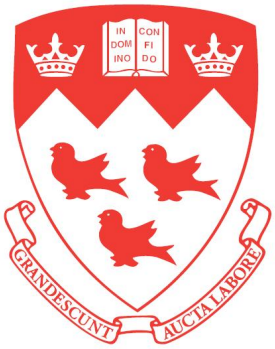


**Integrated Program in Neuroscience**

# Plasticity in adult binocular vision

by

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*A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Doctor of Philosophy in Neuroscience*

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# Abstract

Once thought to be restricted to childhood, adult brain plasticity presents an exciting opportunity to examine how the brain retains the lifelong ability to change and adapt in response to a complex, dynamic environment. Recent work has demonstrated that plasticity is a major guiding principle in the neuronal organization of binocular vision. The neural architecture of the primate visual system provides a fruitful avenue for examining brain plasticity, both due to the fact that it has previously been studied in great detail and to the ability to measure changes in neural function by measuring changes in visual perception. Here we examine adult brain plasticity in the binocular visual system of healthy humans. Specifically, we use the effects of short-term monocular deprivation – an increasingly-studied phenomenon – as a model of plasticity in the binocular visual system. We combine state-of-the-art perceptual and pharmacological methods to infer the neural substrates underlying measurable changes in binocular function. We find new perceptual effects of short-term monocular deprivation that have important consequences on our understanding of its neural mechanism. In addition, we find a profound new role for the cholinergic system in binocular plasticity processes – modulating binocular vision itself. To contextualize these new key insights, we review the previous literature and discuss open questions surrounding adult binocular plasticity, with the ultimate aim of providing a more detailed account of how the adult brain retains a remarkable capacity for malleability and change.

# Abstrait

Autrefois considérée comme limitée à l'enfance, la plasticité corticale à l'âge adulte introduit une intéressante opportunité d'étudier comment le cerveau conserve sa capacité permanente à changer et à s'adapter en réponse à un environnement complexe et dynamique. Des travaux récents ont démontré que la plasticité constitue un principe fondamental dans l'organisation neuronale de la vision binoculaire. L'architecture neuronale du système visuel des primates fournit un terreau fertile pour étudier la plasticité corticale en raison à la fois de son étude extensive et de la possibilité d'évaluer les changements dans les fonctions cérébrales par la mesure des changements de la perception visuelle. Ainsi, nous décidons d'étudier la plasticité corticale à l'âge adulte dans le système visuel binoculaire chez l'humain en santé. Spécifiquement, nous utilisons les effets de la privation monoculaire à court terme – un phénomène dont l'étude est en essor – en tant que modèle de la plasticité dans le système visuel binoculaire. Nous combinons des méthodes perceptives et pharmacologiques de pointe afin d'inférer les substrats neuronaux sous-tendant les changements mesurables des fonctions binoculaires. Nous observons de nouveaux effets perceptifs de la privation monoculaire à court-terme qui impliquent d'importantes conséquences sur notre compréhension de ses mécanismes neuronaux. De plus, nous découvrons un nouveau rôle crucial du système cholinergique dans le processus de la plasticité binoculaire – moduler la vision binoculaire *per se*. Pour mettre en contexte ces nouvelles découvertes clé, nous effectuons une revue de littérature et discutons les questions en suspens autour de la plasticité binoculaire à l'âge adulte, avec pour but ultime de fournir un exposé plus détaillé de comment le cerveau conserve à l'âge adulte une remarquable capacité de malléabilité et de changement.

# Acknowledgements

This thesis is dedicated to my immediate family, whose asylum immigration to North America at the end of the Soviet era made it possible for me to pursue my dreams. I thank my parents, whose tireless work ethic enabled them to support me unconditionally through unending years of education and relocations. I thank my advisor, Robert F Hess, for his mentorship, support, and patience as I matured into a full-fledged scientist, and for his companionship during sub-zero degree runs up Mount Royal in the Montréal winter. I thank Alexandre Reynaud, Alex S. Baldwin, and Sébastien Proulx for their mentorship and comraderie over the course of my degree, as well as Elvire Vaucher for her guidance and support during extensive hours of data collection. Likewise, I thank Fred Kingdom for the countless inspiring conversations we had over the course of my time at McGill. I am also extremely grateful for the mentorship and support I received from role models who believed in me from early on – Michael Silver, Dennis Levi, Rachel Denison, Adrien Chopin, Elise Piazza, and Monica Rivera Mindt. Last but certainly not least, it is nearly impossible to express as much gratitude as I feel towards my partner and best friend, Kaylena Bray, for her kind, loving, support and understanding, especially during the often late hours completing my PhD thesis.

# Contribution to original knowledge

Although there exists a rich foundation on which to build knowledge regarding plasticty in adult binocular vision, a detailed understanding of its neurophysiological underpinnings and perceptual implications is still lacking. The current work constitutes an original contribution to knowledge by offering three examples of scientific inquiry that address these gaps in the literature, and framing these new findings within the existing literature.

Specifically, chapter one presents novel insights regarding mechanims and previously unknown consequences of short-term monocular deprivation, a ubiquitous form of plasticity in binocular vision. Chapter two further expands on the mechanism of short-term monocular deprivation, demonstrating that the acetylcholine is implicated in modulating the magnitude and duration of its effects. Finally, chapter three identifies a previously unknown neurochemical component directly modulating binocular visual plasticity. In summary, the contents of the present work are new and original contributions which address gaps in our present knowledge of plasticity in adult binocular vision.

# Contribution of authors

**Chapter 1** Yasha Sheynin, Sebastien Proulx, and Robert F. Hess collaboratively conceived the project idea. Yasha Sheynin implemented the experiment, conducted the experiments, analyzed the data, and drafted the manuscript. Yasha Sheynin, Sebastien Proulx, and Robert F. Hess contributed to revising the manuscript.

**Chapter 2** Alex S Baldwin, Elvire Vaucher, Mira Chamoun, and Robert F. Hess collaboratively conceived the project idea. Alex S Baldwin and Yasha Sheynin implemented the psychophysical tests. Mira Chamoun, Pedro Rosa Neto, and Yasha Sheynin conducted the experiments. Yasha Sheynin conducted statistical analyses on the data and drafted the manuscript. Alex S Baldwin, Elvire Vaucher, Mira Chamoun, Robert F. Hess, and Yasha Sheynin contributed to revising the manuscript.

**Chapter 3** Yasha Sheynin, Elvire Vaucher, and Robert F. Hess collaboratively conceived the project idea. Yasha Sheynin implemented the experiment,conducted the experiments, analyzed the data, and drafted the manuscript. Yasha Sheynin, Elvire Vaucher, and Robert F. Hess contributed to revising the manuscript.

# Introduction

**Research Problem** Characterizing how changes in sensory experience affect changes in neural structure or function defines a major undertaking in the field of systems neuroscience. Progress in this field presents the possibility to reveal how the brain adapts to the demands of a dynamic and complex environment, as well as to to develop therapies that counteract the negative effects of abnormal experience during development. The neural architecture of the primate visual system provides a fruitful avenue for examining brain plasticity, both due to the fact that it has previously been studied in great detail and to the ability to measure changes in neural function using temporary, noninvasive, behavioural modalities in adult humans. Here we examine adult brain plasticity in the normal binocular visual system – reviewing the previous literature, providing new key insights, and discussing open questions – to provide a more detailed understanding of ways in which the adult brain retains a remarkable capacity for malleability and change.

Recent evidence has demonstrated that experience-driven plasticity is a guiding principle in the neuronal organization of adult binocular vision (Klink et al., 2010). An extraordinary example of this is the short-term perceptual eye dominance plasticity induced by a few hours of monocular patching. In this type of manipulation, patching one eye induces a shift in binocular dynamics such that the deprived eye contributes more to binocular vision (Lunghi et al.; Zhou et al., 2011; 2014). Although the study of this phenomenon has grown substantially in recent years (Lunghi et al.; Lunghi et al.; Lunghi et al.; Daniel Tso, Ronald Miller; Kim et al.; Zhou et al.; Zhou et al.; Zhou et al., 2011; 2015a; 2015a; 2017; 2017; 2013b; 2014; 2019), a thorough understanding of its mechanisms is still lacking. The primary focus of this thesis is to better characterize the mechanism of effect so as to learn more about the limitations and neural substrates of brain plasticity in general.

Similarly, adult brain plasticity is thought to be the result of changes in the functional dynamics of neural populations, however, the precise underpinnings of plasticity in binocular vision remain largely unclear and a more detailed under-

standing of the neurochemical bases is needed. Neural function in visual cortex is modulated by endogenous neurotransmitters like acetylcholine (ACh) and serotonin (5HT) (Shimegi et al., 2016). ACh is particularly interesting in the context of plasticity because it is knwon to be directly implicated in certain visual plasticity processes (Rokem and Silver; Rokem and Silver; Disney et al., 2010; 2013; 2007). While recent work has made substantial progress characterizing ACh's role in the visual system and in visual plasticity, much remains in the hope of gaining a more complete understanding of ACh's effects on binocular vision and on binocular visual plasticity in particular. This thesis addresses this need by directly investigating the role of ACh in the transduction of binocular information and on specifically binocular plasticity processes.

**Aims and Scope** This thesis makes no attempt at an exhaustive review of the available literature regarding plasticity in binocular vision. Rather, this work aims to provide sufficient background information for the reader to understand the motivations driving the research, to expand upon a series of three projects that offer new contributions to the field, to contextualize key insights from these contributions within a larger scope of the field, and to comment on the implications of the new contributions on the field and on possible future avenues of research.

The ultimate aim of this work is to provide new insights on the nature of adult brain plasticity. In the scope of the present work, the term plasticity refers to any changes observed in brain structure or function. These changes can take place across a multitude of timescales, possibly affecting resting cellular membrane potentials, synaptic strength, and structural modifications of both neurons and glial cells. We focus predominantly on plasticity in populations of neurons which, as a whole, produce changes in visual perception. It is important to note that any changes in visual perception that are not attributed to pre-cortical sensory issues (such as eye damage), or to changes in the physical stimulus, are implicitly linked to either changes neural structure/function or to changes in overall network dynamics (del Mar Quiroga et al., 2016).

The purpose of the present work is to better characterize the neural underpinnings of perceptual changes in binocular vision by defining their mechanisms. Specifically, this work aims to better characterize three specific components of plasticity in adult binocular vision that are pertain to existing gaps in the literature. These are: (i) to better understand the neural mechanisms and perceptual consequences of the effects of short-term monocular deprivation, (ii) to determine whether the effects of short-term monocular deprivation can be enhanced pharmacologically with ACh, and (iii) to characterize the role of ACh in binocular plasticity processes. These studies will be discussed in great detail and, hopefully, will sharpen our understanding of neural plasticity in the binocular visual system.

**Outline of the Thesis** The format of this document will follow the general outline of the aims listed above. The first section will review the rich literature, highlighting recent advances in the study of plasticity in binocular vision and emphasizing key articles that motivated the research within. The main body of the thesis will comprise three original scientific studies conducted by the author, each adding unique insights that deepen our understanding of adult binocular visual plasticity.

Specifically, chapter one addresses a novel approach to better characterize the perceptual effects and possible neural underpinnings of short-term monocular deprivation – a model of plasticity in adult binocular vision. In chapter two, we examine whether ACh – a proposed adult brain plasticity enhancer – can enhance the effects of short-term monocular deprivation. Finally, in the third chapter, we investigate a more foundational question about adult binocular plasticity – what is ACh's role in binocular vision in general and how does it affect plasticity? The last section will place the findings of the current thesis within the context of the existing literature, offering comments on the future of the field and on the significance of the new insights.

# Literature Review

## Introduction

Understanding how binocular signals are transduced in the visual cortex constitutes a central focus of the field of visual neuroscience. Roughly speaking, binocular vision first emerges as a function of cells receiving monocular inputs from thalamocortical synapses in layer 4 of the primary visual cortex (Kandel, E, Schwartz, J, Jessel, T, Siegelbaum, A, Hudsputh; Basgoze et al., 2014; 2018). Figure 1 (adapted from Bazgose, et al (2018)) illustrates the field's current understanding of binocular visual transduction, highlighting different pathways that modulate binocular vision as well as possible sights of neural plasticity in the binocular visual system.

Binocular vision provides a unique opportunity to examine experience-dependent plasticity in the brain. The seminal work of Hubel and Wiesel (Hubel and Wiesel, 1970) first characterized binocular neural plasticity via the study of the feline visual system. In these early studies, researchers examined plasticity in binocular visual circuits by artificially occluding one eye of an animal from very early on during the animal's life for a period of days or weeks. Evidence from visually-evoked responses, anatomy, and behavioural data revealed that this type of environmental manipulation causes dramatic and permanent changes to the organization of the binocular visual system. These changes were attributed to both structural and functional alterations in binocular dynamics. Thalamocortical projections from the non-deprived eye grew both in strength and in number, while those from the deprived eye diminished substantially – resulting in changes to ocular dominance, among other features of the animals' vision. Replicating identical experimental designs on older animals did not produce the same results, indicating the existence of a *critical period* for this type of neural plasticity where plasticity is a normal part of early development but becomes restricted after a certain period.

Hubel and Wiesel's discovery of a critical period in visual plasticity initiated the belief that the adult visual system did not exhibit plasticity. With this dogma in

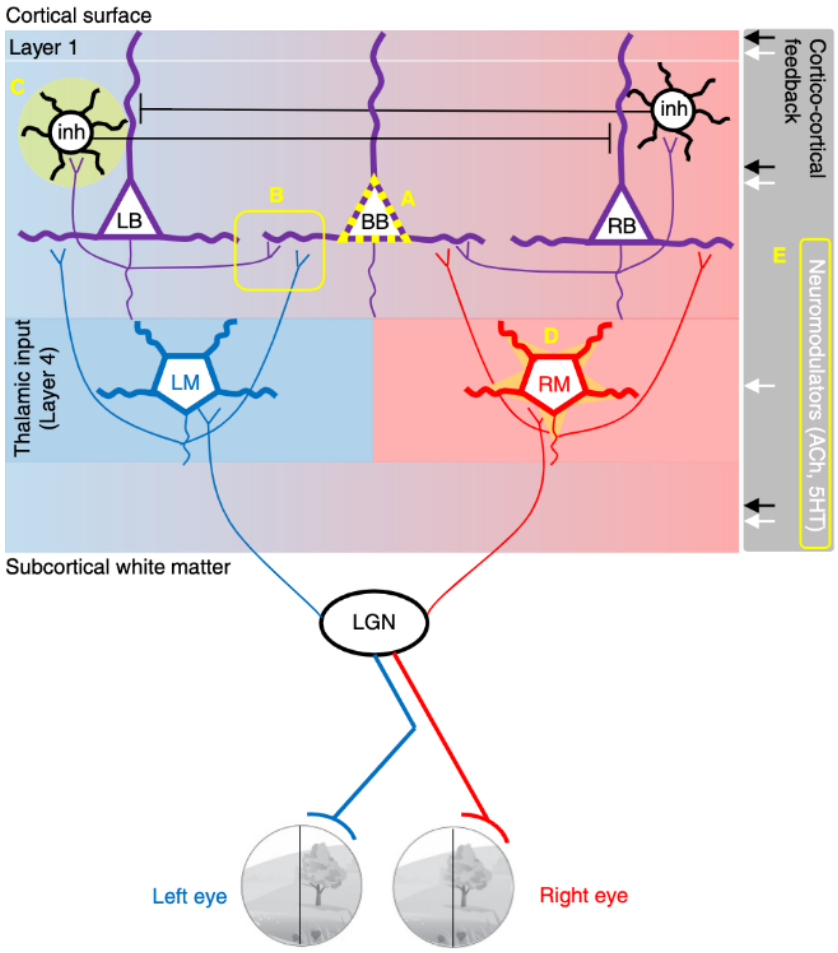


**Figure 1:** Visual stiulation of the left (blue) and right (red) eyes is first processed by cells in the retina. Retinal ganglion cells (RGCs) synapse onto the lateral genicualte nucleus (LGN) after partial decussation such that the left LGN receives monocular input solely from the right visual field, and vice versa. Feedforward signal from the LGN carries information from the left and right eyes into onto cells in layer 4 of the primary visual cortex (V1). These axons are largely (but not entirely) segregated, such that these input layers contain mostly cells driven by one eye or the other, but not both (LM/ RM). Thalamorecipeint cells are generally either pyramidal or stellate neurons, depending on the species. These cells usually project onto synapses in more topical cortical areas, at which stage the largely monocular signals combine onto cells that take input from both eyes, leading to populations of binocularly responsive neurons. Binocular combination occurs via diagonal ascending connections (feedforward) or via horizontal connections within the same layer. Ocular dominance, or the balance of left and right eyes influence on binocular cells is often times variable. Cells may be primarily driven by one eye or the other (LB/RB), or be equally driven by both eyes (BB). In primates, neurons with similar ocular dominance profiles are organized into ocular dominance columns, while in other animals (such as rodents), there is no clear stratification of ocular dominance. Inhibitory interneurons (inh) are believed to be involved in interocular gain control (Sengpiel; Ding and Sperling; Said and Heeger, 2005; 2006; 2013), although inhibitory gain control may also take place in monocular cells. Only layer 1 and layer 4 are labeled due to difference in cortical organizzation across different species. Importantly, feedback from higher order areas and modulatory signals are distributed across the layers of V1 (Shimegi et al., 2016) (acetylcholine / serotonin; ACh, 5HT). Important sites are highlighted as follows: A) cell membranes, B) cortico-cortico synpases, C) inhibitory interneurons, D) peri-neuronal nets, E) neuromodulatory input.

mind, recent discoveries of latent forms of plasticity in adult binocular vision were surprising. In retrospect, however, it is clear that the adult brain retains a remarkable capacity for change, despite incorporating clear restrictions on certain types of plasticity like the type of ocular dominance plasticity described by Hubel and Wiesel. Characterizing these previously unknown forms of adult neural plasticity is an important goal of modern visual neuroscience, with clear clinical implications for the development of treatments for disorders of binocular function.

Formulating a more complete understanding of adult brain plasticity and its consequences on perception is a difficult and ever-evolving endeavor, due in part to the sheer number of observable phenomena and experimental paradigms available for its study. Here we narrow our focus to review the literature regarding plasticity in the binocular visual system, with specific attention to dichoptic adaptation and short-term monocular deprivation paradigms, although other forms of binocular visual plasticity – such as that exhibited in perceptual learning paradigms (Ding and Levi; Li et al., 2011; 2013) – are equally important. We begin by discussing common methodologies used to measure binocular function in the context of dichoptic adaptation and short-term monocular deprivation paradigms. Then, we expand on dichoptic adaptation and how it relates to the effects of short-term monocular deprivation. We also incorporate a review of the literature concerning the role of acetylcholine in binocular vision and in visual plasticity, with the hope of facilitating a comprehensive understanding of the ways in which the cholinergic system may affect binocular visual plasticity specifically. A guiding principle regarding the organization of this work is that the effects of short-term monocular deprivation can be used as a model to understand binocular visual plasticity, and characterizing the neurochemical underpinnings of these effects will no doubt lead to a more complete understanding of binocular plasticity in general.

## Methodological Approaches

### Measuring Binocular Function

The study of binocular visual plasticity requires perceptual measurements of binocular function – discussed here are such measurements often used in conjunction with experimental paradigms that take measurements before and after manipulations that trigger changes in binocular vision. Of the vast array of measurements of binocular visual function, we will focus predominantly on binocular phase combination (Ding and Sperling; Huang et al., 2006; 2009) and binocular rivalry (Wheatstone; Blake and Logothetis, 1868; 2002) as they are most pertinent to the content of the present work. Specifically, we discuss these tasks' theoretical bases and emphasize how they are used in the study of binocular plasticity.

**Binocular Phase Combination** Binocular phase combination refers to a task developed by Ding and Sperling (2006) for the purpose of fitting a computational model of binocular combination. This model posits two basic principles of interocular interactions: in every spatial neighborhood, each eye (i) exerts gain control on the other eye's signal in proportion to the contrast energy of its own input and (ii) additionally exerts gain control on the other eye's gain control (Ding and Sperling, 2006). The model successfully predicts performance on the binocular combination task, utilizing a design in which individuals dichoptically view low spatial frequency patterns that are spatially out of phase by 45 degrees, interocularly. When fusing the two images, the participant is required to use keypresses to move a flanking bar to the perceived center of the sinusoid, such that a balanced binocular visual system would report a phase of 0 degrees for the fused stimulus. The Ding and Sperling (2006) model also predicts the effect of changing the interocular contrast ratio (Huang et al., 2009), where lowering the contrast of one eye's grating shifts the perceived middle of the sinusoid in favour of the monocular grating with the higher contrast.

Plasticity studies utilizing the binocular phase combination task generally eval-

uate plasticity in terms of changes to ocular dominance (ocular dominance). In this way, the phase combination task can effectively demonstrate the relative contributions of the two eyes to a fused binocular percept, and therefore to binocular vision (Chadnova et al.; Zhou et al.; Zhou et al., 2017; 2013b; 2014). Patching an eye for a few hours results in a shift in favour of the deprived eye – similar to the effect of reducing the contrast in the non-deprived eye. These studies generally interpret this finding as a change in the response profile of the interocular gain-control mechanism. In this framework, patching causes a reciprocal inhibition of the non-deprived eye and a dis-inhibition of the deprived eye.

**Binocular Rivalry** Binocular rivalry (Wheatstone, 1868) is a phenomenon that occurs when the two eyes are presented separate, incongruent images. The experience is defined by perceptual alternations that shift perception from one eye's image to the other over the course of stimulus presentation (see Blake and Logothetis (2002) for a review). Studies that use binocular rivalry to measure perceptual eye dominance infer the contributions of the two eyes from the degree to which one eye suppresses the other when competing, or rivaling, for perception.

Binocular rivalry with monochrome gratings – which is often attributed to activity in early areas of visual cortex (Blake; Tong et al., 1989; 2006) – has been explicitly shown to correlate with alterations in steady-state visually evoked potentials (SSVEPs) (Katyal et al., 2016) in V1, as well as with BOLD activity measured in both V1 and the LGN (Blake and Wilson, 2011), indicating its sensitivity for use as a probe of binocular visual processes. Due to these sensitive properties of binocular rivalry, it has also been often used as a probe of neural competition in visual cortex, where changes in binocular rivalry dynamics are interpreted as changes in neural activity and therefore indicative of brain plasticity (Tong et al., 2006). These neural signatures of binocular rivalry have also been modeled extensively using computational methods, incorporating a variety of components such as interocular normalization (Li et al.; Said and Heeger; Wilson, 2015; 2013; 2003), top-down regulation of attention (Li et al.; Carrasco, 2017; 2011), and monocular

normalization (Brascamp et al., 2013).

Although binocular rivalry is often characterized as a series of perceptual alternations between two competing images, the actual visual experience is more extensive and can be separated into three categories: (1) exclusive visibility – when one eye's signal is entirely suppressed by the other eye's image, (2) piecemeal mixed visibility - where information from both eyes is simultaneously visible in smaller spatially segregated areas, sometimes described as local rivalry (Skerswetat et al.; Klink et al., 2017; 2010), and (3) superimposition mixed visibility - where information from both eyes is visible and combined to constitute a fused binocular percept (Brascamp et al.; Liu et al.; Klink et al., 2006; 1992; 2010). Superimposition occurs infrequently (around 10% at common stimulus parameters: 3cpd, 1.5 deg diameter), while piecemeal visibility ranges from 10-60% (Hollins, 1980).

Importantly, mixed visibility highlights instances when complete interocular suppression fails, allowing binocular combination to occur. Stimulus parameters such as contrast, spatial frequency, and field size are known to affect the proportion of mixed visibility during rivalry (Hollins; O'Shea et al., 1980; 1997), suggesting unique neural signatures underlying the phenomenon. In fact, mixed visibility has been shown to be negatively associated with resting-state GABA levels in V1 (Freyberg et al., 2015a), and has likewise been shown to decrease after administration of GABA agonist drugs (Mentch, Jeff., Spiegel, Alina., Ricciardi, Catherine., Kanwisher, Nancy., Robertson., 2018). Dis inhibition of interocular interactions are plausibly responsible for superimposition percepts, while piecemeal percepts are proposed to emerge from a weakening of the spatial coherence of inhibitory interactions (Kovacs, I., Papathomas, T.V., Yang, M., and Feher and Ehe; Lee and Blake; Alais and Melcher, 1996; 2004; 2007).

Relatedly, rivalry has also been used an an assay of E/I balance (Robertson et al.; Robertson et al.; Van Loon et al., 2013; 2016; 2013), an aspect of brain dynamics that is directly linked to plasticity (Bavelier et al., 2010). Recent evidence has found that a slower rate of binocular rivalry and a higher incidence of mixed visibility is linked to an excitation-dominant cortical response profile – a marker of

autism (Robertson et al., 2013). Furthermore, GABA has been shown to modulate the rate and resolution of binocular rivalry (Van Loon et al., 2013). Importantly, manipulations that target cortical E/I balance generally affect the the binocular visual system and subsequently influence binocular rivalry dynamics (Lunghi et al.; Lunghi et al.; Lunghi et al.; Said and Heeger; Mentch, Jeff., Spiegel, Alina., Ricciardi, Catherine., Kanwisher, Nancy., Robertson., 2011; 2015a; 2016; 2013; 2018).

## Experimental Paradigms

The modern study of plasticity in human binocular vision generally falls into three categories of experimental design – (i) dichoptic adaptation, (ii) monocular deprivation, and (ii) dichoptic training (see **Figure** 2). As dichoptic training generally refers to neuroplastic changes in abnormal binocular visual systems (such as in amblyopia), the current work focuses on neuroplasticity in the normal binocular visual system and will therefore focus primarily on key findings of binocular visual plasticity using dichoptic adaptation and short-term monocular deprivation. Additionally, we review the way the endogenous neurotransmitter acetlycholine (ACh) has been used in the study of visual brain plasticity and present possible avenues for its role in modulating binocular plasticity.

**Dichoptic Adaptation** Visual adaptation is a powerful probe of neural function – exemplifying experience-driven changes to neural activity in real time using a non-invasive approach. Adaptation refers to attenuation of neural sensitivity to a particular stimulus after a period of exposure to the same (or similar) stimulus. A straightforward example of this type of neural plasticity is the tilt-aftereffect, where viewing a sinusoidal grating of a particular spatial frequency tilted at a certain orientation for a given period causes the viewer to perceive a neutral, nonoriented bar as tilted in the opposite direction for a short period afterwards. The effects of visual adaptation are reported to last approximately as long as the duration of the initial exposure to the adapting stimulus (Greenlee et al., 1991).

