bottom by their means. Blue dashed lines denote outliers removed from the aforementioned regression analysis. Red dashed lines denote instances of disagreement in ocular dominance directions according to the predefined criterion.

The agreement between two tests was also assessed using ICC. The 95% confidence interval of the ICC estimate (Table 5-4) indicates that the level of repeatability was "moderate to good" (0.535 to 0.829).

Table 5-4. ICC for between-test agreement.

		95% Confidence Interval	
	ICC Estimate	**Lower Boundary**	**Upper Boundary**
Between-Test	0.712	0.535	0.829

With a criterion of 0.04 for between-test differences, most datasets (39 out of 46, 84.78%) exhibited good agreement in ocular dominance directions, with only 7 datasets out of 46 (15.22%) showing disagreement (Figure 5-1B).

In summary, these analyses indicate that the two ocular dominance tests had moderate to good agreement as shown by the Bland-Altman mean differences and the ICC analysis. While 95% of the population's between-test differences were estimated to exceed our pre-established range, the agreement appeared satisfactory for the majority of individuals as shown by the Bland-Altman plot. No proportional bias was observed. Consistent ocular dominance directions were found for the majority of individuals.

5.5 Conclusion

Our comprehensive analyses revealed two main findings: 1) the letter-polarity test exhibited less variability than the grating rivalry test while maintaining a comparable level of repeatability; and 2) these two ocular dominance tests appeared to agree generally well for most individuals.

It has been reported that ocular dominance may be influenced by factors such as individual refractive errors and stimulus sizes (Ito et al., 2013; Laby & Kirschen, 2011; Linke et al., 2012). For instance, high astigmatism or anisometropia (unequal refractive errors between eyes) was found associated with the non-dominant eye (Ito et al., 2013; Linke et al., 2012). In line with the literature (Li et al., 2010; E. Yang et al., 2010), our data show that, while most individuals exhibit balanced or weak ocular dominance, some may have stronger ocular dominance. We did not record participants' refractive errors or perform a comprehensive evaluation of their binocular visual functions. Stereoacuity was reported not to correlate with ocular dominance (Y. Wang et al., 2018), although a sampling bias may derive from the fact that only participants with normal vision were tested. Similarly, our experiments only recruited individuals with a stereoacuity of at least 40 seconds of arc. Therefore, we do not possess insights into the reasons behind the strong ocular dominance observed in some individuals, nor could we confirm whether they had completely normal binocular vision. Due to these uncertainties, these individuals were excluded from participation in our experiments.

Ocular dominance results can vary across tests (Mapp et al., 2003). Some tests have been found to demonstrate more reliability than others (Bossi et al., 2018; Min et al., 2021). Although extensively used for ocular dominance measurement, the grating rivalry test was not ranked among the most reliable tests (Bossi et al., 2018; Min et al., 2021). Aligning with these observations, our comparison suggests that the letter-polarity test may offer greater repeatability than the grating rivalry test. This may be attributed to the straightforwardness of the letter-polarity test employing a two-alternative forced choice task (Bossi et al., 2018). Based on these analyses and the results in our prior experiments, we conclude that the letter-polarity test alone stands as a reliable measure for ocular dominance and is sensitive to changes in short-term ocular dominance plasticity. Therefore, this test was selected for our final experiment.

Chapter 6
The Effect of Repetitive Transcranial Magnetic Stimulation on Ocular Dominance Plasticity in Adults with Normal Vision

This chapter has been submitted for publication in a peer-reviewed journal. Individual author contributions can be found in the Summary of Contributions section above. This work was supported by grants from the Natural Sciences and Engineering Research Council of Canada (NSERC; RGPIN-04404 to WB and RGPIN-05394 and RGPAS-477166 to BT) and the Canadian Foundation for Innovation (34095 to BT). BT was also supported by the Hong Kong Special Administrative Region Government and InnoHK. None of the authors have any conflicts of interest to declare.

6.1 Overview

Short-term monocular deprivation (MD) induces transient ocular dominance changes in favour of the deprived eye. Attempts to augment this plasticity using visual cortex transcranial electrical stimulation did not enhance ocular dominance changes. Inspired by evidence of increased cortical excitability following light deprivation and low-frequency repetitive transcranial magnetic stimulation (rTMS), we investigated whether low- and high-frequency rTMS would augment ocular dominance changes following 1-hour MD. While the ocular dominance shift after MD was statistically significant up to 30 minutes after MD, we did not observe a significant effect of rTMS. Short-term ocular dominance plasticity in the normal visual system does not appear to be modifiable using standard non-invasive brain stimulation techniques delivered to the primary visual cortex.

6.2 Introduction

The adult human visual cortex retains a certain degree of neuroplasticity (Başgöze et al., 2018; Castaldi et al., 2020; Karmarkar & Dan, 2006; Sur et al., 2013). For example, long-lasting Hebbian neuroplastic responses have been demonstrated using visual perceptual learning (Green et al., 2010; Levi & Li, 2009; Polat et al., 2004; Xu et al., 2012; Y. Zhou et al., 2006) and transient homeostatic neuroplasticity can be induced using visual deprivation (Lunghi et al., 2011; Lunghi & Sale, 2015; Ramamurthy & Blaser, 2018; J. Zhou et al., 2017; J. Zhou, Clavagnier, et al., 2013).

A period of monocular deprivation (MD) induces a temporary increase in deprived eye dominance in adults, an effect known as short-term ocular dominance plasticity (Lunghi et al., 2011; Lunghi & Sale, 2015; Ramamurthy & Blaser, 2018; J. Zhou et al., 2017; J. Zhou, Clavagnier, et al., 2013). MD appears to activate homeostatic mechanisms within the early visual cortex that attempt to balance afferent neural activity from the two eyes by modulating GABAergic inhibition within the visual cortex (Binda et al., 2018; X. Chen et al., 2020; Lunghi, Emir, et al., 2015; J. Zhou et al., 2015).

Short-term ocular dominance plasticity is robust and easy to induce. This has made the magnitude of ocular dominance change an attractive outcome measure for studies attempting to modulate adult human neuroplasticity. A number of interventions with the potential to enhance adult neuroplasticity have been assessed using ocular dominance plasticity including physical exercise (Finn et al., 2019; Lunghi & Sale, 2015; J. Zhou et al., 2017), pharmaceuticals (Sheynin, Chamoun, et al., 2019), and non-invasive transcranial electrical stimulation (X. Chen et al., 2022, 2023). Most of these studies found that ocular dominance plasticity could not be augmented, or only to a very limited extent. For example, the non-invasive brain stimulation techniques transcranial random noise stimulation (tRNS) (X. Chen et al., 2022) and anodal transcranial direct current stimulation (tDCS) (X. Chen et al., 2023), which increase cortical excitability and may reduce GABA concentration in the stimulated area, did not enhance ocular dominance plasticity when applied to the visual cortex using standard stimulation parameters.

