Neural Plasticity in Normal and Amblyopic Adult Visual Systems

by

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As someone who plays the clarinet as a hobby, I would like to dedicate my rendition of Flight of the Bumblebee by Rimsky-Korskakov to everyone at the McGill Vision Research unit.

Abstract

The brain is capable of undergoing substantial changes in its organization during childhood. This ability – neural plasticity – declines as we age. However, accumulating evidence shows that adults retain neural plasticity in the visual system. A means to probe neural plasticity in the visual cortex is to deprive the visual input of one eye. Then, the balance between the eyes gets disrupted, which is believed to be driven by mechanisms in the visual cortex. During my doctoral degree, I conducted four studies using psychophysics to explore neural plasticity in the human visual system. For the first study, I investigated the test-retest reliability of tests that have been used to measure the sensory eye balance. This study enabled me to find the most reliable method for my subsequent studies. Then in the second and third studies, I tested whether the neuroplastic changes in the visual system could be magnified and persist in normal observers. For my last study, I examined whether the remnant neural plasticity could be harnessed to benefit the population with amblyopia, which is a brain-based disorder that impairs vision.

Abstrait

Le cerveau est capable de se soumettre à des changements substantiels dans son organisation durant l'enfance. Cette capacité – la plasticité neuronale – périclite avec l'âge. Cependant, les preuves montrant que le système visuel adulte conserve un certain niveau de plasticité neuronale s'accumulent. Un moyen d'évaluer la plasticité neuronale dans le cortex visuel est de dépourvoir l'entrée visuel d'un œil. Ainsi, la balance entre les yeux se retrouve perturbée, vraisemblablement à cause de mécanismes corticaux. Durant ma thèse de doctorat, j'ai mené quatre études psychophysiques afin d'explorer la plasticité neuronale dans le système visuel humain. Pour la première étude, j'ai étudié la fiabilité des tests couramment utilisés pour mesurer la balance interoculaire sensorielle. Cette étude m'a permis de déterminer la méthode la plus fiable pour mes études subséquentes. Ensuite, dans les deuxièmes et troisièmes études, j'ai testé si les changements neuroplastiques dans le système visuel pouvaient être amplifiés et pérennisés chez des sujets sains. Pour ma dernière étude, J'ai étudié si la plasticité neuronale résiduelle pouvait être exploitée dans la population atteinte d'amblyopie, un désordre cortical qui altère la vision.

Contribution to Original Knowledge

My work probes neural plasticity in the human visual system. Contradictory reports regarding the outcome of short-term monocular deprivation have been published in the past. These studies use different measurement techniques. The first study of my thesis examines and compares the reliability of the most popular psychophysical tests. This study resolves and discusses why different methods show discrepancies. The second and third studies test the magnitude and persistence of neural plasticity in normally sighted adults. The fourth study evaluates whether neural plasticity can benefit in the recovery of binocular vision in adults with amblyopia.

Contribution of Authors

Manuscript 1 Seung Hyun Min, Alex S. Baldwin, Alexandre Reynaud and Robert F. Hess conceived the project. Seung Hyun Min and Ling Gong collected the data at Wenzhou, China. Seung Hyun Min, Alex S. Baldwin and Robert F. Hess analyzed the data. Seung Hyun Min drafted the manuscript. All authors edited the manuscript.

Manuscript 2 Seung Hyun Min, Alex S. Baldwin, Alexandre Reynaud and Robert F. Hess conceived the project. Alex S. Baldwin programmed the experiment. Seung Hyun Min collected and analyzed the data, and drafted the manuscript. All authors edited the manuscript.

Manuscript 3 Seung Hyun Min, Alex S. Baldwin, and Robert F. Hess conceived the project. Alex S. Baldwin programmed the experiment. Seung Hyun Min collected and analyzed the data, and drafted the manuscript. All authors edited the manuscript.

Manuscript 4 Seung Hyun Min, Yiya Chen, Jiawei Zhou and Robert F. Hess conceived the project. Seung Hyun Min and Yiya Chen collected and analyzed the data. Seung Hyun Min drafted the manuscript. All authors edited the manuscript.

Introduction

1.1 Rationale and Objective

In the early 1900s, Santiago Ramon y Cajal, the founder of modern neuroscience, observed that the cell body and branches of neurons could undergo structural changes in the adult brain [63]. His work upended the traditional belief that the adult brain was not malleable. This phenomenon of neuronal change would later be referred to as neural plasticity, a term coined by a Polish neuroscientist Jerzy Konorski. After a few decades, Jerzy Konorski [73] discovered that the neural connections could be strengthened or weakened depending on experience, thereby determining how the brain would respond to a particular stimulus. For instance, after a repeated stimulus presentation, the response to the particular stimulus could be reduced. This reduction would reflect neural plasticity, which could exist at all levels of the brain. It could be found from cellular changes in neurons, such as the sprouting of axons or an explosive release of neurotransmitter in the axon terminal, to the general behavior of animals, such as associating an auditory stimulus with the arrival of food after repeated training. In my thesis, I focus primarily on the neural plasticity of the adult visual system, which is responsible for our ability to encode a narrow range of electromagnetic waves into a representation of the world that brims with color, depth, and life.

My thesis focuses on neural plasticity and binocular vision of human adults. Neural plasticity is the ability of the brain to undergo functional or structural changes substantially. One can test the level of neural plasticity of awake humans without directly

invading the brain. For instance, one can measure the balance between the eyes using a psychophysical test. By showing different but fusible stimuli to each eye, the ability of combining inputs from each eye into a binocular image can be measured. This balance can be perturbed manually. For instance, a few hours of monocular deprivation, which involves depriving one eye of its visual input, has been shown to shift the eye balance in favor of the deprived eye in adults [45, 75]. This disruption is believed to be driven by mechanisms in the primary visual cortex [45, 75, 3, 65, 54]. If the disruption from deprivation is long-lasting and large, then we can infer that a high level of neural plasticity exists. If it is short-lived and small, then we can estimate that the brain has a limited neural plasticity. In the four studies of the thesis, psychophysical tests are used to probe neural plasticity because it is non-invasive.

The objective of my thesis is to expand the field of neural plasticity of adults with the hope of finding means to harness remnant neural plasticity to treat the adult population with amblyopia, a neural disorder that impairs vision. Since researchers have estimated the magnitude of neural plasticity by testing eye dominance and the longevity of its disruption from deprivation, the measurement reliability of each test is crucial. For this reason, the first study sets out to compare and contrast different tests for measuring eye dominance. The subsequent studies estimate the level of neural plasticity in the adult brain using the most reliable test as enlightened by the first study. The second study specifically assesses whether the changes in eye balance can be magnified by increasing the duration of monocular deprivation in normally sighted adults. The third study measures whether the changes can be accumulated across multiple days of deprivation in normal observers. The last study investigates whether changes in neural plasticity can be magnified in the adult population with amblyopia.

First, the thesis begins with a literature review that taps into seminal studies since the 1960s. Then, the main body of the thesis – four studies – follows. Next, findings in the thesis are discussed and contextualized within the literature.

1.2 Neural Plasticity in the Visual System of Animals

1.2.1 Long-Term Monocular Deprivation

The cortical visual system establishes the relative weighting of information coming from both eyes during childhood and eventually enables the viewer to achieve a balanced binocular vision. However, this process of visual experience can be interrupted by a process known as monocular deprivation, which means depriving one eye of its visual information. For instance, one could do so by shutting an animal's eyelid with eye suture [33] early in life, thereby causing the shut eye to be dysfunctional. After a few months (i.e., long-term) of monocular deprivation early in life, vision through that eye becomes blind [71]. There can be two explanations for this blindness. First, the eye itself can be damaged. Second, the brain may have stopped processing the visual information from the previously closed eye because it no longer receives input. Hubel and Wiesel noticed no obvious physical or functional change in the eye (i.e. the retina) [71]. The lateral geniculate nucleus (LGN) displayed an anatomical cell shrinkage [26] but no obvious functional change [41]. However, they observed some significant differences in the anatomy and activity of the primary visual cortex (V1) [72]. Therefore, it seems that changes in the primary visual cortex are responsible for the reduction in visual capacity that follows long-term monocular deprivation.

Whether long-term monocular deprivation directly affects LGN has not been clearly determined for two reasons. First, despite the anatomical shrinkage of cells within LGN that receive input from the deprived eye [26], cellular function seems normal [41]. Second, the LGN receives feedback from the cortex via layer 6, so it is possible that LGN deficits could occur and be of cortical origin. Recent fMRI studies of the LGN in adult amblyopes have identified a functional deficit that is confined to the P-cell layers [29]. There is also recent evidence of binocular responses of both excitatory and inhibitory types in the LGN [18]. This study rebuts the argument that the LGN is strictly monocular and

thereby complicates the picture of how ocular dominance is regulated. Therefore, we cannot say the LGN is not involved in the amblyopic deficit at this stage.

In primates, the classical view is that the visual information remains segregated from the eye to the level of the primary visual cortex. Hubel and Wiesel were able to trace neuronal connections and represent the form of segregation by the autoradiographic technique [71, 70] and fibre straining [40]. The geniculate terminals that receive input from one of the two eyes alternate every 0.5 mm. These alternating bands form the ocular dominance columns in layer 4 of the primary visual cortex. In monkeys with normal visual experience during childhood, the distribution of the ocular dominance columns that received input from each eye is balanced. Although the classical view states that cells in layer 4 of V1 that comprise the ocular dominance columns are monocular, more recent findings suggest that they all have a binocular input to some extent [17] exhibiting both facilitatory and inhibitory binocular interactions.

Hubel and Wiesel reported that, in normal monkeys, the number of cells that respond to each eye was quite similar in layer 4 of the primary visual cortex [32]. The characteristic distribution of cells in the cortex that responds to each eye reflects the balance between the two eyes when processing visual information. However, if long-term monocular deprivation was conducted in monkeys, this balanced distribution in the number of cells was no longer observed [32]. Instead, most cells got activated by the non-deprived eye (i.e., normal eye). In other words, monocular deprivation changed the distribution of cells that respond to visual input in each eye, thereby shifting the eye preference in favor of the non-deprived eye [38]. In fact, most geniculate terminals, which contribute to ocular dominance columns, at layer 4 of the primary visual cortex received input from the non-deprived eye rather than from each of the two eyes in a balanced fashion. In other words, the space that would have been occupied by the terminals that receive input from the deprived eye is replaced by those from the non-deprived eye [34, 38]. Therefore, the distribution of cells, and ocular dominance columns, became skewed in animals

with disrupted visual experience. The number of cells in the ocular dominance columns that received input from the deprived eye decreased, and those from the non-deprived eye increased. Hubel and Wiesel showed this anatomical change by autoradiographically labelling neural connections from the eye to the primary visual cortex [70]. This anatomical change in the distribution of ocular dominance columns resulted in a reduced cortical representation of the information from the deprived eye and therefore a loss of vision in the deprived eye.

In short, long-term monocular deprivation early in life causes a profound permanent change to the vision of the deprived eye. These changes are mainly cortical with a possible direct or indirect involvement of the LGN. They are of a competitive nature, the cortical ground lost by the deprived eye is gained by the non-deprived eye. These changes occur early in cortical processing at the geniculocortical synapse in layer 4 of area V1.

1.2.2 The Concept of a Critical Period

Levay, Wiesel and Hubel [34, 40, 38] found that the earlier the visual experience was disturbed, the more severe the damage in visual functions. In fact, an early monocular deprivation resulted in a most drastic change in eye dominance away from the deprived eye. For instance, the changes in eye dominance in monkeys that were deprived at 10 weeks for 4 months resulted in a larger shift of eye dominance than those at 1 year of age for 1 year [38]. On the other hand, an adult monkey at 6 years old with one eye deprived for 1.5 year showed no shift in eye dominance after deprivation [38]. Thus, if vision is interrupted during adulthood, then no significant change occurs. Similar results have been found in monkeys and cats. For example, there is no anatomical or physiological change in the ocular dominance columns in layer 4 of the primary visual cortex after long-term monocular deprivation during adulthood for cats or monkeys. Therefore, the brain has been found to be specifically susceptible to visual experience early rather than

late in life. Hubel and Wiesel coined the term 'critical period' to describe the period during which the brain is susceptible to visual experience.