In terms of plasticity in binocular vision, dichoptic adaptation is used to manip-

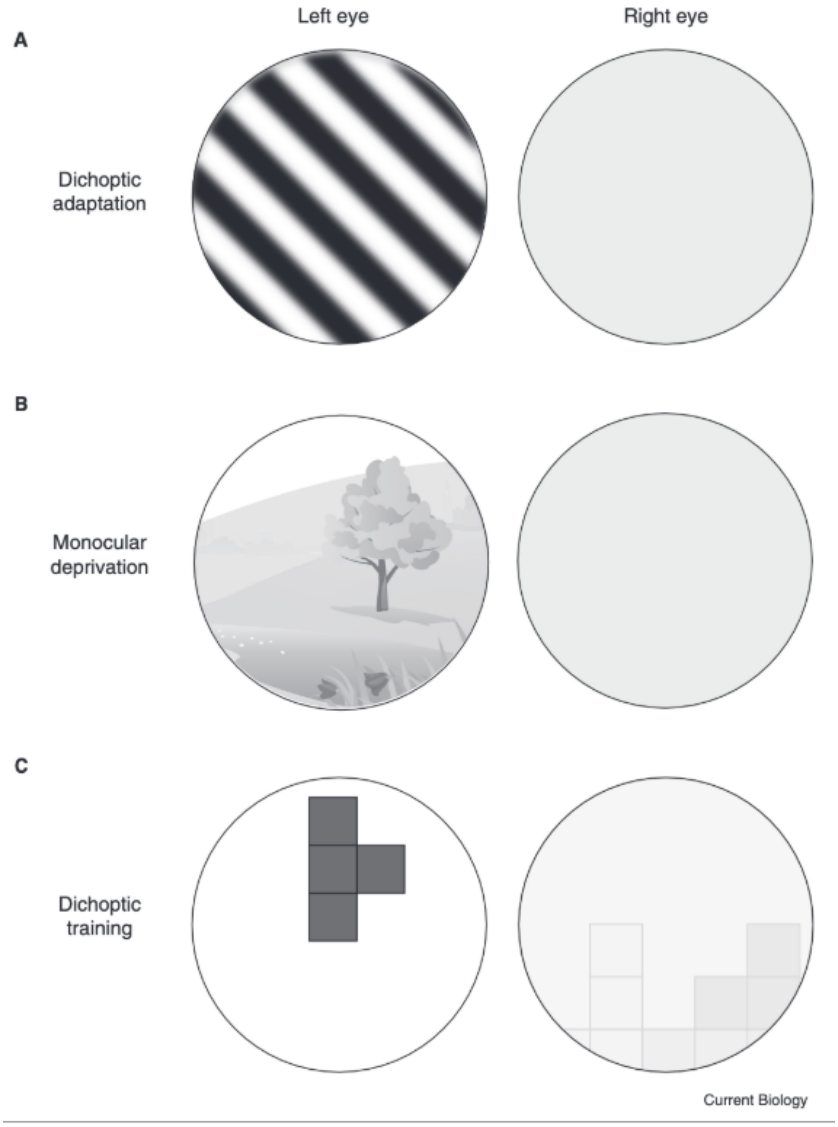


**Figure 2: Illustration of experimental paradigms used to investigate plasticity in adult binocular vision (adapted from Bazgose, et. al., 2018).** (A) Dichoptic adaptation exploits the existence of adaptation in neural circuits. Binocular pathways will change their activity after short periods of adaptation to interocular difference (Kingdom et al., 2018). In this case, one eye views a high contrast high spatial frequency pattern, and the other eye views a uniform field. (b) In monocular deprivation (which is generally on the scale of a few minutes to a few hours in adult humans) (Zhou et al.; Lunghi et al., 2014; 2011), one eye is exposed to all natural scene statistics by staying open and engaging normally, while the other eye is patched with either an opaque patch (eliminating all visual stimulation) or a translucent patch (eliminating all pattern information but retaining luminance information). (C) Dichoptic training paradigms, generally used to improve binocular vision in amblyopia, encourage the eyes to work together by requiring fusion to successfully complete a certain task. The weaker eye (amblyopic eye) generally gets a higher contrast level than the strong (fellow) eye so as to reduce interocular suppression of the amblyopic eye.

ulate the neural activity of binocular populations of cells and then different assessments of binocular function are used to measure the adaptation-induced changes. A simple example of this is illustrated in **Figure** 2, where one eye adapts to a high spatial-frequency pattern and the other views mean luminance. This particular form of dichoptic adaptation results in a reduction of sensitivity to gratings of similar orientation and spatial frequency. Interestingly, these types of manipulations are known to affect both eyes, despite only one eye being adapted to a stimulus – an effect known as interocular transfer (Blakemore and Campbell, 1969). Interocular transfer demonstrates that neurons responsible for producing the viewer's percept are likely binocular cells in V1 or higher that are able to shift their response over the course of stimulus exposure (Howarth et al., 2009).

Binocular rivalry – where the eyes are receiving nonidentical inputs – can be viewed as a type of dichoptic adaptation. Rivalry has been shown to have dramatic effects on binocular function, where prolonged rivalry to orthogonal gratings causes the eyes to inhibit each other less, reducing the visibility of exclusive monocular percepts and facilitating the visibility of mixed, binocular percepts (Klink et al., 2010). Interestingly, patching an eye for up to 24 h after prolonged exposure to rivalrous stimuli enabled the visual system to retain the same dynamics during rivalry measurements afterwards. Only restoring non-rivalrous, normal binocular visual stimulation resulted in a recovery to baseline rivalry dynamics. This finding highlights a central component of binocular vision – namely rapid, experience-driven plasticity that takes place over very short time scales.

Interestingly, a recent article demonstrated that dichoptic adaptation with left- and right-tilted gratings that were (i) flickering interocularly at a rate of 15 Hz and (ii) switching orientation at a rate of .3 Hz, subsequently reduced levels of interocular competition during binocular rivalry (Said and Heeger, 2013). This finding shows that the binocular visual system reduces its sensitivity to interocular difference even after balanced adaptation to the same stimulus in both eyes. The motivation from this work is drawn from a line of work on computational models of binocular rivalry Wilson (2003); Brascamp et al. (2013) whose goal is to determine

the underlying mechanistic components driving binocular rivalry dynamics. The overarching message here is that the binocular visual system is particularly sensitive to detecting differences between the two eyes, such that an adaptive shift in the behaviour of this difference-detecting network may modulate the degree to which the eyes inhibit one another.

Along this line of work, another group also examined adaptation to interocular difference using dichoptic multi-spatial frequency patterns (Kingdom et al., 2018). This work revealed that the binocular visual system can indeed become sensitized to interocular differences, even when both eyes are presented mostly the same image. Together, these findings conclude that (i) there exists a channel in the binocular visual system that is preferentially tuned to interocular difference, and (ii) this channel will change its response profile after the slightest alterations in the environment, exemplifying neural plasticity.

The results of this work align with previous theoretical insights on the existence of a binocular differencing channel in the primate visual system (Li and Atick; May and Zhaoping, 1994; 2016). This differencing channel utilizes an independently-modulated gain-control mechanism that has been theoretically shown to enable the efficient coding of stereoscopic depth perception (Li and Atick; May and Zhaoping, 1994; 2016). In their work, Li and Atick (1994) postulate the existence of a system of efficient stereo coding that relies on two separate binocular channels – one encoding the sum of monocular signals, and the other the difference. In this way, efficient representation of visual depth is achieved by mutually decorrelating otherwise highly-correlated monocular signals. This theory of binocular visual transduction has recently been given new supporting evidence – a novel prediction of the theory, proven true, is that the perceived direction of tilt of a test pattern can be modulated by pre-exposing individuals to dichoptic adaptors (May and Zhaoping, 2016).

Determining the neural mechanisms of this type of adaptation of binocular neurons is an important and non-trivial consideration. Hyperpolarization of binocular neurons (**Figure 1A**) and depression at excitatory cortico-cortical synapses in V1 (**Figure 1B**) are both viable candidates for the site of dichoptic adaptation effects

(Basgoze et al., 2018). The mechanisms underlying interocular gain control in V1 (which are responsible for maintaining a constant visual representation of the world when viewing with one eye or with both) may also play a significant role in this type of adaptation. Imbalanced stimulation of the eyes – like in dichoptic adaptation paradigms – may preferentially target this type of gain-control mechanism. Interocular gain-control processes, such as those described by Ding and Sperling (2006), are thought to be directly linked to levels of the inhibitory neurotransmitter GABA in V1, where inhibitory interneurons mutually inhibit monocular neurons driven by the two eyes (Sengpiel; Said and Heeger, 2005; 2013). This conceptualization aligns itself with the differencing channel idea outlined by Li and Atick (1994) – where populations of neurons become sensitive to the difference of the two eyes' inputs by means of mutual inhibition. It is therefore plausible that dichoptic adaptation phenomena relate back to the two mechanisms described by Li and Atick (1994) corresponding to interocular differencing and interocular summation.

Considering the array of evidence from recent research, it is likely a combination of rapid intrinsic and synaptic changes across different populations of excitatory and inhibitory cells in V1 that contribute to plasticity induced by dichoptic adaptation. Precisely how this is achieved, however, remains unknown. A plausible explanation for the types of changes described in the literature is divisive normalization – where any individual neuron's input-driven activity is divided, or normalized, by some function of the activity of other neurons in the same network (Westrick et al., 2016). These type of network-wide changes may contribute to the binocular system's ability to retain homeostatic stability and constancy between monocular and binocular viewing. Notably, the normalization model of visual adaptation (although not specifically geared towards dichoptic adaptation phenomena) was better at predicting real data than conventional models which assume adaptation is a function of neuronal fatigue or gain-modulation (Basgoze et al., 2018).

**Monocular Deprivation** Another related experimental paradigm used to probe adult binocular vision is short-term monocular deprivation. As mentioned previ-

ously, monocular deprivation of young animals is known to shift ocular dominance at the neural level in favour of the non-deprived eye, while this effect is not observed in older animals (Hubel and Wiesel, 1970). This is traditionally viewed as proof for the existence of a critical period for ocular dominance plasticity. In humans, monocular deprivation is also used during brief periods of childhood to treat amblyopia – a disorder of binocular vision caused by abnormal experience during development, with long-standing success Hess et al. (2010).

Recently, however, perceptual eye dominance plasticity was demonstrated in healthy adults (Lunghi et al.; Zhou et al.; Kim et al.; Zhou et al.; Lunghi et al.; Lunghi et al., 2011; 2014; 2017; 2013a; 2015a; 2015b). To measure perceptual eye dominance, researchers use measurements such as binocular rivalry or binocular phase combination before and after a few (1 - 3) hours of monocular deprivation utilizing either an (i) opaque patch that removes all spatial frequency information (Zhou et al., 2013b), or (ii) a transluscent patch that removes most pattern information (Lunghi et al.; Lunghi et al.; Zhou et al., 2011; 2015b; 2013a). Other manipulations have also been used, where dichoptic goggles present some deprivation configuration using proccessed movies (Zhou et al., 2014).

The most striking result of these experiments is a substantial shift in favour of the *deprived* eye that is noticeable for periods ranging from 15 min - 2 h after the deprivation period. This shift is dependent on an interocular contrast difference between the two eyes (Zhou et al., 2014), where zero contrast in one produces the largest eye dominance shift. The significant shift in favour of the occluded eye was an unexpected result – contrary to the type of plasticity observed during the critical period, where animals' ocular dominance shifts in favour of the non-deprived eye.

It is important to point out that the dissimilar effects of long-term ($>$ 2 days) and short-term monocular deprivation (a few hours) could implicate a different set of neural mechanisms. In the classical model, changes in ocular dominance depend on plasticity brakes and consolidation mechanisms to modify neural activity. Short-term perceptual eye dominance plasticity (Lunghi et al.; Zhou et al.; Chadnova et al., 2011; 2015; 2017), on the other hand, is described as a form of interocular contrast

gain control (Hess et al.; Zhou et al., 2013; 2015), driven by enhanced contrast-gain of signal from the patched eye, as well as a reduction in GABA-ergic inhibition in V1 (Lunghi et al., 2015b).

Physiologically, the effects of short-term monocular deprivation have been observed using MRS (Lunghi et al., 2015b), MEG (Chadnova et al., 2017) and fMRI (Binda et al., 2017) in humans, as well as intrinsic optical imaging in a murine model (Daniel Tso, Ronald Miller, 2017). These studies point to deprivation-induced changes in inhibitory/excitatory dynamics in V1 with observable effects at the level of ocular dominance columns in layer 4c of V1. Importantly, frequency-tagged MEG signal from the non-deprived eye was reported to decrease during short-term deprivation and only begins recovery after restoring binocular visibility (Chadnova et al., 2017). This effect is attributed to an enhanced net inhibition of the non-deprived eye's input relative to the deprived eye.

Fundamentally, ocular dominance is an emergent property of an aggregate population of binocular cells tuned to weighted monocular inputs. The strength of a monocular signal influencing the bias of a specific binocular pyramidal neuron is determined by three main factors: (1) the gain of thalamocortical input from a particular eye, the (2) presynaptic inhibition of the contralateral eye induced by either GABAergic interneurons or recurrent connections, or (3) long-range corticocortical projections. Changes in any or all of these three factors would result in a different perceptual eye dominance profile. Perceptual – or sensory – eye dominance has been considered a proxy for the ratio of synpatic input strength of the eyes. Notably, however, measures of sensory eye dominance are not correlated with monocular measures of contrast sensitivity or brightness perception, indicating that there is no clear link between perceptual eye dominance and the actual strength of neuronal ocular dominance. For this reason, measures of perceptual eye dominance may be a better indicator of interocular inhibition than neuronal ocular dominance (Basgoze et al., 2018).

Interestingly, there is growing evidence that the effects of monocular deprivation do not depend on the duration of the adaptation period Lunghi et al. (2011); Kim

et al. (2017); Min et al. (2018), pointing to the phenomenon as a type of homeostatic plasticity with all-or-none behavior. This new understanding of the effects of monocular deprivation lends reason to examine previous studies that examined adult ocular dominance. Such an early study (Blake and Overton, 1979) demonstrated that interrupting binocular rivalry with 60 seconds of dichoptic adaptation to one of the two rival images causes ocular dominance to shift away from the adapted eye for a period of up to 30 s during subsequent binocular rivalry. This finding is proposed to function as a result of adaptation where populations of neurons responding to the adapted eye exhibit a reduction in activity prior to interocular normalization.

While it may be tempting to consider that the effects of short-term monocular deprivation constitute a form of dichoptic adaptation – **Figure 2B** – there is evidence to the contrary. For example, one study reported that there were no changes to apparent contrast in either eye following monocular deprivation (Lunghi et al., 2011), while other studies indicated a reciprocal increase in contrast sensitivity in the deprived eye and a decrease in the non-deprived eye (Zhou et al.; Zhou et al., 2013a; 2014), likewise reflected in frequency-tagged MEG activity (Chadnova et al., 2017). Indeed, neither monocular adaptation nor interocular transfer are able to explain the binocular effects of monocular deprivation, as visual input is unchanged and there are differential, reciprocal effects in the two eyes. It is therefore imperative for future research to better characterize a mechanistic understanding of the effects of short-term monocular deprivation.

**Pharmacological Enhancement of Acetylcholine** A major undertaking in the visual neurosciences is to characterize the extent to which adult brain plasticity can be enhanced. Treatments that enhance plasticity in adults generally do so by changing long-lasting neuronal responsiveness or by acting on so-called "brakes" on plasticity that develop after the critical period. Some of these brakes on plasticity are structural, such as peri-neuronal nets or myelin, which inhibit synaptogenesis. Others brakes are functional and act on the excitatory/inhibitory balance of neural circuits (Bear and Singer; Kasamatsu et al.; José Fernando Maya Vetencourt et al.;

Morishita et al., 1986; 1991; 2008; 2010). It is widely believed that adult brain plasticity can be enhanced by manipulating excitatory/inhibitory transmitter signalling (Bavelier et al.; Morishita et al.; Baroncelli et al.; Baroncelli et al., 2010; 2010; 2011; 2012).

Treatments that manipulate excitatory/inhibitory balance to alter neural plasticity generally act on endogenous neuromodulator activity. These interventions have, at times, been successful at enhancing cortical functioning and plasticity in both adult human and animal models (Rokem and Silver; Morishita et al.; Chamoun et al.; Rokem and Silver; Bavelier et al.; José Fernando Maya Vetencourt et al.; Bentley et al.; Bear and Singer; Kasamatsu et al., 2010; 2010; 2017a; 2013; 2010; 2008; 2003; 1986; 1991), however this has not universally been the case (Chung et al.; Conner et al., 2017; 2003). Some successful interventions targeting dopaminergic, serotonergic, and cholinergic pathways elicited direct consequences on adult functional and structural brain reorganization (Bear and Singer; Bao et al.; Weinberger; Morishita et al.; Berardi et al.; José Fernando Maya Vetencourt et al.; Gratton et al., 1986; 2001; 2007; 2010; 2000; 2008; 2017). The lack of clarity on the effect of acetylcholine on visual brain plasticity underlines the necessity of pursuing basic research questions, such as determining its role in binocular vision.

Of the known neuromodulators, acetylcholine (ACh) is particularly interesting for plasticity because of its role in modulating excitatory/inhibitory balance in visual cortex as well as mediating long-lasting neuronal responsiveness and structural plasticity throughout the cortex. For instance, genetically removing the expression of Lynx1, a cholinergic brake, reinstates critical-period-like ocular dominance plasticity in adult mice (Morishita et al., 2010), where the non-deprived eye becomes more dominant. Furthermore, multiple administrations of the acetylcholinesterase inhibitor (AChEI) physostigmine (which potentiates and prolonges the action of endogeneous ACh) improves visual function and enhances critical-period-like ocular dominance plasticity after long-term monocular deprivation in a murine model of amblyopia (Morishita et al.; Groleau et al.; Gagolewicz and Dringenberg, 2010; 2015; 2009). ACh is implicated in modulating the E/I balance of primate primary visual

cortex (V1), enhancing the gain of thalamocortical synapses in layer 4c (Disney et al., 2007) while at the same time suppressing the response gain of intracortical interactions (Disney et al., 2012), suggesting it may play an important role in the integration of monocular signals – however this claim has yet to be assessed systematically.

In humans, drugs that increase endogenous ACh signalling have been shown to enhance cortical plasticity and functioning by refining neural circuits' efficacy and enhancing perceptual learning. Donepezil, one such drug, is a reversible, non-competitive, highly selective AChEI with a half-life of 80h and a peak plasma level of 4.1 $\pm$ 1.5h after intake (Rogers et al., 1998). 5 mg of donepezil is the lowest prescribed dose which induces beneficial cognitive effects with very low adverse reaction incidence (Prvulovic and Schneider, 2014), and has produced several reported effects on normal adult vision (Chamoun et al.; Rokem and Silver; Rokem and Silver; Gratton et al.; Silver et al., 2017a; 2010; 2013; 2017; 2008). Importantly, although higher doses of donepezil may yield stronger effects on vision, a lower dose is more physiologically relevant to understanding the underlying, natural mechanisms of the visual system as it would not imbalance cortical neuromdulator levels as dramatically.

5mg of donepezil has benefited a variety of visual plasticity processes in adults, for example, in visual tasks such as motion direction discrimination (Silver et al.; Rokem and Silver; Rokem and Silver, 2008; 2010; 2013) and 3D multiple object tracking (Chamoun et al., 2017a). There are other instances, however, that demonstrate the opposite: a recent study reported that cholinergic enhancement blocked the effect of perceptual learning of a crowding task relative to a placebo control group (Chung et al., 2017).

Nevertheless, pharmacological enhancement of synaptic ACh has been shown to improve visual function, possibly by reducing the spatial spread of visual responses, sharpening visual spatial perception, increasing top-down control of attentional orienting and stimulus discrimination, and enhancing cortical activation in V1 (Gratton et al.; Silver et al.; Kang et al.; Klinkenberg et al., 2017; 2008; 2014; 2011). Although cholinergic potentiation has been implicated in mediating several types of visual per-

ceptual learning and enhancing visual neural responsiveness, its exact role in adult binocular visual plasticity *per se* remains unclear.

## Preliminary Conclusions and Open Questions

It is evident that the visual system employs different strategies that facilitate change in response to the demands of the visual world. However – given the scale of the neural networks needed to produce human vision, as well as the number of possible neuroplastic mechanisms that could be implicated – correctly linking neural activity to changes in visual perception requires careful consideration. The purpose of the present work is to review preliminary insights from the previous literature and to present questions that logically follow for future investigation. The current work uses the effects of monocular deprivation as a model system for plasticity in adult binocular vision and also examines the role of ACh in facilitating these effects. As such, here we review preliminary conclusions and gaps in the literature with regard to the effects of short-term monocular deprivation and on the role of ACh in adult binocular plasticity.

There is general consensus that patching targets a mechanism separate from the type of adaptive effects demonstrated in monocular – or dichoptic – adaptation paradigms (Basgoze et al., 2018). This is attributed to the fact that patching causes differential effects in the two eyes (Zhou et al., 2014), measurable using neuroimaging techniques (Chadnova et al., 2014), as well as with optical imaging in mice (Daniel Tso, Ronald Miller, 2017). The precise mechanism of the underlying plasticity, however, is still unclear, and will require more work to better characterize the neural substrates and perceptual implications of the effects of short-term patching.

Is the mechanism of short-term monocular deprivation related to interocular gain control, where a bi-directional inhibitory circuit is asymmetrically adapted? Or is it more complicated, where dichoptic adaptation to natural scenes in one eye and a uniform field in the other induces a homeostatic plasticity to balance out the eyes' inputs? In order to confidently link the perceptual effects of monocular patching on binocular vision to an actual neural substrate, future work must implement designs

that preferentially tease out (i) how patching affects perception across a variety of different stimuli and binocular functions, (ii) how long the effects of patching across these domains are measurable, and (iii) whether its effects can be amplified or reduced with different experimental procedures. Such work will produce a more complete understanding of the mechanistic basis for the effects of monocular deprivation on binocular vision.

In terms of amplifying the effects of patching, ACh can be seen as a good contender based on several of its characteristics that are generally agreed upon in the literature: (i) ACh modulates feed forward gain(Disney et al., 2007), (ii) suppresses intracortical interactions(Disney et al., 2012), (iii) facilitates some forms of perceptual learning in healthy adults (Rokem and Silver; Chamoun et al., 2010; 2017a), (iv) is important in the consolidation of ocular dominance during development (Morishita et al., 2010), (v) plays a role in spatial visual processing (Silver et al.; Gratton et al.; Roberts, 2008; 2017; 2004), and (vi) modulates visual arousal (Klinkenberg et al., 2011).A fundamental next question to ask is – what about ACh's role in binocular vision, specifically? Can it enhance the effects of adult short term monocular deprivation, as it has shown to reinstate juvenile ocular dominance plasticity in adult rodents?

Although perceptual learning studies utilizing motion direction discrimination tasks (Rokem and Silver, 2010) reveal that ACh enhances the effects of neuronal plasticity by facilitating long-lasting learning effects (Rokem and Silver, 2013), the ubiquity of this effect is unclear. A recent article demonstrated that cholinergic enhancement does not improve (and may actually block) the effects of perceptual learning on a crowding task for adults with amblyopia (Chung et al., 2017). The science of ACh's effect on binocular vision is inconclusive – with virtually nothing in the literature linking ACh to binocular visual processes. However, there is ample reason to believe that ACh plays a central role in modulating binocular processes, beginning with the fact that it is known to modulate feed forward thalamocortical projections to V1 and also suppresses activity in other laminae of visual cortex (Disney et al.; Disney et al., 2007; 2012).

There are several possible avenues to address gaps in the literature. A starting point to better characterize the neural mechanisms of the effects of patching in human adults would be to determine whether there are other perceptual changes besides the shift in perceptual eye dominance. Additional perceptual effects can be assessed within the context of patching's known effects to constitute a more complete list, facilitating the search for a conclusive neural substrate.

As discussed earlier, perceptual changes in binocular rivalry are a sensitive indicator of plasticity in visual cortex (Wilson; Klink et al.; Said and Heeger; Tong et al.; Blake; Blake and Overton, 2003; 2010; 2013; 2006; 1989; 1979), where both the rate of rivalry and the overall proportion of exclusive dominance are proxies of E/I balance in visual cortex (Robertson et al.; Robertson et al.; Mentch, Jeff., Spiegel, Alina., Ricciardi, Catherine., Kanwisher, Nancy., Robertson., 2013; 2016; 2018). Although previous studies used binocular rivalry to probe the effects of monocular deprivation, many of these focused solely on shifts in ocular dominance at the expense of a more complete understanding of its effects on rivalry dynamics (Lunghi et al.; Lunghi et al.; Lunghi et al.; Lunghi et al., 2011; 2015a; 2016; 2015b). A clear gap in the literature that must be addressed is to determine how short-term monocular deprivation affects other aspects of binocular rivalry dynamics besides ocular dominance.

A logical next step would also be to determine whether the effects of short-term monocular deprivation could be enhanced pharmacologically through the use of the AChEI donepezil. Determining whether enhanced potentiation of ACh facilitates – or detracts from – the effects of monocular deprivation will enable us to learn more about both the neural mechanisms of patching and about ACh's role in binocular vision. Such work also has the dual benefit of characterizing the effects of ACh on binocular visual plasicity while also progressing the field towards a possible therapeutic modality for the treatment of amblyopia. Indeed, several recent studies have already promoted an inverse occlusion therapy that utilizes the effects on short-term monocular deprivation to treat adult ambyopia (Lunghi et al.; Zhou et al., 2018; 2019). Determining whether this effect cam be amplified pharmacologically

has clear clinical implications. In addition, characterizing the role of ACh in binocular processes is central to the development of the field of adult binocular plasticity. Utilizing binocular rivalry – a sensitive probe of visual neural function and of binocular vision itself (Tong et al., 2006) – can reveal the effects of ACh on binocular vision. Linking such foundational knowledge into the other known aspects of binocular plasticity will be helpful in defining the neural substrates of a of different forms of adult binocular plasticity.

The subsequent three sections of this thesis offer new insights into these open questions, expanding on experimental protocols to better characterize the mechanistic basis of the effects of monocular deprivation using binocular rivalry as a probe, to determine whether ACh can enhance the plasticity effects implicit in short-term monocular deprivation, and to characterize the effects of ACh on adult binocular vision.

# 1. Temporary monocular occlusion facilitates binocular fusion during rivalry

## Introduction

Short-term monocular deprivation (MD) is known to have several effects on adult human vision (see Baldwin and Hess, 2018 for an overview). MD, or patching, can shift perceptual eye dominance at the neural level (Hubel and Wiesel; Daniel Tso, Ronald Miller, 1970; 2017). In childhood, long-term ($>$ 1 week) MD causes a shift in favour of the non-deprived eye, while temporarily patching an eye for a few hours in adulthood results in a shift in favour the *deprived* eye that is observable up to at least an hour after deprivation (Lunghi et al., 2011). The ability of the adult visual system to temporarily shift perceptual eye dominance points to a latent functional plasticity whose mechanism is currently unknown. While the jury is still on out on the precise mechanism of this plasticity, there is empirical evidence implicating changes in excitatory/inhibitory (E/I) balance in V1 (Lunghi et al.; Chadnova et al., 2015b; 2017). Further work on the effects of temporary (a few hours) MD will help produce a more comprehensive mechanistic model for this type of adult brain plasticity.

Patching studies generally measure perceptual eye dominance behaviorally with either binocular rivalry (Kim et al.; Binda et al.; Lunghi et al.; Lunghi et al.; Lunghi et al., 2017; 2017; 2011; 2016; 2015b) or binocular phase combination (Baldwin and Hess; Chadnova et al.; Zhou et al., 2018; 2017; 2015) tasks. For the purpose of the current paper, we will focus on binocular rivalry. Binocular rivalry is defined by perceptual alternations that shift perception from one eye's image to the other over

the course of stimulus presentation (see (Blake and Logothetis, 2002) for a review). Studies that use binocular rivalry to measure perceptual eye dominance infer the contributions of the two eyes from the degree to which one eye suppresses the other when competing, or rivaling, for perception.