Both tRNS and tDCS involve head mounted electrodes that deliver electrical stimulation through the skull. Repetitive transcranial magnetic stimulation (rTMS) is an alternate form of non-invasive brain stimulation that uses electro-magnetic induction to stimulate superficial cortical structures (Antal et al., 2022; Wassermann, 1998). Brief magnetic fields are generated within a hand-held coil. When the coil is positioned above a brain region and activated, a series of electrical currents, or pulses, are generated within the targeted cortical tissue that modulate neuronal activity. Based on the pulse frequency, rTMS may produce different effects (Sabel et al., 2020). Typically, in the motor cortex, high-frequency rTMS (e.g. 10 Hz) is found to increase cortical excitability whereas low-frequency rTMS (e.g. 1 Hz) has the opposite effect (Fitzgerald et al., 2006; Klomjai et al., 2015; Oberman, 2014; Sabel et al., 2020). While some studies have reported an inhibitory effect of low-frequency rTMS in the visual cortex (Bocci et al., 2011; Hirose et al., 2007; Kosslyn et al., 1999; Saint-Amour et al., 2005; Tashiro et al., 2007), to our knowledge, there is currently no evidence that supports an excitatory effect of high-frequency rTMS on the human visual cortex. In fact, Fierro et al. (2005) found an opposite effect. In their study, light deprivation decreased participants' phosphene threshold (PT), indicating increased cortical excitability.

Low-frequency (1-Hz) rTMS to the early visual cortex prolonged this effect, while high-frequency (10-Hz) rTMS reduced the excitatory effect of light deprivation. The authors suggested that the effect of rTMS might be dependent on the activation state of the stimulated cortex, which had been modified by light deprivation. Given the evidence that both light deprivation (Boroojerdi et al., 2000; Fierro et al., 2005; S. Huang et al., 2015) and monocular deprivation (Lunghi, Emir, et al., 2015) appear to reduce GABAergic inhibition, we hypothesised that 1-Hz rTMS would also enhance the effects of monocular deprivation.

To test this hypothesis, we conducted an experiment using three types of rTMS, i.e., high-frequency (10-Hz), low-frequency (1-Hz) and sham stimulation, using a similar design to the one employed by Fierro et al. (2005). Participants with measurable phosphene thresholds received MD for 1 hour and rTMS for 15 min on each visit. The sequence of rTMS types was randomized across three visits. Ocular dominance was measured before and for 30 min after MD in 10-minute intervals.

6.3 Methods

6.3.1 Participants

All participants had visual acuity (corrected or uncorrected) ≤ 0.0 logMAR in each eye and stereoacuity reaching 40 seconds of arc, tested using an ETDRS chart (Precision Vision, Woodstock, IL) and the Titmus circle test (Stereo Optical Company, Inc., Chicago, IL). Participants who showed relatively strong ocular dominance (> 0.6 as measured by our computerized test described below) at baseline and those whose phosphene threshold was not obtained below 80% maximum stimulator output (MSO) as described below were excluded. All participants were in good general health with no history of epilepsy or seizures, no history of hearing loss, no recurring headaches, no metal implants on the head, no head injury and no psychoactive medication. Participants were asked not to consume more than one standard alcoholic drink per hour within 24 hours before each visit, not to consume caffeinated beverages within 3 hours before each visit and to have at least 5 hours of sleep the night before each test session.

This study was approved by the University of Waterloo Research Ethics Board and conformed to the Declaration of Helsinki. All participants gave written informed consent prior to participation.

6.3.2 Computerized ocular dominance test

Ocular dominance in this study was measured by the letter-polarity test. For detailed descriptions of this test, please refer to Section 3.3.2. Stimuli were generated in Python 3.6.6 with PsychoPy and presented on an Asus VG279 monitor (60 Hz refresh rate, 1920×1080 resolution). A chin rest was provided to maintain a viewing distance of 86 cm.

6.3.3 TMS equipment

The TMS configuration is shown in Figure 6-1. A MagPro X100 Pro stimulator (MagVenture, Farum, Denmark) was used to control the delivery of TMS pulses. For phosphene threshold measurement, a figure-of-eight coil (MCF-B65, MagVenture, Farum, Denmark) was used. For rTMS, a double-blind figure-of-eight coil (COOL-B65, MagVenture, Farum, Denmark) was used and stabilized using a mechanical arm. Neuro-navigation (Brainsight®, Rogue Research, Montréal, QC) was utilized to mark each participant's phosphene hotspot. Ear plugs were provided during stimulation. A chin rest was used during rTMS to help stabilize participants' head position.

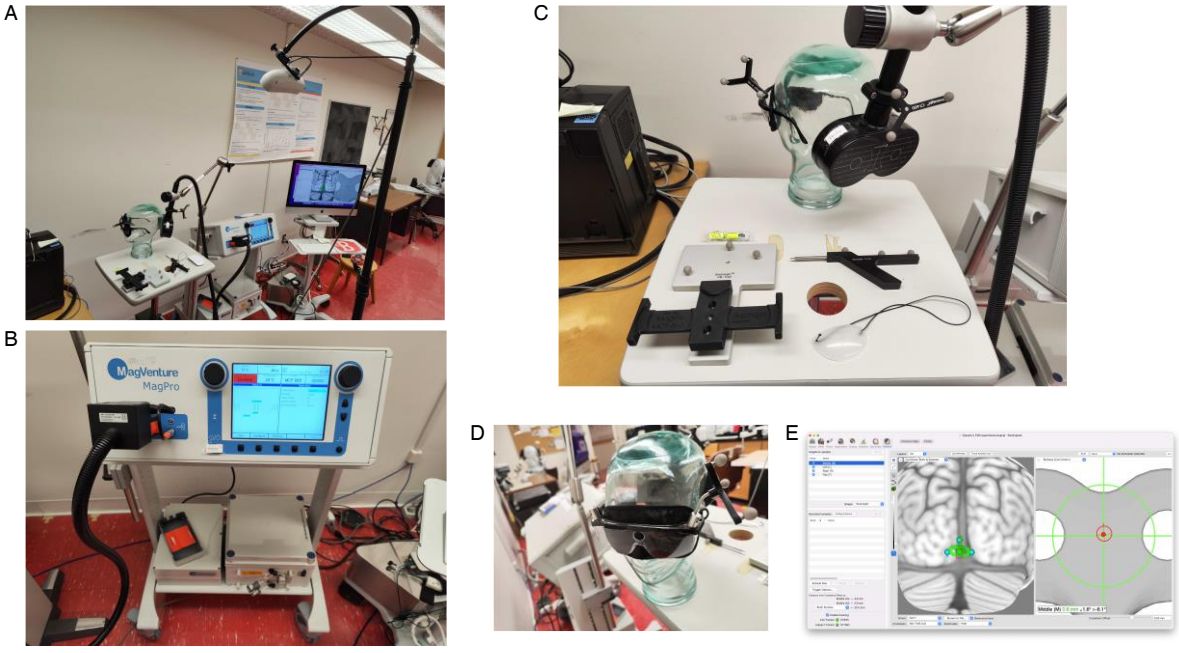

Figure 6-1. TMS configuration. (A) Left to right: TMS coil and related apparatus, magnetic stimulator, mobile computer (27″ iMac™, Apple Inc., Cupertino, CA) with Brainsight® software,