By comparing the firing activity [72] and the anatomical structure of the visual cortex [40, 41, 70] before and after monocular deprivation, researchers have found that the largest changes from deprivation are induced during the critical period but not after when the level of plasticity is low. These findings further support the notion that the brain is most susceptible to visual experience early in life but not after the critical period. For example, the firing of neurons in the visual cortex in response to visual input can inform about the state of the visual cortex. After monocular deprivation, the firing rate of cells is decreased in the cortical regions that receive input from the deprived eye [72]. This physiological change indicates a shift in eye dominance in favor of the non-deprived eye. Moreover, the anatomical organization of the visual cortex and its connection to each eye can be traced via an autoradiography technique. By doing so, researchers have successfully quantified the number of cells that respond to visual input from either the deprived or non-deprived eye [31, 34, 70]. Long-term monocular deprivation skews the distribution of cells that receives input from each eye [34, 38]. By using these two techniques, Hubel and Wiesel [33, 71] were able to observe a larger change from deprivation during childhood but not adulthood.

The critical period varies amongst species. For instance, in rodents, the critical period occurs in the first 35 days upon birth [25]. In cats, it can start as early as 3 weeks after birth and end at around 3 months of age [13]. In macaque monkeys, it spans from birth to about a year of age. In humans, the plasticity level peaks at around at the age of 1-2 but remains substantial until the age of 8-9. However, the commonality of all these species is that monocular deprivation causes a maximal shift in the eye balance during the critical period.

Moreover, the critical period is different at each level of the visual pathway. A low visual area simply responds to luminance and contrast, whereas a high visual area can

process a complicated stimulus such as face. To begin with, the retina, which is sensitive to mean luminance and contrast changes, is hardwired at birth and shows no plasticity [58]. LGN show a moderate level of plasticity and has a short critical period [59]. The input layer (layer 4 of V1) of the visual cortex, which is the entry point of the primary visual cortex from LGN, has a shorter critical period than the output layers (layers 2, 3, 5 and 6), which represent the point of exit from the primary visual cortex to higher visual areas. The inferior temporal cortex, which is responsible for processing faces and objects, is one of the higher visual areas and demonstrates a relatively long critical period [55]. Moreover, the temporal cortex projects to the hippocampus, which has been shown to be plastic even in the adult brain [13]. In short, the lower visual areas such as the retina and LGN exhibit a small degree of plasticity, whereas higher visual areas such as the output layers of V1, temporal cortex and hippocampus exhibit a large degree of plasticity which can extend over different time periods depending on the visual area concerned.

The organization of the brain has been revealed to be hierarchical and modular [48]. Hierarchy is also found in the visual system, from the retina to higher visual areas such as the temporal cortex. As previously mentioned, the span of the critical period varies at each level of the visual system. Due to its processing modularity, different visual functions are associated with different sites along the cortical pathway. For this reason, the critical period is also distinct for different visual functions. In other words, some visual functions are simple (i.e., low level), whereas others are more complex (i.e., high level). For example, low level visual functions include direction and orientation selectivity because they are processed monocularly in early cortex. On the other hand, ocular dominance can be categorized as a more high-level visual function because it involves binocular processing. In fact, studies have shown that the critical period for direction and orientation selectivity end earlier than that for ocular dominance in cats and ferrets [10, 36, 14]. These findings support the idea that the critical periods last longer for

visual functions that are processed at a higher level along the cortical pathway [13]. Monocular deprivation can affect various visual functions depending on when it occurs during the critical period [13]. If monocular deprivation/suture is performed before, but not after, 3 months of age in monkeys, the sensitivity of light in dark-adapted state (i.e., scotopic vision) gets diminished. However, it does not if the deprivation occurs later. Furthermore, if deprivation occurs within 6 months of age, it reduces the sensitivity of increments above background at light-adapted state. Moreover, contrast sensitivity for high spatial frequency gets reduced if deprivation occurs within 18 months of age. Lastly, binocular summation can be disturbed even if monocular deprivation is completed within 25 months of age [13]. In sum, since each visual function has a different critical period due to the hierarchical processing of the visual system, the timing of monocular deprivation will determine which functions will be affected.

In summary, the critical period is a length of time when there is a high level of neural plasticity. The critical period at each level of the visual system, and therefore, for each visual function varies. Low visual areas such as the LGN exhibit a low level of plasticity, whereas output layers of V1 exhibit a higher level of plasticity. A low-level visual function such as orientation selectivity also exhibits a short critical period, whereas face recognition (which is processed in the temporal cortex) exhibits a relatively long critical period. Hence, the time when monocular deprivation takes place determines what visual functions will be affected. If an eye is deprived exceptionally early in life, both low- and high-level visual functions will be affected. However, if it occurs relatively late in life, then only the high-level functions will be influenced.

1.2.3 Mechanism of Long-Term Monocular Deprivation

After depriving one eye for a long period of time during the critical period, vision through that eye is permanently lost. Animal studies report that the cause of the blindness lies in changes within the primary visual cortex rather than the eye itself [71]. However, what

underlies the blindness from the deprivation is not simple. There are two possibilities to describe the blindness: (1) disuse of one eye and (2) competition between the eyes. If the disuse of one eye directly causes blindness, binocular deprivation should blind both eyes. However, Blakemore and Sluyter [6] showed that both eyes of binocularly deprived monkeys remained normal. Also, their results indicate that cells in the primary visual cortex fired readily to monocular visual input from each eye; however, very few cells responded to binocular visual input, thereby indicating that binocular function was compromised during binocular deprivation. In addition, Guillery [26] observed that monocular, but not binocular, function of cats remained functional after binocular deprivation. Therefore, competition, rather than disuse, drives the changes in ocular dominance during monocular deprivation in critical period.

In summary, depriving an eye makes it blind due to the loss of relative, rather than absolute, stimulation in cortical cells. The information from the two eyes is competitively combined at the first synapse in layer 4 of area V1. The nature of the functional deficit depends on how early the deprivation occurs and how long it lasts.

1.3 Monocular Deprivation in Humans

1.3.1 Long-Term Monocular Deprivation in Children

Children can be naturally deprived of their entire visual field of one or both eyes by either a congenital cataract or a unilateral ptosis. Congenital cataract refers to a lenticular opacity [27], and ptosis refers to a drooping of the upper eyelid [47]. Both produce monocular deprivation and can cause permanent consequences in the visual system if they occur early in life. However, individuals who do have cataracts or ptosis during adulthood will not be functionally affected. In other words, as long the visual experience early in life is normal, monocular deprivation does not permanently affect the visual function.

From what we have already discussed from the animal literature, monocular deprivation during childhood most likely increases the number of cells in ocular dominance columns for the non-deprived eye and decreases those for the deprived eye [33]. However, the relationship between the number of cells and visual sensitivity for each eye is not simple. Freeman and Bradley [20] suggested that subjects who had been monocularly deprived in childhood exhibited superior to normal vernier acuity for the non-deprived eye. This finding supports the argument that the anatomical gain in cells by the non-deprived eye results in functional benefits. However, two subsequent studies show that the vernier acuity does not improve in the non-deprived after deprivation of the other eye [24, 35]. Therefore, the literature shows that the non-deprived eye does not necessarily gain in function, although the deprived eye certainly loses function.

1.3.2 Long-Term Monocular Deprivation in Adults

Although animal studies show that monocular deprivation perturbs the visual system minimally after the critical period, there have been laboratory studies on the short-term effect of long-term monocular deprivation in human adults.

To begin with, researchers have recorded the changes in the excitability of the cortical regions that receive input from the normal and deprived eye after long-term monocular deprivation. An increase in cortical excitability of the brain for one eye's input is seen as an increased activity of stimulation for that eye. For instance, Tyler and Kaitz [66] recorded visual evoked potentials (VEPs), which are a gross index of cortical excitability, in the normal and dysfunctional eyes of two adults, to study the effect of 9-hour monocular deprivation. They found a significant decrease in the amplitude of VEP response from the deprived eye and a significant increase of the non-deprived eye during the deprivation. Moreover, they observed that deprivation of form information (high spatial frequency content) also increases the response amplitude of the non-deprived eye. This finding suggests a competitive interaction with reciprocal changes in the VEPs from

both eyes. However, the sample size is small (n = 2) and the VEP is a gross potential with a wide spatial resolution (1 cm).

In addition, Transcranial Magnetic Stimulation (TMS) has been used to study the effect of long-term monocular deprivation (i.e., 48 hours) in adult humans [43]. They observed that monocular deprivation for 48 hours reduced the excitability in both hemispheres of the occipital cortex that receive input from the deprived eye. However, this change in excitability was short-lived because it returned to the baseline level of excitability within 3 hours after removal of the deprivation. This study uses a phosphene detection approach which itself is open to criticism. However, the direction of the effect reported was what might have been predicted on the basis of the earlier animal studies where deprivation was within the critical period. The fact that the effects were so short-lived reinforces the notion that neural plasticity is limited in the adult brain to bring about a permanent change after monocular deprivation.

In summary, recent studies show that long-term monocular deprivation (9 to 48 hours) in adults reduces, in the short-term, the cortical response from the deprived eye [43, 66]. These findings agree with the animal studies that indicate either a loss of functional connectivity from the deprived eye after long-term monocular deprivation [33] or an inhibitory interaction between the two eyes after deprivation [49, 56, 62]. This finding is in contrast with those that conclude that the non-deprived eye does not gain in function [24, 35].

Perceptual learning is a process by which the sensory system changes its response level to a stimulus after training [23]. For instance, after perceptual training, one can "learn" to detect a visual stimulus better than before training. Although a specific task is used for a perceptual training protocol, studies show that perceptual learning for a specific task can be generalized to other visual functions [30, 81, 82]. For instance, perceptual training for contrast sensitivity at high spatial frequency improves not only the contrast sensitivity for said frequency but also acuity for letters and gratings [30, 81, 82].

Moreover, a recent study reports that V1 neurons mediate perceptual learning for an orientation identification task in the feline visual system [52]. This indicates that the type of neurons that underlie perceptual learning depend on which visual task is used for training. Since orientation identification is a low-level visual function, it seems that V1 neurons are involved. In addition, monocular deprivation of one eye facilitates perceptual learning of the other (non-deprived) eye [60]. To illustrate, Shibata et al. (2012) conducted a study to measure the influence of long-term monocular deprivation (for three days) on perceptual learning of both deprived and non-deprived eyes in normal adults [60]. They measured contrast detection thresholds, which are the minimum detectable contrast level of the visual stimulus, to assess the detection ability of observers. First, the baseline contrast detection threshold was measured for each eye before deprivation. Then, after 3 days of monocular deprivation, each subject underwent perceptual training for 12 days. On each day of the training, they performed the contrast detection task for each eye. The researchers observed that the performance of the non-deprived eye was significantly better than that of the deprived eye during the early and middle period of the training (12 days). This finding suggests that long-term monocular deprivation of one eye can potentiate the effect of perceptual training for the other (non-deprived eye) in normal adults. Along with the study of Tyler and Kaitz [66], this finding shows that monocular deprivation induces a competitive change of function between the non-deprived and deprived eyes. The direction of the change is again consistent with what we know of monocular deprivation from the animal literature; the deprived eye shows a poorer response.

1.3.3 Short-Term Monocular Deprivation in Adults

Over the past decade, studies have identified a new form of neural plasticity in the visual system of human adults, termed ocular dominance plasticity. The original study of Lunghi et al. [45] shows the influence of short-term monocular deprivation on the

dynamics of binocular rivalry in normal adults. In a binocular rivalry task, each eye is shown an orthogonal sinusoidal grating. Six subjects reported over time the frequency with which they perceived a visual stimulus from the deprived eye, non-deprived eye or a fused visual stimulus from both eyes. The researchers measured the duration of each visual percept before and after short-term monocular deprivation and normalized each subject's response relative to baseline. They observed that the phase duration of the deprived eye significantly increased while that of the non-deprived eye decreased. However, it is important to note that, by the nature of their binocular rivalry task, the finding of a reciprocal change (increase in the deprived eye, decrease in the non-deprived eye) is simply reflecting an imbalance in the binocular rivalry response. Hence, even if the deprived eye alone experiences a change, the result will be reflected in a decrease frequency for one eye and an increased frequency for the other eye. They postulated that the change in sensory eye dominance in favor of the deprived eye could be due to the contrast gain control mechanism, during which the perceived contrast of a visual stimulus for each eye either weakens or strengthens in response to the mean contrast level in the surroundings [22]. This change (functional increase in the deprived eye) is in the opposite direction to that of the loss of visual function in the deprived eye from long-term monocular deprivation during childhood.