Although binocular rivalry is often often characterized as a series of perceptual alternations between two competing images, the actual visual experience is more extensive and can be separated into three categories: (1) exclusive visibility – when one eye's signal is entirely suppressed by the other eye's image, (2) piecemeal mixed visibility - where information from both eyes is simultaneously visible in smaller spatially segregated areas, sometimes described as local rivalry (Skerswetat et al., 2017), and (3) superimposition mixed visibility - where information from both eyes is visible and combined to constitute a fused binocular percept (Brascamp et al.; Liu et al., 2006; 1992). Importantly, mixed visibility highlights instances when complete interocular suppression fails, allowing binocular combination to occur. In fact, mixed visibility has been shown to be negatively associated with resting-state GABA levels in V1 (Freyberg et al., 2015a), and has likewise been shown to decrease after administration of GABA agonist drugs (Mentch, Jeff., Spiegel, Alina., Ricciardi, Catherine., Kanwisher, Nancy., Robertson., 2018). Disinhibition of interocular interactions are plausibly responsible for superimposition percepts, while piecemeal percepts are proposed to emerge from a weakening of the spatial coherence of these inhibitory interactions (Kovacs, I., Papathomas, T.V., Yang, M., and Feher and Ehe; Lee and Blake; Alais and Melcher, 1996; 2004; 2007).

Our study on the effects of patching was inspired, in part, from the finding that the predominance of mixed visibility can be altered in real-time by recent visual experience (Klink et al., 2010). This finding demonstrated that the proportion of mixed percepts increases over the course of continuous exposure to rivalrous stimuli (found with both gratings and natural images) and, importantly, that presentation of non-rivalrous binocular stimuli is necessary to restore this proportion back to baseline levels. This study highlighted a central role for experience-driven plasticity in adult binocular vision, causally linking recent visual experience to changes in

binocular rivalry dynamics. For the purposes of our investigation, it may be useful to consider the effects of several hours of MD as a form of experience-driven plasticity.

Studies using binocular rivalry to investigate the effects of MD (Binda et al.; Kim et al.; Lunghi et al.; Lunghi et al.; Lunghi et al., 2017; 2017; 2015a; 2011; 2015b) have not explored the role of mixed percepts in the effect of patching, focusing instead on using the exclusive percepts to quantify shifts in perceptual eye dominance. While a previous rivalry study on patching (Lunghi et al., 2011) reported that their stimulus did not produce much mixed visibility (less than 20%), an earlier article (O'Shea et al., 1997) highlighted up to 60% mixed visibility using similar stimulus parameters (1.5 deg diameter sinusoidal gratings, 3cpd, presented dichoptically). This discrepancy may be due to differences in task instructions and response options, however, given that MD alters binocular rivalry dynamics and that the predominance of mixed visibility is known to be directly influenced by recent visual experience, we felt it would be pertinent to conduct a systematic investigation of patching-induced changes in rivalry dynamics using task instructions that require attending to mixed percepts.

To do so, we designed two experiments that permitted us to simultaneously quantify patching-induced changes in perceptual eye dominance and mixed visibility. Specifically, experiment I utilized a novel rivalry task to quantify patching-induced changes in five different rivalry percept states: the exclusive percepts of the left and right eyes' image, the mixed percept biased in favor of the left and right eye's image, and a balanced mixture of the left and right eye's images. Our rationale for using this task design was to encourage participants not to classify mixed percepts biased in favour of one eye as an exclusive percept. This approach allowed us to more reliably estimate the relative predominance of mixed and exclusive visibility during rivalry while also allowing us to measure changes in perceptual eye dominance.

Experiment II was a follow-up to experiment I to determine whether piecemeal or superimposition percepts were specifically targeted by the effects of deprivation. To investigate this, we used a task adapted from (Skerswetat et al., 2017) that allowed us to simultaneously measure patching-induced changes in perceptual eye

dominance as well as the relative predominance of superimposition and piecemeal percepts.

Due to the findings that recent visual experience can alter binocular rivalry dynamics (Klink et al.; Freyberg et al., 2010; 2015b) and that monocular patching alters E/I balance in visual cortex (Binda et al.; Lunghi et al.; Chadnova et al., 2017; 2015b; 2017), we predicted that patching would significantly increase the proportion and median duration of mixed percepts while simultaneously shifting perceptual eye dominance in favour of the deprived eye. Likewise, under the assumption that patching weakens interocular inhibition, we predicted that patching would selectively increase the proportion and median duration of superimposition, rather than piecemeal percepts.

# Experiment I

We designed experiment I to investigate the effects of short-term monocular patching on mixed visibility during rivalry. This experiment used a 5-AFC binocular rivalry task to evaluate patching induced changes in rivalry dynamics along a discretized spectrum of percept-states that ranged from the exclusive percepts from the left eye's image to that from the right eye's image, including three intermediate mixed percept states.

## Methods and Materials

**Observers** A total of 16 individuals enrolled in Experiment I (8 women, 22 $\pm$ 2.3, one author). Two participants were excluded from the study due to data collection errors during baseline measurements, and one participant was excluded because their median rivalry phase durations at baseline were greater than 4 standard deviations of the group mean. In sum, 13 individuals participated in the study. A subset of our participants (N = 5, 3 women, 24, $\pm$ 1.3) completed additional post-deprivation measurements that were taken over the course of an hour after removing the eye patch to evaluate the decay of the patching-induced changes in rivalry dynamics.

All participants had normal or corrected-to-normal visual acuity and were free

from ocular diseases. Normal stereo vision was confirmed through the Randot task. This research was approved by the Ethics Review Board of the McGill University Health Center and was performed in accordance with the ethical standards laid down in the Code of Ethics of the World Medical Association (Declaration of Helsinki). Subjects gave written informed consent prior to the experiment. All participants except for the author YS were naive to the purpose of the experiment.

**Apparatus** Each session took place in a quiet room with dim light. Visual stimuli for the binocular rivalry experiments were generated and controlled by an Apple MacBook Pro 2008 computer (MacOSX; Cupertino, CA, USA) running MATLAB R2012B (MathWorks, Natick, MA) with the Psychtoolbox psychophysics toolbox (Brainard, 1997; Kleiner, Brainard & Pelli, 2007; Pelli, 1997). Stimuli were displayed on a wide 2300 3D-Ready LED monitor ViewSonic V3D231, gamma corrected with a mean luminance of 100 $cdm^2$. Subjects viewed the stimuli at a viewing distance of 70 cm with passive polarized 3D glasses so that the left image was only seen by the left eye and the right image by the right eye. The polarized filters had the effect of reducing the luminance to about 40%, measured with a photometer.

The stereo image input was in top-down VGA format and was displayed in interleaved line stereo mode at a resolution of 1920 x 1080p and a refresh rate of 60 Hz: the left eye image was displayed in even scanlines and the right eye image was displayed in odd scanlines. Crosstalk levels for polarizing filter and passive goggle systems such as the one we used are known to be low, (luminance crosstalk: 1.14%, CI: [1.13, 1.15], contrast crosstalk: - 0.04%, CI: [-0.28, 0.18], (Baker et al., 2016)).

**Stimulus** The dichoptic stimulus was composed of two orthogonal ($\pm$ 45 degree) sinusoidal gratings. These gratings were 3 cycles per degree, subtending a diameter of 1.5 degrees with a raised cosine annulus blurring the edges, Michelson contrast = 75 %, presented inside a black-and-white noise pattern frame (side = 10°) (**Fig.** 1.1a).

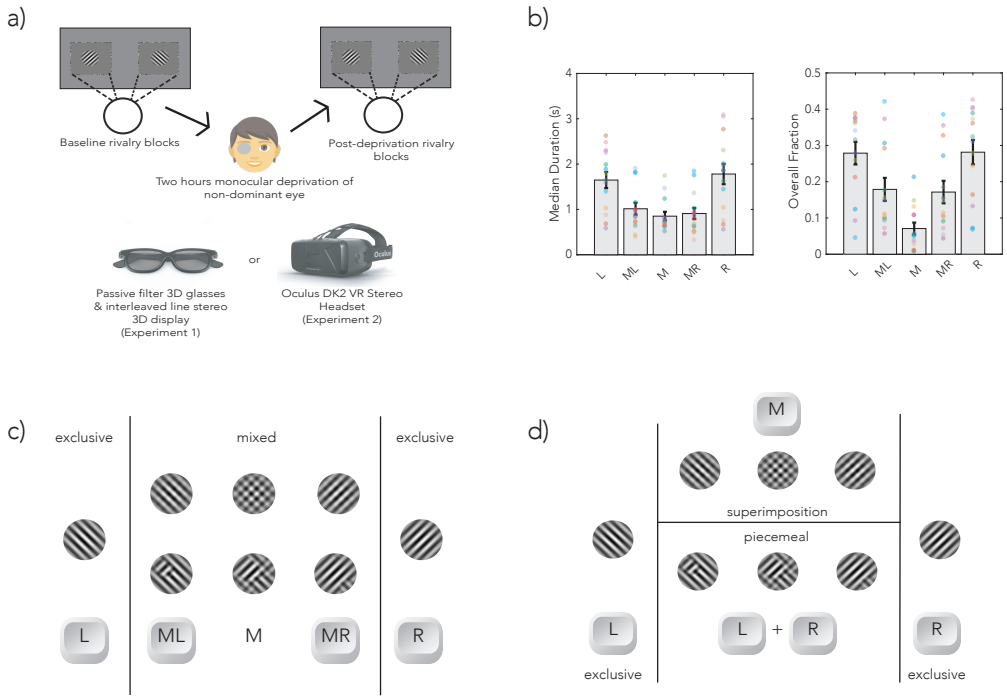


**Figure 1.1: Methods. a) Experimental Protocol.** Baseline rivalry data was obtained from four 180-second rivalry blocks, each consisting of two 90-second rivalry runs. The first block of the baseline measurements was discarded. The baseline measurements were calculated by taking the median of the three remaining blocks. Following baseline testing, we patched the participants' non-dominant eye with a diffuser eye patch for two hours. After this we continued with three post-patching rivalry blocks over the course of nine minutes after removing the patch, and extracted our main post-patching measurement by taking the median of these blocks. **b) Baseline data.** Median phase durations(left) and overall fractions (right) (mean ± SEM) for the five percept states obtained using the binocular rivalry task in experiment I. Individual colored dots indicate unique participants. **c) Experiment I: 5AFC Binocular Rivalry Task.** Participants were instructed to continuously indicate whether they were seeing (L) an exclusively left-oriented grating, (ML) a mostly left-oriented grating with some right-oriented lines, (M) a balanced left-and-right oriented grating (indicated by the absence of a key press), (MR) a mostly right-oriented grating with some left-oriented lines, or (R) an exclusively right-oriented grating. **c) Experiment II: 4AFC Superimposition versus Piecemeal Rivalry Task.** Participants were instructed to continuously indicate whether they were seeing (L) an exclusively left-oriented grating, (R) an exclusively right-oriented grating, pressing both (L+R) simultaneously to indicate they were seeing a piecemeal percept, or (M) a superimposition percept.

**Monocular Deprivation** Using the Miles test for sensory eye dominance (W. R. Miles, Ocular dominance in human adults, J. Gen. Psychol., vol. 4, pp. 412-430, 1930), we identified the dominant eye for each participant. We confirmed perceptual eye dominance with baseline binocular rivalry data for each subject and proceeded to

patch the non-dominant eye for each experimental session in which they participated. If the baseline rivalry perceptual eye dominance did not align with the dominant eye identified with the Miles test, or if the baseline rivalry blocks did not produce a clearly defined ( >75% of blocks ) dominant eye, we patched the non-dominant eye identified with the Miles test. We chose to patch the non-dominant eye with the rationale that it has more capacity to increase its dominance, however this claim has not been systematically evaluated. We used a diffuser eye patch that preserved most luminance information (40 % luminance reduction), but eliminated all pattern information as confirmed by a Fourier decomposition of a natural image viewed through the patch. While most studies use a patching duration of 2.5 hours, recent investigations have shown comparable effects after two hours of patching (Lunghi et al., 2016). To minimize the amount of time it would take to complete a single session, we monocularly deprived the non-dominant eye for two hours.

**Binocular Rivalry Task and Experimental Protocol** We designed the five alternative forced choice (5AFC) binocular rivalry task used in Experiment I to extract more reliable information about rivalry dynamics than the conventional 2- (left versus right) or 3- (left versus mixed versus right) AFC approach (**Fig.** 1.1c). Reports of lower-than-expected levels of mixed visibility at baseline in other 2- or 3-AFC rivalry studies (Lunghi et al., 2011) using similar stimulus parameters could be attributed to the fact that participants begin to miscategorize their rivalry percepts, reporting a mixed percept biased in favour one eye's image as that eye's exclusive percept. Our task design stresses attention to the phenomenological difference between mixed and exclusive percepts. An earlier article regarding the effect of stimulus parameters on the predominance of mixed visibility (O'Shea et al., 1997) was reported to be approximately 40% (SF: 3cdp, field size: 1.5°). Our dataset produced a similar figure, with an average fraction of mixed visibility at baseline at 42% ± 5.76% (SEM).

At the beginning of each session, participants were told that they would see a dynamic stimulus during the experiment and that their task was to track what they

were seeing, with particular attention to timeliness and accuracy. Participants were given an illustration (**Fig.** 1.1c) of the types of stimuli they would be seeing so as to better categorize their responses during the task.

Participants were instructed to continuously indicate whether they were seeing either (1) an exclusively left-tilted grating, (2) a mixed but predominantly left-tilted grating, (3) a mixed but predominantly right-tilted grating, or (4) an exclusively right-tilted grating, using four separate keys. In our instructions, we specified that exclusive percepts were those with 90% or more left or right-tilted lines, while the mixed percepts were between 50-90% left- or right-tilted lines. If the participants could not discriminate a mixed percept as predominantly left- or right- oriented, they were instructed not to respond, consituting our 'balanced' mixed percept state.

Each rivalry measurement began with a dichoptic nonius cross presented inside a 3-degree oval surrounded by a black-and-white noise (1 cycle per degree) frame (side = 10 deg). The observer was asked to make keypresses to adjust the position of the two frames to calibrate the optimal position for comfortable fusion. After confirmation, the participant was instructed to fixate at a fixation dot (0.2 deg) and place their hands on the appropriate keys to begin responding to the rivalry task. After a keypress, the dichoptic stimulus appeared and participants began responding to what they were observing on the monitor using the keypress instructions we provided at the beginning of each session. Subsequent blocks were initiated after a brief break where subjects viewed a mean-gray background screen. Subjects performed blocks of the binocular rivalry task before and after two hours of MD of the non-dominant eye. During deprivation subjects were instructed to keep both eyes open and do normal activities such as watching a movie or doing computer work in a well-lit room.

All participants were trained with up to five rivalry training blocks before beginning baseline measurements. We provided a break of 15 minutes between training and baseline blocks. Baseline measurements were drawn from 4 180-second rivalry blocks, each consisting of 2 90-second rivalry runs. The orientation of the gratings seen by the eyes was flipped between the two runs in each block to counterbalance

possible orientation-eye biases and to interrupt any possible adaptation effects that would result in an increase in mixed visibility (Klink et al., 2010). We discarded the first rivalry block to account for possible errors made in the beginning of the task. All participants completed three post-patching measurements over the course of nine minutes after patching. Five subjects completed additional post-patching rivalry blocks conducted at 30 and 60 minutes after removing the eye patch.

**Preprocessing and Statistical Analysis** The goal of preprocessing the raw rivalry time series data was to extract key features of the data usable for our analyses. Our main points of interest for analysis were patching-induced differences in: (1) the median durations of the percept states, defined as the median of the distribution of durations spent perceiving each percept category, (2) the overall fraction of each percept state, and (3) perceptual eye dominance, defined as the ratio of the total durations spent viewing the two exclusive percepts.

The preprocessing pipeline consisted of four stages: (1) remove the first and last percept states in the time series as well as all percept states shorter than 250ms to obtain the preprocessed time series, (2) extract the distribution of percept phase durations for each state from the processed time series, (3) calculate the median and sum of these distributions to obtain the median and overall fraction of each of the states in each rivalry block.

Using this paradigm, we computed median phase durations as well as overall fractions for each of our five percept states (i.e. left, right, balanced mixed, mixed left, and mixed right) (**Fig.** 1.2b), allowing us to calculate ratios between the median phase durations of exclusive percepts (exclusive left vs. exclusive right) and mixed percepts (mixed left vs. mixed right). Although mean rivalry phase durations are used commonly in the literature to quantify perceptual dominance during rivalry (Lunghi et al.; Sheynin et al.; Klink et al.; Zhou et al.; Blake and Logothetis, 2011; 2019; 2010; 2004; 2002), calculating the mean of the original distribution is prone to be biased in favor of longer phase durations (Zhou et al., 2004), therefore to account for this, we used the median rather than the mean of the phase duration

distributions as a measure of perceptual dominance for each category.

In addition, our main measure of perceptual eye dominance was defined by:

$$\mathrm{ODI} = \left(\frac{\bar{d}_{\mathrm{non-deprived}} - \bar{d}_{\mathrm{deprived}}}{\bar{d}_{\mathrm{non-deprived}} + \bar{d}_{\mathrm{deprived}}}\right), \tag{1.1}$$

where the two $\bar{d}$ variables are the overall fractions for the exclusive percepts from the non-deprived and deprived eye. This ratio computed a value between -1 to 1, the extreme values indicating completely monocular vision for the non-deprived and deprived eye, respectively. To evaluate deprivation-induced changes in these indices we subtracted the baseline ratio from each post-patching measure.

Importantly, our 5-AFC design allowed us to re-partition the three intermediate mixed percepts into a single variable: mixed visibility. This was achieved by concatenating adjacent mixed percepts in the original rivalry time series data (i.e. mixed left + balanced mixed + mixed right) to obtain a single mixed percept state. We then administered our preprocessing paradigm on this repartitioned time series to obtain distributions of phase durations **Fig.** 1.2c) for three percept states: exclusive left eye, mixed, and exclusive right eye. We used the distribution corresponding to the repartitioned 'mixed' category to calculate the overall fraction and median duration of mixed visibility.

To asses patching-induced effects across subjects and to account for inter-subject variability at baseline, we calculated a normalized value that represented the magnitude of the effect of patching on each dependent variable for each individual. These values were obtained by dividing post-patching measures by those at baseline and then subtracting the normalized baseline. We conducted null hypothesis pairwise t-tests on these normalized post/baseline values that determined whether deprivation significantly shifted the mean with respect to baseline (zero). We used the initial post-deprivation value for each dependent variable under the *a priori* assumption that the effect was maximal immediately after removing the patch. P-values were corrected for multiple comparisons using the False Discvocery Rate (FDR) correction method outlined in Benjamini et al., 1995 (Benajmini and Hochberg, 1995). We obtained 95% confidence intervals and the standard deviation of a 1000-bootstrap

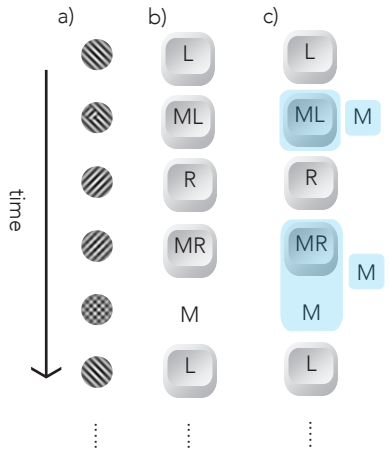


**Figure 1.2: Partitioning original rivalry data into different dependent variables. a) Observer's rivalry percept. b) Ideal observer's keypress response corresponding to percept. c) Obtaining phase durations of overall mixed visibility** We concatenated adjacent mixed percepts reported using the three mixed states in the original task to compute a new aggregated mixed percept state from which we extracted the median duration of mixed visibility.

distribution (with replacement) of the normalized post/baseline values for each dependent variable. All SEMs in the current paper are equivalent to the standard deviation of the respective bootstrap distribution.

Further, we also conducted a one-way repeated measures ANOVA on the post-deprivation measures from the subset of observers who completed additional rivalry blocks over the course of an hour after patching. This analysis, administered on normalized post/baseline values at 0, 30, and 60 minutes after patching, was used to establish the time course of the decay of the effects of patching. We compared the normalized post/baseline values across the three measured time points to determine the time course of the decay, and then administered post-hoc t-tests to determine which time points were significantly shifted with respect to baseline.

Finally, we implemented a principal component analysis (PCA) to analyze the median duration data drawn from the reduced rivalry time series illustrated in **Fig.** 1.2c. PCA is a statistical procedure that uses an orthogonal transformation to

convert a set of observations of possibly correlated variables into a set of values of linearly uncorrelated variables called principal components (PCs). We observed that the median durations of the two exclusive percepts at baseline were highly correlated with one another (Spearman rho = 0.93, $p < 0.0001$), therefore a PCA transformation of the data would assist in mining statistically uncorrelated variables from the data that are arguably more informative of the neural processes underlying rivalry than the original variables used for analysis.

We used MATLAB's built-in PCA function, specifying a singular value decomposition (SVD) algorithm to extract the $3 \times 3$ coefficient matrix of three PCs (three PCs explain 100% of the variance in a three dimensional dataset) from the baseline median duration data. We then used this coefficient matrix to project both the baseline and post-patching median duration data into the principal component space defined at baseline using the procedure:

$$\mathbf{A}_i = \mathbf{X}_i \cdot \mathbf{C} \tag{1.2}$$

where $\mathbf{A}_i$ is the representation of median duration data $\mathbf{X}_i$ at time point $i$, in the PC space defined at baseline by the PC coefficient matrix $\mathbf{C}$. Both $\mathbf{A}_i$ and $\mathbf{X}_i$ are $N \times 3$ matrices, where N represents the total number of participants. The columns of $\mathbf{X}_i$ correspond to the median durations of the three percept categories (exclusive left, mixed, exlcusive right), while the columns of $\mathbf{A}_i$ correspond to the PC scores for the three PCs extracted at baseline defined by coefficient matrix $\mathbf{C}$. We then conducted FDR-corrected pairwise t-tests on the post - baseline values for each PC column $j$ in $\mathbf{A}_i$, (i.e. $\mathbf{A}_{2j} - \mathbf{A}_{1j}$) to evaluate patching-induced changes in the relative weight of each component's influence on binocular rivalry dynamics with respect to baseline. Unlike more conventional analyses, this PCA approach does not rely on our *a priori* assumptions of the underlying processes driving rivalry phase durations. On the contrary, the PCA uncovers statistically uncorrelated components of rivalry phase duration data that may then map on to our understanding of the neural mechanisms involved in binocular rivalry, allowing us to evaluate patching-induced changes within those components.

## Results

We first analyzed the processed rivalry time-series data to obtain median phase durations and overall fractions for each of our five percept states. We were interested to see how patching affected the fractions (**Fig.** 1.3a) and median phase durations (**Fig.** 1.3b) for the original five percept categories.

In contrast with previous findings (Lunghi et al., 2011), our results indicate that neither the fraction nor median duration of the deprived eye's exclusive percept increase significantly after deprivation (fraction: M = 0.03, 95% CI: [-0.10, 0.16], FDR-corrected $p > 0.05$; median duration: M = 0.06, 95% CI: [-0.05, 0.18], FDR-corrected $p > 0.05$). However, we do find that the fraction and median duration of the exclusive percept of the non-deprived eye decrease significantly (fraction: M = -0.31, 95% CI: [-0.41, -0.20], t(12) = -5.41, FDR-corrected $p < 0.001$; median duration: M = -0.15, 95% CI: [-0.24, -0.04], t(12) = -2.91, FDR-corrected $p < 0.05$). This implies that the shift in perceptual eye dominance observed after patching may be driven by a decrease in the input strength of the non-deprived eye's image rather than a reciprocal increase in the deprived eye's contribution.

Further, the median duration of the mixed percepts biased in favour of the non-deprived eye's image increased significantly after patching (mean difference = 0.30, 95% CI:[0.17, 0.46], t(12) = -4.09, FDR-corrected $p < 0.01$), as did that of the deprived eye's image (mean difference = 0.28, 95% CI:[0.09, 0.51], FDR-corrected $p > 0.05$). Increases in the overall fractions of all three mixed percepts were also observed (frac. mixed (non-deprived eye): M = 0.46, 95% CI: [0.15, 0.89], t(12) = 3.19, FDR-corrected $p < 0.05$; frac. mixed (balanced): M = 0.72, 95% CI: [0.11, 1.55], FDR-corrected $p > 0.05$; frac. mixed (deprived eye): M = 0.47, 95% CI: [0.21, 0.75], t(12) = 3.19, FDR-corrected $p < 0.05$). While it is possible that our task did not accurately measure bias within the mixed percepts (see **Discussion**), these results indicate that the mixed percepts were enhanced without the introduction of eye-specific bias. To further investigate, we analyzed changes in the overall fraction (**Fig.** 1.4a) and median duration (**Fig.** 1.4b) of overall mixed visibility (extracted

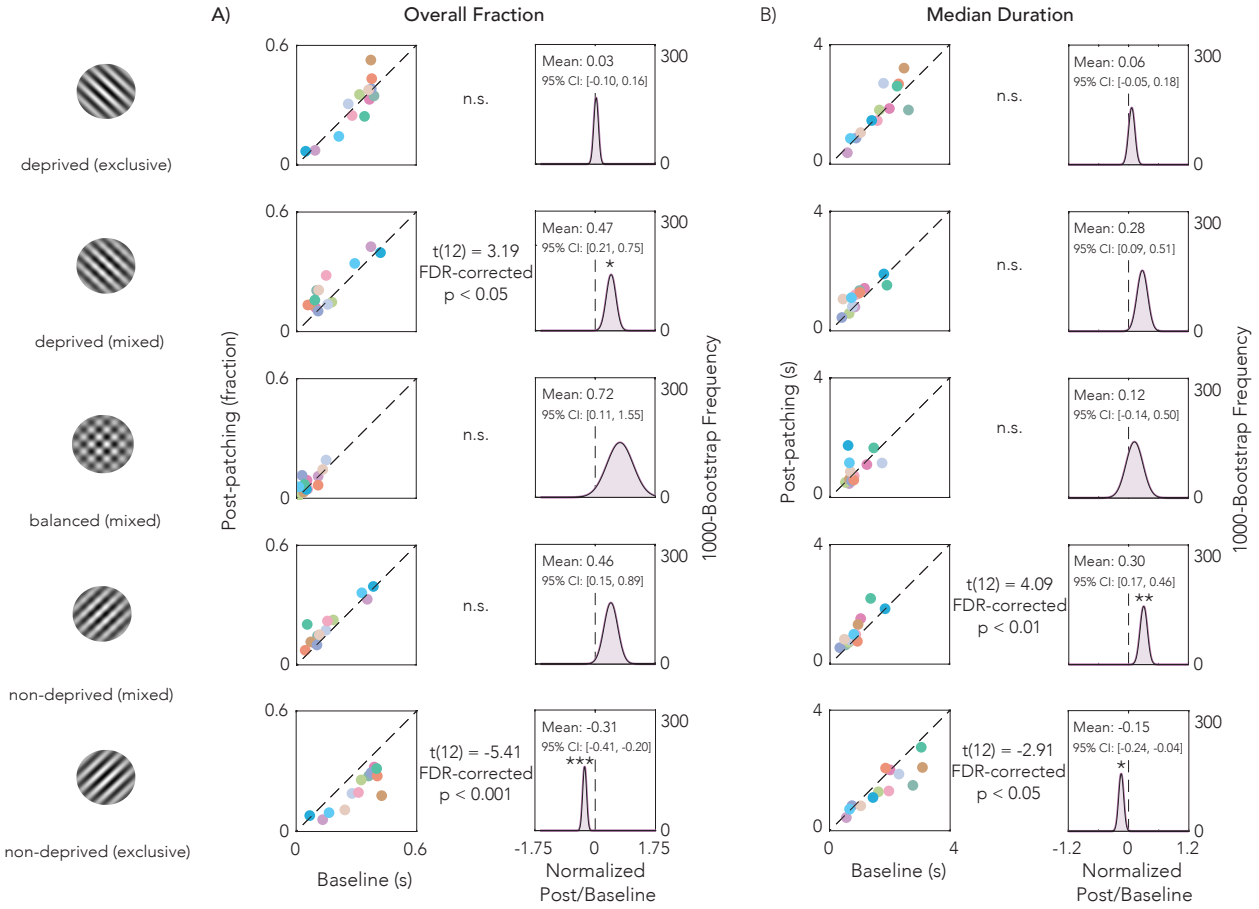


**Figure 1.3: Patching-induced changes in overall fractions and median phase durations.** From the top down, the five percept states are (1) exclusive percepts from the deprived eye, (2) the mixed percepts biased in favour of the deprived eye, (3) the balanced mixed percepts, (4) the mixed percepts biased in favour of the non-deprived eye, and (5) the exclusive percept from the non-deprived eye. **a) Overall fractions.** The left column shows individual participants' baseline fraction durations for each percept plotted against their post-deprivation fraction durations, the right column illustrates the output of a 1000-iteration nonparametric bootstrapping implementation (with replacement) on the pooled normalized post/baseline values for each percept category. A gaussian function was fit to a 20-bin histogram of the bootstrap distributions, illustrating the spread of the distributions. We used these bootstrap distributions to obtain 95% confidence intervals and the standard error (equivalent to the standard deviation of the bootstrap distribution) for the mean post/baseline values. Individual colored dots indicate unique participants. **b) Median phase durations.** see panel **a**. for corresponding information. N = 13; * = FDR-corrected $p < 0.05$, ** = FDR-corrected $p < 0.01$, *** FDR-corrected $p < .001$

from the reduced time series illustrated in **Fig.** 1.2c).