position sensor camera (Polaris Vicra®, Northern Digital Inc., Waterloo, ON) affixed to a stand. (B) The magnetic stimulator (MagPro X100) on a movable trolley. Below shows a coil cooler equipped with liquid cooling media. The cooler was connected to the double-blind coil during rTMS to prevent overheating. (C) Left to right: earplugs, calibration jig for calibrating coil position, participant head position tracker on a model head, pointer for calibrating participant's head position, translucent eye patch for monocular deprivation, figure-of-eight coil mounted on a mechanical arm with a coil tracker. Signals from reflective spheres on these trackers were captured by the position sensor camera to determine spatial locations. Note that during the experiment, the thresholding coil was hand-held, while the double-blind coil was affixed to the mechanical arm for rTMS. An "earplug" reminder was attached to the coil to ensure the use of earplugs. (D) Close-up of the participant head position tracker mounted on goggles. A blindfold was worn by participants during phosphene thresholding, with room lights turned off. (E) A screenshot of Brainsight® software interface. The PT hotspot was saved on the left. To stimulate, the position and orientation of a coil were adjusted to align the bullseye with the crosshair centre.

6.3.4 Phosphene threshold (PT) measurement

Participants dark adapted with eyes closed under a blindfold for at least 5 minutes prior to PT measurement. Single TMS pulses at least 3 seconds apart were used for phosphene thresholding. Participants were first familiarized with phosphene perception by receiving TMS between 60%-80% maximum stimulator output (MSO) at a site 2 centimetres above the inion or 1 cm laterally to the initial site. They were instructed to report the presence or absence of a phosphene after each pulse. Positive reports were verified by flipping the coil and checking that the report was now negative. Participants who did not report genuine phosphenes were excluded.

After familiarization, PT measurement was performed. First, the intensity was increased from low to high (up to 80% MSO), until participants reported phosphene perception. A PT hotspot was determined as the spot (either the initial site, or 1 cm to the left, right or above) that induced reliable phosphenes with the lowest intensity. After finding the hotspot, the intensity was reduced in steps of 5% until no phosphenes were reported and, then increased in steps of 1-2% until reaching PT. PT was defined as the minimum intensity required for participants to report phosphene perception for 5 out of 10 pulses. The hotspot was saved in Brainsight® software and the PT intensity was recorded for use in subsequent visits. Participants from whom a PT was not obtained below 80% MSO were excluded.

6.3.5 Repetitive transcranial magnetic stimulation (rTMS)

rTMS was delivered at 100% phosphene threshold during the final 15 minutes of each MD visit at the hotspot location. At each visit, participants received either 10-Hz rTMS, 1-Hz rTMS, or sham stimulation. Following Fierro et al. (2005), 10-Hz rTMS involved 18 five-second stimulation trains separated by 45 seconds of rest. 1-Hz rTMS was delivered continuously for 15 minutes. Both protocols resulted in 900 pulses delivered over 15 minutes. Sham stimulation was delivered using the placebo side of the double-blind coil, randomly in the form of 10-Hz or 1-Hz trains. Both participants and the experimenter were masked to stimulation type.

6.3.6 Experimental procedures

Each participant had one PT visit and three MD visits (Figure 6-2). During the PT visit, after health and vision screening, PT measurement was performed as described above. Eligible participants with a reliable PT were invited to participate in three MD visits. In those visits, baseline ocular dominance was measured using the letter-polarity test. Participants' dominant eye, as determined by this test, was then deprived using a translucent eye patch for 1 hour. 15 minutes before the end of MD, participants received one of three types of rTMS. When MD was finished, ocular dominance was measured again every 10 minutes up to half an hour; thus, there were four post-intervention time points (Post 0, Post 10, Post 20 and Post 30). An adverse effect questionnaire was given after the Post 0 measurement for each visit. All visits happened at least 48 hours apart.

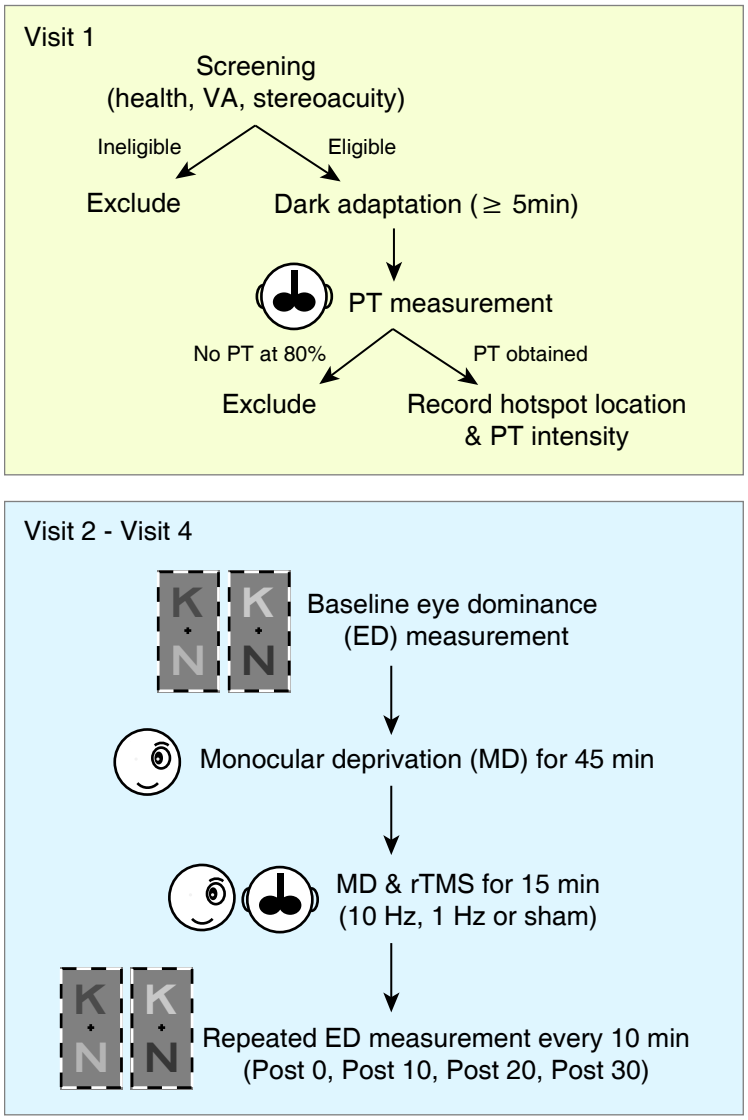

Figure 6-2. Procedures in this study. After confirming participants' eligibility in this study, PT was measured on the first visit. The most reliable location for inducing phosphenes and the PT intensity were recorded for use in subsequent visits. Participants then received MD for one hour and one of three types of rTMS (10 Hz, 1 Hz or sham) for the final 15 minutes of MD on three different days. Ocular dominance was measured using a computerized letter-polarity test before and every 10 minutes after MD. All visits happened at least 48 hours apart.