As previously noted, binocular rivalry does not directly measure the contribution of each eye in binocular vision. For this reason, Zhou et al. (2013) conducted a similar study using three tasks that were designed to measure the relative contribution from each eye to binocular visual tasks [75]. First, they used binocular phase combination, which measures the perceived binocular phase of a fused percept from two separate visual stimuli of slightly different phases shown to each eye. This task enabled them to measure the relative contribution of each eye in binocular vision. Second, they used a dichoptic global motion coherence task; it measured the motion detection threshold when both eyes were shown motion stimuli at different contrast levels. Finally, they performed a

binocular contrast matching task to directly measure the changes in perceived contrast in both eyes after short-term deprivation. From all these different tasks, they observed that the sensory eye dominance shifted in favor of the deprived eye (150 minutes). By using various visual tasks, they demonstrated that the effect of short-term deprivation could take place at multiple levels of the visual system. However, all these three tasks were relative measures. The study indicates that there is a change in eye balance in favour of the previously deprived eye.

To see whether a reciprocal change occurs in the non-deprived eye's (i.e., a contralateral change) contribution to binocular vision after short-term monocular deprivation, a monocular visual function was tested. Zhou et al. (2013) measured the contrast detection threshold of both deprived and non-deprived eyes after short-term deprivation [75]. They observed that the contrast threshold decreased for the deprived eye, whereas it increased for the non-deprived eye. Moreover, Reynaud et al. (2020) measured the contrast detection threshold of the non-deprived eye while the other was deprived [53] and noticed a gradual increase in the contrast threshold of the non-deprived eye during the short-term deprivation of the other eye. These psychophysical observations indicate that the sensory eye dominance changes in a reciprocal fashion between eyes after short-term deprivation in adults. The deprived eye's contribution becomes stronger and the non-deprived eye's contribution weaker.

A. Amblyopia

Amblyopia, which is a neurodevelopmental disorder, originates from abnormal binocular experience early in life [28, 61, 79], thereby impairing the function of one eye (amblyopic eye) relative to the other eye (fellow eye). There are three types of amblyopia: strabismic, anisometropia and deprivation amblyopia. To begin with, in strabismic amblyopia, the amblyopic eye has a squint. In the central visual system of both eyes, the visual input across eyes becomes mismatched, more so in the central visual field [61] than the periph-

ery. Due to the misalignment, binocular rivalry occurs to prevent diplopia (i.e., double image of a single visual target). The input within the amblyopic eye's central visual field gets strongly suppressed, resulting in abnormal binocular interaction between the eyes. The permanent suppression of the central visual field of the amblyopic eye causes a string of visual disturbances, such as poor monocular visual acuity and poor stereopsis, which characterize amblyopia. Moreover, in anisometropia amblyopia, one eye is blurred. To prevent diplopia, binocular rivalry occurs between the blurred (amblyopic eye) and in focus (fellow eye) visual input. Due to the binocular rivalry in favor of the fellow eye, suppression of the amblyopic eye becomes permanent. However, unlike in strabismic amblyopia, both the central and peripheral visual field get suppressed equally [61]. In deprivation amblyopia, the eye with either a cataract or ptosis gets continually suppressed. The continual inhibition shapes the binocular interaction in favor of the fellow eye permanently. Therefore, one can aim to restore the binocular interaction of the amblyopic visual system and then target the secondary visual consequence, such as visual acuity.

In amblyopes, the eye dominance is not balanced due to the abnormal suppression. To treat amblyopia, an intervention should take place during the critical period but not later [13]. In a typical therapy, the fellow eye is patched for 40-50% of the awake time for months in an attempt to restore the visual acuity of the non-derived (i.e., amblyopic) eye [13, 57]. Moreover, the patching therapy loses its effectiveness after about 10 years of age [21, 64]. This protocol is referred to as "reverse deprivation" in the animal literature because it reverses the effect of monocular deprivation, which causes amblyopia. Studies have shown that reverse deprivation is effective if it done during the critical period in cats and monkeys [6, 38, 5, 12].

Short-term monocular deprivation has also been studied in adults with amblyopia with the hope of re-balancing the binocular inputs. In this case, the amblyopic eye which has the weaker input is patched with the aim to strengthen its contribution to binocular

vision. Zhou et al. (2013) deprived the amblyopic eye of adults with a translucent patch for 150 minutes (i.e., short-term duration) [80]. This is referred to as an inverse patching therapy because in a traditional patching therapy the fellow eye would be deprived rather than the amblyopic eye [6]. Zhou et al (2013) observed that the deprived eye's contribution to binocular vision improved as a result of the period of short-term deprivation [80]. Moreover, the improvement was more significant and long-lasting in amblyopes than that in normal adults. Recently, two clinical studies have been conducted for amblyopic children in which short-term patching (2 hrs) of the amblyopic eye has been conducted every day for 1-2 months [46, 76]. In the study of Lunghi et al. (2019), five amblyopic patients were recruited for six sessions of patching (2h each) the amblyopic eye over 4 weeks [46]. They measured stereo-threshold and visual acuity of the amblyopic eye before and after the inverse patching therapy. They observed a small improvement in visual acuity (gain of 0.06 logMar) of the amblyopic eye and no improvement in stereo-threshold. In addition, Zhou et al. (2019) performed a clinical study in which the amblyopic eye of 18 amblyopes was patched everyday for 2 hrs for 2 months [76]. They reported a significant improvement in the binocular balance as measured with a binocular phase combination task, visual acuity of the amblyopic eye (0.15 logMAR) and stereoacuity. However, the issue with this study is that they did not make measurements throughout the study, so we could not infer the degree to which the benefits accumulated over the 2-month period. Nevertheless, a new therapeutic approach by patching the amblyopic eye has gained traction in recent years.

Bangerter introduced the idea of depriving the amblyopic eye [2]. However, depriving the normal eye became more popular since it improved the visual acuity of the amblyopic eye more [8, 42, 68]. Back then, visual acuity of the amblyopic eye was the primary outcome of interest. However, in light of the recent literature, it seems more appropriate to target the abnormal binocular interaction to treat amblyopia. One approach to redress the imbalance is to patch the amblyopic eye.

B. Mechanism from Psyhophysical Evidence

Short-term monocular deprivation can affect a wide range of visual information. Is a deprivation of all types of visual information necessary to change the sensory eye balance in favor of the deprived eye in adults? By selectively removing different types of visual information, one can assess which type of visual information is critical for maintaining sensory eye balance. Throughout the thesis, I will refer to this change in eye dominance from short-term monocular deprivation as the *patching effect*.

Zhou et al. (2014) selectively removed different types of visual information as a more refined approach to deprivation as opposed to the all-or-none effect of an eye patch [77]. They did this by having the subjects view dichoptic movies where different types of visual information were filtered from the frames of one eye's view over a 2-hr period [77]. They used six subjects who viewed dichoptic movies through head-mount goggles. On different runs they selectively removed orientation, spatial frequency, phase coherence, and contrast to determine which of them were critical for inducing a change in binocular balance in the short term (i.e. the patching effect). They used a binocular combination task to measure the change in contribution that each eye made to binocular perception. During the task, two fusible horizontal sinusoidal gratings of 0.3 cycles per degree (low frequency) of slighting different spatial phase were shown, one to each eye. First, they selectively removed all orientations except for horizontal orientations in the dichoptic movie for one eye as an alternative to short-term monocular deprivation. In other words, since the binocular combination task only showed horizontal gratings, it tested for the sensitivity of the subjects to horizontal information. Since there was no deprivation of horizontal information during the movie viewing, the sensitivity should not have changed if there was orientation selectivity in the patching effect. However, Zhou et al. (2014) observed the patching effect because the eye dominance was shifted in favor of the filtered eye [77]. This finding suggests little or no orientation selectivity in the patching effect. A subsequent study using optical filtering by the same laboratory group corroborates

the initial finding that the patching effect does not show a selectivity to orientation [69].

Next, they examined the role of spatial frequency content in the patching effect. They selectively removed either the low or high spatial frequency content to determine which one had to be removed to replicate the patching effect. They discovered that the removal of high, but not low spatial frequency information is crucial to drive the change in eye dominance in favor of the deprived eye after short-term monocular deprivation.

Moreover, Zhou et al. randomized the phase of the video for one eye while the other eye viewed the movie normally [77]. This disruption of the video which reduced the phase coherence, was performed by scrambling the Fourier phase domain. As a result, information of contours and higher-level spatial shape representations were removed in the filtered eye. However, removal of coherent phase information did not result in inducing the patching effect, suggesting that the image amplitude information is sufficient to maintain a normal interocular balance.

Lastly, Zhou et al. (2013) was able to induce the patching effect by depriving one eye with either an opaque or translucent patch [75]. An opaque patch blocks both the contrast and luminance, whereas a translucent patch reduces only the contrast. Removal of contrast alone was sufficient to produce a patching effect. Subsequently, Zhou et al. (2014) examined the role of contrast for inducing a patching effect [77]. They compared the patching effect across 3 conditions: 1) normal viewing, 2) 60% contrast, and 3) 20% contrast. The largest patching effect was observed when only 20% of contrast remained for one eye in the dichoptic movie stimulus.

In summary, along with the general body of literature, the study of Zhou et al. (2014) elucidates the mechanism of the patching effect and suggests where in the brain it takes place [77]. Studies have shown that the patching effect is a binocular process because the deprived and non-deprived eyes experience a reciprocal change in their functions after short-term deprivation [53, 75]. This suggests that a binocular neural site such as V1 or higher is associated with the patching effect. In addition, the patching effect is not

orientationally selective [69, 77]. Hence, it seems that the neural site for the patching effect is in early visual cortex where cells are binocular but non-orientationally selective, such as 4C-beta of V1 [77]. Lastly, removal of high spatial frequency and contrast is crucial to induce the patching effect. This explains how a translucent patch, which removes form information and contrast but not luminance, can drive a strong patching effect.

C. Contrast Gain vs. Response Gain mechanisms

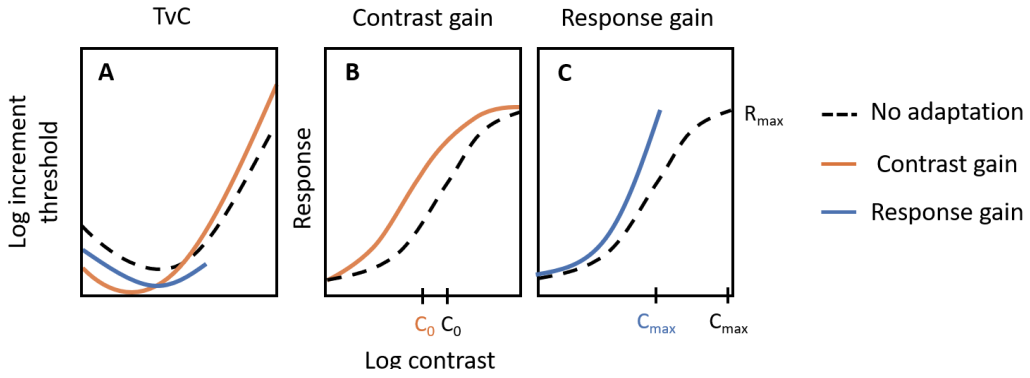

Figure 1.1: **Two possible models of short-term monocular deprivation.** This figure has been modified from Kwon et al. [37]. **(A)** Threshold vs. Contrast function (TvC). **(B)** Contrast response function described by the contrast gain model. **(C)** Contrast response function described by the response gain model.

The original study of Lunghi et al. (2011) shows that short-term monocular deprivation increases the phase duration of the deprived eye using a binocular rivalry paradigm [45]. Lunghi et al. (2011) postulated that the increase in the deprived eye's strength may be attributed to "increasing cortical contrast gain of the deprived eye," which is an attempt to "optimize weak or absent information" occurring as a result of the deprivation [45]. A neuroimaging study [37] supports the premise that contrast deprivation (i.e., contrast adaptation) is driven by an increase in the response gain, which results in an increased neuronal activity/response to a given range of contrast. Both contrast- and

response-gain mechanisms could in principle describe the patching effect, specifically in how the deprived eye gains in function. In this section, we explore each of them in the context of the recent literature.

Contrast gain refers to the level of sensitivity to a range of contrast. Studies have shown that a shift in the mean contrast level in the surroundings can modulate contrast gain [1, 22, 51]. For instance, if the mean contrast level is decreased, the contrast gain increases to maintain an stable level of response at a lower contrast. Conversely, if the mean contrast is increased, the contrast gain decreases. This enables the visual system to maintain its optimal sensitivity to the prevailing contrast level. This shift in contrast gain is known as contrast gain control, which can be graphically represented (see Figure 1.1B). The x-axis is the contrast on log scale, ranging from 0 to C_{max}, where in between resides the mean contrast C_0. At C_0, the contrast response function shows a steep curve because visual system has been designed to be most sensitive to changes around the mean contrast. The y-axis represents the response, ranging from 0 to R_{max}. Hence, the response to the stimulus increases non-linearly as the mean contrast increases. When the mean contrast (C_0) is reduced (orange plot in Figure 1.1B), the contrast response function shifts to the left. This represents an increase in the contrast gain. A situation where the mean contrast decreases is short-term monocular deprivation. Indeed, the deprived eye experiences an increase in the contrast gain as a result of the reduced mean contrast level during deprivation. This has been shown with measurements using binocular rivalry and binocular combination [19, 78] as well as contrast detection tests [53, 75].