Patching significantly increased both the overall fraction of mixed visibility (**Fig.** 1.4a, M = 0.33 , bootstrapped 95% CI:[ 0.19, 0.52], t(12) = 3.51, FDR-corrected $p < 0.01$) and the median duration of mixed visibility (**Fig.** 1.4b, M = 0.30 , bootstrapped

95% CI:[ 0.17, 0.44], t(12) = 4.17, FDR-corrected p < 0.01). The shift in perceptual eye dominance, calculated using the ratio of the fractions of the exclusive percepts, was also highly significant (M = 0.20, 95% CI: [ 0.11, 0.29], t(12) = 4.42, p < 0.001) **Fig.** 1.4c. Interestingly, we did not observe a significant shift in perceptual eye dominance within the mixed percepts (mean difference = 0.03, 95% CI: [ -0.04, 0.11], t(13) = 0.78, p > 0.05), further suggesting that the shift in perceptual eye dominance and the increase in mixed visibility may be separate effects of patching.

For five out of the thirteen participants we collected data from rivalry blocks at 0, 30, and 60 minutes after patching to determine the time course of the decay of the patching-induced effects. For these data we conducted repeated-measures ANOVAs on group means for the three post-deprivation measurements to evaluate whether the patching-induced shifts changed significantly over the course of the experiment. Due to the small number of participants in this subset, most of our statistical tests for these analyses were underpowered. They still, however, give a noteworthy insight into both the inter-subject variability of these effects and their time courses over an hour after patching.

The main effect of time on the overall fraction of mixed visibility across these three time points was not significant for this subset of observers (Wilks' lambda = 0.60, F(2,10) = 1.30, p < 0.05, $\eta_p^2$ = 0.21, **Fig.** 1.4a, right panel), indicating that the mean normalized post/baseline overall fraction of mixed visibility was not significantly different across the three post-deprivation time points for this subset of observers. Post-hoc t-tests on the post/baseline values for each time point did not yield statistically significant results (FDR - corrected ps > 0.05), however there was an observable trend of recovery to baseline levels over the course of an hour after patching (t0: M = 0.74, 95% CI: [-0.22, 1.71]; t30: M = 0.65, 95% CI: [0.06, 1.23]; t60: M = 0.31, 95% CI: [-0.37, 0.99] ). Likewise, the effect of time on the median duration of mixed visibility across these four time points was also not significant for this subset of observers (Wilks' lambda = 0.60, F(2,8) = 1.55, p > 0.05, $\eta_p^2$ = 0.28, **Fig.** 1.4b), indicating that the average post-baseline median duration of mixed visibility did not change significantly across our post-deprivation measurements for

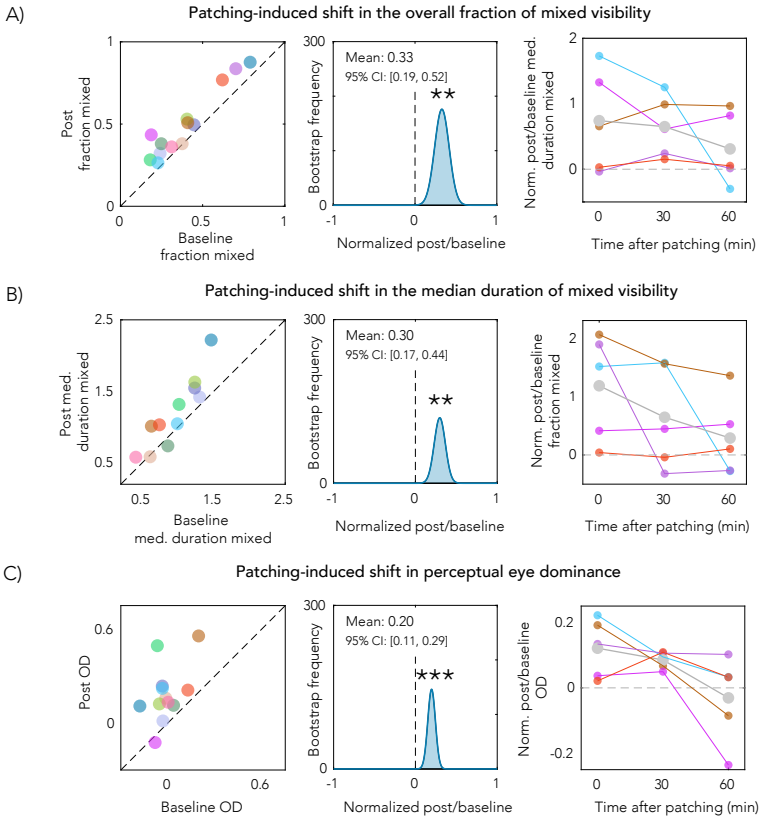


**Figure 1.4: Patching-induced changes in mixed visibility and perceptual eye dominance a) Normalized post/baseline overall fraction of mixed visibility.** Scatter plot (left) illustrating individual subjects' baseline fraction of mixed visibility (N = 13), plotted against their initial post-deprivation fraction of mixed visibility; middle panel illustrates the output of a 1000-iteration nonparametric bootstrapping implementation on the post-baseline differences. A gaussian function was fit to a 20-bin histogram of the bootstrap distributions, illustrating the spread of the distributions. We used these bootstrap distributions to obtain 95% confidence intervals and the standard error (equivalent to the standard deviation of the bootstrap distribution) for the mean post-baseline differences.; right panel demonstrates individual normalized post/baseline overall fractions of mixed visibility at 0, 30, and 60 minutes after deprivation. The gray markers indicate the group mean. n = 5 (3 women, age 24 $\pm$ 2.1) **b) Normalized post/baseline overall median duration mixed visibility.** See panel **a** for corresponding information. **c)Normalized post/baseline perceptual eye dominance over the course of one hour after deprivation.** Positive values indicate shifted bias in favour of the deprived eye. The perceptual eye dominance index (ODI) used to calculate these means utilized the median duration of the exclusive percepts from the deprived and non-deprived eyes. See panel **a** for corresponding information. Asterisks indicates means significantly shifted with respect to baseline. Individual colored dots indicate unique participants. * indicates FDR-corrected $p < 0.05$, ** indicates FDR-corrected $p < 0.01$., *** indicates FDR-corrected $p < 0.001$

this subset of participants. Additional post-hoc t-test on the post-baseline difference indicated that no individual post measurements were significantly shifted from baseline (FDR-corrected ps $> 0.05$), however there was also an observable trend of recovery to baseline levels over the course of an hour after patching (t0: M = 1.18, 95% CI: [0.06, 2.30]; t30: M = 0.64, 95% CI: [-0.43, 1.74]; t60: M = 0.28, 95% CI: [-0.55, 1.13]. Finally, the effect of time for perceptual eye dominance across the three post-patching time points was not significant for this subset (Wilks' lambda = 0.27, $F(2,8) = 1.78$, $p > 0.05$, $\eta_p^2 = 0.30$, **Fig.** 1.4c, right panel), indicating that the overall shift in perceptual eye dominance did not change significantly throughout the post-deprivation assessments. Perceptual eye dominance was significantly shifted with respect to baseline immediately after removing the eye patch (M = 0.12, 95% CI: [0.10, 0.23], $t(4) = 3.1$, FDR-corrected $p < 0.05$), as well at 30 minutes after removing the patch (M = 0.08, 95% CI: [ 0.05, 0.11], $t(4) = 7.37$ FDR-corrected $p < 0.01$), but not at 60 minutes (FDR-corrected $p > 0.05$), suggesting this effect of patching also decayed over time.

Our initial analyses found that the median durations of the two exclusive percepts are highly correlated with one another (Spearman rho = 0.93, $p < 0.001$). This led us to use a PCA approach to transform the variables in our median duration dataset (exclusive left, mixed, exclusive right) into a new set of statistically uncorrelated variables that are possibly more informative of neural processes underlying rivalry. We administered a descriptive PCA on the baseline median durations extracted from the processed time series illustrated in **Fig.** 1.2c to uncover three principal components which explained 100% of the variability in our data (**Fig.** 1.5a). The PCA coefficients indicate the degree to which each principal component (PC1-3) is associated with the original percept variables. PC1 is most closely associated with the median duration of mixed visibility and explains 70.10% of the variability in the baseline data. For the purpose of this analysis, PC1 can be interpreted as the binocular combination component underlying rivalry phase durations. For PC2, The PCA extracted the correlation between the two exclusive percept variables – PC2 is most closely associated with the median duration of both exclusive percepts

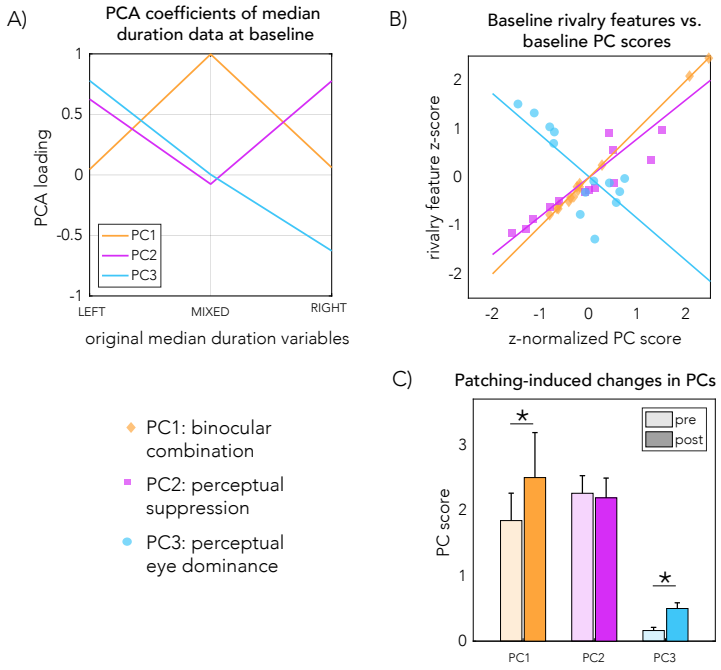


**Figure 1.5: Pricipal components analysis (PCA) on median rivalry phase duration data. a) Output of the PCA.** The PCA was administered on baseline rivalry phase durations drawn from the reduced processed time series illustrated in **Fig.** 1.2c. The components are statistically uncorrelated, pointing to three unique processes underlying the phase duration data. The PCA coefficients indicate the degree to which each principal component (PC1-3) is associated with the median durations of each percept type. PC1 is most closely associated with the median duration of mixed visibility, PC2 is most closely associated with the median duration of complete perceptual suppression, and PC3 is plausibly interpreted as ocular imbalance, or perceptual eye dominance (see **Methods** for more information on the PCA). **b) Correlating baseline PCA scores with baseline binocular rivalry features.** The x-axes indicates z-normalized PCA scores for each principal component across subjects, y-axis values indicate z-normalized values corresponding to the following baseline median phase duration data: PC1 – median duration of mixed visibility, PC2 – median duration of exclusive visibility (the arithmetic mean of the exclusive percepts' median durations), and PC3 - the ratio of the median durations of the exclusive percepts, defined in equation 1. PCR betas are highly correlated with their respective binocular rivalry features.**c) Comparing post-baseline PC scores** Pre- and post- patching PC scores were obtained using the method outlined in the methods section. PC scores indicate the degree to which each PC weighs on an individual's rivalry data. Each bar indicates the group mean ± SEM.
See panel **c** for corresponding information. Asterisks indicate significant interactions. * indicates FDR-corrected $p < 0.05$

and explains 28.94% of variability in the data. PC2 can then be feasibly regarded as
2 the perceptual suppression component underlying rivalry phase durations. Finally, PC3 is anti-correlated between the two exclusive percepts and uncorrelated with

mixed visibility; this PC explains the remaining 0.95% of the variability in the data. PC3 points to interocular balance, or perceptual eye dominance, as an underlying component in the baseline rivalry phase duration data.

We transformed both the baseline median duration data and the post-patching median duration data by projecting them into the PC space defined by the coefficient matrix extracted from the baseline data. This procedure yielded two datasets, corresponding to the PC scores for each participant for each PC before and after monocular patching (see **Methods** for more details). As a sanity check, we ran correlations between these PC scores and the features we believed they represented in the baseline data. For PC1 this was the median duration of mixed visibility, for PC2 this was the median duration of exclusive visibility (the arithmetic mean of the median durations of the two exclusive percepts), and for PC3 this was perceptual eye dominance, calculated using the procedure outlined in equation 1. We z-normalized both the PC scores and their corresponding features in the original dataset to ensure both sets were scaled similarly for comparison. The PC scores were all significantly correlated with the features we extrapolated from the original dataset ($Fs(1,12) \geq 21.4$, $ps < 0.001$, adjusted $R^2 \geq 0.61$), indicating the PCA successfully extracted meaningful components underlying the phase duration data at baseline (**Fig.** 1.5c).

FDR-corrected pairwise post-baseline t-tests were conducted on the PC scores. We found that patching significantly increases the PC score of PC1 (M = 0.65; 95% CI: [0.09, 1.21]; t(13) = 2.52; FDR-corrected $p < 0.05$ ) and PC3 (M = 0.33; 95% CI: [0.11, 0.55]; t(13) = 3.31; FDR-corrected $p < 0.05$ ), but not PC2 (M = -0.06; 95% CI: [0.-44, 0.30]; t(13) = -0.40; FDR-corrected $p > 0.05$ ). This analysis confirms and extends the insights of the previous analyses - binocular combination and perceptual eye dominance weigh more heavily on rivalry phase durations as a result of short-term patching. Unlike our more conventional analyses, this PCA approach does not rely on our *a priori* assumptions of the underlying processes driving rivalry phase durations. On the contrary, the PCA uncovered statistically uncorrelated components of rivalry phase duration data that map on quite well to our understanding of the neural mechanisms involved in binocular rivalry – binocular

combination, perceptual suppression, and perceptual eye dominance – allowing us to evaluate patching-induced changes within these components.

## Experiment II

We designed experiment II to investigate whether short-term monocular patching preferentially affects superimposition versus piecemeal mixed percepts during binocular rivalry. This experiment used a 4-AFC binocular rivalry task, adpated from (Skerswetat et al., 2017), to evaluate patching-induced changes in rivalry dynamics.

### Methods and Materials

**Observers** A total of 11 individuals enrolled in Experiment I (8 women, 21, ± 2.1, one author). One participants was excluded from the study due to a failure to complete the full experiment, therefore in sum, 10 individuals participated the study. Two participants completed both experiments I and II.

**Apparatus** Each session took place in a quiet room with dim light. Stimuli were displayed on the Oculus DK2 VR headset to dichoptically present the binocular rivalry stimuli generated and controlled by the same computer system as described in Experiment I. The Oculus was gamma-corrected with a mean luminance of 90 cd/m2, driven at a resolution of 960 x 1080 per eye, with a refresh rate of 60Hz and a nominal Field of View (FoV) of 100 degrees. The left and right eye images were separated by a divider such that the left eye only viewed the left side of the goggles and the right eye only viewed the right side.

**Stimulus** The dichoptic stimulus used in experiment II was identical to that of experiment I with the exception that we used a larger stimulus (4 cycles per degree, subtending a diameter of 2 degrees with a raised cosine annulus blurring the edges, Michelson contrast = 80 %), due to the pixel density limitations of the Oculus DK2 headset.

**Binocular Rivalry Task and Experimental Protocol** We adapted a 4AFC binocular rivalry task used by (Skerswetat et al., 2017) (**Fig.** 1.1d) to quantify the overall fraction duration of exclusive, piecemeal, and superimposition mixed percepts. At the beginning of each session, participants were shown images on a document that illustrated the differences between the left-oriented, right-orineted, and superimposition versus piecemeal mixed percepts. Participants were told that they would see a dynamic stimulus during the experiment and that their task was to track what they were seeing, with particular attention to timeliness and accuracy. Aside from the response criteria, all other aspects of the stimulus and task were identical to that described for experiment 1.

Participants were given the option to continuously indicate whether they were seeing either (i) an exclusively left-tilted grating, (ii) an exclusively right-tilted grating, (iii) a superimposition mixed percept, or (iv) a piecemeal mixed percept. Participants used three adjacent keys for the task, using the left to indicate exclusive left-tilt, right for right-tilt, a holding down a combination of the left and right keys for the piecemeal percepts, and the middle key for the superimposition percepts. In our instructions, we specified that exclusive percepts were those with 90% or more left or right-tilted lines, while the mixed percepts were between 50-90% left- or right-tilted lines. Post - deprivation assesments were administered at 0, 15, 30, and 60 minutes after patching.

**Preprocessing and Statistical Analysis** We used the same preprocessing paradigm described in experiment I, however we also developed an additional dependent variable to investigate post-baseline differences in the mixed percept ratio (MPR) defined by the equation:

$$\mathrm{MPR} = \left(\frac{d_{\mathrm{superimposition}} - d_{\mathrm{piecemeal}}}{d_{\mathrm{superimposition}} + d_{\mathrm{piecemeal}}}\right), \tag{1.3}$$

where the two d variables indicate the overall duration reported for seeing superimposition and piecemeal percepts, respectively. Negative values in the MPR indicated bias in favour of superimposition percepts, while positive values indicated

bias in favour of piecemeal percepts. Patching-induced changes in the MPR were obtained by subtracting baseline from post-patching values.

We conducted pairwise t-tests on the first post-patching measurement and baseline for (1) the overall fraction of mixed visibility, (2) the median duration of mixed visibility,(3) the MPR, and (4) the ODI. We also conducted a repeated measures ANOVA with complementary post-hoc paired t-tests on the MPR and ODI values to determine the time course of the decay of the effect of patching on these variables.

## Results

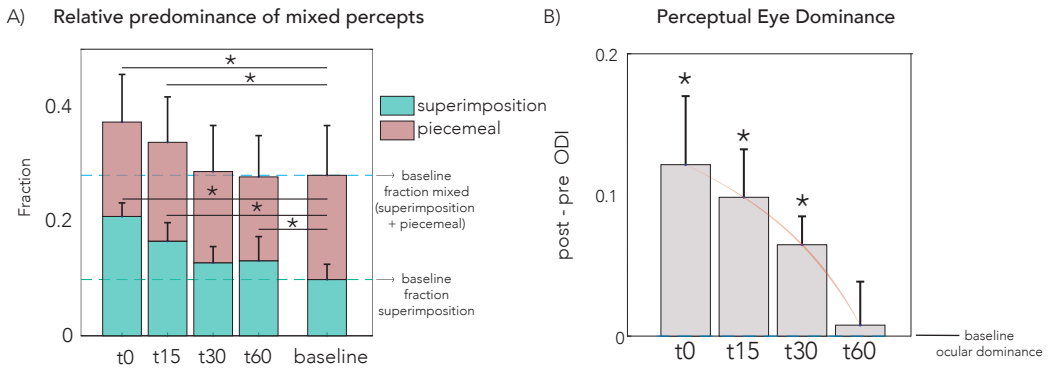


**Figure 1.6: Experiment II: Patching induced changes in superimposition versus piecemeal mixed visibility during rivalry a) Decay of patching-induced effect on fraction mixed visibility and MPR.** The fraction of mixed visibility is the sum of the absolute predominance of superimposition percepts (green) and that of the piecemeal percepts (red). The top rows of asterisked interactions indicate a significant increase in the fraction of mixed visibility at t0 and t15 with respect to baseline. The bottom row of asterisked interactions indicates an increase in the absolute predominance of superimposition percepts at t0, t15, and t60 with respect to baseline. Piecemeal percepts did not shift significantly with respect to baseline. **b) Decay of patching-induced effect on perceptual eye dominance.** Perceptual eye dominance gradually recovers to baseline. Asterisks indicate significant differences with respect to baseline. * indicates $p < 0.05$.

We first wanted to see if the results observed in experiment I were also measurable using a a binocular rivalry task with different response instructions. Using this rivalry task, we replicated the finding that two hours of MD increases both the fraction ($M = 1.09$, 95% CI: [0.24, 1.93], $t(9) = 2.98$, $p < 0.05$) and median duration ($M = 0.24$ , 95% CI: [0.04, 0.43], $t(9) = 2.74$, $p < 0.05$) of mixed visibility during rivalry. Perceptual eye dominance was also significantly shifted in favour of the

deprived eye with respect to baseline (M = 0.12, 95% CI: [0.01, 0.23], t(9) = 2.52, $p < 0.05$).

Furthermore, we also found that the mixed percept ratio (MPR) shifts significantly in favor of superimposition immediately after MD (M = -0.25, 95% CI:[ -0.62, -0.12], t(9) = -2.75, $p < 0.05$). This indicates that the increase in mixed visibility observed in this experiment and in experiment I is likely due to increases in the superimposition percepts, rather than piecemeal percepts. This was confirmed by separate paired t-tests on the normalized post/baseline fractions for both superimposition and piecemeal percepts immediately after deprivation (superimposition: M = 0.08, 95% CI: [0.03, 0.12], t(9) = 4.01, FDR-corrected $p < 0.01$; piecemeal: M = -0.02, 95% CI: [-0.07, 0.02], t(9) = -1.06, FDR-corrected $p > 0.05$).

To determine the time course of this effect of deprivation, we also conducted repeated-measures ANOVAs on the the change in the overall fraction of mixed visibility, the shift in the MPR **Fig.** 1.6a), and the shift in perceptual eye dominance **Fig.** 1.6b) across four post-deprivation time points (at 0 , 15, 30, and 60) minutes after removing the patch. The effect of time on the shift in perceptual eye dominance across these four time points was not significant for these observers (Wilks' lambda = 0.47, F(3,27) = 0.38, $p > 0.05$, $\eta_p^2 = 0.13$, **Fig.** 1.6b), indicating that the overall shift in perceptual eye dominance did not change significantly throughout the post-deprivation assessments. However the perceptual eye dominance shift was significant immediately after removing the eye patch and remained significant until 30 minutes after removing the patch (t9) > 2.98, FDR-corrected ps < 0.05). Likewise, the main effect of time on the overall fraction of mixed visibility across the five time points was also not significant (Wilks' lambda = 0.39, F(3,27) = 1.30, $p > 0.05$, $\eta_p^2 = 0.13$, **Fig.** 1.6a), although there was a significant increase in the overall fraction of mixed visibility immediately after removing the patch (mean = 0.31, 95% CI: [ 0.06, 0.56], t(9) = 2.8, FDR-corrected $p < 0.05$), as well as at 15 minutes after removing the patch (mean = 0.30, 95% CI: [ 0.15, 0.45], t(9) = 4.65, FDR-corrected $p < 0.01$). These analyses reveal that time decays the initial effects of deprivation to baseline over the course of an hour after patching, mirroring the

results in experiment 1.

The effect of time across the five time points was also not significant for the shift in the MPR (Wilks' lambda = 0.63, F(3,27) = 0.70, p > 0.05, $\eta_p^2$ = 0.07, **Fig.** 1.6a), suggesting the ratio of superimposition to piecemeal percepts did not change significantly over the course of our post-deprivation measurements. The MPR, did, however shift significantly in favour of superimposition with respect to baseline across three out of four of our measure time points: 0, 15, and 60 minutes after deprivation (t(9) > 2.98, FDR-corrected ps < 0.05). This finding indicates that the most consistent and long-lasting effect of MD in our data is to enhance the absolute predominance of superimposition percepts during rivalry.

## Discussion and Conclusion

We conducted two experiments to characterize the effects of short-term monocular patching on the occurrence of mixed percepts during binocular rivalry. Our investigation was inspired by recent findings that patching alters E/I balance in visual cortex (Lunghi et al.; Chadnova et al.; Binda et al., 2015b; 2017; 2017), and that the absolute predominance of mixed visibility during rivalry can be modified through recent visual experience (Klink et al.; Said and Heeger, 2010; 2013) as well as with neuromodulators (Mentch, Jeff., Spiegel, Alina., Ricciardi, Catherine., Kanwisher, Nancy., Robertson., 2018).

Experiment I utilized a rivalry task that enabled us to accurately quantify patching-induced changes in perceptual eye dominance as well as in the overall fraction and median duration of mixed visibility during rivalry. Our results from this experiment demonstrated that patching causes enhancements in both the fraction and median duration of mixed visibility during rivalry. Further, our data also suggest that patching acheives a perceptual eye dominance shift in favour of the deprived eye by reducing the overall predominance and median duration of the non-deprived eye's image while simultaneously reallocating its responses among the mixed percepts.