6.3.7 Data analysis

Data analysis was performed in JASP. $P < 0.05$ was considered statistically significant. Shapiro-Wilk tests were used to test data normality, and Mauchly's sphericity tests were used to confirm the sphericity of data. Non-spherical data were corrected using the Greenhouse-Geisser method. A repeated measures ANOVA with a factor of condition (10-Hz, 1-Hz versus Sham) and a factor of time (Baseline, Post 0, Post 10, Post 20 versus Post 30) was performed to examine the effect of rTMS on ocular dominance plasticity. The effect size was reported with omega squared (ω^2). Post hoc tests were performed using Bonferroni correction.

6.4 Results

28 healthy adults were recruited. 10 of them were excluded due to PT not acquired below 80% MSO. 3 were excluded due to vision not reaching 0.0 logMAR in at least one eye, and 1 due to high baseline ocular dominance (> 0.6). 4 withdrew due to personal reasons. The remaining 10 participants (age: 20-24 years, mean 22 years, 9 females) completed the study.

As shown in Figure 6-3, deprived eye dominance increased significantly after 1-hour MD (main effect of time: $F(4,36) = 46.24$, $p < 0.001$, $\omega^2 = 0.338$). Post hoc tests indicated that the increase was largest immediately following MD, after which deprived eye dominance dropped and remained broadly constant. Deprived eye dominance was still significantly different from baseline at 30 minutes post-intervention.

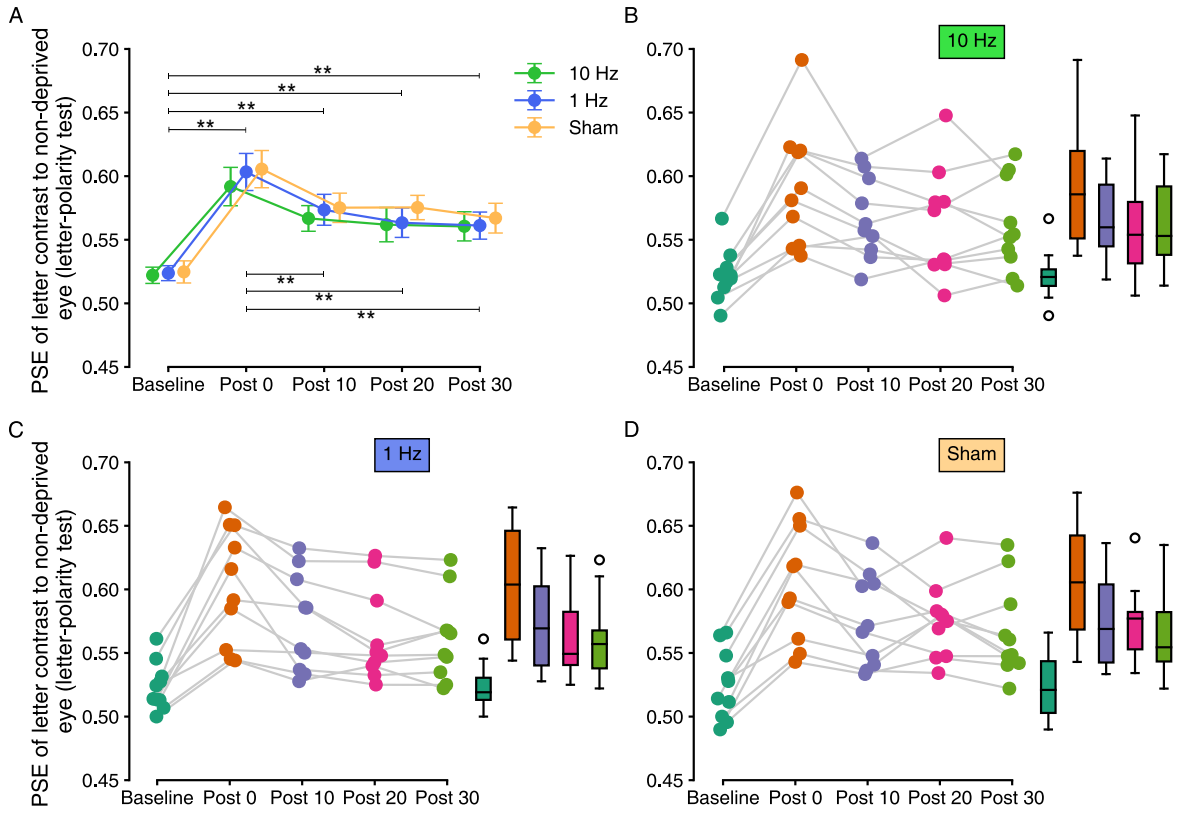

Figure 6-3. Deprived eye dominance data at different time points for three conditions in Experiment 3. Panel A shows group mean data. Error bars denote standard errors of the mean. Asterisks denote statistical significance by post hoc tests on the main effect of time (** $p < 0.001$). Panels B to D shows individual data for the 10-Hz, 1-Hz and sham stimulation conditions, respectively. Box plots indicate the median, quartiles and range of group data at each time point. Empty circles in the box plots denote outliers determined using the interquartile range (IQR) method (values more than 1.5 × IQR outside the IQR).

There was a significant main effect of condition ($F(2,18) = 3.694$, $p = 0.045$, $\omega^2 = 0.009$). Post hoc tests indicated that there was a significant difference between 10-Hz and sham conditions. However, we did not observe any interaction between the two factors (condition & time, $F(4.083, 36.744) = 0.466$, $p = 0.764$, $\omega^2 < 0.001$), suggesting that the pre-post ocular dominance changes were not significantly different across conditions. Therefore, the significant main effect of condition was likely due to the individual variability in baseline ocular dominance rather than an effect of brain stimulation.