However, the contrast sensitivity of the non-deprived eye decreases after short-term monocular deprivation even though the mean contrast level does not change [53, 75]. In addition, Chadnova et al. (2017) also reported a decrease in the electrophysiological response in the non-deprived eye and an increase in the deprived eye [9]. These studies show that the contrast gain change in the deprived eye is not independent to what

occurs in the non-deprived eye. The contrast gain model by Ding et al. (2006) could potentially explain this intriguing effect [16]. In their binocular gain control model, each eye influences two factors: (i) the other eye's signal in proportion to the contrast energy of its own input and (ii) the other eye's contrast gain [16]. In short, when the contrast of stimuli to one eye is high, it has the ability to significantly inhibit the other eye's processing of stimuli. For instance, its signal level and contrast gain are reduced. This interocular (i.e., between the eyes) inhibition may be the source of the reciprocal relationship between the contrast gains across the eyes. Therefore, when the contrast gain of the deprived eye increases, the contrast gain of the non-deprived eye is reciprocally reduced. This interocular inhibition between the eyes, as explained by the reciprocal contrast gain model, can explain why the sensitivity of the non-deprived eye gets worse while that of the deprived eye is improved following short-term deprivation in adults.

Contrast gain changes are usually invoked to explain the phenomenon of contrast adaptation which is a short-term event with a time scale in minutes [1, 51]. On the other hand, short-term patching, which involves contrast deprivation, is often applied for hours [19, 74, 75, 77]. Another difference between contrast adaptation and ocular dominance plasticity (i.e., the patching effect) is that the latter involves, by definition, imbalanced binocular stimulation and for this reason involves reciprocal binocular interactions. For this reason, the more prolonged deprivation associated with ocular dominance plasticity might affect the contrast response function differently to that of short-term contrast adaptation. Thus, a response gain model seems more appropriate for the patching effect. If the contrast gain control is truly what happens during short-term monocular deprivation, then only the mean contrast (C_0) should be changed but not the minimum and maximum contrast (i.e., the range of the x-axis). However, short-term deprivation reduces the contrast, often to zero (opaque patching) for hours, thereby reducing the range of the contrast itself. In fact, after contrast deprivation, the

response-gain model shows that the contrast range is narrowed and that the contrast response function becomes steeper around C_0 (see blue plot in Figure 1.1C). Kwon et al. measured the discrimination threshold of three normal adults and the activity of V1 using fMRI [37]. They found that contrast deprivation improved the sensitivity for contrast discrimination and increased the gain of contrast response function in such a way that it could be described by a response-gain model (Figure 1.1C). However, in their study, both eyes were deprived of contrast; therefore, the experimental design was not identical to that of short-term monocular deprivation, during which one eye's contrast would not be deprived. Nevertheless, this study shows that the response gain model can be a suitable model to describe what occurs during a form of contrast deprivation.

In summary, the current body of literature does not conclusively show whether the contrast- or response-gain models is more apt to describe the process of short-term monocular deprivation. In some respects, the nature of the total deprivation over an extended period is more suited to response-gain explanation where the contrast range has been narrowed. On the other hand, a contrast gain model within the context of the reciprocal network proposed by Ding and Sperling [16] can provide a satisfactory explanation of the reciprocal changes in sensitivity that characterize ocular dominance plasticity. A future study should investigate whether a reciprocal model of response-gain is appropriate to describe the changes in ocular dominance that are associated with short-term monocular deprivation. This could be achieved by measuring the threshold of contrast discrimination in both the deprived and non-deprived eyes (see Figure 1.1A). The plots in Figure 1.1A illustrate the contrast increment threshold (ΔT, y-axis) as a function of baseline (pedestal) contrast (C, x-axis). The functions have a dipper shape [39, 50] where the increment contrast threshold is at its minimum. If contrast gain control solely modulates the patching effect, then we can expect the TvC curve (Threshold vs Contrast) to shift downward and slightly leftward in the deprived eye (orange plot in Figure 1.1A). However, if it is driven by response gain mechanism, then the TvC curve

will shift downward for the deprived eye (blue plot in Figure 1.1A).

D. Mechanism from Physiological Evidence

Psychophysical studies of the effects of short-term monocular deprivation have demonstrated that the sensitivity of the deprived eye increases, whereas that of the non-deprived eye decreases [53, 75]. Moreover, a reciprocal contrast gain model would successfully predict that the gain of the non-deprived eye decreases due to the increased gain of the deprived eye [16]. Besides psychophysics, one can utilize electrophysiology to investigate the inhibitory relationship between the two eyes during short-term monocular deprivation. To illustrate, Lunghi et al. used electroencephalogram (EEG) to record the visual evoked potential (VEP) in the primary visual cortex before and after short-term monocular deprivation [44]. EEG has a spatial resolution of 1 cm and, therefore, can only capture the generalized activity of the cortex [7]. The higher the amplitude of VEP, the higher the excitability of the cortex. The amplitude increased by 66% for the cortical regions associated with the deprived eye and decreased by 29% for the non-deprived eye after short-term deprivation (150 minutes). This reinforces the initial findings from psychophysics that the deprived eye gains in function, whereas the non-deprived loses function. In addition, Zhou et al. also measured the VEP using EEG in the primary visual cortex before and after short-term monocular deprivation (150 minutes) [74]. Although they observed an increase in VEP in the cortical regions that are associated with the deprived eye, they observed no decrease in VEP in regions for the non-deprived eye. The reason that they were not able to observe a contralateral change in the eyes could be due to the poor spatial resolution of EEG. Magnetoencephalography (MEG) has also been used to address this issue. As a more sensitive method of electrophysiology, it has a spatial resolution of 1 mm, which is much finer than that of EEG [7] and a better signal-to-noise ratio. By measuring the frequency-tagged steady state VEP, Chadnova et al. showed an increase in the response in cortical regions for the non-deprived eye

and a decrease for the deprived eye [9]. Their findings confirm the observation from psychophysical studies that the deprived eye gains in its function, whereas the non-deprived eye loses in its function after short-term monocular deprivation. In sum, electrophysiological studies of the human visual cortex corroborate the reciprocal relationship of the sensitivity changes between the two eyes following short-term monocular deprivation (i.e., the patching effect).

Furthermore, functional magnetic resonance imaging (fMRI) technique has been used to study the effect of short-term monocular deprivation in the human brain. fMRI has a fine spatial resolution (1 mm) [7]. Binda et al. (2018) showed that the reassignment of neurons in the ocular dominance column underlies the increase in the response for the deprived eye and decrease for the non-deprived eye [4]. In other words, a population of neurons that originally represents the non-deprived eye is reassigned to the deprived eye during deprivation. However, they observed no shift in ocular preference for those that already prefer the deprived eye before deprivation, thereby maintaining their allegiance to the deprived eye. This neuroimaging study also illustrates the reciprocal change in the function of the two eyes during short-term monocular deprivation.

In addition, there have been studies that investigate the physiological changes in the ocular dominance column during short-term monocular deprivation in monkeys. To begin with, Begum and Tso performed optical imaging experiments (spatial resolution: 1 mm) to monitor the effect of short-term monocular deprivation in V1 ocular dominance columns of macaque monkeys [3]. Intrinsic optical imaging is a non-invasive technique that allows the recording of neural activity by monitoring the blood flow in the brain [67]. They observed an increased response for deprived eye columns and decreased response for non-deprived eye columns in layer 4 of area V1 after deprivation. Moreover, Tso et al (2017) found from single unit recording experiments that the strength of the deprived eye's input increases and that of the non-deprived eye's input decreases in macaque V1 [65]. Furthermore, Reynaud et al. [54] used a voltage-sensitive dye imaging technique,

which has a very fine spatial resolution (< 50 μm) [11], to measure the cortical response of separated, frequency-tagged eye domains following short-term monocular deprivation [54]. They found that the population activity in V1 driven by the undeprived eye is suppressed whereas that driven by the deprived eye is enhanced. This finding confirms the antagonistic relationship between the two eyes inputs in cortex. Lastly, Reynaud et al. (unpublished) have measured the population activity of awake macaque's ocular dominance columns in V1 using functional ultra-sound imaging (FUS), which allows one to measure local changes in the blood flow at a very high resolution (50-200 μm) [15]. They confirmed the reciprocal relationship between the two eyes at the level of the ocular dominance columns in V1. In sum, the physiological studies in non-human primate agree with the physiological results in humans; the relationship between the deprived eye and non-deprived eye seems to be reciprocal and the site of this effect is the ocular dominance columns in V1.

1.4 Summary

Two different types of ocular dominance plasticity exist. One occurs early in the critical period, during which the brain learns to encode visual information from each eye properly and establish sensory eye balance. If an eye is deprived during the critical period, it can become permanently blind while the non-deprived eye does not deteriorate or improve. Another type occurs during adulthood, much later than the critical period. As a result of this type of plasticity, the sensitivity of the deprived eye and its contribution to binocular vision improve, whereas the sensitivity of the non-deprived eye decreases. This reciprocal relationship has been verified in both psychophysical, neuroimaging and electrophysiological studies in both humans and primates. These changes can be potentially explained by either a contrast- or a response-gain model. Short-term monocular deprivation in adulthood provides a method to manipulate the balance of left/right eye contributions to binocular function. This then raises the possibility of implementing

what would be an inverse patching protocol to restore the binocular function of adult amblyopes who have not been successfully treated in childhood whose binocular vision is severely out of balance (amblyopic eye suppressed). However, before one applies the protocol in the clinical setting, one has to answer the following questions, which will be addressed in the subsequent manuscripts.

1. Which test is most reliable to measure sensory eye dominance and its changes after short-term monocular deprivation? (Manuscript 1)

2. Does a longer duration of short-term deprivation induce a larger change in sensory eye dominance in adults, be they normal or amblyopic? (Manuscripts 2 and 4 respectively)

3. Can the changes in eye dominance from short-term deprivation be maintained across days in adults with normal vision? (Manuscript 3)

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Manuscript 1. Ocular Dominance Plasticity: Measurement Reliability and Variability

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2.1 Abstract

In the recent decade, studies have shown that short-term monocular deprivation strengthens the deprived eye's contribution to binocular vision. However, the magnitude of the change in eye dominance after monocular deprivation (i.e., the patching effect) has been found to be different between for different methods and within the same method. There are three possible explanations for the discrepancy. First, the mechanisms underlying the patching effect that are probed by different measurement tasks might exist at different neural sites. Second, the test-retest variability of the same test can produce inconsistent results. Third, the magnitude of the patching effect itself within the same observer can vary across separate days or experimental sessions. To explore these possibilities, we assessed the test-retest reliability of the three most commonly used tasks (binocular rivalry, binocular combination, and dichoptic masking) and the repeatability of the shift in eye dominance after short-term monocular deprivation for each of the task. Two variations for binocular phase combination were used, at one and many contrasts of the stimuli. Also, two variations for dichoptic masking were employed; the orientation of the

mask grating was either horizontal or vertical. So, five different tasks were evaluated. We hoped to resolve some of the inconsistencies reported in the literature concerning this form of visual plasticity. In this study, we also aimed to recommend a measurement method that would allow us to better understand its physiological basis and the underpinning of visual disorders.