This finding contrasts with previous rivalry studies on patching which found that

the shift in perceptual dominance is caused by an increase in the strength of the deprived eye and a reciprocal decrease in the non-deprived eye (Lunghi et al.; Lunghi et al.; Lunghi et al., 2011; 2015b; 2016). It is important to note, however, that the conclusions drawn from our data are not entirely in disagreement with these previous results due to the fact that the previous studies monocularly deprived the dominant eye while our study always deprived the non-dominant eye. This distinction is possibly related to Levelt's Proposition II (Levelt, 1965), or more appropriately Modified Proposition II (Brascamp et al., 2015), which states that when the input strength of the two eyes are independently altered, the dominance duration of the eye with the stronger input will be maximally affected. In the context of our study, it is reasonable to consider the non-deprived (dominant) eye as the eye with the stronger input at baseline. It is therefore plausible that patching-induced changes in the signal strength of the deprived eye would preferentially affect the dominance duration of the non-deprived eye, as we observe in our results.

Our study also demonstrated that perceptual eye dominance shifts within the exclusive percepts while the two biased mixed percept categories increase independently of eye-of-origin. This finding presents the possibility that deprivation impacts exclusive dominance and mixtures differently. It is possible, however,that our participants did not accurately classify the three fractional mixed percept categories due to the fact that they alternated faster and were more difficult to keep track of than the exclusive percepts. While our task design sought to ensure that participants do not miscategorize 'biased' mixed percepts as exclusive percepts, it also introduced a possible source of error in the categorization of the three mixed percept categories. For this reason, it may be fruitful for future studies utilizing our task to employ a 'replay' rivalry control condition to evaluate possible criterion effects latent in the task. Relatedly, an unpublished experiment conducted by the authors demonstrated that five minutes of monocular deprviation did not change the response criterion for mixed visibility during replay rivalry (although it did shift perceptual eye dominance and also enhance mixed visibility in normal rivalry). Our approach to circumnavigate this issue in the present study, however, was to implement a PCA that aimed to

transform the original data into statistically uncorrelated components underlying rivalry phase durations which were invariant to eye-of-origin. Using this approach, we identified three components which corresponded to several hypothesized mechanisms involved in producing the rivalry states: (i) binocular combination, (ii) perceptual suppression (agnostic to eye-of-origin), and (iii) perceptual eye dominance. This approach, which has previously been used to infer neural mechanisms from behavioral data (Reynaud and Hess, 2017), offered additional evidence for the idea that MD has two identifiable and statistically distinguishable effects on binocular rivalry dynamics: (i) an increase in ocular imbalance, and (ii) an increase in binocular combination.

The main conclusions drawn from experiment I can be plausibly understood by the idea that MD achieves its effects by weakening interocular inhibition. We designed experiment II to assess this idea. We adapted a rivalry task previously developed by Skerswetat, et. al. (2017) to investigate patching-induced changes in the relative predominance of superimposition and piecemeal mixed percepts. Whereas superimposition percepts can be thought of as fully fused binocular percepts, the result of weakened interocular suppression, piecemeal percepts can be considered to be intermediary binocular percepts, where rivalry is still occurring in smaller subregions (Kovacs, I., Papathomas, T.V., Yang, M., and Feher and Ehe; Lee and Blake; Alais and Melcher; Klink et al., 1996; 2004; 2007; 2010). Superimposition and piecemeal mixed percepts have been previously attributed to arise from two different but related aspects of interocular inhibition – gain and spatial coherence, respectively (Klink et al., 2010). Superimposition percepts would then indicate a reduction in the overall gain of interocular inhibition while picemeal perception points to reduced spatial coherence of interocular inhibition. The finding that patching enhances the relative predominance of superimposition percepts, while not significantly affecting piecemeal visibility, adds complementary evidence to the idea that MD attenuates the gain of interocular inhibitory interactions.

It is also noteworthy to add that superimposition percepts during binocular rivalry are known to appear infrequently with the stimulus parameters used in our

study (Hollins, 1980), and when they are visible the component gratings often do not appear equal in clarity and contrast (Yang et al., 1992). Assuming the neural mechanisms underlying superimposed visibility immediately after patching are the same ones promoting those states at baseline, the significant increase in superimposition visibility implicates patching as a potent method to reduce interocular inhibition. In this way, our results are related to previous investigations evaluating the role of inhibitory interocular interactions in rivalry, where prolonged exposure to rivalrous binocular stimuli also causes an increase in superimposed mixed visibility (Klink et al.; Said and Heeger, 2010; 2013).

While the effects of short-term patching on perceptual eye dominance are well-documented (Lunghi et al.; Lunghi et al.; Hess et al.; Kim et al.; Baldwin and Hess, 2011; 2015a; 2013; 2017; 2018), the current study presents the first evidence that monocular patching also enhances binocular combination. Previous studies using binocular rivalry with similar stimulus parameters to assess the effects of monocular patching (Lunghi et al.; Lunghi et al.; Lunghi et al., 2011; 2016; 2015b) excluded participants with greater than 20% overall predominance of mixed visibility at baseline. While such exclusion criteria may improve accuracy in measures of perceptual eye dominance, it also reduces the generalizability of these results to the overall population, where the average proportion of mixed visibility using the stimulus parameters mentioned in our paper ranges between 30% - 60% (O'Shea et al., 1997).

**Theoretical Implications** Importantly, our main findings are compatible with several proposed computational frameworks of binocular rivalry. For instance, the patching-induced increase in mixed visibility aligns well with the work done by Brascamp et. al. (2013). In this paper, the authors present an experimentally-derived model of rivalry where eye-specific neural events in early processing areas contribute to perceptual competition during stimulus rivalry (where incongruent images are continuously swapped between the two eyes but representations of the images rival as in binocular rivalry). As patching likely causes changes in early eye-specific cor-

tical areas (Lunghi et al.; Chadnova et al.; Daniel Tso, Ronald Miller, 2015b; 2017; 2017), our data contribute to the idea that changes in monocular neural activity can modulate the resolution of binocular rivalry. This model contrasts with other computational approaches to binocular rivalry which attribute perceptual competition to exclusively higher-order binocular areas (Wilson, 2003). An interesting avenue of future study will be to investigate whether patching also affects perceptual eye dominance and mixed visibility during stimulus rivalry. Such work can further reveal the neural loci of the two identifiable effects of monocular patching on rivalry dynamics mentioned in the current study.

Likewise, the finding that patching enhances binocular combination is compatible with computational frameworks of rivalry that include opponency neurons (Blake; Said and Heeger; Li et al.; Katyal et al., 1989; 2013; 2017; 2016). Opponency neurons, or XOR neurons, detect interocular conflict and play a role in the resolution of binocular rivalry. In the Said and Heeger model of binocular rivalry (2013), opponency neurons inhibit preceding feedforward units such that an adaptive reduction in the activity of these inhibitory interneurons results in a facilitation of binocular combination. This model succeeds at predicting experimental evidence in which adaptation to interocular flicker of left- and right-oriented monocular gratings (targeting opponency neurons) subsequently produces more mixed visibility during rivalry than a binocular adaptor of the same stimuli (not targeting opponency neurons). Similarly in our case, temporarily depriving one eye of input can be conceived of as (i) preferentially adapting binocular opponency neurons and also (ii) adapting the feedforward monocular signal of the non-deprived eye. Removing the eye patch subsequently causes a relative enhancement in (i) the perception of mixtures and (ii) a shift in balance in favour of the deprived eye. It is worth mentioning that recent physiological evidence has identified populations of neurons that are synchronized with the intermodulation of monocular SSVEP signals during rivalry (Katyal et al., 2016), in line with these theoretical insights (Blake; Said and Heeger; Li et al., 1989; 2013; 2017).

Finally, it is feasible to consider that the two effects of MD on binocular rivalry

dynamics discussed in this dissertation emerge, in part, as a result of the type of attentional gain mechanism described in Li et. al. (2017). Attention is a well-established factor influencing binocular rivalry dynamics (see (Dieter and Tadin; Dieter et al.; Carrasco, 2011; 2016; 2011)). In their model, Li et. al. (2017) propose attentional modulation from higher-order visual areas amplifies perceptual competition by biasing attentional gain to one of the rival stimuli. According to the model, prolonged adaptation of such an attentional mechanism would subsequently result in a decrease of perceptual suppression during rivalry. A patching-induced adaptation of this type of attentional mechanism could account for the reduction of perceptual exclusivity we observe in our experiments. Taking this possibility a step further, our findings may contribute new evidence for the existence of eye-specific attentional channels (Self; Saban et al., 2010; 2018), where adaptation of the non-deprived eye's attentional channel subsequently shifts perceptual balance in favour of the deprived eye.

**Conclusion** In summary, our study provides new insights on the effects of short-term adult MD. While we have known for some time that patching causes a temporary shift in perceptual eye dominance, we now know that some of this shift is attributed to a reallocation of responses towards the perception of mixtures. The findings of the present study contribute to the growing evidence that short-term MD causes a temporary functional plasticity observable at the level of excitatory/inhibitory balance in early visual cortex. It will be beneficial for future rivalry studies on MD to take advantage of a detailed account of the intermediary mixed percepts to further advance our knowledge of the underlying brain mechanisms and to sharpen our understanding of binocular visual plasticity in general.

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# Rationale for Subsequent Study

To briefly review, we have found that two hours of monocular deprivation with a translucent eye patch reduces interocular suppression – with increases in the perception of superimposition mixed percepts pointing to changes in excitatory/inhibitory (E/I) balance. This constitutes an additional and important effect of deprivation that has not yet been reported in the literature. Likewise, our main results from chapter one also demonstrated that monocular patching achieves a shift in perceptual eye dominance during binocular rivalry by reallocating responses corresponding to the non-deprived eye among those corresponding to the mixed percepts and the deprived eye. This finding offers additional evidence to the idea that patching is related to dichoptic adaptation, where binocular vision shifts as a result of one eye's reduced strength.

With these findings in mind, our subsequent study was motivated by the idea that patching changes visual brain activity via changes to cortical E/I balance. Here, we determine whether cholinergic enhancement with the acetylcholinesterase inhibitor donepezil – which is known to alter cortical E/I balance – enhances or detracts from the effects of monocular deprivation. For this study, we primarily focus on donepezil's effect on the the shift in perceptual eye dominance induced by temporary monocular patching. Determining whether acetylcholine facilitates or reduces this effect of patching will better characterize the precise mechanism of patching's action and will also help to inform us whether the potentially therapeutic aspects of short-term patching can be enhanced pharmacologically.

# 2. Cholinergic potentiation alters perceptual eye dominance induced by a few hours of monocular patching in adults

## Introduction

Changes in ocular dominance are perhaps the most widely studied form of brain plasticity, illustrating the causal links between experience and neuronal organization (Hubel and Wiesel; Wiesel; Fagiolini and Hensch; Gilbert and Li; Zucker and Regehr; Bavelier et al., 1970; 1982; 2000; 2012; 2002; 2010). Ocular dominance arises from the relative tuning of binocular neurons in the visual cortex to feedforward inputs from both eyes. Downstream competition (in the form of mutual inhibition) and integration (or binocular summation) of these monocular inputs presents an opportunity to understand the mechanisms of binocular visual processing and to explore the dynamics of experience-driven plasticity, a defining feature of the adult binocular visual system (Klink et al., 2010). A commonly used way to dissect these processes is through monocular deprivation (MD). Extended ($>$ 2 days) MD within the critical period, for instance, results in a permanent shift of perceptual eye balance in favour of the non-deprived eye that is measurable at the level of individual neurons' responses in V1. (Hubel and Wiesel; Wiesel, 1970; 1982).

In addition to plasticity during the critical period, recent investigations have also found residual plasticity in adults using short-term (a few hours) MD (Lunghi et al.; Zhou et al.; Zhou et al.; Hess et al.; Lunghi et al.; Lunghi et al.; Kim et al.; O'Shea and O'Shea, 2011; 2015; 2013; 2013; 2015b; 2015a; 2017; 2017); for an overview of

short-term MD's effects see (Baldwin and Hess, 2018). In this case, patching an eye for a period of two hours results in a temporary shift in favour of the *deprived* eye that is measurable for a duration of at least 1.5 hours (Lunghi et al., 2011). Importantly, this temporary shift in perceptual eye dominance points to a latent plasticity in the adult visual system that is categorically unique from OD plasticity within the critical period because contrary to the latter, this plasticity enhances the contribution of the *deprived* eye. In an effort to avoid confusion with the classical OD plasticity examined by (Hubel and Wiesel, 1970), which enhances the *non-deprived* eye, we will refer to the effect examined in the present study as short-term perceptual eye dominance plasticity.

Furthermore, it is important to point out that the dissimilar effects of long-term ($> 2$ days) and short-term MD (a few hours) could implicate a different set of neural mechanisms. In the classical model, changes in OD depend on plasticity brakes and consolidation mechanisms to modify neural activity. The short-term perceptual eye dominance plasticity observed in the present study and others (Lunghi et al.; Zhou et al.; Chadnova et al., 2011; 2015; 2017) is described as a form of interocular contrast gain control (Hess et al.; Zhou et al., 2013; 2015), driven by enhanced contrast-gain of signal from the patched eye as well as a reduction in GABA-ergic inhibition in V1 (Lunghi et al., 2015b). Physiologically, the effects of short-term monocular deprivation have been observed using MRS (Lunghi et al., 2015b), MEG (Chadnova et al., 2017) and fMRI (Binda et al., 2017) in humans, as well as intrinsic optical imaging in a murine model (Daniel Tso, Ronald Miller, 2017). These studies point to deprivation-induced changes in inhibitory/excitatory dynamics in V1 with observable effects at the level of ocular dominance columns in layer 4c of V1. Importantly, frequency-tagged MEG signal from the non-deprived eye was reported to decrease during short-term deprivation and only begins recovery after restoring binocular visibility (Chadnova et al., 2017), likewise attributed to an overall enhanced net inhibition of the non-deprived eye's input relative to the deprived eye.

While mechanisms underlying neural plasticity are generally more active during

development, recent investigations have demonstrated that enhanced plasticity may be restored in adulthood, albeit to a lesser degree (Bavelier et al., 2010). Treatments that enhance plasticity in adults generally do so by changing long-lasting neuronal responsiveness or by acting on so-called "brakes" on plasticity that develop after the critical period. Some of these brakes on plasticity are structural, such as peri-neuronal nets or myelin, which inhibit synaptogenesis. Others brakes are functional and act on the excitatory/inhibitory balance of neural circuits (Bear and Singer; Kasamatsu et al.; José Fernando Maya Vetencourt et al.; Morishita et al., 1986; 1991; 2008; 2010). It is widely believed that adult brain plasticity can be enhanced by manipulating excitatory/inhibitory transmitter signalling (Bavelier et al.; Morishita et al.; Baroncelli et al.; Baroncelli et al., 2010; 2010; 2011; 2012).

Treatments that manipulate excitatory/inhibitory balance to alter neural plasticity generally act on endogenous neuromodulator activity. These interventions have, at times, been successful at enhancing cortical functioning and plasticity in both adult human and animal models (Rokem and Silver; Morishita et al.; Chamoun et al.; Rokem and Silver; Bavelier et al.; José Fernando Maya Vetencourt et al.; Bentley et al.; Bear and Singer; Kasamatsu et al., 2010; 2010; 2017a; 2013; 2010; 2008; 2003; 1986; 1991), however this has not universally been the case (Chung et al.; Conner et al., 2017; 2003). Some successful interventions targeting dopaminergic, serotonergic, and cholinergic pathways elihcited direct consequences on adult functional and structural brain reorganization (Bear and Singer; Bao et al.; Weinberger; Morishita et al.; Berardi et al.; José Fernando Maya Vetencourt et al., 1986; 2001; 2007; 2010; 2000; 2008).

Of the known neuromodulators, acetylcholine (ACh) is particularly interesting for visual plasticity because of its role in modulating excitatory/inhibitory balance in visual cortex as well as mediating long-lasting neuronal responsiveness and structural plasticity throughout the cortex. For instance, genetically removing the expression of Lynx1, a cholinergic brake, reinstates critical-period-like OD plasticity in adult mice (Morishita et al., 2010), where the non-deprived eye becomes more dominant. Furthermore, multiple administrations of the acetylcholinesterase inhibitor (AChEI)

physostigmine (which potentiates and prolonges the action of endogeneous ACh) improves visual function and enhances critical-period-like ocular dominance plasticity after long-term MD in a murine model of amblyopia (Morishita et al.; Groleau et al.; Gagolewicz and Dringenberg, 2010; 2015; 2009).

In humans, drugs that increase endogenous ACh signalling have been shown to enhance cortical plasticity and functioning by refining neural circuits' efficacy and enhancing perceptual learning. This has been assessed, for example, in visual tasks such as motion direction discrimination (Silver et al.; Rokem and Silver; Rokem and Silver, 2008; 2010; 2013), and 3D multiple object tracking (Chamoun et al., 2017a). There are other instances, however, that demonstrate the opposite: a recent study reported that cholinergic enhancement blocked the effect of perceptual learning of a crowding task relative to a placebo control group (Chung et al., 2017). Nevertheless, pharmacological enhancement of synaptic ACh has been shown to improve visual function, possibly by reducing the spatial spread of visual responses, sharpening visual spatial perception, increasing top-down control of attentional orienting and stimulus discrimination, and enhancing cortical activation in V1 (Gratton et al.; Silver et al.; Kang et al.; Klinkenberg et al., 2017; 2008; 2014; 2011). Although cholinergic potentiation has been implicated in mediating several types of visual perceptual learning and enhancing visual neural responsiveness, its exact role in adult visual plasticity *per se* remains unclear.

In the present study, we used the AChEI donepezil to investigate the effects of cholinergic enhancement on adult perceptual eye dominance plasticity. In a double-blind crossoever design, we provided a placebo pill or donepezil and compared the effect of a few hours monocular patching on perceptual eye dominance in the two experimental conditions. Under the assumption that cholinergic potentiation enhances visual neural responsiveness (Kang et al., 2014), we hypothesized that donepezil would (1) enhance the strength of the patched eye's contribution to binocular vision after patching and would also (2) reduce the amount of time necessary to elicit the shift in perceptual eye dominance relative to the placebo control. We were surprised to find that donepezil in fact *reduces* both the magnitude and duration of the shift of

binocular response in favour of the deprived eye. We found this to be the case when patching for both 1 and 2 hours, and with two separate tasks measuring perceptual dominance.

## Materials and Methods

***Table 2.1: Demographic data: participant characteristics and involvement in binocular combination and binocular rivalry experiments, mean ± SEM (range).*** *BPC2: Binocular Phase Combination Task – 2 hours monocular deprivation; BPC1: Binocular Phase Combination Task – 1 hour monocular deprivation; RIV2: Binocular Rivalry Task – 2 hours monocular deprivation*

| Experiment | N | Age | Height(cm) | Weight (kg) | BMI (kg/m) |
|---|---|---|---|---|---|
| Total | 13 | 23 ± 1 (19 - 31) | 169 ± 4 (152 - 193) | 66 ± 2 (43 - 77) | 23 ± 1 (18 - 26) |
| BPC2 | 12 | 23 ± 1 (19 - 31) | 170 ± 1 (152 - 193) | 64 ± 1 (43 - 90) | 22 ± 1 (18 - 26) |
| BPC1 | 7 | 25 ± 1 (20 - 31) | 174 ± 2 (158 - 193) | 68 ± 2 (56 - 90) | 22 ± 1 (19 - 24) |
| RIV2 | 6 | 24 ± 1 (20 - 28) | 171 ± 2 (152 - 193) | 62 ± 2 (43 - 90) | 21 ± 1 (18 - 24) |

Sixteen young adults participated in the study. Two participants were excluded from the study due to data collection errors. One additional subject was excluded from analysis on the basis that he was an author and aware of the motivation of the investigation. Thirteen participants (2 Men, age: 19-31 years , BMI: 18-26 kg/m$^2$, see **Table** 2.1 completed the study. Twelve subjects completed the first experiment which used the binocular phase combination task to measure perceptual eye dominance before and after two hours of deprivation. Seven participants completed the second experiment which also used the phase combination task to measure perceptual eye dominance after one hour of deprivation. Finally, six participants completed a different experiment which used binocular rivalry to measure the shift in perceptual eye dominance after two hours of monocular deprivation. Only two subjects were able to participate in all three experiments.

All subjects met the inclusion criteria (**Table** 2.2. The body-mass-index range

was specified as 17–26 kg/m$^2$ to ensure a similar distribution of the drug across subjects. All subjects were naive to the purpose of the experiment. A standard clinical and neurological examination, a stereoacuity test and an ECG recording were performed before the beginning of the experiment. Subjects were monitored for their safety during the experimental sessions with several blood pressure measurements taken.

Subjects gave written informed consent prior to the experiment. Data were collected and kept secure in the laboratory of author EV. Participants were enrolled by the student researcher YS, and their random allocation sequence was carried out by EV and MC by assigning drug/placebo in numbered containers. Subjects received financial compensation to cover travel expenses and time spent participating in the experiment at a rate of $15/hour. The procedures were in accordance with the Helsinki Declaration of 2013 and the ethical standards of the Comité d'éthique de la recherche en santé, Université de Montréal, approval #12- 084-CERES-P.

We used a double-blind within-subject crossover design where each participant completed two experimental sessions. Subjects were randomly assigned to either the donepezil or control group for their first session and then switched to the other group for their second session which occurred approximately 21 days after the first. In each session, participants completed baseline testing on either a binocular phase combination or binocular rivalry task. This provided an index of their baseline perceptual eye dominance. This was followed by donepezil or placebo administration and two hours of monocular deprivation. The patch was then removed, and subsequent tests of perceptual eye dominance were made over the next hour.

In experiment two, subjects underwent an identical protocol to that of experiment one, with the exception of adjusting the incubation period – where subjects awaited the activation of the drug – to two hours and the deprivation duration to one hour. A third experiment was also conducted where a binocular rivalry task was used instead of a binocular combination task. Previous studies on short-term monocular deprivation have found different results with the two tasks (Bai et al., 2017) – depriving one eye of Fourier phase information for two hours produced a

shift in perceptual eye dominance in favor of the deprived eye as measured with binocular rivalry but not with binocular phase combination. We were interested to determine whether donepezil had a different effect on plasticity as measured through rivalry versus binocular phase combination.

***Table 2.2: Inclusion and exclusion criteria***

| **Inclusion criteria** | **Exclusion criteria** |
|---|---|
| Good health | Attention deficit |
| Body mass index between 17 and 26 | Smoker |
| No visual impairment or ocular pathology not corrected by glasses or contact lenses | Pregnant, breast feeding or planning a pregnancy |
| Good stereo vision | Unable to do task |
| | Lactose intolerant (lactose pills as placebo) |

### Donepezil Pharmacological Enhancement

Donepezil is a reversible, non-competitive, highly selective AChEI with a half-life of 80h and a peak plasma level of 4.1 $\pm$ 1.5h after intake (Rogers et al., 1998). 5 mg of donepezil is the lowest prescribed dose which induces beneficial cognitive effects with very low adverse reaction incidence (Prvulovic and Schneider, 2014). This dose is shown to be effective in improving visual attention and the neural plasticity associated with perceptual learning in young adults (Rokem and Silver; Rokem and Silver, 2010; 2013). Three hours before the patch removal, subjects ingested one capsule containing either 5 mg donepezil (ARICEPT, Pfizer, Canada) or lactose placebo with water (Rokem and Silver, 2010). The experimenter and subjects were naive to the experimental conditions.

### Monocular Deprivation

Using the Miles test for sensory eye dominance (W. R. Miles, Ocular dominance in human adults, J. Gen. Psychol., vol. 4, pp. 412-430, 1930), we identified the

dominant eye for each participant. We then patched the *non*-dominant eye for each experimental session they participated in. We chose to patch the non-dominant eye with the rationale that it has more capacity to increase its dominance, however this has not been yet been assessed systematically. We used a diffuser eye patch that eliminated all spatial frequency information as confirmed by a Fourier decomposition of a natural image viewed through the patch. While most studies use a patching duration of 2.5 hours, recent investigations have seen comparable effects after two hours of patching (Lunghi et al., 2016). To minimize the amount of time it would take to complete a single session, we administered monocular deprivation for two hours for Experiments 1 and 3. For Experiment 2 we reduced the duration to one hour to assess whether donepezil accelerates the rate of plasticity.

## Experimental Protocol

The general protocol of each session is outlined in **Figure** 2.1A. For each of the three experiments, participants were randomly allocated to either Group 1 (Donepezil first session, Placebo second session) or Group 2 (Placebo first session, Donepezil second session). The experimenter was not aware of participants' group assignments until after data collection was complete. For safety purposes, the experimenter recorded the participant's systolic blood pressure at baseline and monitored blood pressure levels throughout the experiment. Baseline psychophysical testing took place over the course of five to ten minutes on either the binocular phase combination task in Experiments 1 and 2 or binocular rivalry in Experiment 3. The half-life of donepezil is $4.1 \pm 1.5$ hours after intake. We therefore chose to begin post-deprivation testing at three hours after drug administration to maximize the potency of the drug at the time of testing. For Experiments 1 and 3 this required that our participants wait one hour before beginning their two hours of deprivation. For Experiment 2 participants waited two hours before beginning one hour of deprivation.

After the drug incubation period, participants were provided with a diffuser eye patch to wear on the non-dominant eye. During the drug incubation period and subsequent monocular deprivation, participants were instructed to keep their eyes

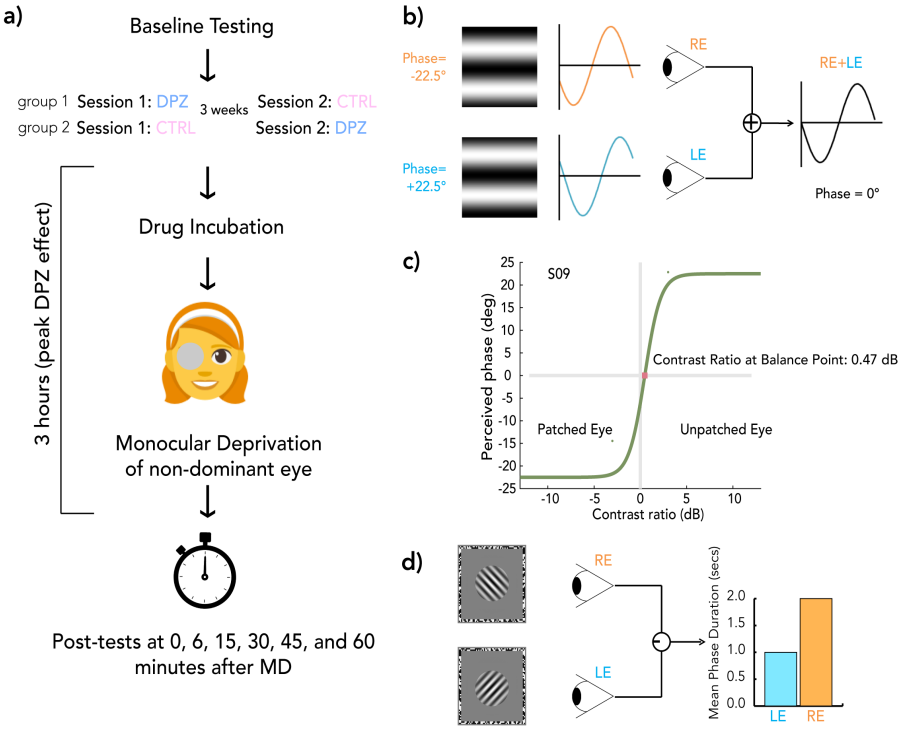


**Figure 2.1: General Protocol and Methods. a) Schema of experimental session.** For each experiment, participants were randomly allocated to either group 1 or group 2, indicating whether they take donepezil (DPZ) or placebo on the first day and then the reverse on the second day which occurs 21 days later. After baseline testing, participants take their assigned pill. Both the experimenter and participant are unaware of the participant's group assignment. After a drug incubation period (1 hour for experiments 1 and 3, 2 hours for experiment 2), Monocular deprivation (MD) with a diffuser eye patch begins (2 hours for experiments 1 and 3, 1 hours for experiment 2). Post-MD testing begins 3 hours after taking the pill. **b) Binocular phase combination task.** The participant views two sinusoidal gratings presented individually to each eye through a modified Wheatstone stereoscope. The gratings have phase-shifts in opposite directions of the same magnitude (22.5°). The observer is asked to use keypresses to move a flanking bar to the middle of the trough of the fused sinusoid. This gives an estimate of the perceived phase of the grating after binocular combination. In this example, the participant sees a fully balanced fusion of the two gratings, resulting in a perceived phase difference of 0°. **c) Psychometric curve for binocular combination task.** Psychometric function for one subject at baseline. Curves were generated by fitting data from each measurement to a model of binocular combination (see methods). The CR at the balance point was used to determine ocular dominance for each measurement. **d) Binocular rivalry task.** Two orthogonal sinusoidal gratings ± 45° were presented dichoptically through a modified Wheatstone stereoscope for 180 seconds per measurement. The participant continuously indicated whether they were seeing a (1) predominantly left-tilted grating, (2) a balanced fusion of right and left lines, or (3) a predominantly right-tilted grating for the entire duration of the stimulus presentation. The ratio of median rivalry phase durations for each eye was used to quantify ocular dominance for each measurement.

open and do activities that require visual perception such as watching a movie, doing homework, or walking around the lab.