6.5 Discussion

Consistent with the literature, we replicated short-term ocular dominance plasticity and observed an increase in deprived eye dominance up to 30 minutes after 1-hour MD. By adding rTMS to MD, we anticipated that the modulation of inhibitory and excitatory circuits in the visual cortex might influence the extent to which neurons respond to MD. Our study used a similar design and the same rTMS protocol as Fierro et al.'s work (2005). Their study employed light deprivation, which has been shown to increase cortical excitability and to reduce GABAergic inhibition in the visual cortex (Boroojerdi et al., 2000; Fierro et al., 2005; S. Huang et al., 2015). Based on the idea of state-dependency, reduced GABAergic inhibition during light deprivation may have caused an excitatory effect of low-frequency rTMS (Fierro et al., 2005). Given the evidence that MD also reduces GABA levels in V1 (Lunghi, Emir, et al., 2015), we anticipated that a similar excitatory effect of 1-Hz rTMS may enhance ocular dominance plasticity. However, we did not observe any effect of either 1-Hz or 10-Hz rTMS.

One possible reason for the null effect would be that ocular dominance plasticity might not be easily modulated. In fact, our group has previously tested the effects of two types of electrical stimulation on the magnitude ocular dominance plasticity, transcranial random noise stimulation (X. Chen et al., 2022) and transcranial direct current stimulation (X. Chen et al., 2023). These types of electrical stimulation are reported to modulate GABA concentration, which was our premise for their interaction with MD. However, we observed no effect. Similarly, studies that investigated the integration of physical exercise (Finn et al., 2019; J. Zhou et al., 2017), the use of a cholinesterase inhibitor (Sheynin, Chamoun, et al., 2019) and the use of attentionally demanding video games (X. Chen et al., 2020). have also observed no effects on ocular dominance plasticity. In contrast, other studies have observed strengthening of ocular dominance plasticity induced by physical exercise (Lunghi & Sale, 2015), neural states (Y. Chen et al., 2023), metabolic states (Animali et al., 2023) and sleep (Menicucci et al., 2022). The characteristics of interventions that can modulate ocular dominance plasticity remain unclear and are the subject of debate in the literature. However, across three available studies, it appears that non-invasive brain stimulation does not influence ocular dominance plasticity.

The magnitude of ocular dominance plasticity is modulated by the duration of MD (Min et al., 2022; Prosper et al., 2023; Ramamurthy & Blaser, 2021), raising a concern that ocular dominance changes might already have reached the ceiling with long durations of MD. We previously investigated the effect of electrical stimulation with both 2-hour and 0.5-hour MD (X. Chen et al., 2023). While confirming a modulatory effect of MD duration, we did not observe any modulation by electrical stimulation, suggesting that a potential ceiling effect does not explain the lack of ocular dominance

plasticity changes (X. Chen et al., 2023). The present study, which employed 1-hour MD to replicate the period of binocular deprivation used by Fierro et al. (2005), adds to this collective evidence that short-term ocular dominance plasticity is not affected by brain stimulation.

Another possibility is that our stimulation might not have been delivered to V1. The primary visual cortex is believed to be the cortical area where short-term ocular dominance plasticity originates (X. Chen et al., 2020; Lunghi, Berchicci, et al., 2015; Lunghi, Emir, et al., 2015). It has been shown that the simple use of an anatomical landmark has been reported to be insufficient for the selective stimulation of V1 (Salminen-Vaparanta et al., 2012). The utilization of functional magnetic resonance imaging (fMRI) was recommended instead (Salminen-Vaparanta et al., 2012). fMRI was not available for our study. However, instead of the simple use of the anatomical landmark, we located V1 by means of a mapping approach, i.e., through identifying the hotspot for inducing reliable phosphenes around the initial landmark, an approach that have been commonly used in other studies, most of which have reported a modulatory effect of brain stimulation (Brückner & Kammer, 2014, 2015; Clavagnier et al., 2013; Franca et al., 2006; Rahnev et al., 2013; Tashiro et al., 2007). In addition, our search grid was restricted to the occipital pole, and was only 2 cm^2 in size (1 cm to the left, top and right of the initial spot). Although more focal than other coil types, figure-of-eight coils are reported to have a spatial spread larger than 5 cm^2 (Deng et al., 2013; Thielscher & Kammer, 2004), much larger than our search grid. Therefore, it is likely that stimulation was successfully delivered to V1 in our study.

It is noteworthy that, in electrical stimulation studies, current amplitudes are generally the same across participants and not individualized. One study (van der Groen & Wenderoth, 2016) found that the optimal intensities in transcranial random noise stimulation (tRNS) varied across participants, though some of them did share a common optimal intensity of 1 mA. Individualized intensities for tDCS, on the other hand, have been reported to show no effect for the motor cortex (Sallard et al., 2021). It is possible that individual differences in optimal stimulation intensity affected the results of our previous electrical stimulation studies (Pavan et al., 2019; Smucny, 2021; van der Groen & Wenderoth, 2016). However, in the present study rTMS intensities were individually calibrated using 100% PTs. This use of normalized intensities helps to account for differences in individual cortical excitability (Siebner et al., 2022; Valero-Cabré et al., 2017).

State-dependency is an important factor to consider when interpreting the results of brain stimulation studies because it means that the same stimulation protocol applied to the same cortical area does not always yield the same effects. Rather, the effects are dependent on the activation state of the stimulated area prior to stimulation (Rotenberg et al., 2014; Silvanto & Pascual-Leone, 2008). Our null findings,

compared with an excitatory effect of 1Hz rTMS observed in (Fierro et al., 2005), may suggest that despite both monocular deprivation and light deprivation reducing GABA levels in the visual cortex, these two visual deprivation regimes may lead to different cortical states for rTMS. It is possible that complete light deprivation has pronounced effects on cortical excitability that interact with rTMS whereas the smaller excitability effects induced by monocular deprivation do not.

6.6 Conclusions

High-frequency and low-frequency rTMS did not strengthen short-term ocular dominance plasticity. Along with evidence from other studies (X. Chen et al., 2020, 2022, 2023; Finn et al., 2019; Sheynin, Chamoun, et al., 2019; J. Zhou et al., 2017), we conclude that this homeostatic plasticity is not easily modulated with non-invasive brain stimulation.