2.2 Introduction

In the recent decade, there has been increasing evidence that a new form of temporary binocular plasticity exists in human adults. For instance, patching an eye for a short period strengthens that eye's contribution to binocular vision [14, 30]. This has been demonstrated for a patching duration as short as 15 minutes [12, 21]. Here, we will refer to this neuroplastic change in ocular dominance as a result of short-term monocular deprivation as the patching effect. The patching effect lasts for 30-90 minutes [11, 14, 21]. It can be induced by both opaque and translucent patches, and by dichoptic video presentation [1, 32]. The patching effect has been demonstrated with psychophysical, electrophysiological [13, 29] and neuroimaging [3, 6, 16] studies. The change in sensory eye dominance as a result of short-term patching seems to be reciprocal between the eyes: the contrast gain of the patched eye is enhanced and that of the non-patched eye weakened [6, 30]. In general, studies agree that patching enhances the contribution of the deprived eye to binocular vision. However, the magnitude of the patching effect has been found to be different. For instance, inconsistent results have been found between different methods and within the same method. There are three possible explanations for the discrepancy. First, the patching effect might be a complex phenomenon rather than a change in a single factor (ex. an increase in one eye's input gain). In other words, mechanisms underlying the patching effect that are probed by different measurement tasks might exist at different neural sites. For example, removal of phase information induces the patching effect if it is measured with a binocular rivalry task [1] but not

so with a binocular combination task [1, 32]. Moreover, the patching effect has been shown to be of larger and longer lasting in the chromatic visual pathway than in the achromatic visual pathway if it is measured with binocular rivalry [15] but not so with binocular combination [33]. Furthermore, the site of action is believed to be at an early stage (i.e. striate) in cortical processing by some groups [26, 28, 32] and at a later stage (i.e. extra-striate) by others [1, 12, 25]. Second, the test-retest variability of one method might yield inconsistenct data [11, 17]. Third, the patching effect itself in the same subject might fluctuate across separate days or experimental sessions. This possibility has not been explored in the literature. Some studies have measured the effect of short-term patching for each subject and experimental condition without repeating the entire experiment. This practice assumes that the respective psychophysical methodology is reliable and that the patching effect is consistent across days for each subject. In this study, we question this assumption. We repeat all of our experiments using each task twice on separate days. The test-retest reliability of the three most commonly used tasks (binocular rivalry, binocular combination, and dichoptic masking) and the repeatability of the patching effect for each of the task is evaluated. Two variations for binocular phase combination are used, at one [30] and many contrasts of the stimuli [21]. Also, two variations of the dichoptic masking task are tested, in which the orientation of the mask grating is either horizontal or vertical [2]. This makes five different measurement methods in all. We hope to resolve some of the inconsistencies reported in the literature concerning this form of visual plasticity. We also aim to recommend a measurement method that will allow us to better understand its physiological basis and the underpinning of visual disorders. To do so, we assess four properties of each task:

1. *Baseline reliability*: how well is the baseline performance (i.e., no patching) correlated for each subject between repeated experiments?

2. *Patching effect reliability*: How well is the magnitude of the patching effect corre-

lated for each subject between repeated experiments?

3. *Baseline measurement variability*: What is the expected measurement variability from the task alone, and how does this compare to the overall variability in the baseline conditions?

4. *Patching effect measurement variability*: What is the expected measurement variability from the task alone in the patched conditions, and how does this compare to the overall?

2.3 Materials and Methods

2.3.1 Subjects

We used data from 104 adults (age range = 18-33) with normal or corrected-to-normal vision in this study. Data of 78 subjects have already been reported in publications [2, 21, 11, 20]. For this study alone, we recruited 26 additional subjects. This study adhered to the Declaration of Helsinki and was approved by the Institutional Review Boards at McGill University and Wenzhou Medical University. All subjects provided informed written consent.

Power analysis was not used to determine our sample size because we did not expect to see a statistically significant difference between two repeated experiments. The difference between two experiments could be statistically unsignificant, and yet be just large enough to reduce the replicability of the task. Moreover, we did not introduce the effect of treatment on one of the two groups. Since many laboratory groups have recruited between 10 and 20 subjects for an experimental condition, we decided that 15 subjects per task would be sufficient. For all methods, subjects were trained extensively before they began the actual experiment and repeated the experiment on a separate day (each session separated by 24 hours) at a similar time.

2.3.2 Monocular Deprivation

In all experiments, the dominant eye of all observers was deprived with a translucent patch, which deprived all form information and reduced the luminance by 20%. . The eye dominance was determined by the Miles test [19]. In this test, the subjects were asked to form a peephole with their index finger and the thumb. After placing a visual target within the peephole at arm's length, they alternatively closed each eye. When the dominant eye was closed, the visual target was displaced more within the peephole. For some psychophysical tasks, we tested different patching durations (30, 120 and 150 minutes). Subjects repeated each experiment twice (i.e., two sessions of the same patching duration) on separate days. During patching, subjects browsed the web with either their computer or phone. We were only interested in the immediate patching effect (within 10 minutes), so we did not test the patching effect long after patch removal.

2.3.3 Psychophysical Tasks

In this study, we evaluated five psychophysical tasks. Each task is described in detail in this section. Moreover, we extracted a subset of data from four published studies [2, 21, 11, 20]. We additionally recruited 15 subjects (in all, 26 unique individuals) for three experimental tasks (see Figs. 1-2). In this section, we elaborate on the rationale for the data extraction, the process of data analysis, and the experimental procedure for each psychophysical method.

1. Binocular rivalry

In this method, non-fusible stimuli were shown to the two eyes. The relative strength of each eye was assessed by measuring the length of time for which each eye suppresses the other. Data from 30 subjects were collected for a previous study [11]. We reused the baseline measurements from Finn et al [11]. An additional 15 subjects were then tested as part of the current study. Therefore, data from 45 subjects were included in

the binocular rivalry analysis.

Stimuli In the binocular rivalry task used in the study of Finn et al., (2019), two oblique Gabor patches at $+45°$ and $-45°$ were shown separately to the two eyes. The experiment randomly assigned the two orientation of the Gabor patches to remove orientation bias. They Gabor patches had a spatial frequency of 1.5 c/deg, a spatial sigma of 1.3 degrees of visual angle and a contrast of 50%. Shutter glasses were used for the stimulus presentation. Each test block lasted for 180 seconds. Subjects reported continuously using the keyboard whether they perceived a left oblique grating, right oblique grating, or mixed percept throughout the test.

In the new experiment, two orthogonal Gabor patches (0.46 cycle/deg, $4.33° \times 4.33°$) were dichoptically presented to the two eyes using head-mount goggles (details in the section entitled Apparatus for the New Experiments). The contrast of the Gabor presented on the non-patched eye was fixed at 80%, and that of the Gabor on the eye to be patched was set so that each subject perceived an equal visibility of the Gabor patches between the two eyes. In short, the ratio of the duration between the eyes was close to 1 after adjusting the contrast for the eye to be patched. This contrast was used throughout the experiment on the same day and was individually established for each subject. The contrast was re-established on the second day of the experiment (i.e., second session). Each testing block had two segments of 90-seconds trial. Therefore, a single test block lasted for 180 seconds. In the first segment, the orientation of the Gabor was $-45°$ in the non-patched eye and $+45°$ in the patched eye. In the second segment, the orientation of the Gabor was $+45°$ in the non-patched eye and $-45°$ in the patched eye. Subjects were asked to report continuously using the keyboard whether they perceived a left-, right-tilted or mixed Gabor throughout the test.

Each eye was displayed with one of the two possible orientations of the Gabor patches. Hence, we processed the data by designating the two Gabor gratings at different ori-

entations to each eye's percept (patched or non-patched), and then computed ocular dominance index, which represents sensory eye dominance (see below).

Procedure In the study of Finn et al. [11], the patching effect was measured in two experimental conditions. The goal of the study was to examine whether exercise during patching potentiated the patching effect. Since the experimental conditions were not identical, we could not use the post-patching data for our analysis. However, since the baseline measurements made on the two testing days were identical, we included the baseline data in our analysis (n = 30).

However, since we also wanted to evaluate the repeatability of the patching effect, we tested 15 additional subjects. The subjects first performed the baseline measurement during which the binocular rivalry task was performed four times (Figure 2.1). The binocular rivalry task was interleaved with a binocular combination task (the data from the combination task were not used for analysis due to technical mishap). This was to make the procedure here more comparable with that used to compare two forms of the combination task (as described in the next section). The baseline tests therefore consisted of four experimental blocks of binocular combination and binocular rivalry tasks. After patching for 120 minutes, the subjects were tested again using binocular combination and binocular rivalry for two experimental blocks (two blocks per task).

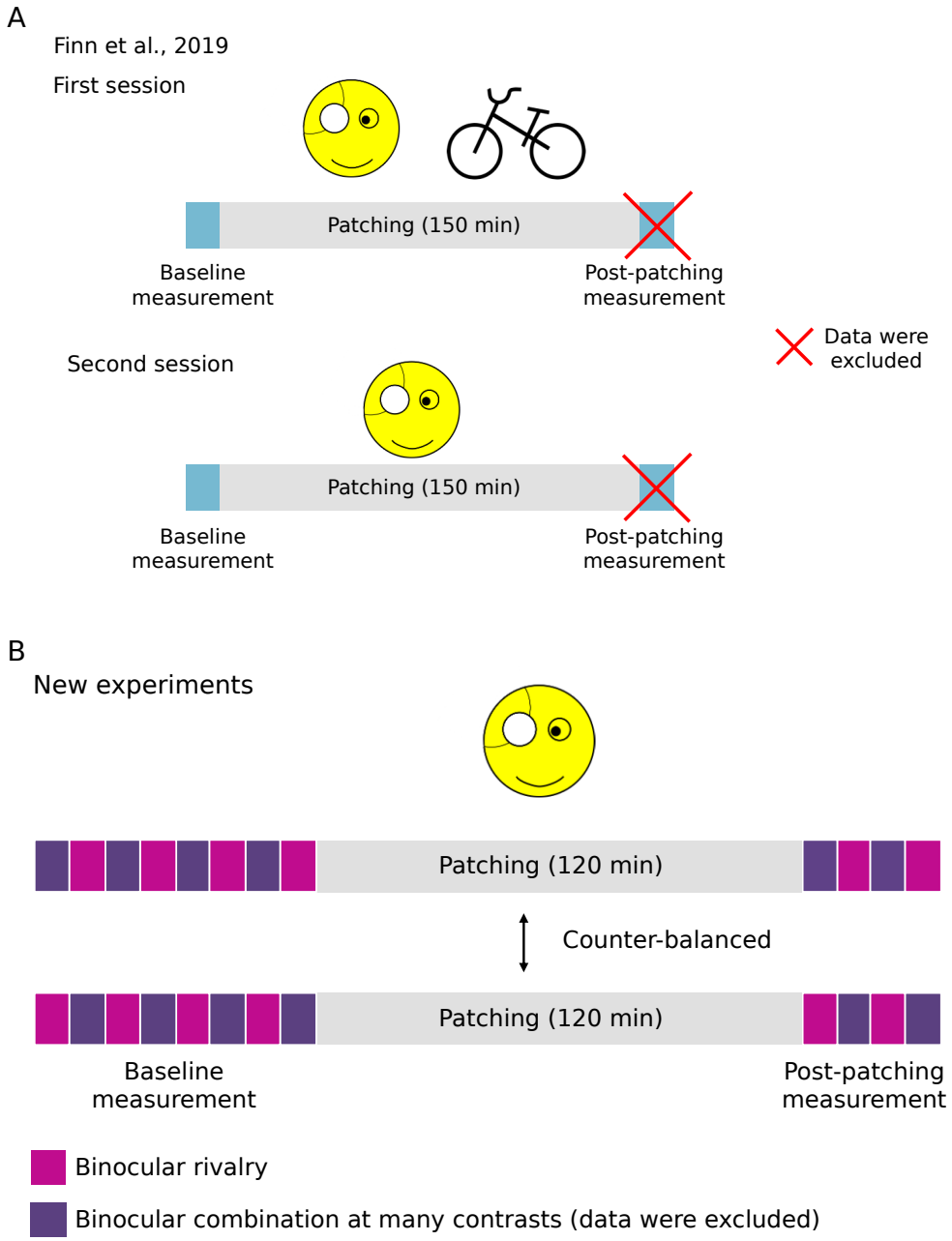

Figure 2.1: **Procedures of experiments using binocular rivalry. (A)** Procedure of the experiment in the study of Finn et al. [11] **(B)** Procedure of the new experiments in our study.

Data Analysis We computed the ocular dominance index (ODI) as follows:

$$ODI = \frac{d_p - d_n}{d_p + d_n + d_m}, \tag{2.1}$$

where d_p, d_n and d_m are the total response durations of the percept perceived by the patched eye, non-patched eye and both eyes (i.e., mixed percept), respectively. When ODI is positive, the total response duration for the percept perceived by the patched eye is longer than that for the non-patched eye's percept. When ODI is negative, the total response duration for the percept perceived by the non-patched eye is longer than that by the patched eye.

2. Binocular phase combination task at one contrast

For this method, 15 subjects were recruited. We had not had any data to extract from previous studies.