After the full duration of monocular deprivation (two hours for Experiment 1 and 3, one hour for Experiment 2), participants were instructed to remove the eyepatch and begin psychophysical testing. Psychophysical measurements were taken at five timepoints (0, 15, 30, 45, and 60 minutes) after deprivation. Each measurement took approximately three minutes to complete, and participants were instructed to keep their eyes open in between measurements. After completing the first session of an experiment, participant were assigned a scheduled date to return for completing their second session. To ensure there was no residual effects from the previous session, all sessions were spaced roughly three weeks apart from one another.

## Apparatus

Each session took place in a quiet room with dim light. Visual stimuli for both binocular combination and binocular rivalry experiments were generated and controlled by an Apple MacBook Pro 2008 computer (MacOSX; Cupertino, CA, USA) running MATLAB R2012B (MathWorks, Natick, MA) with the Psychtoolbox psychophysics toolbox (Brainard, 1997; Kleiner, Brainard & Pelli, 2007; Pelli, 1997). Stimuli were presented on a gamma-corrected cathode ray tube monitor (LG, Seoul, South Korea) driven at a resolution of 1024 x 768 pixels, with a refresh rate of 75 Hz and a measured mean luminance of 60cdm$^{-2}$. Participants viewed stimuli through an eight-mirror modified Wheatstone stereoscope so that the left image was only seen by the left eye and the right image by the right eye. The position of the participant's head was stabilized with a chin rest at a viewing distance of 57cm.

## Binocular Phase Combination Task

The binocular phase combination task (Ding and Sperling, 2006) is outlined in **Figure** 2.1B. Each measurement began with a dichoptic nonius cross presented inside a 3° oval surrounded by a black-and-white noise (1 cycle per degree) frame (side = 10°). The observer was asked to make keypresses to adjust the position

of the two frames to calibrate the optimal position for comfortable fusion. After calibration, two horizontal sine-wave gratings (0.3 cycles per degree, 6° x 6°) with phase-shifts in opposite directions of the same magnitude (22.5°) were presented dichoptically through the stereoscope.

The physical sum of two sinusoidal gratings of the same frequency is another sinusoidal grating with a phase and amplitude that depend on the phases and amplitudes of the two inputs. This behavior has also been shown to hold for the perception that arises from the summation of gratings presented to the two eyes (Ding and Sperling, 2006). For our stimuli, the perceived phase of the perceived grating depends on the internal weighting of the inputs from each eye. Therefore, variations in perceptual eye dominance can be quantified by the change in the perceived phase (**Figure**2.1b).

To account for any potential bias, two configurations were used for assessing the perceived phase in any given trial. The first configuration gave a phase-shift of +22.5° in the dominant eye and -22.5° in the non-dominant eye. The second reversed the two, giving a phase-shift of -22.5° in the dominant eye and +22.5° in the non-dominant eye. In each trial, participants were asked to indicate the location of the central dark bar of the fused grating by adjusting the location of a flanking bar on the screen with a keyboard. The vertical position of the flanking bar was converted into degrees of phase of the combined gratings. This phase offset provided a subjective measure of perceived phase in each trial. An increase of the perceived phase (i.e. more positive) after deprivation indicates an enhanced contribution of the eye that was not patched, whereas a decrease of the perceived phase (i.e. more negative) indicates a shift of dominance towards the patched eye. After each trial, the nonius calibration screen was presented for the observer to re-calibrate if necessary and begin the next trial.

To fit our data to psychometric curves defined by a model of binocular combination (Ding and Sperling; Huang et al., 2006; 2009), we modulated the interocular contrast ratio around a mean contrast of 50% across trials (**figure**2.1c). For baseline measurements, each of the following ratios were tested eight times by method of constant stimuli: 1:2, 1:$\sqrt{2}$ ,1:1, $\sqrt{2}$:1, 2:1. Due to the time-sensitive nature of

OD plasticity after removing the eye-patch, post-test measurements were reduced to three ratios: 1:$\sqrt{2}$ ,1:1, $\sqrt{2}$ : 1. Baseline data consisted of perceived phases collected from 80 trials (5 contrast ratios x 8 repetitions x 2 configurations), and post-deprivation measures consisted of perceived phases from 30 trials (3 contrast ratios x 5 repetitions x 2 configurations). Data were fit to a function of the form

$$\Phi_A = 2\tan^{-1}\left[\frac{f(\alpha,\delta,\gamma)-\delta^{1+\gamma}}{f(\alpha,\delta,\gamma)+\delta^{1+\gamma}}\tan\left(\frac{\theta}{2}\right)\right], \tag{2.1}$$

where

$$f(\alpha,\delta,\gamma) = \frac{1+\delta^{\gamma}}{1+\alpha\delta^{\gamma}}, \tag{2.2}$$

and $\Phi_A$ is the perceived phase of the fused image, $\theta$ is the constant phase displacement between eyes (45°), $\delta$ is the interocular contrast ratio, and the two free parameters, $\gamma$ and $\alpha$ are the slope of the function and the contrast ratio when the two eyes contribute equally to binocular vision. $\alpha$ is represented in log units (dB relative to a 1:1 contrast ratio between the two eyes), calculated as

$$\alpha_{\mathrm{dB}} = 20 \times \log_{10}\left(\delta_{\mathrm{balanced}}\right) \tag{2.3}$$

such that an $\alpha$ of 0 dB indicates that both eyes are contributing equally to binocular combination, while an $\alpha$ of -6 dB indicates that input from the deprived eye is weighted roughly twice as much as that from the non-deprived eye. Changes in $\alpha$ provide a measure of the shift in perceptual eye dominance from baseline. Our main measure of deprivation-induced changes in dominance as measured by the binocular phase combination task was obtained by subtracting each participant's baseline $\alpha$ from each post-patching $\alpha$.

### Binocular Rivalry

In Experiment 3 subjects performed a binocular rivalry task (see **Figure** 2.1d) instead of a phase combination task. After calibration (as above), two orthogonal ( $\pm$ 45° ) sinusoidal gratings (3 cycles per degree, subtending a diameter of 1.5°, with a raised cosine annulus blurring the edges, contrast = 75%) were presented inside a

black-and-white noise pattern frame (1 cycle per degree, 10 °, one side) individually to each eye. The participant was asked to continuously indicate whether they were seeing a (1) predominantly left-tilted grating, (2) a balanced fusion of right and left tilted gratings, or (3) a predominantly right-tilted grating. Baseline measurements were made from six 90-second rivalry blocks. Each post-patching measure was made using two 90-second rivalry blocks.

A commonly used measure of perceptual eye dominance when analysing rivalry data is the mean phase duration (Lunghi et al.; Lunghi et al.; Lunghi et al., 2011; 2015b; 2016). This measure is defined as the average amount of time spent viewing a percept by one eye. Rivalry phase durations generally follow a log-normal distribution (Zhou et al., 2004). Because of this property, mean phase durations are generally influenced more by longer phase durations. The median phase duration is arguably a better measure of centrality for these distributions, so our analysis used the median phase durations to compute an perceptual ocular dominance index (ODI), bounded by [-1, 1], for each rivalry measurement that was defined by the equation:

$$\mathrm{ODI} = \left(\frac{\bar{d}_{\mathrm{non-deprived}} - \bar{d}_{\mathrm{deprived}}}{\bar{d}_{\mathrm{non-deprived}} + \bar{d}_{\mathrm{deprived}}}\right), \tag{2.4}$$

where the two $\bar{d}$ variables are the mean phase durations for the non-deprived and deprived eyes. Negative and positive ODIs indicate bias in favour of the deprived and non-deprived eyes, respectively. To evaluate deprivation-induced changes in the index we then subtracted baseline values from each post-patching measure.

### Statistical Analyses

Each experiment provided measures of perceptual eye dominance at baseline and at five time points (0, 15, 30, 45, 60 minutes) after treatment. For our analyses, we subtracted baseline ODIs from each post-deprivation ODI to obtain five treatment-induced differences in perceptual eye dominance over the course of an hour after removing the patch. We implemented a two-factor (treatment × time) repeated measures ANOVA on these post - baseline differences to investigate whether

there was an interaction between the donepezil and placebo control treatments over the course of our measurements. Separately, we applied one-way repeated measure ANOVAs for each treatment condition to determine whether treatment significantly shifted perceptual eye dominance at the initial time point after patching with respect to baseline. The results of our ANOVA analyses for the three experiments are summarized in **Table** 2.3. If the effect of treatment was significant for either of the experimental conditions, we conducted follow-up FDR-corrected (Benajmini and Hochberg, 1995) t-tests on the post - baseline differences to determine which time points were significantly shifted with respect to baseline. In addition, we computed the area under the curve generated by drawing a line through each treatments's post - baseline differences as a function of time. This measure, calculated by estimating the integral (via the trapezoidal method) of the curve, can be used as an estimate of the overall effect size for each treatment (donepezil or placebo). We applied Wilcoxon signed-rank tests on these areas to determine if there were significant differences in (1) the mean ranks of the areas from those at baseline and (2) between the mean ranks of the areas of the two treatment conditions.

## Results

### Experiment 1: Two hours of MD with Binocular Phase Combination Task

Two hours of patching induced a shift in perceptual dominance for both donepezil and placebo control conditions (CTRL: Wilks' lambda = 0.22, F(1,11) = 38.3, FDR-corrected $p < 0.01$, $\eta_p^2 = 0.77$; DPZ: Wilks' lambda = 0.50, F(1,11) = 10.63, FDR-corrected $p < 0.05$, $\eta_p^2 = 0.49$) that was maximal immediately after removing the patch (CTRL: M = -3.06, 95% CI: [-4.1, -1.9]; DPZ: M = -1.5, 95% CI: [-2.5, -0.48], dB with respect to baseline). We performed a two-factor (session $\times$ time) repeated measures ANOVA (see **Table** 2.3 for statistics) on the post-baseline ODIs computed for measurements taken at 0, 15, 30, 45, and 60 minutes after removing the patch. The results of this analysis yielded significant main effects for both session (Wilks'

***Table 2.3: ANOVA Summary Table.*** *The left column shows the results of a two-factor (session x time) repeated-measures ANOVA for the three separate experiments. The right column shows results from one-factor (time) repeated measures ANOVAs conducted for individual sessions (donepezil/control) for each experiment to determine whether the effect of treatment was significantly different from that measured at baseline. BPC2: Binocular Phase Combination Task – 2 hours monocular deprivation; BPC1: Binocular Phase Combination Task – 1 hour monocular deprivation; RIV2: Binocular Rivalry Task – 2 hours monocular deprivation*

| | **Donepezil versus placebo** | | | | | | **Initial effect of treatment** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Source** | **df** | **MS** | **F** | **p** | $\eta_p^2$ | **Source** | **df** | **MS** | **F** | **p** | $\eta_p^2$ |
| **BPC2** | Session | 1 | 48.50 | 11.10 | **0.00*** | 0.50 | DPZ | 1 | 13.50 | 10.63 | **0.00*** | 0.49 |
| | Time | 4 | 6.62 | 4.60 | **0.00*** | 0.30 | CTRL | 1 | 56.20 | 38.30 | **0.00*** | 0.77 |
| | Session x Time | 4 | 1.25 | 0.83 | 0.51 | 0.07 | | | | | | |
| **BPC1** | Session | 1 | 7.90 | 5.40 | **0.06** | 0.47 | DPZ | 1 | 4.36 | 6.70 | **0.04*** | 0.46 |
| | Time | 4 | 2.67 | 7.80 | **0.00*** | 0.50 | CTRL | 1 | 7.00 | 17.20 | **0.00*** | 0.74 |
| | Session x Time | 4 | 0.53 | 0.91 | 0.47 | 0.13 | | | | | | |
| **RIV2** | Session | 1 | 0.03 | 1.19 | 0.32 | 0.19 | DPZ | 1 | 0.08 | 0.91 | 0.38 | 0.15 |
| | Time | 4 | 0.10 | 3.32 | **0.03*** | 0.40 | CTRL | 1 | 0.25 | 8.00 | **0.03*** | 0.61 |
| | Session x Time | 4 | 0.01 | 1.41 | 0.28 | 0.35 | | | | | | |

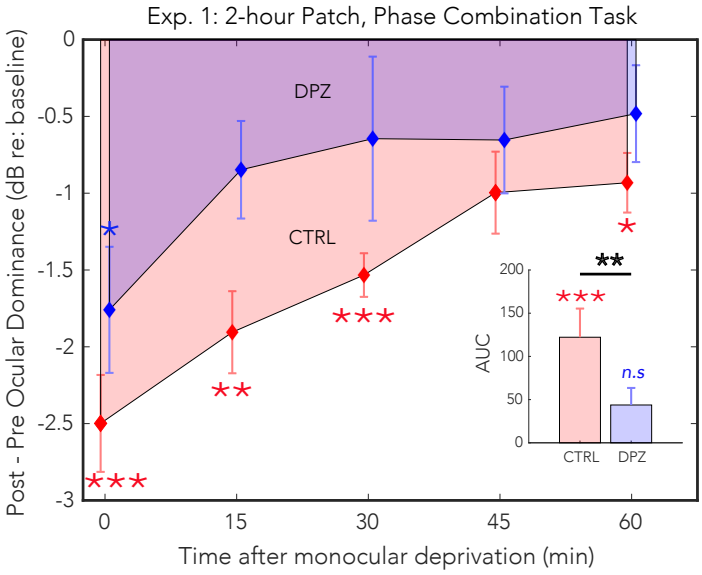


**Figure 2.2: Experiment 1: The effect of donepezil on the shift in ocular dominance that occurs after two hours of monocular deprivation, measured by binocular phase combination. Donepezil reduces both the magnitude and the duration of the shift in ocular dominance that results from monocular deprivation relative to placebo control.** N = 12. Red and blue diamonds indicate the mean difference in ocular dominance from that measured at baseline using the contrast ratio index described in equation 3 for control (CTRL) and donepezil (DPZ) conditions. Errorbars are bootstrapped SEMs. Red and blue asterisks indicate means that are significantly different from baseline for CTRL and DPZ conditions, respectively. Black asterisks indicate means that are significantly different from one another. *** FDR-corrected $p < 0.001$, ** FDR-corrected $p < 0.01$, * FDR-corrected $p < 0.05$

lambda = 0.5, F(1, 11) = 11.1, $p < 0.01$, $\eta_p^2 = 0.50$ ) and time (Wilks' lambda = 0.08, F(4, 44) = 4.6, $p < 0.01$, $\eta_p^2 = 0.30$), however the interaction term was not significant (F(4,44) = 0.83 $p > 0.05$) (**Figure 2.2**.

A post-hoc paired t-test examining the main effect of session indicated that the mean post-baseline difference across all measured time points observed when subjects were treated with donepezil was significantly reduced relative to the placebo control condition (t(11) = -4.9, $p < 0.001$, M = -1.27, 95% CI: [-1.79, -0.75]). Subsequent FDR-corrected paired t-tests on the post - baseline ODIs in the donepezil condition indicated that the mean shift in perceptual eye dominance was significant only during the first measured time point after removing the patch (t(11) = - 3.2, FDR-corrected $p < 0.05$). No other measured time points in the donepezil condition

were significantly shifted from baseline (FDR=adjusted ps $< 0.05$). Post-baseline differences in the placebo control condition, on the other hand, remained significant until up to at least 60 minutes minutes after removing the patch (FDR=adjusted ps $< 0.05$), indicating that donepezil significantly reduced the duration that the mean shift in perceptual eye dominance was significantly shifted from baseline compared to the placebo control.

Furthermore, a two-tailed paired Wilcoxon signed-rank test on the mean ranks of the areas under the curves generated by the post-baseline ODIs in each condition revealed that the mean rank area observed in the placebo control condition was significantly greater than zero (FDR-corrected $p < .001$), while the mean rank area observed in the donepezil condition was not significantly different from zero (FDR-corrected $p > 0.05$). An additional signed-rank test on the mean ranks of the areas of the two experimental conditions revealed that the mean rank area observed in the donepezil condition was significantly reduced relative to placebo control ($p < 0.01$), demonstrating that the magnitude of the effect of patching treatment across the five measured time points was significantly reduced in the donepezil condition compared to placebo. Together, the results of these analyses indicate that donepezil significantly reduces the magnitude and duration of the shift in perceptual eye dominance that occurs after two hours of monocular deprivation.

## Experiment 2: One hour of MD with Binocular Phase Combination Task

As in the first experiment, one hour of patching induced a shift in perceptual eye dominance for both donepezil and placebo control conditions (CTRL: Wilks' lambda = 0.26, $F(1,6) = 17.2$, FDR-corrected $p < 0.01$, $\eta_p^2 = 0.74$; DPZ: Wilks' lambda = 0.47, $F(1,6) = 6.7$, FDR-corrected $p < 0.05$, $\eta_p^2 = 0.52$) that was maximal immediately after removing the patch (CTRL: M = -1.4, 95% CI: [-2.3, -0.6]; DPZ: M = -1.1, 95% CI: [-2.1, -0.06], dB with respect to baseline). We performed a two-factor (session $\times$ time) repeated measures ANOVA (see **Table** 2.3 for statistics) on the post-baseline ODIs computed for measurements taken at 0, 15, 30, 45, and 60 minutes after removing the patch. The results of this analysis yielded a significant main

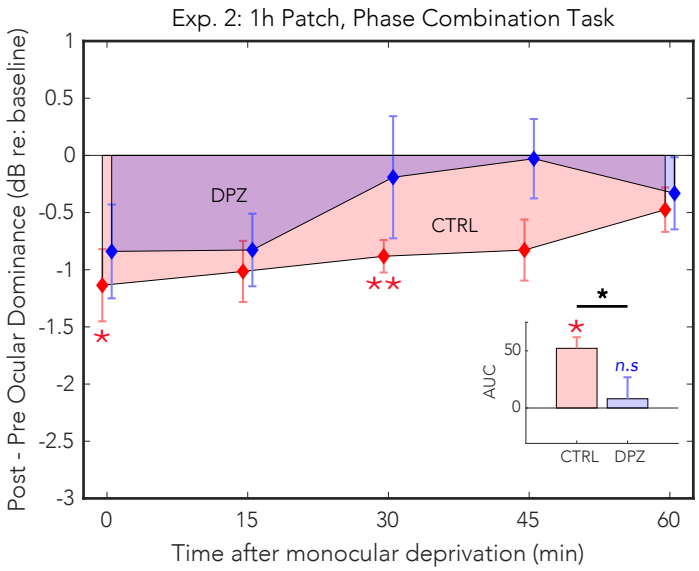


**Figure 2.3: Experiment 2: The effect of donepezil on the shift in ocular dominance that occurs after one hour of monocular deprivation, measured by binocular phase combination. Donepezil reduces the magnitude and duration of the shift in ocular dominance induced by on hour of monocular patching.** N = 7. For further details see **Figure 2.2** caption.

effect of time (Wilks' lambda = 0.10, F(4, 24) = 7.8, p < 0.001, $\eta_p^2 = 0.57$), and a trend towards a significant main effect of session (Wilks' lambda = 0.53, F(1, 6) = 5.4, p = 0.06, $\eta_p^2 = 0.47$, however the interaction term was not significant (F(4,24) = 0.9, p > 0.05) (**Figure 2.3**

Post-hoc paired t-tests examining the main effect of session yielded a trend that the mean post-baseline difference observed when subjects were treated with donepezil was reduced relative to the placebo control, (M = -0.66, p = 0.06, 95% CI: [-1.4, 0.03]). Subsequent FDR-corrected paired t-tests on the post - baseline ODIs indicated that the mean shift in perceptual eye dominance was was significant at 0 and 30 minutes after patching in the placebo control condition (FDR-corrected ps < 0.05), however no individual time points were significantly shifted from baseline in the donepezil condition (FDR-adjusted p > 0.05). As in experiment 1, this indicates that donepezil reduced the duration that perceptual eye dominance was shifted from baseline compared to the placebo control.

A two-tailed paired Wilcoxon signed-rank test on the mean ranks of the areas

under the curves generated by the post-baseline ODIs in each condition revealed that the mean rank area observed in the placebo control condition was significantly greater than zero (FDR-corrected $p < 0.05$), while the mean rank area observed in the donepezil condition was not significantly different from zero (FDR-corrected $p > 0.05$). Likewise, an additional Wilcoxon signed-rank test on the mean ranks of the areas in the two experimental conditions revealed that the mean rank area of the donepezil condition was reduced relative to the placebo control ($p < 0.05$), further demonstrating that the overall magnitude of the effect of one hour of patching on perceptual eye dominance was reduced in the donepezil condition. Together, the results of these analyses indicate that donepezil significantly reduces the magnitude and duration of the shift in perceptual eye dominance that occurs after one hour of deprivation.

### Experiment 3: Two hours of MD with Binocular Rivalry

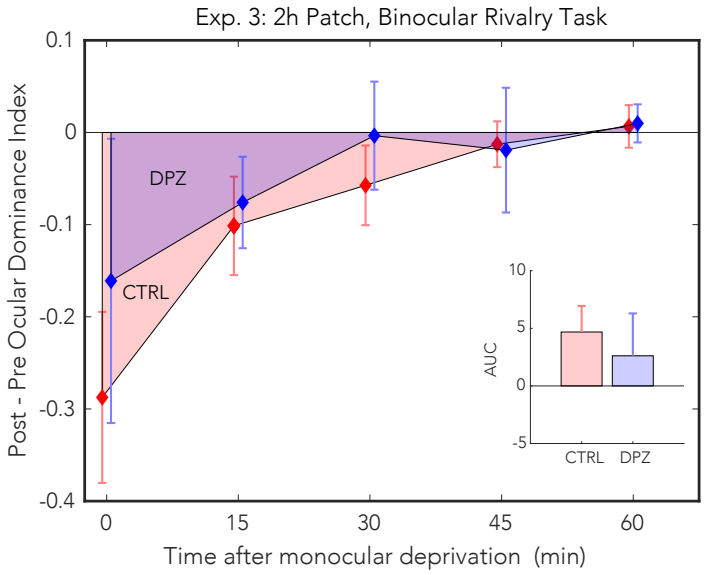


**Figure 2.4: Experiment 3: The effect of donepezil on the shift in ocular dominance that occurs after two hours of monocular deprivation, measured by binocular rivalry. Donepezil reduces the shift from baseline ocular dominance relative to placebo control.** N = 6. Red and blue diamonds indicate the mean difference from baseline OD ratio in described in equation 4 for control and DPZ conditions, respectively.Errorbars are bootstrapped SEMs.

For experiment 3, we used a binocular rivalry task to measure perceptual eye

dominance before and after two hours of monocular deprivation. We administered a repeated measures ANOVA on the initial ODI measured after deprivation versus baseline to assess the initial effect of patching in the two experimental conditions. Ocular dominance shifted significantly with respect to baseline in the placebo control condition, however not in the donepezil condition (CTRL: Wilks' lambda = 0.38, F(1,5) = 7.91, FDR-corrected $p < 0.05$, $\eta_p^2 = 0.61$, M = -0.29, 95% CI: [-0.55, -0.30]; DPZ: Wilks' lambda = 0.85, F(1,6) = 0.91, FDR-corrected p = 0.38, $\eta_p^2 = 0.15$, M = -0.16, 95% CI: [-0.59, 0.27]).

In addition, we performed a two-factor (session × time) repeated measures ANOVA (see **Table** 2.3 for statistics) on the post-baseline ODIs computed for measurements taken at 0, 15, 30, 45, and 60 minutes after removing the patch. The results of this analysis yielded a significant main effect of time (Wilks' lambda = 0.41, F(4, 20) = 3.32, $p < 0.05$, $\eta_p^2 = 0.40$), however neither the effect of session nor the interaction term were significant (ps $> 0.05$) (**Figure 2.3**. While the mean shift in perceptual eye dominance across all time points was greater in the placebo control condition (M = -0.09, 95% CI: [ -0.20, .02], than in the donepezil condition (M = -0.05, 95% CI: [-0.23, 0.13]), the lack of a significant main effect of session indicates that any observed differences between the two experimental conditions in this experiment constitute a weak effect. In addition, a two-tailed paired Wilcoxon signed-rank test on the mean ranks of the areas under the curves generated by the post-baseline ODIs in each condition did not yield a significant difference for this experiment ($p > 0.05$).

The results from our binocular rivalry experiment are less conclusive than those in the phase combination experiments, possibly due to technical limitations of our implementation of the binocular rivalry task. Although the effects observed in this experiment are weak, they nevertheless trend in the same direction as the previous experiments, namely that donepezil reduces the overall magnitude of the shift in perceptual eye dominance that occurs after temporary monocular patching.

## Discussion and Conclusion

We conducted three experiments to investigate whether cholinergic enhancement via the AChEI donepezil could enhance the short-term perceptual eye dominance plasticity induced by two hours of monocular patching. In Experiment 1, we used a binocular phase combination task and found that donepezil decreases the magnitude of the shift in perceptual eye dominance induced by two hours of monocular deprivation relative to control. Importantly, donepezil also appeared to reduce the amount of time for which perceptual eye dominance was shifted. In Experiment 2, we reduced the patching duration to one hour. We found that donepezil reduced the magnitude and duration of the shift here as well. Finally, we assessed whether the effects we observed using the binocular phase combination task were also seen using different measure of perceptual eye dominance, binocular rivalry. Our binocular rivalry result demonstrated that the magnitude of the shift in perceptual eye balance in favour of the deprived eye was reduced with donepezil compared to the placebo control. These findings agreed with that from Experiments 1 and 2. Donepezil appeared to reduce the effect of 1 and 2 hours of monocular deprivation, while the effect of treatment in the control condition was significant relative to baseline.