Chapter 7
General Discussion

7.1 Summary of Findings

Since its discovery by Lunghi et al. (2011), short-term ocular dominance plasticity has been investigated by research groups worldwide. This thesis focused on the investigation of whether NIBS can be employed to enhance short-term ocular dominance plasticity, as an index of visual cortex plasticity, in adults with normal vision. The first study investigated the effects of hf-tRNS and physical exercise, which demonstrated ocular dominance plasticity but revealed no significant effects of either intervention. The second study examined the effect of a-tDCS and whether a potential ceiling effect with 2-hour MD might have limited the effectiveness of NIBS through two experiments. This study showed that the magnitude of ocular dominance shift was indeed smaller after 30-min MD than after 2-hour MD. However, we did not observe any changes in ocular dominance shifts across stimulation conditions, even with 30-min MD, indicating no influence of a-tDCS on this plasticity. In the third study, we explored the impact of rTMS on the MD effect. Using individualized magnetic intensities, we did not find any effect of high- or low-frequency rTMS on ocular dominance plasticity. Collectively, these studies converge on a conclusion that neither tES nor rTMS appears to modulate short-term ocular dominance plasticity in adults with normal vision. These null findings, contrary to our hypotheses of positive effects, are addressed below.

7.1.1 Rethinking short-term ocular dominance plasticity: is V1 crucially involved?

Short-term ocular dominance plasticity has been believed to occur in early visual areas. There are multiple sources of support for this hypothesis. Firstly, V1 is the first visual area to integrate binocular inputs and contains ocular dominance columns (Daw, 2014; Tovée, 2008; Werner & Chalupa, 2013). Secondly, in human adults, the C1 component of visual evoked potentials, which reflects V1 activity, has been shown to decrease after MD for the deprived eye (Lunghi, Berchicci, et al., 2015). Elevated V1 activity with deprived eye viewing has also been detected using BOLD signals measured through functional magnetic resonance imaging (fMRI) (Binda et al., 2018). Moreover, a reduction in resting GABA levels (i.e., when both eyes are closed) in V1 has been observed following MD, with a significant correlation to ocular dominance changes (Lunghi, Emir, et al., 2015), suggesting that reduced GABAergic inhibition in V1 may underlie ocular dominance shifts following MD. Finally,

ocular dominance plasticity has been observed with a variety of ocular dominance tasks, as discussed in Chapter 3, suggesting that MD may indeed modify a fundamental aspect of binocular vision, presumably within V1.

Despite this evidence, short-term ocular dominance plasticity may not solely involve V1. Two recent studies have provided further insights. One study utilized a kaleidoscopic lens, where both eyes received similar images, except that the image presented to one eye was scrambled (Ramamurthy & Blaser, 2018). In the other study, researchers employed an inverting prism technique, where both eyes received the same input, except the input to one eye was entirely inverted (M. Wang et al., 2021). With these innovative monocular disruption techniques, both studies observed robust ocular dominance plasticity, despite visual inputs being similar between the eyes, thus bypassing low-level mechanisms (Ramamurthy & Blaser, 2018; M. Wang et al., 2021). Furthermore, M. Wang et al. (2021) compared the effects of engaging in a jigsaw task and passive viewing of a plain curtain during MD. The results showed a significant ocular dominance shift with the active task, while no such effect was observed with the passive viewing task. These findings suggest that top-down attentional processes may play a crucial role in ocular dominance plasticity, although it is unclear why MD with the passive viewing task did not lead to any ocular dominance shift. Indeed, although interocular suppression has generally been thought to occur in V1 and V2, higher visual areas have been reported to influence eye selection when visual inputs are disrupted, which can lead to the suppression of one eye (Kiorpes & Daw, 2018). In short-term ocular dominance plasticity, while changes in V1 activity have been correlated with ocular dominance shifts, a causal link has not yet been established, and V1 activity might not be the critical site for this plasticity. It may thus be understandable why stimulating V1 did not enhance short-term ocular dominance plasticity in our studies.

7.1.2 Rethinking short-term ocular dominance plasticity: is GABA crucially involved?

Let us assume that V1 activity is indeed critical for short-term ocular dominance plasticity. A second question arises: is GABAergic activity in V1 crucial for this plasticity? Currently, the only direct evidence on this subject comes from Lunghi, Emir, et al. (2015). As discussed above, while a significant correlation was revealed, Lunghi, Emir, et al.'s study (2015) study did not establish a causal link between the reduction in GABA levels and the magnitude of ocular dominance shifts. In addition, despite an increase in GABA levels with age (Pitchaimuthu et al., 2017), the magnitude of ocular dominance plasticity has been found to remain similar across adolescents, younger adults and older

adults (B. N. Nguyen et al., 2021, 2023). NIBS techniques, particularly hf-tRNS and a-tDCS, have been reported to alleviate GABAergic inhibition, yet our own studies did not demonstrate any enhancement of ocular dominance plasticity through these NIBS techniques. The lack of a role for GABA in this plasticity may help provide an explanation for our null findings. Hence, it is worth reconsidering the role of GABA in short-term ocular dominance plasticity.

It is possible that ocular dominance plasticity may rely on other neurotransmitters. Acetylcholine (ACh) has been reported to enhance cortical plasticity, with evidence primarily reported in the somatosensory and auditory cortices (Sur et al., 2013). In the visual cortex, one study (Sheynin, Chamoun, et al., 2019) explored the effects of donepezil, a cholinesterase inhibitor that elevates ACh activity. Instead of enhancing ocular dominance plasticity, the authors found that the intake of donepezil diminished ocular dominance shifts. They argued that increased ACh levels might have facilitated neural processing for signals from both the deprived and non-deprived eyes, resulting in an overall shift of ocular dominance in favour of the non-deprived eye (Sheynin, Chamoun, et al., 2019). Given the limited literature on the role of neurotransmitters in short-term ocular dominance plasticity, no conclusion can be drawn yet on this subject. More research is needed to comprehensively understand the mechanisms of this type of plasticity.

7.1.3 Rethinking NIBS: does NIBS modulate GABA in the human visual cortex?

Again, let us assume that reduced GABAergic inhibition in V1 is crucial for short-term ocular dominance plasticity. It is reasonable to hypothesize that interventions capable of reducing GABA levels may enhance this plasticity. As reviewed in Chapter 2, the reduction of GABA has been identified as an important mechanism underlying the excitatory offline effects of NIBS techniques. To briefly recapitulate, evidence supporting the reduction in GABA concentration following tRNS has been observed in the motor cortex and the prefrontal cortex (Chaieb et al., 2015; Sánchez-León et al., 2021). For a-tDCS, such evidence has been reported in the human motor cortex (Stagg et al., 2009, 2011) and the cat visual cortex (Zhao et al., 2020). However, these studies were not conducted in the human visual cortex. Although it initially seems plausible, results from the motor cortex may not necessarily generalize to the visual cortex. For instance, c-tDCS, which employs the opposite direction of electric current, compared to a-tDCS, and is considered inhibitory in the motor cortex, has been found to improve visual performance in patients with proliferative diabetic retinopathy (de Venecia & Fresnoza, 2021). Another study also observed a facilitatory effect of c-tDCS in V1, although the authors attributed

this effect to a suppressive impact of c-tDCS on interhemispheric inhibitory circuits (Bocci et al., 2018). Additionally, a recent study found that a-tDCS did not appear to significantly alter GABA concentration in human V1, as measured by magnetic resonance spectroscopy (MRS) (Abuleil, 2020). These inconsistencies in findings between the motor cortex and the visual cortex may indicate differences in underlying neural mechanisms of NIBS across difference cortical regions, which could contribute to our null findings regarding NIBS effects.