Stimuli Two fusible, separate, and horizontal sine-wave gratings (0.46 cycle/°, 4.33° × 4.33°) with equal and opposite phase shifts (+22.5° and −22.5°) relative to the center of the screen were presented to the two eyes. The perceived phase of fused stimuli was 0° if the two eyes contributed equally to binocular fusion (see Figure 2.5). The subjects were asked to locate their perceived middle portion of the dark patch in the fused grating by positioning a flanking 1-pixel reference line. The stimuli were displayed until subjects completed the tasks. The contrast of the stimuli shown to the non-dominant eye (i.e., non-patched eye) was set at 100% for each subject. Moreover, the contrast of the stimuli shown to the dominant eye (i.e., patched eye) was set so that both eyes contributed equally to binocular vision (i.e., binocularly perceived phase = 0). The contrast of the stimuli shown to the non-dominant eye was not uniform across subjects. Therefore, there was only one contrast ratio between the stimuli shown separately to the eyes for every subject.

Procedure As Figure 2.2 shows, the experimental protocol is identical to the interleaved design described in Figure 2.1. The subjects performed baseline measurements with psychophysical tasks of binocular combination at one and multiple contrasts (another variation of binocular phase combination, described later). They completed four test blocks of the two different binocular combination tasks (four blocks per task). Each block lasted for about 3-5 minutes. Then they were patched for 120 minutes. During patching, they performed tasks such as reading and web browsing. After patching, they were tested again using the two methods of binocular combinations for two experimental blocks (Figure 2.2). We randomized the order of the task to be tested and maintained the order across two repeated experiments for each subject.

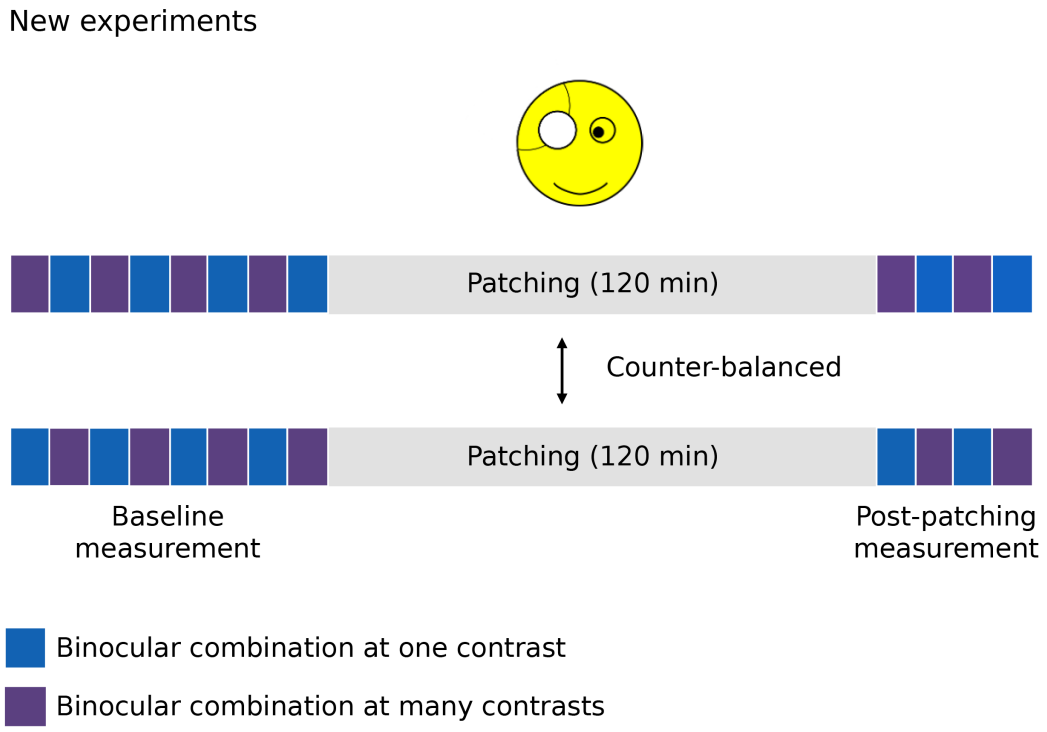

Figure 2.2: **Procedure of the new experiments using, but not limited to, binocular combination at one contrast**

3. Binocular Phase Combination Task at Many Contrasts

Data from 19 subjects were extracted from previous studies [21, 20]. These participants had been patched for 30 or 120 minutes. 15 more subjects were additionally recruited (see Figure 2.2) and were patched for 120 minutes. In sum, there are 34 unique data points.

Stimuli The stimuli were very similar to those in binocular combination at one contrast. Two slightly offset horizontal sinusoidal gratings were presented to the two eyes. The phase difference was 45°: +22.5°) for one eye and −22.5°) for the other eye. If the two eyes contributed equally to binocular vision, the fused phase percept appeared as exactly the average of the two gratings phases. This was equivalent to the perceived phase of zero (see Figure 2.5).

The interocular contrast ratio between the eyes was changed by increasing the contrast of one eye's stimulus while decreasing the contrast of the other eye's stimulus (see Figure 2.1). Then, the interocular contrast ratio at a perceived phase of 0 degrees was estimated using a contrast gain model [10]. By comparing the binocular balance before and after patching, we calculated the shift in ocular dominance.

We set five interocular contrast ratios ($1/2$, $1/\sqrt{2}$, 1, $\sqrt{2}$, 2) for baseline measurement, and three for post-patching measurement ($1/\sqrt{2}$, 1, $\sqrt{2}$). TA baseline test book took about 5 minutes to complete, whereas the post-patching test block took 3 minutes. On the other hand, in the binocular phase combination at one contrast task (Section 2), only a single ratio (i.e., 1) was used.

Procedure From two previous studies [21, 20], we extracted data of 19 subjects who had been patched for two patching durations (30 and 120 minutes). We discarded remaining data of the participants who had been patched for other durations (from Min et al. [21]) in order for us to not violate the assumption of independence. That is, each

data point could only be used once in data analysis. Prior to patching, the subjects performed the baseline experiments (see Fig. 2.3). After patching for an assigned duration, they completed post-patching experiments at several timepoints between 0 to 48 or 96 minutes after patching. All subjects repeated the experiment twice. Therefore, we were able to include data from baseline and post-patching assessments to evaluate the test-retest repeatability of the task. We only extracted post-patching data at the first three measured post-patching timepoints (0 to 6 minutes) and averaged the values.

As described in Section 3.2.2, we tested 15 more subjects to directly compare the test-retest repeatability between the two variations of binocular phase combination. Data had been first collected previously in the procedure described in Section 3.1.1 (Fig. 2.1). We had first designed the experiment to directly compare between binocular rivalry and combinations at multiple contrasts. However, due to the improper display of the gratings for binocular combination that we found out after we had finished collecting the data, we decided to discard the data of binocular combination and keep those of binocular rivalry. After resolving the screen issue, we decided to maintain a comparable task design by interleaving two different tasks in the same manner as the procedure described in Section 3.1.1 (Fig. 2.1). Therefore, we included a binocular phase combination at one contrast, and interleaved it with binocular phase combination at many contrasts (Fig. 2.2).

Data Analysis We averaged the perceived phases across two configurations from each subject. We then fitted these means of perceived phases into a contrast gain control model introduced by Ding and Sperling [10]:

$$\phi_A = 2\tan^{-1}\left[\frac{f(\alpha,\beta,\gamma)-\delta^{1+\gamma}}{f(\alpha,\beta,\gamma)+\delta^{1+\gamma}}\tan(\frac{\theta}{2})\right], \tag{2.2}$$

ϕ_A = perceived phase from the fused percept of two stimuli, α = gain factor which determines the contrast balance ratio when both eyes contribute equally to binocular vision, γ = slope of the function when both eyes contribute equally to binocular vision,

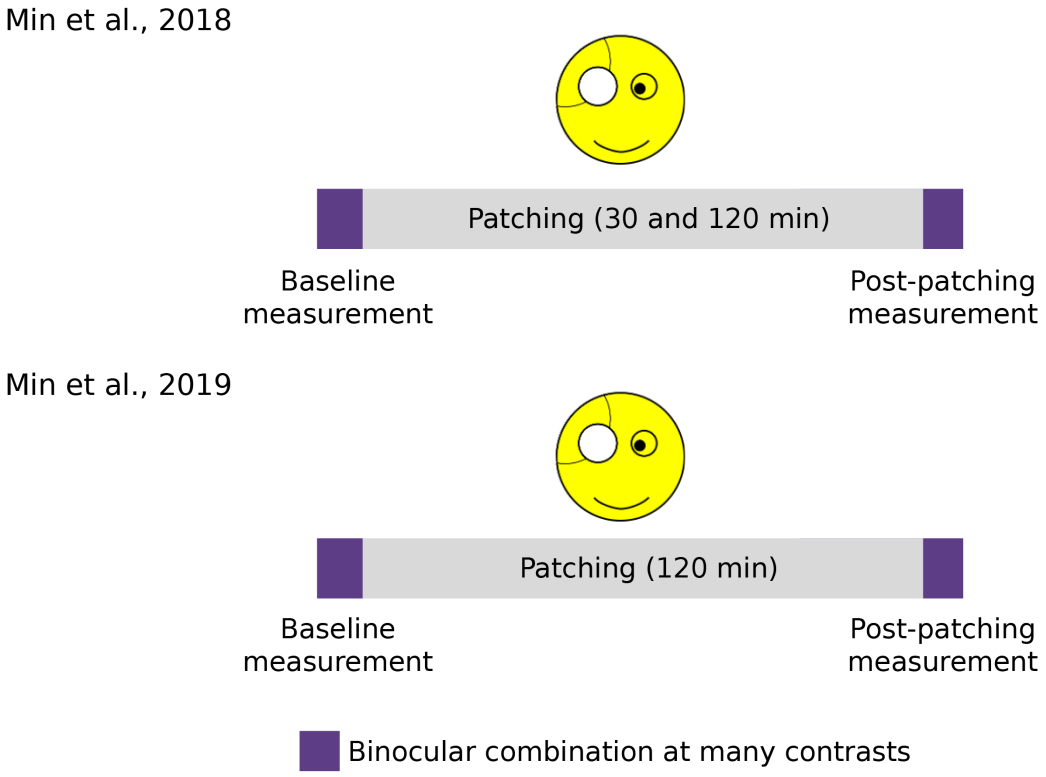

Figure 2.3: **Procedure of experiments using binocular combination at many contrasts.**

θ = fixed phase displacement between eyes (45°), δ = interocular contrast balance ratio. After we fitted our data to the contrast gain model function [10], we estimated the two free parameters α and γ. We bootstrapped responses trial-to-trial and generated each measurement's sample of α values to generate standard errors for each data point.

α was transformed into log scale as following:

$$\alpha_{dB} = 20 \times log_{10}(\alpha_{ratio}), \tag{2.3}$$

where

$$\alpha_{ratio} = \frac{\alpha_{DE}}{\alpha_{NDE}}, \tag{2.4}$$

α_{ratio} = contrast balance ratio when both eyes contribute equally to binocular vision

in linear scale, $\alpha_{dB} = \alpha_{ratio}$ in log scale. When the contrast shown to the dominant eye is twice as strong as the non-dominant to reach the balance point ($\alpha_{DE} = 2\alpha_{NDE}$), then $\alpha_{ratio} = 2$, thereby resulting in $\alpha_{dB} = 6dB$. We converted α_{ratio} into α_{dB} to avoid bias for the dominant eye when we quantify binocular balance. We normalized the contrast balance ratios by calculating for the differences in contrast balance ratios between baseline and after patching (dB). Therefore, when Δ contrast balance ratio = 0, it represents no change after patching. While a positive Δ contrast balance ratio indicates the shifting of ocular dominance favors the dominance eye (the patched eye).

4. Parallel- and Cross-Oriented Dichoptic Masking Task

Data of 14 subjects were extracted from a previous study [2]. No additional subjects were tested.

Stimuli One sinusoidal grating of 0.5 c/deg was presented to each eye. Gratings were presented in a circular raised-cosine envelope. The diameter was 5 degrees of visual angle. The temporal envelope for presenting the gratings was a Gabor (temporal frequency of 2 Hz, duration sigma 500 ms). The contrast in log units (dB) was computed as:

$$c_{dB} = 20 \times log_{10}(c_{\%}), \tag{2.5}$$

A contrast of 1% translates to 0 dB. A twofold threshold elevation from masking gives a 6 dB difference between detection thresholds with and without the mask.