Our study was motivated by recent findings regarding the role of cholinergic potentiation in adult visual plasticity. Specifically, repeated days of cholinergic enhancement has been shown to improve visual perceptual learning for a number of tasks in observers with normal vision (Chamoun et al.; Rokem and Silver; Kang et al., 2017a; 2010; 2014), suggesting a central role of the neurotransmitter in modulating plasticity processes. In the rat, cholinergic potentiation also improves visual recovery (Chamoun et al., 2017b) and visual processing (Chamoun et al.; Kang et al.; Soma et al., 2016; 2015; 2013), due, in part, to enhancing the responsiveness of visual neurons to their tuned stimuli. Based on these findings, we expected a reinforcement of the shift in perceptual eye dominance in favour of the deprived eye. However, the present findings indicate that donepezil actually reduces the expected gain of the deprived eye over the non-deprived eye relative to placebo control.

There are many possible mechanisms by which ACh enhancement could cause the results we observed in our study. First, consider perceptual eye dominance as an emergent property of an aggregate population of binocular cells tuned to weighted monocular inputs. The strength of a monocular signal influencing the bias of a specific binocular pyramidal neuron is determined by three main factors: (1) the gain of thalamocortical input from a particular eye, the (2) presynaptic inhibition of the contralateral eye induced by either GABAergic interneurons or recurrent connections, or (3) long-range corticocortical projections. Changes in any or all of these three factors would result in a different perceptual eye dominance profile. Due to the presence of nicotinic and muscarinic receptors on thalamocortical fibers, inhibitory neurons and pyramidal cells, ACh is likely to influence every level of binocular summation (Groleau et al., 2015).

Notably, ACh has been shown to enhance feedforward inputs to cortex while also suppressing lateral connections within the cortex (Disney et al.; Disney et al., 2007; 2012). Other studies report ACh-induced increases in cortical excitation as well (Groleau et al.; Gil et al.; Thiele; Hasselmo and Bower, 2014; 1997; 2013; 1992). As cholinergic receptors are located at every level of the cortical circuitry (Groleau et al.; van Kempen et al., 2015; 2017), it is clear that ACh plays a crucial role in modulating the excitatory/inhibitory balance. We speculate that cholinergic potentiation might actually enhance feedforward thalamocortical contrast-gain, facilitating the deprived-eye's signal while simultaneously reducing the patching-induced inhibition of the non-deprived eye, causing an overall reduction in the ocular dominance shift as we observed in our study. It is likely that AChEIs affect monocular responses at the level of the lateral geniculate nucleus (which is also highly cholinoceptive), modulating monocular signal to the visual cortex. Due to the differential role of ACh in subcortical and intracortical circuits, the net reduction of the shift we observe after administration of donepezil is compatible with the idea that reduced GABAergic inhibition in early visual cortex is partially responsible for the shift in perceptual eye dominance induced by patching (Lunghi et al., 2015b).

Furthermore, it is possible that higher doses of AChEI for multiple days would

have a different effect from the results we report in this article. Although the dose we administered has been shown to be effective in enhancing neural plasticity associated with perceptual learning and other aspects of visual perception in other studies (Rokem and Silver; Rokem and Silver; Chamoun et al.; Chamoun et al., 2010; 2013; 2017a; 2016), these studies provided multiple days of cholinergic enhancement while the present study only provided a single dose. This possibility has been called into question due to findings from a recent study (Chung et al., 2017) which reported that multiple administrations of donepezil blocked perceptual learning of a crowding task in adult human amblyopes relative to a placebo control. The finding from this study mirrors that from our own – cholinergic potentiation can reduce certain aspects of adult visual plasticity.

It may also be worthwhile to consider ACh's role in reinstating juvenile OD plasticity as a factor in our results. A previous study (Morishita et al., 2010) examining the effect of extended (30 days) MD on ocular dominance plasticity in mice found that ACh reinstates classical OD plasticity where the non-deprived eye strengthens its relative contribution to binocular vision. It is possible that our conclusions are not in conflict with the findings of this animal study. The short-term perceptual eye dominance plasticity investigated in the present study causes a shift in favour of the deprived eye. It is likely that the mechanism underlying this type of temporary visual plasticity is categorically unique from the canonic OD plasticity evaluated in the aforementioned study. The present study demonstrated that ACh impedes the consolidation of the deprived eye's enhancement after a few hours patching, causing a net shift in favour of the *non-deprived* eye relative to the placebo control. We speculate that the failure to consolidate the deprived eye's enhancement is due, in part, to two conflicting mechanisms at play: (1) the short-term perceptual eye dominance plasticity attempting to consolidate the deprived eye's enhancement and (2) the classical juvenile OD plasticity, enhanced by ACh, attempting to augment the responsiveness of the non-deprived eye. It is possible that that an ACh-modulated enhancement of juvenile OD plasticity could account for the unexpected results of the present study.

Likewise, it is plausible that ACh-mediated effects on visual attention can be a confounding factor in our results. Cholinergic potentiation is known to play a critical role in the top-down control of attentional orienting and stimulus discrimination (Klinkenberg et al.; Groleau et al., 2011; 2015). While our binocular rivalry results are consistent with those reported in our binocular phase combination results, it remains an open question whether short-term monocular deprivation alters fused or eye-specific attentional dynamics, and yet another question is whether cholinergic enhancement affects these dynamics.

Our finding that donepezil reduces the magnitude and duration of the perceptual eye dominance plasticity induced by a few hours of monocular patching contributes to the growing evidence that cholinergic potentiation enhances some aspects of adult visual function and plasticity at the expense of others. Further work is necessary to determine whether the short-term perceptual eye dominance plasticity evaluated in this study can be enhanced pharmacologically. This line of research has the dual benefit of adding to possible clinical therapies for visual disorders while also enhancing our understanding of the limitations and mechanisms of adult neural plasticity.

## Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Author Contributions

ASB, EV, MC, and RFH collaboratively conceived the project idea. ASB and YS implemented the psychophysical tests. MC, PRN, and YS conducted the experiments. YS conducted statistical analyses on the data and drafted the manuscript. ASB, EV, MC, RFH, and YS contributed to revising the manuscript.

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# Rationale for Subsequent Study

To summarize the main conclusions of this thesis so far: (i) in addition to shifting perceptual eye dominance, a few hours of monocular deprivation also reduces the gain of interocular inhibition by enhancing the visibility of superimposition mixed percepts during rivalry, (ii) the shift in eye dominance is likely due to an enhanced suppression of the non-deprived eye's image rather than a boost of the deprived eye's image, and is (iii) reduced in both magnitude and duration by means of cholinergic potentiation when measuring with both binocular rivalry and binocular phase combination tasks.

To understand why cholinergic potentiation reduces the magnitude and duration of the effects of monocular deprivation, it is imperative to ask a more basic neuroscience question – what is the role of acetylcholine in the transduction of binocular information? Understanding what role acetylcholine plays in the relative balance of binocular inhibition and excitation may (i) reveal a presently unknown neurochemical component in the convergence of monocular inputs and (ii) inform our understanding of the mechanisms of the effect of short-term monocular deprivation by contextualizing the results in the preceding chapter.

# 3. Cholinergic modulation of binocular vision

## Main Text

Binocularity, a defining feature of human vision, is predicated on the ability to combine inputs from the two eyes via cortical modulation of the excitatory/inhibitory (E/I) balance of interocular interactions. The endogenous neuromodulator acetylcholine (ACh) is implicated in the E/I balance of primate primary visual cortex (V1), enhancing the gain of thalamocortical synapses in layer 4c (Disney et al., 2007) while at the same time suppressing the activity of intracortical interactions (Disney et al., 2012). Here we use binocular rivalry - a proxy of neural competition in the visual cortex (Tong et al., 2006) – to characterize ACh's role in the transduction of binocular information. Utilizing a double-blind placebo-controlled crossover design, we demonstrate that a single administration of the acetylcholinesterase inhibitor (AChEI) donepezil (5mg, oral) strongly affects binocular rivalry dynamics, with important perceptual implications for binocular vision. We report that donepezil attenuates interocular competition by enhancing the visibility of mixed binocular percepts, thereby reducing the amount of time one eye suppresses the other. Furthermore, donepezil also reduces the rate of interocular competition – a sensitive parameter of cortical E/I balance (Robertson et al.; Van Loon et al., 2013; 2013). Together, these results indicate that the primary modality of ACh's effect on interocular dynamics is to shift the visual cortex towards an excitation-dominant response profile. Our findings suggest that ACh plays a fundamental role in modulating binocular vision, providing new insights on the neurophysiological basis of human

binocularity and on ACh's role in visual perception.

23 individuals each completed two experimental sessions where binocular rivalry measurements were obtained before and after taking either donepezil or a placebo (lactose) pill. The binocular rivalry task consisted of a dichoptic stimulus where participants viewed a left-tilted grating in one eye and a right-tilted grating in the other for 90 seconds, continuously indicating whether they were seeing (i) the left eye's image, (ii) the right eye's image, (iii) a piecemeal mixture of the two images, or (iv) a superimposed mixture of the two images (**Figure 3.1A**). We used this 4-AFC task to characterize the mixed percepts – a sensitive probe of E/I balance (Robertson et al., 2016) – and to encourage participants not to miscategorize a mixed percept as exclusive (see **Supplemental Experimental Procedures** in **Supplemental Information** for details).

**Figure 3.1B** illustrates the effect of donepezil on rivalry dynamics, separately for exclusive visibility, mixed visibility, and the rate of rivalry. Each bar represents the average of three binocular rivalry runs conducted three hours after ingesting a donepezil/placebo pill, divided by the average of three identical rivalry runs at baseline, averaged across participants. Compared to placebo control, donepezil enhances the predominance of mixed visibility during rivalry by 42% ($F(1,22) = 12.4$, $p < 0.01$, $\eta_p^2 = 0.36$), and increases the median duration of mixed visibility by 78% ($F(1,22) = 7.18$, $p < 0.05$, $\eta_p^2 = 0.25$; see **Table 3.1** and **Supplemental Experimental Procedures** for details). These changes were reciprocated in measurements of exclusive visibility, where donepezil reduces the fraction of exclusive dominance by 35% ($F(1,22) = 11.80$, $p < 0.01$, $\eta_p^2 = 0.35$) and the median duration by 20% ($F(1,22) = 6.40$, $p < 0.05$, $\eta_p^2 = 0.23$). The rate of binocular rivalry also decreased by 15% in the donepezil condition relative to placebo ($F(1,22) = 4.90$, $p < 0.05$, $\eta_p^2 = 0.18$), suggesting attenuation of cortical inhibition (Van Loon et al., 2013). **Figure 1C** illustrates the distribution of the effect of donepezil on the fraction of mixed visibility during rivalry. Relative to placebo, the fraction of mixed visibility increases for 19 out of 23 participants – where 8 of these individuals exhibited donepezil-induced increases of more than 50% (see **Figure 3.2** in the Supplemental Information for

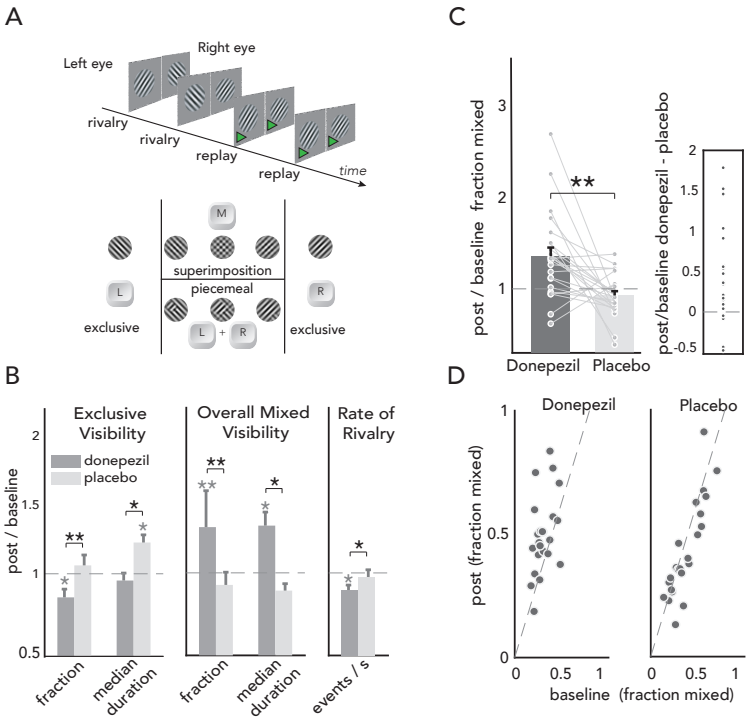


**Figure 3.1: Effect of donepezil on binocular rivalry dynamics. (A)** Top: Each block consisted of two rivalry runs (where participants viewed left- and right-tilted gratings presented individually to the two eyes) and two replay runs (where participants watched computer-generated videos of simulated binocular rivalry, presented identically to both eyes), each lasting 90 s. Bottom: Participants were instructed to press and hold the key that corresponded to what they were perceiving during both rivalry and replay runs. **(B)** Each bar represents the average of three binocular rivalry runs conducted three hours after ingesting either a donepezil/placebo pill, divided by the average of three identical rivalry runs at baseline, and averaged across participants. Gray asterisks indicate statistical significance re: baseline, black asterisks indicate significant session interactions. Errorbars are bootstrapped SEM. ** = $p < 0.01$, * = $p < 0.05$ **(C)** (left) See **B**. (right) Donepezil - placebo post/baseline values represent the magnitude of the effect of donepezil on the fraction of overall mixed visibility. Higher values indicate donepezil increases mixed visibility. **(D)** Raw data for the overall fraction of mixed visibility during rivalry. X-axis indicates baseline fracion mixed visibility, y-axis represents that 3 h after taking donepezil/placebo.

raw data). Together, these results point to an ACh-induced facilitation of binocular combination, likely due to a cortical shift in favour of excitation.

Despite the dramatic increase in the visibility of mixed percepts, these changes were not reflected in individuals' self-report of their experience after the experiment, nor during a control condition where we generated rivalry playback videos and measured the criterion used for categorizing a percept as mixed (see **Supplemental**

**Information** for information on the rivalry replay condition). While mixed visibility increased substantially on donepezil, the criterion used to categorize a percept as mixed did not change significantly (8%, F(1,22) = 1.34, p > 0.05, $\eta_p^2$ = 0.18), indicating that the perceptual changes we observe in the donepezil condition can not be caused by changes in subjects' response criteria, and can only be attributed to changes in neural activity.

Our task allowed us to measure the relative predominance of piecemeal and superimposition mixed percepts during rivalry. Piecemeal percepts – where the two images appear combined as in a mosaic – are proposed to emerge from a reduction of the spatial coherence of interocular inhibition, whereas superimposition percepts – where the two component gratings appear overlaid as in a plaid – likely correspond to decreases in the gain of interocular inhibition (Klink et al., 2010) (see **Figure 3.1A** for illustrations). Donepezil greatly enhances the visibility of piecemeal percepts (70%, (F(1,22) = 14.20, p < 0.01, $\eta_p^2$ = 0.39), while not significantly affecting the overall visibility of superimposition percepts (14%, (F(1,22) = 0.20, p > 0.05, $\eta_p^2$ = 0.01); see **Figure 3.2** in the Supplemental Materials). These findings indicate that ACh – which has previously been implicated in visual spatial processing in V1 (Roberts; Silver et al., 2004; 2008) – predominantly modulates the spatial coherence of interocular inhibition, as opposed to its gain.

Importantly, our findings can not be attributed solely to an increase in the gain of purely monocular signals, as previous work has demonstrated that enhanced stimulus contrast – which increases monocular gain – actually reduces mixed visibility during rivalry (Hollins, 1980). Our results are therefore aligned with the notion that cholinergic potentiation also suppresses inhibitory intracortical interactions. Furthermore, our work demonstrates a foundational role for ACh in the neural substrate of binocular vision, with direct perceptual consequences – modulating the degree to which the two eyes' images are combined or suppressed. Future work will reveal the extent to which specific aspects of binocular vision – such as stereopsis or summation – can be shaped by cholinergic potentiation, as well as whether donepezil can be used therapeutically for disorders of binocular function.

# Supplemental Information

## Supplemental Experimental Procedures

A total of 24 individuals enrolled in the study. One participant was excluded from the study due to a failure to complete the full experiment, therefore in sum, 23 individuals participated the study (13 male; age: 25 ± 3 (20 - 32)).

All subjects met the inclusion criteria (non-smoker, normal or corrected-to-normal visual acuity, normal stereo vision, no history of any neurological or ocular diseases). The body-mass-index range was specified as 17–26 kg/m$^2$ to ensure a similar distribution of the drug across subjects. All subjects were naive to the purpose of the experiment. A standard clinical and neurological examination, a stereoacuity test, and an ECG recording were performed before the beginning of the experiment. Subjects were monitored for their safety during the experimental sessions with several blood pressure measurements taken.

Subjects gave written informed consent prior to the experiment. Data were collected and kept secure in the laboratory of author EV. Participants were enrolled by the student researcher YS, and their random allocation sequence was carried out by YS by assigning drug/placebo in numbered containers. Subjects received financial compensation to cover travel expenses and time spent participating in the experiment at a rate of $15/hour. The procedures were in accordance with the Helsinki Declaration of 2013 and the ethical standards of the Comité d'éthique de la recherche en santé, Université de Montréal, approval #12- 084-CERES-P.

**Apparatus** Each session took place in a quiet room with dim light. Visual stimuli were generated and controlled by an Apple MacBook Pro 2008 computer (MacOSX; Cupertino, CA, USA) running MATLAB R2012B (MathWorks, Natick, MA) with the Psychtoolbox psychophysics toolbox (Brainard, 1997; Kleiner, Brainard & Pelli, 2007; Pelli, 1997). Stimuli were presented on a gamma-corrected cathode ray tube monitor (LG, Seoul, South Korea) driven at a resolution of 1024 x 768 pixels, with a refresh rate of 75 Hz and a measured mean luminance of 60cdm$^{-2}$. Participants

viewed stimuli through an eight-mirror modified Wheatstone stereoscope so that the left image was only seen by the left eye and the right image by the right eye. The position of the participant's head was stabilized with a chin rest at a viewing distance of 57cm.

**Donepezil Pharmacological Enhancement** Donepezil is a reversible, non-competitive, highly selective AChEI with a half-life of 80h and a peak plasma level of 4.1 ± 1.5h after intake (Rogers et al., 1998). 5 mg of donepezil is the lowest prescribed dose which induces beneficial cognitive effects with very low adverse reaction incidence (Prvulovic and Schneider, 2014), and has produced several reported effects on adult vision (Chamoun et al.; Rokem and Silver; Rokem and Silver; Gratton et al.; Silver et al., 2017; 2010; 2013; 2017; 2008). Importantly, although higher doses of donepezil may yield stronger effects on vision, a lower dose is more physiologically relevant to understanding the underlying, natural mechanisms of the visual system as it would not imbalance cortical neuromodulator levels as dramatically. Three hours before post-treatment testing, subjects ingested one cellulose capsule containing either 5 mg donepezil (ARICEPT, Pfizer, Canada) or lactose placebo with water (Rokem and Silver; Sheynin et al.; Chamoun et al., 2010; 2019; 2017). The experimenter and subjects were naive to the experimental conditions.

**Binocular Rivalry Task** We adapted a 4AFC binocular rivalry task developed by Skerswetat et. al. (2017) ((Skerswetat et al., 2017); **Fig. 3.1A** in main text) to quantify the fractions and median durations of exclusive, piecemeal, superimposition, and overall mixed percepts . At the beginning of each session, participants were shown images on a document that illustrated the differences between the left-oriented, right-orineted, and superimposition versus piecemeal mixed percepts. Participants were told that they would see a dynamic stimulus during the experiment and that their task was to track what they were seeing, with particular attention to timeliness and accuracy.

Participants were given the option to continuously indicate whether they were seeing either (i) an exclusively left-tilted grating, (ii) an exclusively right-tilted grat-

ing, (iii) a superimposition mixed percept, or (iv) a piecemeal mixed percept. Participants used three adjacent keys for the task, using the left to indicate exclusive left-tilt, right for right-tilt, a holding down a combination of the left and right keys for the piecemeal percepts, and the middle key for the superimposition percepts. In our instructions, we specified that the criterion for exclusive percepts should be approximately 90% left- or right-oriented.

**Rivalry Replay Control** We utilized a rivalry replay control condition to characterize the criterion used for categorizing a percept as mixed and to quantify the latency of binocular rivalry responses (Robertson et al.; Robertson et al., 2013; 2016). The replay control consisted of computer-generated videos presented binocularly, where we oscillated the stimulus from left-oriented gratings to right-oriented gratings along a continuous scale, such that the midpoint of this oscillation would produce a complete mixture of the two gratings. Each experimental block consisted of two binocular rivalry runs followed by two rivalry replay runs, where each replay run was generated using the time series extracted from the participants's data in a preceding binocular rivalry run within the same block, replaying the participant's rivalry dynamics so as to reduce the likelihood that the participant was aware of the fact that the replay control was a different experimental condition. One of the replay runs in each block was generated with piecemeal mixed visibility as the mixed category, and the other with superimposition mixed visibility, so as to be able to characterize differences in criterion or response latency for these two different percept types. We extracted the average criterion used to categorize a percept as mixed by taking the mean value of the physical stimulus across all timepoints when the participant indicated they switched from exclusive to mixed visibility. The response latency was extracted by finding the time value corresponding to the minimum root mean square error (RMS) between the participant's responses and the physical stimulus. To obtain an estimate of the overall criterion and response latency for binocular rivalry (where piecemeal and superimposition both appear within a single run), we averaged the criterions and latencies across the two piecemeal and

superimposition runs in each block.

**Experimental Protocol** Participants were randomly allocated to either Group 1 (Donepezil first session, Placebo second session) or Group 2 (Placebo first session, Donepezil second session). Group assignment was counterbalanced across participants to control for possible session-order effects. The experimenter was not aware of the treatment condition of the two group assignments until after data collection was complete. For safety purposes, the experimenter recorded the participant's systolic blood pressure at baseline and monitored blood pressure levels throughout the experiment.

The general protocol of each experimental block is outlined in **Figure 3.1A** in the main text. Each block consisted of two binocular rivalry runs followed by two rivalry replay runs, each lasting 90 s. We confirmed subjects correctly learned the key mapping corresponding to the percept categories by administering two replay runs at the beginning of every session, one run corresponding to the piecemeal mixed category, and the other to the superimposition catgegory.

Each run (rivalry and replay) began with a dichoptic nonius cross presented inside a 3-degree oval surrounded by a black-and-white noise (1 cycle per degree) frame (side = 10 deg). The observer was asked to make keypresses to adjust the position of the two frames to calibrate the optimal position for comfortable fusion. After confirmation, the participant was instructed to fixate at a fixation dot (0.2 deg) and place their hands on the appropriate keys to begin responding to the rivalry task. After a keypress, the dichoptic stimulus appeared and participants began responding to what they were observing on the monitor using the keypress instructions we provided at the beginning of each session. Subsequent runs were initiated after a brief break where subjects viewed a mean-gray background screen. Subjects performed four experimental blocks before and after taking donepezil/placebo (after a three hour drug incubation period). During the incubation period subjects were instructed to keep both eyes open and do normal activities such as watching a movie or doing computer work in a well-lit room.

Baseline and post-treatment measurements were drawn from 4 blocks, each block consisting of 2 90 s rivalry runs and 2 90 s replay runs. We implemented a mandatory 2-minute break between each experimental block to prevent fatigue. The orientation of the gratings seen by the eyes during the rivalry runs was flipped between the two runs in each block to counterbalance possible orientation-eye biases and to interrupt any possible adaptation effects that would result in an increase in mixed visibility (Klink et al., 2010). We discarded the first experimental block in both baseline and post-treatment measurements to account for possible errors made in the beginning of the task.

Baseline and post-treatment measurements took place over the course of approximately 30 minutes. The half-life of donepezil is 4.1 $\pm$ 1.5 hours after intake. We therefore chose to begin post-deprivation testing at three hours after drug administration to maximize the potency of the drug at the time of testing. During the drug incubation period, participants were instructed to keep their eyes open and do activities that require visual perception such as watching a movie, doing homework, or walking around the lab. Participants were also given a brief questionnaire before and after each experimental session that utilized a Likert scale (1 - 5) to quantify levels of arousal, along with short answer questions to characterize whether they noticed any perceptual differences between the morning and afternoon sessions, and between the two experimental sessions after both were completed.

After completing the first session of an experiment, each participant was assigned a scheduled date to return for completing their second session. To ensure there was no residual effects from the previous session, all sessions were spaced at least one week apart from one another.

**Preprocessing and Statistical Analysis** Using the preprocessing methodology described in detail in Sheynin, Proulx, and Hess (2019), we extracted key aspects of binocular rivalry dynamics corresponding to the overall fractions and median durations of (i) exclusive visibility, (ii) piecemeal visibility, (iii) superimposition visibility, and (iv) overall mixed visibility (Figure 2). In addition, we extracted the overall

rate of rivalry, defined as the total amount of events in a rivalry run (switches + reversions) divided by the run duration (Robertson et al.; Robertson et al., 2013; 2016). In order to quantify the magnitude of the effect of the two treatment conditions relative to baseline, we divided mean post-treatment values by the mean baseline values to obtain post/baseline ratios for each dependent variable across both experimental conditions. We conducted repeated-measures ANOVAs on the post-baseline values to evaluate the effect of each treatment condition with respect to baseline (**Table** 3.1, right column). To evaluate the magnitude of the effect of donepezil relative to placebo control, we conducted a repeated measures ANOVA on the post/baseline ratios for each dependent variable (**Table 3.1**, left column). We obtained 95% confidence intervals and the standard deviation of a distribution of 1000 bootstrapped resamples (each drawing 23 subjects, with replacement) of the normalized post/baseline values for each dependent variable. All confidence intervals ($\alpha = 0.05$) in the current paper are equivalent to the 2.5th and 97.5th percentiles of the respective bootstrap distribution.