Another piece of evidence that suggests NIBS might not modulate GABAergic activity in V1 is derived from our findings on mixed percept durations. As elaborated in Chapter 1, GABAergic inhibition influences binocular rivalry dynamics (Mentch et al., 2019; Pitchaimuthu et al., 2017; Robertson et al., 2016; van Loon et al., 2013). According to the energy landscape theory (Kang & Blake, 2011; Skerswetat et al., 2018; Werner & Chalupa, 2013), alleviated interocular inhibition can lead to the partial or complete fusion of binocular inputs, resulting in mixed percepts. Therefore, the duration of mixed percepts can be indicative of the level of GABAergic inhibition. Indeed, MD was shown to increase mixed percept durations (Sheynin, Proulx, et al., 2019), which was consistent with the reduction of GABA levels observed following MD (Lunghi, Emir, et al., 2015). However, our studies, as presented in Chapters 3 and 4, did not reveal any significant changes in mixed percept durations. This indirectly suggests that GABAergic activity might not have been modulated by tES. It is noteworthy that, as extensively discussed in Chapter 3, the choice of visual stimuli can affect the dynamics of binocular rivalry (Kang, 2009; O'Shea et al., 1997; Qiu et al., 2020; Skerswetat et al., 2016, 2018). Therefore, it remains possible that, our null findings regarding mixed percept durations could be a result of the rivalry stimulus that we used rather than indicating no effect of tES on GABA in V1.

7.1.4 NIBS settings matter

With all the above discussed, let us now assume that NIBS does reduce GABA in the visual cortex and has the potential to enhance short-term ocular dominance plasticity. Yet it is crucial to keep in mind that the outcomes of NIBS can be influenced by various factors, as discussed in Chapter 4. For tES, these factors include the polarity of electric current (anodal vs cathodal stimulation), the relative locations of the stimulation and reference electrodes, electrode sizes, current intensity, and the duration of stimulation (Thair et al., 2017). For rTMS, factors include the orientation of the coil, the intensity and frequency of magnetic pulses, the duration of TMS trains, and the length of pauses between trains

(inter-train intervals) (Klomjai et al., 2015; Oberman, 2014; Taylor et al., 2018). Discrepancies in these NIBS settings as well as individual differences in cortical and cranial anatomy (Parazzini et al., 2015) may contribute to the inconsistent findings across studies.

Another variable that may influence NIBS effects is the timing of its application. tDCS timing, as discussed in Chapter 4, has been reported to affect the enhancement on motor training, although evidence is conflicting regarding whether tDCS is more beneficial before or during motor training (Buchwald et al., 2019; Jin et al., 2019; Jo et al., 2021; Liao et al., 2020; Sriraman et al., 2014). In the adult cat visual cortex, high-frequency rTMS has been shown to result in expanded representation of gratings with a single orientation, suggesting a brief period of elevated cortical plasticity following rTMS (Kozyrev et al., 2018). The authors suggest that leveraging this brief window of heightened plasticity may be more likely to enhance the effects of perceptual learning (Kozyrev et al., 2018). Our studies mirrored the design of Fierro et al. (2005), a study that demonstrated increased visual cortex excitability following low-frequency rTMS by the end of light deprivation. While our studies observed no significant effect, it remains possible that NIBS could modulate ocular dominance plasticity when applied at a different time, such as before MD.

In sum, our null findings regarding NIBS effects on ocular dominance plasticity must be considered within the context of the specific NIBS protocols that we employed. Different NIBS protocols may still be able to produce modulatory effects on ocular dominance plasticity.

7.1.5 State-dependency of NIBS

A final consideration for our null effect of NIBS arises from the concept of state-dependency. As reviewed in Chapter 2, reports of the state-dependency of NIBS in the visual cortex predominantly come from single-pulse TMS studies. For rTMS, no studies, except for Fierro et al. (2005), have reported its state-dependency in the visual cortex. As discussed in Chapter 6, our findings that rTMS did not influence ocular dominance plasticity may suggest that monocular deprivation induced a different cortical state prior to stimulation, compared to light deprivation. This difference in the cortical state could explain our failure to replicate the facilitatory effect of low-frequency rTMS observed by Fierro et al. (2005).

7.2 Impact of Work

Short-term ocular dominance plasticity has gathered significant attention from various research groups due to its potential application in the treatment of amblyopia in adulthood. Indeed, there has been initial evidence that this plasticity can be employed to improve patients' visual performance (Lunghi, Sframeli, et al., 2019; J. Zhou et al., 2019). A deeper understanding of the underlying mechanisms of this plasticity and the interventions that can enhance it will significantly augment its clinical relevance. In this thesis, for the first time in the literature, we investigated the enhancement of this plasticity in adults with normal vision using NIBS techniques. While we observed no significant effects of NIBS (Objective 1), our findings suggest that the neural mechanisms governing this plasticity may be more complex than a simple reduction in GABA levels (Objective 2). We also propose that it is necessary to reevaluate the role of V1 in this plasticity and reconsider the modulatory effects of NIBS on GABA in the visual cortex. While this thesis does not furnish direct evidence of the state-dependency of NIBS, we posit that the particular cortical state induced by MD may partially explain our null findings (Objective 3). Along with prior research (Min et al., 2018; Sheynin, Chamoun, et al., 2019), we corroborate that the magnitude of ocular dominance shifts depends on the length of MD. These findings provide valuable reference points for future studies investigating the enhancement of this plasticity. In addition, our experiments confirm that the letter-polarity test, introduced by Bossi et al. (2018), is reliable as a measuring tool for assessing ocular dominance and is suitable for quantifying ocular dominance shifts following MD (Objective 4).

7.3 Limitations and Future Directions

There are two main limitations in our experiments. One limitation is that these experiments, except for Experiment 2a, had relatively small sample sizes. Nevertheless, it is important to note that we did not observe any trend of differences across NIBS conditions in these experiments. Hence, recruiting more participants would likely not alter our findings. Another limitation is that we did not directly quantify GABAergic changes. Therefore, we do not possess direct evidence regarding whether NIBS modulated GABAergic inhibition in these experiments.