The experiment used a two-interval forced choice procedure. Contrast detection thresholds were measured under three conditions: i) monocularly in the eye to be patched (no mask), ii) monocularly in the eye to be patched with a dichoptic mask grating shown to the other eye that had the same orientation as the target (parallel), iii) similar to ii), but with the mask having an orthogonal orientation (if the left eye's grating were 45°, the right eye's grating would be −45°). The mask contrast was fixed at 4%. When

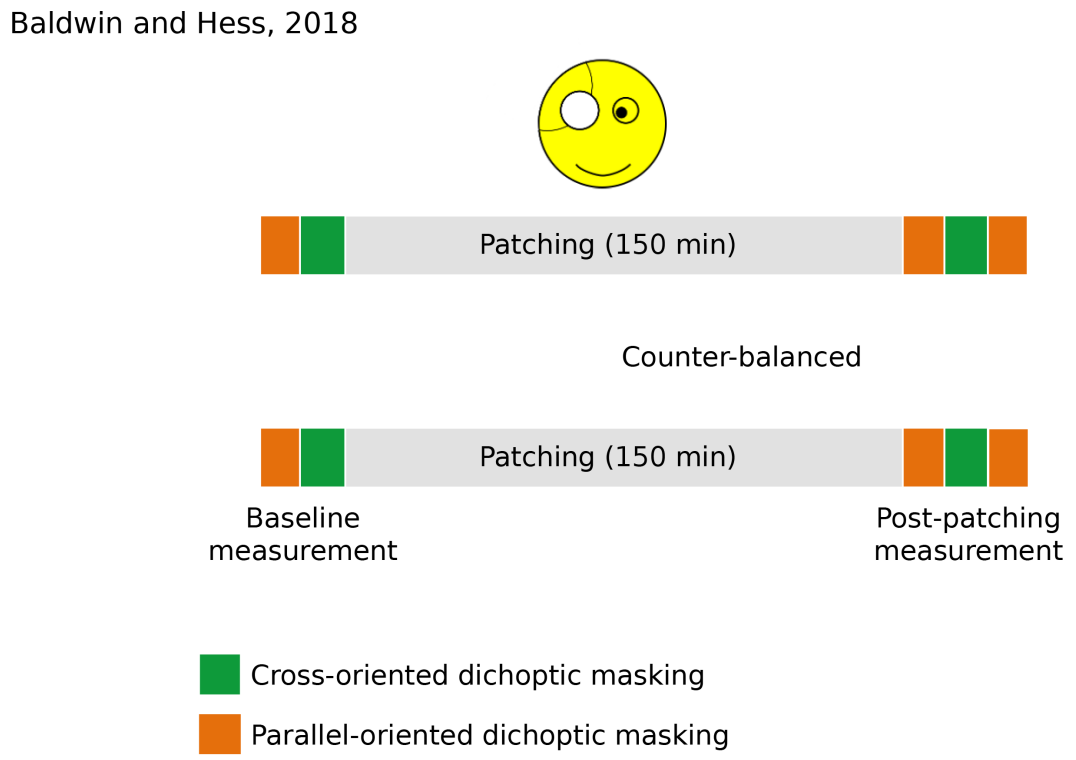

Figure 2.4: **Procedure of experiments using dichoptic masking.** The figure has been adapted from the previous study by Baldwin and Hess [2]

a mask was shown, it would be presented to the non-patched eye in both intervals. In only one of the intervals, the target grating would be shown (to the patched eye). The subject reported the interval (first or second) in which the target grating was presented.

During baseline measurement, we measured the detection threshold of the patched eye and that of the patched eye when the mask grating was shown to the non-patched eye (i.e., masked threshold) in two different orientations (parallel and cross). Then the dominant eye was patched for 150 minutes. After patch removal, subjects were asked to immediately perform three blocks of post-patching measurements. The post-patch tests included three test blocks and measured masked threshold of the patched eye. The sequence of one testing block was either parallel-cross-parallel or cross-parallel-cross for the mask orientation. Each testing block lasted for about 5 minutes. All subjects com-

pleted both sequences in a randomized order across the two repeated experiments. The sequence order of the post-test was counterbalanced because the shift in eye dominance after patching would decay over time.

2.3.4 Apparatus for the New Experiments

For our new experiments, we measured changes in eye balance after patching using binocular rivalry, binocular combination at one contrast, and binocular combination at many contrasts. We set up the tasks in MATLAB 2012a using PsychToolBox 3.0.9 [24]. We presented the stimuli on a Mac computer with gamma-corrected head mounted goggles (NED Optics Groove pro, OLED). They had a refresh rate of 60 Hz and resolution of 1920 x 1080 to the screen for each eye. The maximum luminance of the goggles was 150 cd/m^2.

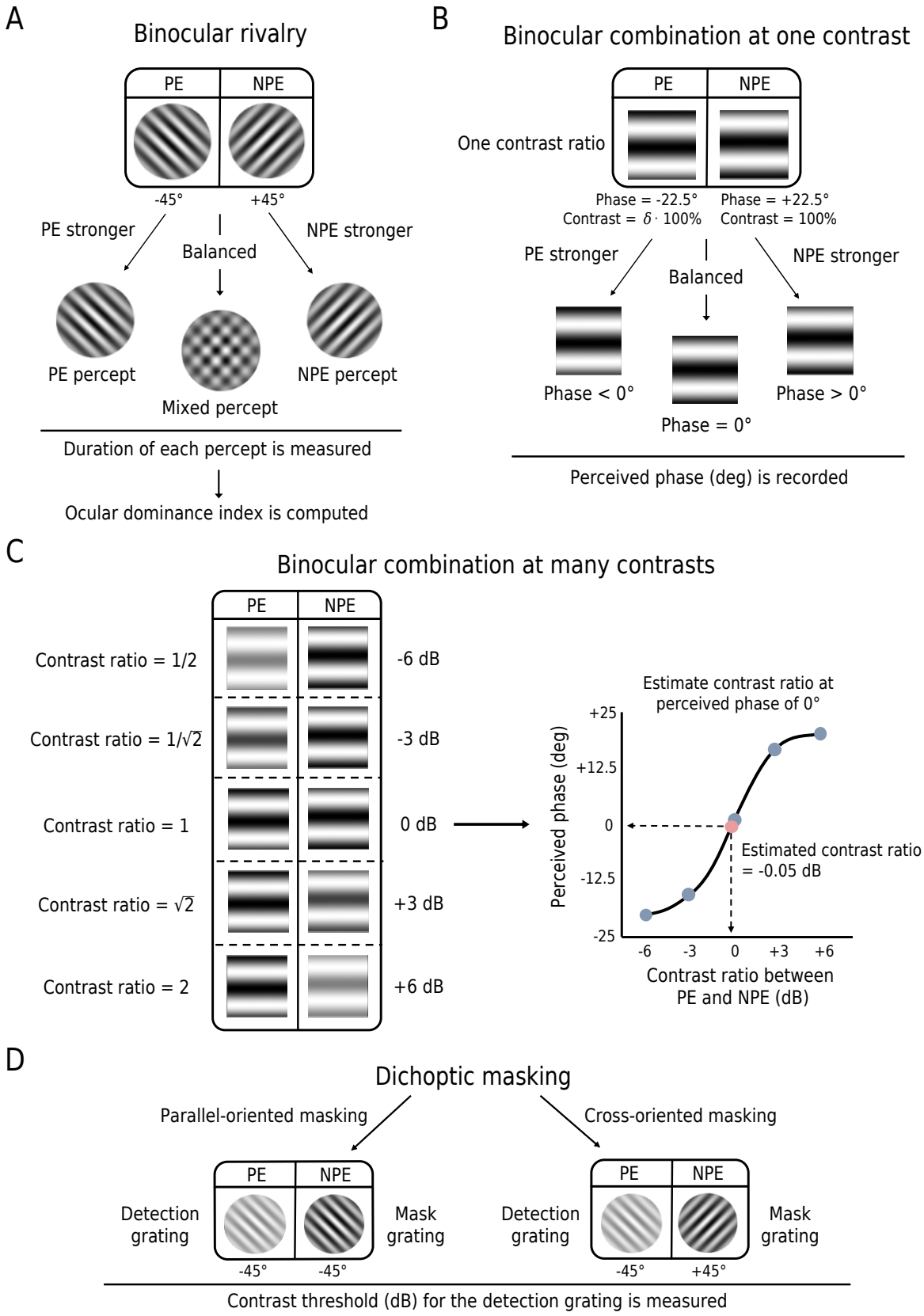

Figure 2.5: Stimuli in all five psychophysical tasks

(A) Binocular rivalry. Two gratings in different orientations were shown separately to both eyes. When the patched eye was dominant, the grating shown to the patched eye would dominate the conscious visual awareness. **(B)** Binocular phase combination at one contrast. Two fusible gratings were shown dichoptically. Subjects were asked to locate using the keyboard the center of the darkest strip within the middle segment of the fused grating. **(C)** Binocular combination at many contrasts. Two fusible gratings were shown separately to both eyes. Subjects were asked to locate using the keyboard the center of the darkest strip within the middle segment of the fused grating. Five contrast ratios were tested for baseline. Three contrast ratios were used for post-patching measurement. **(D)** Dichoptic masking. The subjects were asked to detect in which of two intervals the detection grating appeared. Two types of dichoptic mask were used. The parallel mask had the same orientation as the target. The cross-oriented mask had an orthogonal orientation.

2.3.5 Apparatus in the Previous Studies

Binocular rivalry (Finn et al., 2019)

During the rivalry task, the gratings were displayed on a projector screen at 2.3 m from the subjects by an Optoma HD26 DLP projector. The subjects wore a pair of Optoma ZD302 DLP Link Active Shutter 3-D glasses so that the gratings would be displayed dichoptically. For every degree of visual angle, there was 75 pixels in the resolution of the projector. The mean luminance of the screen was set at 95 cd/m^2. The experiment was set up in MATLAB and PsychToolBox [24].

Binocular combination task at many contrasts (Min et al., 2018; Min et al., 2019)

The gratings were displayed dichoptically using head-mount goggles with a refresh rate of 60 Hz, resolution of 800 $\times$ 600 pixels and a mean luminance of 59 cd/m^2. For all

subjects tested in Min et al. (2018) and for five of the 10 subjects tested in Min et al. (2019), the stimuli were displayed through the eMargin Z800 pro goggles. However, due to the equipment failure, GOOVIS Cinego G2 goggles were used for the remaining five subjects. These goggles had a resolution of 1920 x 1080 pixels, a refresh rate of 60 Hz and a mean luminance of 60 cd/m^2.

Dichoptic masking tasks (Baldwin and Hess, 2018)

The detection and mask gratings were displayed on a gamma-corrected Clinton Monoray CRT monitor with a resolution of 800 × 600 pixels and a refresh rate of 150 Hz. The subjects completed the task at a viewing distance of 70 cm. There were 27 pixels per degree of visual angle at this viewing distance. To dichoptically display the stimulus, a ViSaGe (Cambridge Research Systems Ltd., Kent, UK) was implemented using FE-1 ferro-electric shutter goggles. The goggles had a refresh rate of 75 Hz.

2.3.6 Standardized Data Analysis

Data were analyzed using R and Python. Since the five methods have different units, we standardized the raw data into z-score for each dataset. For instance, z-score was computed for the dataset of the first session using binocular rivalry for baseline measurement. A z-score of 0 would indicate data that are identical to the mean of the particular dataset (such as our example here). A z-score of 1 would denote that a particular datum is 1 standard deviation away from the mean of a particular dataset. The z-score was calculated with this formula:

$$z = \frac{x - \mu}{\sigma} \tag{2.6}$$

where x is the raw data, μ is the mean of the sample, σ is the standard deviation of the sample. The results from each task are analysed in a similar way. Below we describe each column of our figures in Results (Figures 2.6 and 2.7).

Column (i): Baseline and Patching Effect Reliabilities

To assess test-retest repeatability, Pearson's correlation was calculated using raw data. A strong correlation indicates that a subject's performance from the first experimental session is a good predictor of that in the second session. In this column, figures also show the conversion of raw data into z-scores. Correlation, however, does not guarantee replicability of data. A few extreme points can determine the fate of a correlation. Also, when the means of two samples are significantly different, the data from these samples can still have a strong correlation. Therefore, a strong correlation (r ¿ 0.7) does not directly signify that the test-retest replicability is superior. Column (ii) aims to address the inadequacy of correlation.

Column (ii): Baseline and Patching Effect Measurement Variabilities

Since correlation is not sufficient to test for replicability, Bland-Altman plots are plotted in Column (ii) with the z-score. They illustrate the measurement variability (i.e., test-retest replicability) of either baseline or the patching effect. The y-axis is the difference between the z-scores from the first and second experiments (i.e., sessions). The x-axis is the mean z-score across the two sessions. The mean difference of z-score between the two days (across subjects) is indicated by the central horizontal dashed line. 95% limits of agreement are shown by the upper- and lower-dashed lines; they represent the range within which the difference is most likely to fall for most observers. The wider the limits of agreement, the larger the measurement variability between the tasks. The mean difference (i.e., middle-dashed line) is always set to 0 because all the raw data are converted to z-score. Mathematically, the mean of z-scores from one sample has to be 0. Hence, the mean difference of z-scores between two samples also has to be 0.