## Supplemental Figures and Tables

***Table 3.1: ANOVA Summary Table.*** *Left column shows the reuslts of a repeated measures ANOVA conducted between donepezil and placebo conditions for each dependent variable. Right column shows the output of a repeated measures ANOVA on the magnitude of the effect of treatment for donepezil and placebo conditions with respect to baseline, seperately.*

| | **Donepezil versus placebo** | | | | | | **Treatment versus baseline** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Measure** | **M** | **95% CI** | **F** | **p** | $\eta_p^2$ | **Session** | **M** | **95% CI** | **F** | **p** | $\eta_p^2$ |
| **Overall Mixed** | **Fraction** | 0.42 | [0.19, 0.69] | 12.4 | ***<0.01** | 0.36 | **DPZ** | 0.38 | [0.18, 0.56] | 13.3 | ***<0.01** | 0.37 |
| | | | | | | | **CTRL** | -0.07 | [-0.17, 0.02] | 2.16 | >0.05 | 0.09 |
| | **Duration** | 0.78 | [0.17, 1.39] | 7.18 | ***<0.05** | 0.25 | **DPZ** | 0.80 | [0.36, 1.36] | 8.68 | ***<0.01** | 0.28 |
| | | | | | | | **CTRL** | 0.02 | [-0.22, 0.17] | 0.09 | >0.05 | 0.00 |
| **Exclusive** | **Fraction** | -0.34 | [-0.54, -0.13] | 11.80 | ***<0.01** | 0.35 | **DPZ** | -0.18 | [-0.30, -0.06] | 9.30 | ***<0.01** | 0.30 |
| | | | | | | | **CTRL** | 0.16 | [-0.0, 0.31] | 4.20 | >0.05 | 0.16 |
| | **Duration** | -0.20 | [-0.37, -0.04] | 6.40 | ***<0.05** | 0.23 | **DPZ** | -0.03 | [-0.14, 0.09] | 0.24 | >0.05 | 0.01 |
| | | | | | | | **CTRL** | 0.18 | [0.05, 0.30] | 9.00 | ***<0.01** | 0.30 |
| **Piecemeal** | **Fraction** | 0.70 | [0.31, 10.10] | 14.20 | ***<0.01** | 0.39 | **DPZ** | 0.47 | [0.12, 0.82] | 7.80 | ***<0.05** | 0.26 |
| | | | | | | | **CTRL** | -0.22 | [-0.26, -0.08] | 11.0 | ***<0.01** | 0.33 |
| | **Duration** | 0.40 | [-0.02, 0.82] | 3.91 | >0.05 | 0.15 | **DPZ** | 0.52 | [0.16, 0.90] | 8.83 | ***<0.01** | 0.29 |
| | | | | | | | **CTRL** | 0.13 | [-0.05, 0.31] | 2.20 | >0.05 | 0.01 |
| **Superimposition** | **Fraction** | 0.14 | [-0.50, 0.71] | 0.20 | >0.05 | 0.01 | **DPZ** | 0.35 | [-0.17, 0.88] | 1.90 | >0.05 | 0.08 |
| | | | | | | | **CTRL** | 0.20 | [-0.16, 0.57] | 1.32 | >0.05 | 0.06 |
| | **Duration** | 0.54 | [-0.03, 1.10] | 3.90 | >0.05 | 0.15 | **DPZ** | 0.59 | [0.10, 1.10] | 6.19 | ***<0.05** | 0.22 |
| | | | | | | | **CTRL** | 0.06 | [-0.12, 0.23] | 0.45 | >0.05 | 0.02 |
| **Rivalry Rate** | **Rate** | -0.15 | [-0.30, -0.01] | 4.90 | ***<0.05** | 0.18 | **DPZ** | -0.14 | [-0.22, -0.07] | 14.70 | ***<0.01** | 0.40 |
| | | | | | | | **CTRL** | 0.01 | [-0.10, 0.12] | 0.06 | >0.05 | 0.00 |
| **Replay** | **Criterion** | 0.08 | [-0.07, 0.23] | 1.34 | >0.05 | 0.06 | **DPZ** | 0.07 | [-0.05, 0.18] | 1.40 | >0.05 | 0.06 |
| | | | | | | | **CTRL** | -0.02 | [-0.12, 0.08] | 0.15 | >0.05 | 0.01 |
| | **Delay** | 0.05 | [-0.03, 0.12] | 1.80 | >0.05 | 0.07 | **DPZ** | 0.03 | [-0.08, 0.03] | 1.16 | >0.05 | 0.05 |
| | | | | | | | **CTRL** | -0.02 | [-0.08, 0.04] | 0.52 | >0.05 | 0.02 |

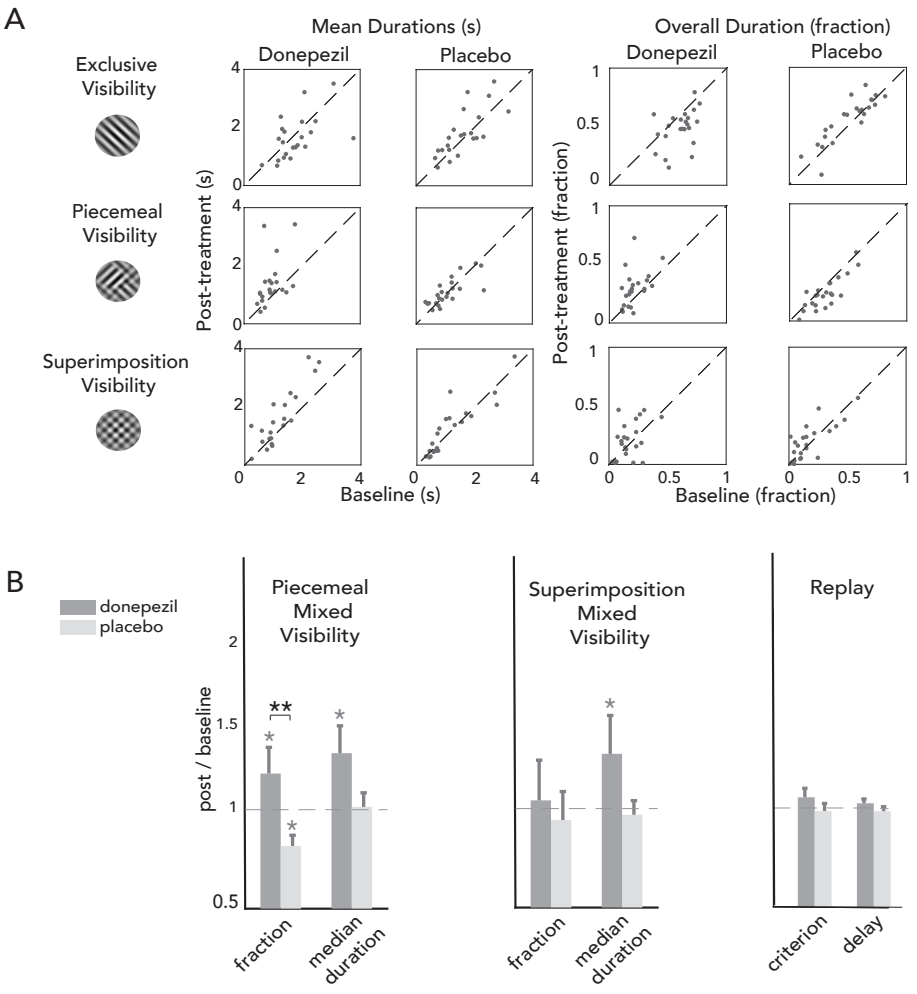


**Figure 3.2: The effect of donepezil on binocular rivalry dynamics (continued). (A)** The scatter plots illustrate the distribution of individuals' shift induced by either donepezil or placebo for each percept category and for both fractions and median durations. **(B)** See **Figure 3.1A** in main text for more information. Piecemeal, and not superimposition visibility during rivalry, was preferentially enhanced on donepezil. Neither the criterion of mixed visibility nor the response latency changed in either experimental condition, suggesting that other effects on rivalry dynamics can not be attributed to changes in criterion or latency.

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# Discussion

In the present thesis, we investigated underlying neural processes of plasticity in adult binocular vision. To briefly review the aims of the current work, chapter one addressed a novel approach to better characterize the perceptual effects and possible neural underpinnings of short-term monocular deprivation – a model of plasticity in adult binocular vision. In chapter two, we examined whether acetylcholine (ACh) – a proposed adult brain plasticity enhancer – can enhance the effects of short-term monocular deprivation. Finally, in the third chapter, we investigated a more foundational question about adult binocular plasticity – what is ACh's role in binocular vision in general and how does it affect plasticity? Here we review the main findings from the three studies and evaluate how they fit into our current understanding of the field. We conclude with practical implications of the research conducted and offer suggestions for future study.

## Research Aims

**Characterizing the effects of short-term monocular deprivation** As established previously, this thesis utilized the perceptual effects of short-term monocular deprivation as a model of plasticity in binocular vision. Though studied increasingly in research labs globally, the perceptual effects and neural substrates of the effects of deprivation are, so far, unclear. To better characterize the mechanisms of the effects of short-term patching, we investigated whether there are other perceptual changes associated with short-term monocular deprivation besides the shift in perceptual eye dominance. Additional perceptual effects can be assessed within the context of patching's known effects to constitute a more complete list, facilitating the search for a conclusive neural substrate. Using binocular rivalry – a sensitive probe of plasticity and competition in visual cortex (Wilson; Klink et al.; Said and Heeger; Tong et al.; Blake; Blake and Overton, 2003; 2010; 2013; 2006; 1989; 1979) – we found that (i) short-term monocular deprivation attenuates interocular inhibition by increasing the visibility of fused, binocular percepts and (ii) achieves a shift in

eye dominance by suppressing the activity of the non-deprived eye.

Our findings regarding these effects of patching on rivalry dynamics are, to an extent, controversial. While we have known for some time that patching causes a temporary shift in perceptual eye dominance, we now know that some of this shift is attributed to a reallocation of responses towards the perception of mixtures. Importantly, our findings contrast with previous studies implicating either (i) reciprocal changes in the two eyes (Zhou et al., 2014) or exclusive boosts to the deprived eye (Lunghi et al., 2011). The interpretation that the shift in perceptual eye dominance is predominantly due to an enhanced suppression of the non-deprived eye, rather than an increase in the deprived eye, suggests the possibility that patching may after all be an unique form of dichoptic adaptation, rather than constituting a unique phenomenon. In this conceptualization, adapting one eye to natural viewing reduces its sensitivity and gain prior to the level of interocular gain control (as in dichoptic adaptation paradigms) resulting in the shift in eye dominance that occurs for approximately the duration of the deprivation period (Greenlee et al., 1991).

With our discoveries from chapter one in mind, it becomes slightly more difficult to determine whether the effects of short-term monocular deprivation are truly categorically unique from those in conventional dichoptic adaptation paradigms, such as those described in Blakemore and Campbell (1969) and Kingdom et al. (2018). One important consideration that lends substantial evidence in support of the idea that patching is categorically unique from adaptation is the time scale of the effects of dichoptic adaptation compared with those in patching. Whereas dichoptic adaptation effects are generally discussed at very short timescales ($< 1$ min), the effects of patching are usually between 15 min - 2 h (Kim et al.; Lunghi et al.; Zhou et al., 2017; 2011; 2014). Similarly, patching effects measured using phase combination and MEG have reported reciprocal changes in the two eyes, likewise differentiating the two effects. These discrepancies complicate the issue and require further work. Nevertheless, our findings point to important and substantial similarities between the effects of dichoptic adaptation and short-term monocular patching.

Importantly, our interpretation of the perceptual results we discuss in chapter

one is compatible with several proposed computational frameworks of binocular rivalry. For instance, the patching-induced increase in mixed visibility aligns well with the work done by Brascamp et. al. (2013). In this paper, the authors present an experimentally-derived model of rivalry where eye-specific neural events in early processing areas contribute to perceptual competition during stimulus rivalry (where incongruent images are continuously swapped between the two eyes but representations of the images rival as in binocular rivalry). As patching likely causes changes in early eye-specific cortical areas (Lunghi et al.; Chadnova et al.; Daniel Tso, Ronald Miller, 2015b; 2017; 2017), our data contribute to the idea that changes in monocular neural activity can modulate the resolution of binocular rivalry – akin to that which occurs in dichoptic adaptation paradigms. While our results point to short-term deprivation as a dichoptic adaptation-like phenomenon, other studies offer diverging views, and the precise nature of the debate must be the topic of subsequent studies. An interesting avenue of future study will be to investigate whether patching also affects perceptual eye dominance and mixed visibility during stimulus rivalry. Such work can further reveal the neural loci of the two identifiable effects of monocular patching on rivalry dynamics mentioned in the current study.

Relatedly, the finding that patching reduces perceptual suppression during binocular rivalry is compatible with several computational frameworks of rivalry that incorporate populations of neurons which are sensitive to interocular differences. Over the last 30 years, several such theoretical constructs have emerged. If we consider, for example, that the populations of X0R neurons discussed by Blake (1989), opponency neurons in Said and Heeger (2013), and B- cells in Li and Atick (1994), are related populations of cells (each sensitive to some form of interocular difference) then we begin to see a pattern emerge that relates to our results. Specifically, in all three of these frameworks, these cells perform neural computations that amounts to the difference – either full-wave or half-wave rectified – between two monocular inputs. This computed difference then affects binocular vision in a certain way. In the case of Blake (1989) and Said and Heeger (2013), these cells play a role in driving the inhibition needed to produce perceptual suppression during binocular

rivalry, while in Li and Atick (1994) they play a role in the effective transduction of stereoscopic information by decorrelating binocular signals.

If these cells – plausibly inhibitory interneurons – inhibit preceding feed-forward inputs as a function of the magnitude of the interocular difference, an adaptive reduction in the activity of these inhibitory interneurons would result in a facilitation of binocular combination, as we observe in the effects of short-term patching. When we consider, also, that patching may indeed be a form of dichoptic adaptation, it becomes theoretically plausible that temporary deprivation (i) preferentially adapts binocular differencing neurons while also (ii) adapting the feed-forward monocular signal of the non-deprived eye. Removing the eye patch subsequently causes a relative enhancement in (i) the perception of mixtures and (ii) a shift in balance in favour of the deprived eye. It is worth mentioning that recent physiological evidence has identified populations of neurons that are synchronized with the intermodulation of monocular SSVEP signals during rivalry (Katyal et al., 2016), in line with these theoretical insights (Blake; Said and Heeger; Li et al., 1989; 2013; 2017). These pieces of theoretical and electrophysiological evidence align quite nicely with our result that monocular patching reduces perceptual suppression during rivalry.

It is import to consider that the two effects of MD on binocular rivalry dynamics discussed in chapter one emerge, in part, as a result of the type of attentional gain mechanism described in Li et al. (2017). Attention is well-known to be an important factor influencing binocular rivalry dynamics (see Dieter and Tadin (2011); Dieter et al. (2016); Carrasco (2011)). In their model, Li et al. (2017) propose attentional modulation from higher-order visual areas amplifies perceptual competition by biasing attentional gain to one of the rival stimuli. According to the model, prolonged adaptation of such an attentional mechanism would subsequently result in a decrease of perceptual suppression during rivalry. A patching-induced adaptation of this type of attentional mechanism could account for the reduction of perceptual exclusivity we observe in our experiments. Taking this possibility a step further, our findings may contribute new evidence for the existence of eye-specific attentional channels (Self; Saban et al., 2010; 2018), where adaptation of the non-deprived eye's

attentional channel subsequently shifts perceptual balance in favour of the deprived eye.

**Mechanisms of short-term monocular deprivation: lessons from the cholinergic system** Furthermore, our findings from both chapter one and chapter two contribute to the growing evidence that short-term MD causes a temporary functional plasticity observable at the level of excitatory/inhibitory (E/I) balance in early visual cortex. In chapter one, we demonstrated that patching attenuates interocular inhibition by facilitating the visibility of fused, binocular percepts and suppressing the activity of the non-deprived eye. Superimposition percepts, which increased in our study as a result of patching, are thought to occur when the gain of interocular inhibition is reduced (Klink et al., 2010), although a more systematic assessment of this claim is needed. When we add enhanced cholinergic potentiation into the equation, ACh reduces the magnitude and duration of the shift in perceptual eye dominance – indicating that ACh plays an important role in the E/I balance of binocular interactions, a topic that formulated the core of our investigation in chapter three.

Our study of the cholinergic system was motivated by recent findings regarding the role of cholinergic potentiation in adult visual plasticity. Specifically, repeated days of cholinergic enhancement has been shown to improve visual perceptual learning for a number of tasks in observers with normal vision (Chamoun et al.; Rokem and Silver; Kang et al., 2017a; 2010; 2014), suggesting a central role of the neurotransmitter in modulating plasticity processes. Based on these findings, we expected a reinforcement of the shift in perceptual eye dominance in favour of the deprived eye. However, the findings in chapter two indicate that donepezil actually reduces the expected gain of the deprived eye over the non-deprived eye relative to placebo control.

There are many possible mechanisms by which ACh enhancement could cause the results we observed in this thesis. First, if we consider perceptual eye dominance as an emergent property of an aggregate population of binocular cells tuned to

weighted monocular inputs, the strength of a monocular signal influencing the bias of a specific binocular pyramidal neuron can be determined by three main factors: (1) the gain of thalamocortical input from a particular eye, the (2) presynaptic inhibition of the contralateral eye induced by either GABAergic interneurons or recurrent connections, or (3) long-range corticocortical projections. Changes in any or all of these three factors would result in a different perceptual eye dominance profile. Due to the presence of nicotinic and muscarinic receptors on thalamocortical fibers, inhibitory neurons and pyramidal cells, ACh is likely to influence every level of binocular summation (Groleau et al., 2015).

Indeed, when we consider the main findings from all three chapters, a clearer image begins to emerge regarding the neurophysiological basis for the effects of patching. ACh, which we now know modulates spatial scale of interocular inhibition, also reduces the shift in perceptual eye dominance induced by patching. As we now also know that the shift in eye dominance induced by patching is predominantly due to enhanced suppression of the non-deprived eye, we can form an informed hypothesis that ACh reduces the magnitude of the patching-induced shift by dis-inhibiting the intracortical pathways resposible for suppressing the non-deprived eye.

If we take this idea a step forward we can consider these effects are occurring in the type of gain control mechanism expanded on theoretically in Ding and Sperling (2006). To review, Ding and Sperling (2006) suggest that each eye (i) exerts gain control on the other eye's signal in proportion to the contrast energy of its own input and (ii) additionally exerts gain control on the other eye's gain control. Within this framework, it is feasible that patching selectively targets the neural circuit corresponding to the deprived eye exerting inhibitory gain control on the non-deprived eye, such that the non-deprived eye's signal is dramatically reduced relative to the deprived eye. This type of network-wide effect would result in an eye dominance shift. Enhanced cholinergic potentiation, on the other hand, disrupts this prolonged inhibitory process and reduces the shift in eye dominance while also reducing interocular inhibition by dis-inihibiting both eyes' gain-control.

Despite this plausibility, it is nevertheless difficult to reconcile the fact that both cholinergic potentiation and short-term monocular deprivation reduce levels of interocular suppression by enhancing mixed visibility during rivalry. Additional evidence describes GABAergic reductions in visual cortex using magnetic resonance spectroscopy (Lunghi et al., 2015b). Intuitively, if both of these paradigms inherently reduce interocular suppression, then combining them should simply amplify their individual effects. In fact, this is not the case. Cholinergic potentiation reduces the perceptual eye dominance shift while also reducing intracortical inhibition. That said, our results across all three studies lend evidence for the idea that patching achieves it's shift, in part, via intracortical inhibition of the non-deprived eye.

Likewise, it is also plausible that ACh-mediated effects on visual attention can be a confounding factor in our results. Cholinergic potentiation is known to play a critical role in the top-down control of attentional orienting and stimulus discrimination (Klinkenberg et al.; Groleau et al., 2011; 2015). While the binocular phase combination task is robust to changes in attentional control since it does not require substantial stimulus discrimination or attentional orienting, it is now widely agreed that binocular rivalry is highly influenced by attention (see (Dieter et al., 2016) for a review). While our binocular rivalry results are consistent with those reported in our binocular phase combination results, it remains an open question whether short-term monocular deprivation alters fused or eye-specific attentional dynamics, and yet another question is whether cholinergic enhancement affects these dynamics.

**A new role for acetylcholine in binocular vision** Last but not least, a major finding of this thesis is that the cholinergic system modulates binocular vision at a foundational level. Although the central role of ACh in human vision has been established in the literature, the specific role ACh plays in binocular visual transduction has not been described until now. A central aspect of binocular vision is that E/I balance in cortex controls the flow of binocular information. Now, however, we know ACh plays a central role in the E/I balance of interocular interactions – and the current work establishes a direct link between cholinergic potentiation and

binocular function.

Placing this finding within the literature reveals complementary evidence for our results. Indeed, previous evidence has demonstrated that ACh is implicated in feed-forward thalamocortical gain (Disney et al., 2007) while also suppressing intracortical interactions (Disney et al., 2012). Our results demonstrate the perceptual implications of this neurochemical mechanism in the context of binocular vision. Indeed, our results present the possibility that a significant role of ACh in the visual system is to modulate the degree to which the eyes are suppressing one another's images – implicating the choinergic system as a component in influencing interocular gain-control as in Ding and Sperling (2006). In this framework, ACh would be a major neurochemical component influencing the degree to which one eye exerts inhibitory gain-control on the other.

## Practical Implications

The main content of this thesis concerns the effects of short-term monocular deprivation, a form of binocular plasticity that can be useful in the treatment of abnormal binocular vision. The basic premise behind the therapeutic use of short-term monocular deprivation is that strengthening a weaker eye will improve binocular function. In fact, daily treatments of short-term monocular deprivation have recently been proposed as a therapy for adult amblyopia Zhou et al. (2019), with some success.

As such, a major outcome of this thesis is a better characterization of the precise neural mechanisms responsible for the effects of monocular deprivation. With the new-found understanding that patching achieves its effects via intracortical inhibition of the non-deprived eye, it becomes possible to design therapeutic modalities that specifically target enhanced inhibition of the non-amblyopic, fellow, eye. Such targeted therapeutic modalities will no doubt benefit the effectiveness of the use of short-term monocular deprivation as a treatment for adult amblyopia.

Moreover, a major implication of the current thesis is the finding that cholinergic potentiation modulates binocular interactions. In the context of therapies for adult amblyopia, dichoptic training or perceptual learning paradigms improve binocular

vision by forcing the two eyes of the amblyopic visual system to cooperate to solve a perceptual task that requires binocular fusion. Such dichoptic training paradigms often work to improve the acuity of the amblyopic eye by reducing contrast in the fellow eye (Levi and Li; Li et al., 2009; 2013). It is plausible to imagine a therapeautic modality incorporating perceptual learning or dichoptic training paradigms in conjunction with cholinergic potentiation. Reducing levels of interocular suppression is invaluable for treating disorders of binocular function. Such a therapy – combining dichoptic training and cholinergic enhancement – would facilitate the recovery of binocular function by reducing the degree to which the eyes are inhibiting one another, thereby promoting healthy binocular vision. Combining the use of such treatment modalities with the use of cholinergic drugs may therefore improve treatment outcomes and reduce the duration of treatment.

## Future Research

There are several clear opportunities for future study of plasticity in adult binocular vision. One clear path to solidify the conclusions of the current thesis is to examine whether the implications of our behavioural work extends to electrophysiological work done on primates or rodents. While likely very challenging to implement, our work predicts that patching an eye reduces the activity of the non-deprived eye. Theoretically, this shift in E/I balance would be observable using electrophysiological methods in animal models. Such work will improve our understanding of the neural bases for the effects of short-term monocular deprivation and progress the field by enhancing our understanding of the electrophysiological underpinnings of binocular vision in general.

Relatedly, some clear next steps would be to investigate the role of attention in the effects of short-term monocular deprivation. As mentioned previously, attention is known to greatly affect binocular rivalry dynamics (Dieter and Tadin, 2011). ACh, a major topic of the present work, is also directly implicated in endogenous attention and spatial perception (Thiele; Silver et al., 2013; 2008). Importantly, recent evidence for the existence of monocular (possible sub-cortical) pathways of

attention (Saban et al., 2018) may also implicate the role of attention in producing the effects of patching. Because of this, it is possible that our results are conflated with attentional effects that were beyond the scope of the experimental designs employed here. It will be critical for future work to examine whether patching targets attentional pathways in binocular vision, as this is a major component of human vision that has, as of yet, not been evaluated in the context of binocular plasticity.

In terms of therapeutic modalities, it will be critical for future studies to take advantage of our finding that cholinergic potentiation reduces interocular suppression during rivalry. It will be critical to first establish the effect of donepezil on other facets of binocular vision, such as a binocular summation or stereopsis. Indeed, our results justify the pursuit of experimental designs that examine the effect of cholinergic potentiation on different aspects of binocular function. Importantly, there is a serious interest within the visual neuroscience community to devise manipulations that enhance binocular function such as steropsis (Levi and Li; Ding and Levi, 2009; 2011). The implications of the cholinergic effects on binocular vision are yet unclear – precisely how ACh would affect stereopsis needs to be fully characterized, as a beneficial outcome would be hugely beneficial for millions with poor stereopsis in the general population (Hess et al., 2015).

As mentioned earlier, a randomized controlled trial for the use of acetylcholinesterase inhibitors (AChEIs) alongside dichoptic training paradigms for the treatment of adult amblyopia are a clear next step. Reducing interocular inhibition is a valuable effect that, theoretically, should have positive consequences on dichoptic training paradigms, such as those employed to treat adult amblyopia. Characterizing whether cholinergic drugs can improve treatment outcomes for such training paradigms may permanently change the way adult amblyopia is approached in the clinic.

# Conclusion

At this point in the history of visual neuroscience, proving the existence of plasticity in adult binocular vision is no longer sufficient and instead we must focus on where, how, and for how long neural changes occur in the binocular visual system (Basgoze et al., 2018). This is the primary motivation for the current work and, hopefully, we have succeeded in progressing, however incrementally, our knowledge of where, how, and for how long.

The current work evaluated plasticity in the context of the effects of short-term monocular deprivation – an increasingly-studied phenomenon that demonstrates the adult brain's latent ability to change and adapt in response to a dynamic visual world. In addition, this thesis incorporated pharmacological work to better characterize the role of acetylcholine (ACh) – a purported cortical plasticity enhancer (Kang et al., 2014) – in binocular vision and, importantly, in binocular plasticity processes such as those in short-term patching.

In chapter one, we found that short-term patching achieves its perceptual eye dominance effect predominantly by suppressing the activity of the non-deprived eye. Importantly, we demonstrated that the responses originally corresponding to the non-deprived eye were allocated among the mixed percepts – suggesting a reduction in perceptual suppression during rivalry. We also found that short-term patching preferentially increases the visibility of fused, superimposition mixed percepts – further indicating that patching reduces levels of interocular inhibition. These effects were observable approximately as long as the eye dominance shift, indicating a related neural basis.

We subsequently examined whether cholinergic enhancement would facilitate the plasticity effects induced by short-term patching. In chapter two, to our surprise, we found that ACh actually reduces the magnitude and duration of the effects of patching. To determine *why* this occurred, we conducted an additional experiment in chapter three, using binocular rivalry as a probe of neural function to evaluate ACh's role in binocular vision. We found that ACh modulates the degree to which

the eyes suppress one another – constituting an important finding regarding an integral neurochemical component of primate binocularity. Reincorporating this finding into our previous result suggests that patching enhances inhibition of the non-deprived eye – a process that ACh attenuates – causing a reduction of the magnitude and duration of the effects of patching.

As short-term monocular deprivation is presently being developed as a treatment for those suffering from adult amblyopia (Zhou et al., 2019), it is imperative to gain a more complete understanding of the neural underpinnings of this phenomenon. With this in mind, the contents of this thesis present new and important insights regarding the neural basis for the plasticity exhibited in the effects of patching. As we have demonstrated that ACh attenuates levels of interocular inhibition, future work will benefit from a comprehensive investigation regarding the use of cholinergic drugs alongside perceptual training paradigms to improve binocular function in clinical populations such as amblyopia.

Building towards a more complete science of plasticity in binocular vision will progress the field towards a deeper knowledge of the mechanisms, limitations, and chemical substrate of adult brain plasticity in general. It is my personal hope that such work will have consequences on the way clinicians address disorders of brain function – the result of faulty neural pathways. It is the utmost importance to build towards a deeper understanding of brain plasticity so as to improve prognosis and treatment outcomes of individuals with disorders of brain function, be that in amblyopia or in Parkinson's.

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