Future research may investigate the existence of a causal link between GABA activity and ocular dominance plasticity using antagonists and agonists of GABAergic receptors. In addition, measuring changes in GABA concentration in V1 before and after MD and brain stimulation could provide insights into potential interactions between these two types of interventions and the state-dependency

of NIBS. Future studies may also investigate whether different NIBS protocols could enhance ocular dominance plasticity. Furthermore, as we did not conduct these experiments in patient populations, future studies should explore whether NIBS could enhance ocular dominance plasticity and improve visual functions, such as visual acuity and contrast sensitivity, in patients with amblyopia. Lastly, while ocular dominance plasticity was intended as an index of visual cortex plasticity, our null findings do not rule out the potential of NIBS to augment visual cortex plasticity in general. Future studies could further investigate the effects of NIBS on other types of visual cortex plasticity, such as perceptual learning, in both patient and control populations.

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Appendix A

Supplementary Tables

Supplementary Table 1. Individual raw baseline eye dominance measures for each visit for both the grating rivalry and the letter-polarity tests. Values > 0.5 indicate right eye dominance. Data have been rounded to two decimal places. Datasets from excluded participants or those who withdrew were marked blue.

Experiments	Participants	Letter-Polarity Test				Grating Rivalry Test			
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4
Exp 1	A01	0.53	0.49	0.50	0.50	0.51	0.44	0.48	0.47
	A02	0.52	0.49	0.47	0.46	0.47	0.36	0.32	0.32
	A03	0.48	0.51	0.50	0.44	0.49	0.63	0.47	0.48
	A04	0.52	0.49	0.49	0.50	0.48	0.46	0.46	0.46
	A05	0.48	0.49	0.52	0.52	0.53	0.57	0.54	0.61
	A06	0.44	0.50	0.53	0.50	0.45	0.54	0.51	0.51
	A07	0.50	0.53	0.54	0.53	0.53	0.54	0.56	0.50
	A08	0.50	0.53	0.53	0.53	0.54	0.54	0.56	0.48
	A09	0.49	0.51	0.50	0.55	0.52	0.44	0.54	0.48
	A10	0.50	0.47	0.46	0.47	0.39	0.44	0.48	0.51
	A11	0.71	0.71	0.65	0.68	0.78	0.75	0.72	0.77
	A12	0.57	0.53	0.56	-	0.58	0.56	0.57	-
	A13	0.47	0.46	0.42	-	0.41	0.35	0.38	-
	A14	0.48	0.36	-	-	0.57	0.40	-	-
	A15	0.81	0.57	-	-	0.75	0.84	-	-
	A16	0.57	-	-	-	0.55	-	-	-
	A17	0.47	-	-	-	0.43	-	-	-
	A18	0.46	-	-	-	0.42	-	-	-
	A19	0.57	-	-	-	0.55	-	-	-
	A20	0.51	-	-	-	0.73	-	-	-
Exp 2a	B01	0.47	0.50	0.47		0.52	0.52	0.51	
	B02	0.52	0.52	0.51		0.51	0.48	0.47	

	B03	0.49	0.47	0.47	0.47	0.51	0.50
	B04	0.49	0.48	0.50	0.50	0.43	0.45
	B05	0.49	0.57	0.53	0.55	0.59	0.51
	B06	0.46	0.42	0.44	0.38	0.37	0.35
	B07	0.49	0.52	0.51	0.52	0.54	0.54
	B08	0.48	0.47	0.51	0.48	0.50	0.49
	B09	0.53	0.52	0.52	0.53	0.55	0.58
	B10	0.39	0.40	0.43	0.49	0.48	0.49
	B11	0.50	0.50	0.50	0.50	0.53	0.53
	B12	0.51	0.49	0.51	0.52	0.52	0.52
	B13	0.54	0.54	0.54	0.50	0.48	0.51
	B14	0.46	0.46	0.47	0.46	0.47	0.47
	B15	0.48	0.49	0.49	0.48	0.46	0.54
	B16	0.53	0.53	0.55	0.54	0.50	0.50
	B17	0.44	0.46	0.45	0.47	0.47	0.48
Exp 2b	C01	0.48	0.49	0.50	0.52	0.52	0.50
	C02	0.48	0.48	0.50	0.53	0.53	0.48
	C03	0.48	0.52	0.49	0.47	0.51	0.47
	C04	0.52	0.54	0.53	0.50	0.54	0.50
	C05	0.48	0.47	0.47	0.52	0.51	0.50
	C06	0.47	0.48	0.50	0.52	0.50	0.48
	C07	0.54	0.49	0.51	0.53	0.52	0.52
	C08	0.55	0.52	0.52	0.54	0.49	0.54
	C09	0.50	0.51	0.52	0.53	0.57	0.50

Supplementary Table 2. Participant reports of adverse effects of tDCS.

Anodal	**Cathodal**	**Sham**
Skin redness (21/26)	Skin redness (21/26)	Skin redness (12/26)
Tingling (3/26)	Tingling (7/26)	Tingling (2/26)

Itching (5/26)	Itching (4/26)	Itching (1/26)
Headache (4/26)	Headache (1/26)	Headache (2/26)
Scalp pain (1/26)	Scalp pain (4/26)	Scalp pain (0/26)
Burning sensation (0/26)	Burning sensation (2/26)	Burning sensation (0/26)
Neck pain (1/26)	Neck pain (0/26)	Neck pain (0/26)
Sleepiness (4/26)	Sleepiness (4/26)	Sleepiness (5/26)
Trouble concentrating (2/26)	Trouble concentrating (2/26)	Trouble concentrating (2/26)

All reports were rated as mild, except for a total of six moderate-level reports of "skin redness" (one anodal, one cathodal), "tingling" (one anodal), "sleepiness" (one anodal and one sham) and "trouble concentrating" (one sham). The prevalent reports of mild skin redness in this study could be partially due to the tightness of bands holding the electrodes in place and manual pressing on the electrodes to improve conductivity, as corroborated by 12 reports in the sham condition.

Supplementary Table 3. Participant reports of adverse effects of rTMS.

10 Hz	**1 Hz**	**Sham**
Skin redness (4/10)	Skin redness (3/10)	Skin redness (1/10)
Scalp pain (3/10)	Scalp pain (0/10)	Scalp pain (0/10)
Sleepiness (3/10)	Sleepiness (2/10)	Sleepiness (1/10)
Trouble concentrating (2/10)	Trouble concentrating (0/10)	Trouble concentrating (1/10)
Neck pain (1/10)	Neck pain (3/10)	Neck pain (3/10)
Headache (1/10)	Headache (1/10)	Headache (1/10)
Tingling (0/10)	Tingling (0/10)	Tingling (1/10)
Itching (0/10)	Itching (0/10)	Itching (0/10)
Burning sensation (0/10)	Burning sensation (0/10)	Burning sensation (0/10)

Moderate neck pain was reported by one participant after 1-Hz rTMS and another participant after all types of stimulation, despite that a chinrest had been provided during TMS. All other adverse effect reports were rated as mild.