Two experimental sessions were separated by at least 24 hours. So, we reasoned that the variability indicated by the outer dashed lines can arise from various factors. The first of these could be the measurement error from the task design and testing

procedure. The second could be the day-to-day variability in the measured physiological mechanism. In our case, the former was of more interest. For this reason, we estimated the first of these factors by computing the expected standard error that arose from only the psychophysical task of interest. To obtain the representative standard error for each task, the median of the standard error from each testing block of the task was obtained either directly from testing (binocular phase combination at one contrast) or estimated by bootstrapping. This was the standard error for a single measure. However, as the Bland Altman plots analyse the difference between two measurements the standard errors of both needed to be accounted for. Sp, we scaled the single standard error by multiplying it by $\sqrt{2}$. To convert this "difference standard error" to a 95% confidence interval, we multiplied it by 1.96. In short, we calculated the range between the mean of the differences between the two sessions and the expected 95% confidence interval from the measurements. Finally, this was scaled into the z-scores since Bland-Altman plots were plotted in z-scores. We subsequently shaded this range in grey (see Figures 2.6 and 2.7). This shaded grey region represents the expected measurement variability from the psychophysical task itself. In short, the narrower the grey region, the better the test-retest replicability of the test. If the range enclosed by the dashed lines indicating the limits of agreement is wider than the shaded region (i.e., measurement variability), then an additional source of variability beyond the measurement alone exists.

Column (iii): Baseline and Patching Effect Correlations

Finally, whether the performance of a single subject across experimental sessions was significantly more correlated than a mismatched pair of subjects was evaluated. To do so, the correlation coefficient was computed from two samples. The first sample was the first session of all subjects (i.e., orderly sample) and the second sample was a randomly sampled data from the second session of all subjects. The resampling of the second sample created a mismatched pair of subjects. If these samples are correlated, then the

mismatch will destroy their linear relationship. The second sample was resampled 1000 times, so we were able to compute 1000 correlation coefficients, most of which had a weak linear relationship. The histogram (i.e., distribution) of the correlation coefficients from random sampling is plotted in Column (iii) from Figures 2.6 and 2.7. Also, the actual correlation coefficient from Column (i) is marked in the histogram. If the actual correlation is robust, then the correlation coefficient will be located in the outer edge of the histogram. However, if the correlation is weak, then the correlation coefficient will reside within the middle of the histogram.

2.4 Results

To assess the test-retest variability of the psychophysical tasks, we incorporated data from baseline measurement into our data analysis. Each subject performed two experimental sessions that were separated by at least 24 hours.

2.4.1 Baseline measurement

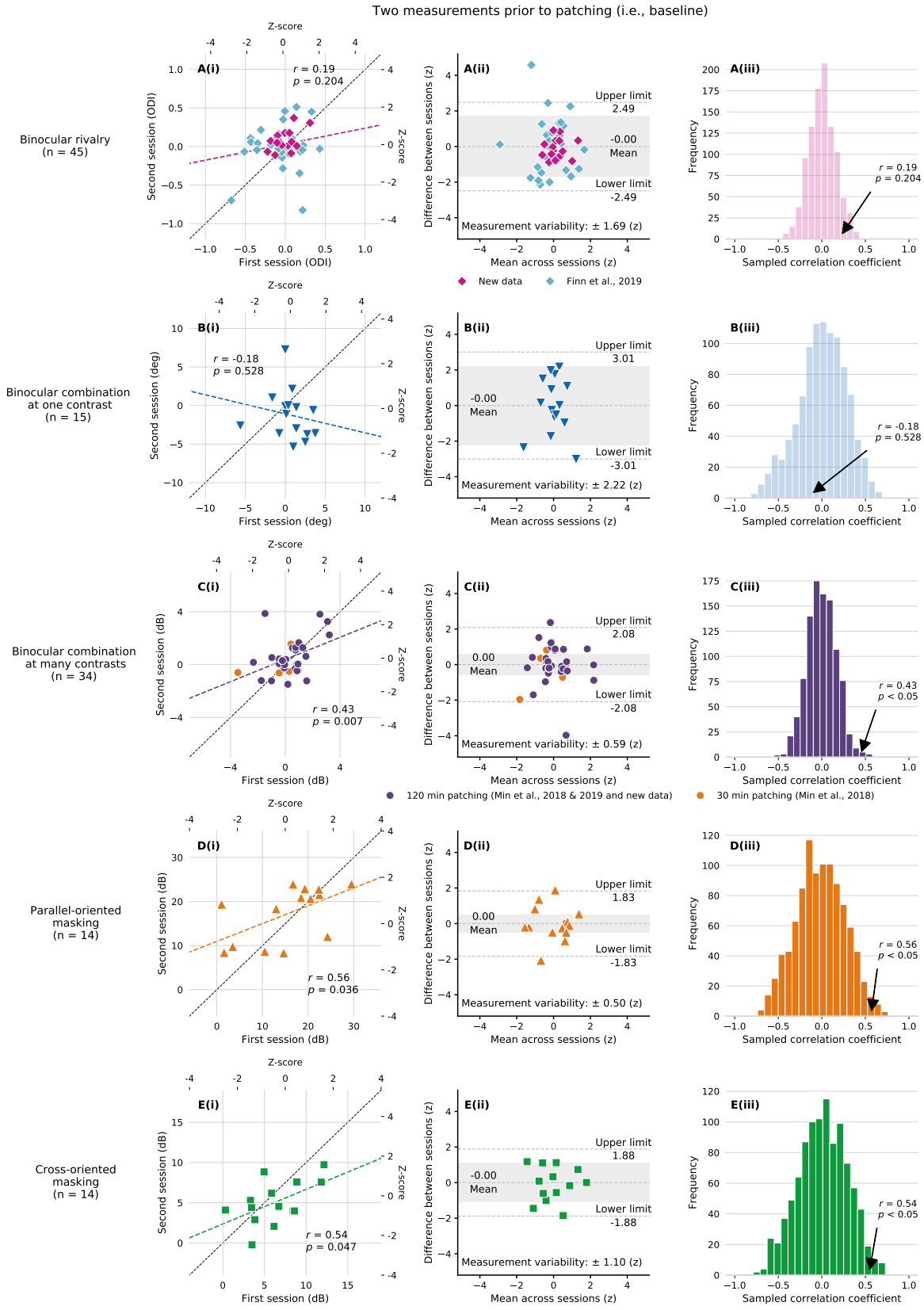

Figure 2.6: Evaluation of baseline measurement (i.e., no patching) with the five psychophysical task variations.

Figure 2.6: **Evaluation of baseline measurement (i.e., no patching) using the five psychophysical tasks.** This figure is divided into five rows (task) and three columns (as described in the Standardized Data Analysis section). Row **(A) Binocular rivalry.** Pink points represent data from the new experiments, blue points from the study of Finn et al. (2019). Row **(B) Binocular phase combination at one contrast.** Row **(C) Binocular phase combination at many contrasts.** Different durations of patching are represented in different colors. Row **(D) Parallel-oriented dichoptic masking.** Row **(E) Cross-oriented dichoptic masking.** Column **(i) Baseline reliability.** The x-axis represents results (e.g., ocular dominance index from binocular rivalry) from the first experiment session, and the y-axis denotes results from the second session. The secondary x- and y-axes represent z-scores from the raw data of ocular dominance index. The black dashed line represents the line of equality (1st session = 2nd session) and has a slope of 1. The colored dashed line represents the regression line from Pearson's correlation test. Each diamond represents a data point of one subject. Column **(ii) Baseline measurement variability** in a Bland-Altman plot. Difference in z-scores between the first and second session is plotted as a function of the mean of z-scores across two sessions. The outer horizontal dashed lines indicate 95% limits of agreement. The dashed line in the middle indicates the mean difference of z-scores across the subjects. The gray shaded region within the limits of agreement represents measurement variability of baseline (i.e., the testing variability stemming from only the binocular rivalry task). The unshaded regions within the limits of agreement represent test-retest variability from external factors beside the task itself. Column **(iii) Baseline reliability** illustrated in a histogram. The sampled reliability coefficients are plotted as a histogram, where the y-axis represents the frequency and the x-axis the sampled correlation coefficient ranging from -1 to 1. The single line value represents the within-subject correlation and this is compared to the distribution of between-subjects correlations.

1. Binocular Rivalry

For a typical measurement of binocular rivalry, the ocular dominance index (ODI) indicates the relative length of the percepts (patched or non-patched eye) shown separately to both eyes during one test block.

Pearson's correlation was calculated to assess whether the baseline performance of a subject in one day was correlated to that of the same subject from another day. The correlation was not significant (n = 45, r = 0.19, p = 0.204, see Figure 2.6A(i)). Next, the raw data of ocular dominance index were converted into the z-score for standardization.

First, we investigated whether binocular rivalry is a reliable tool to study ocular dominance plasticity. To begin with, Pearson's correlation was calculated to assess whether the baseline performance of a subject in one day is correlated to that of the same subject from another day. The correlation was not significant (n = 45, r = 0.19, p = 0.204, see Figure 2.6A(i)). Next, the raw data of ocular dominance index were converted into z-scores. All points except one seem to reside within the range of z-scores ± 1. This indicates that most points are within 1 standard deviation from the mean of the dataset for each session.

To see if there was a good agreement between the two experimental sessions, we created a Bland-Altman plot. Figure 2.6A(ii) indicates that the 95% limits of agreement are ± 2.49 (z-scores). The limits of agreement (dashed lines) represent the test-retest variability that originate from multiple factors, such as day-to-day variability between the two experimental sessions and the variability from the psychophysical measurement itself. Therefore, we computed the measurement variability of binocular rivalry, which is the median of the bootstrapped standard errors for each test block from baseline measurement. This range, which is shown as a grey shaded area in Figure 2.6B(ii), is ± 1.69 (z-scores). Most area within the limits of agreement (i.e., dashed lines) is taken up by the shaded region. This suggests that most of the test-retest variability originates from the binocular rivalry measurement itself rather than the variability from

physiological factors.

One might be concerned about the noticeable difference in the spread of the points between the data from Finn et al. (light-blue diamonds) and our more recent data (pink diamonds; see Figure 2.6A(i)) and in the spread of the mean difference from the Bland-Altman plot (Figure 2.6A(ii)). The correlation of the data from our new data is robust (n = 15, r = 0.52, p = 0.043). However, two samples can have a strong correlation even if their means are significantly different. For this reason, the measurement variability is more representative of replicability than correlation. The measurement variability (grey area) of the data from Finn et al. alone is comparable (± 1.72 z-scores) to that of the combined (Finn et al. + new data) baseline dataset (± 1.69 z-scores). Even if the new dataset has a robust correlation, the measurement variability for each testing block is still large.

Lastly, we evaluated whether the performance of a subject from the first experimental session was more correlated to that same subject's performance from the second experimental session rather than that from another, randomly selected subject. The distribution of the 1000 sampled correlation coefficients is plotted in the histogram (see Figure 2.6A(iii). As we expected from Figure 2.6A(i), the correlation between the performance scores in both experimental sessions is weak. So, the correlation coefficient from Figure 2.6A(i) resides close the middle of the histogram. Our histogram indicates that the test-retest difference is so large that there is little to be gain from using a within-subject protocol to make comparisons.

2. Binocular Combination at One Contrast

In this task, a phase of 0 degree indicates that both eyes are contributing equally to binocular vision. Pearson's correlation revealed a weak correlation (n = 15, r = -0.18, p = 0.528) for the baseline data from the binocular combination task at one contrast.

The Bland-Altman plot (Figure 2.6B(ii)) shows that the limits of agreement are ±

3.01 (z-scores). The measurement variability expected only from the task (grey region) is ± 2.22 (z-scores). Since the shaded area makes up most of the area within the limits of agreement (dashed lines), most of the test-retest variability originates from the task measurement variability rather than from other factors.

The sampled correlation coefficients are plotted in histogram (Figure 2.6B(iii)). The weak correlation coefficient obtained from Figure 2.6B(i) resides in the middle of the histogram. This suggests the test-retest difference is so considerable that within-subject designs offer little, if any, advantage.

3. Binocular Combination at Many Contrasts

In this task, 0 dB indicates that both eyes contribute equally to binocular vision. This task is different from binocular phase combination task at one contrast because it makes measurements at multiple contrast ratios and calculates the shift in ocular dominance using a model.

Pearson's correlation (see Figure 2.6C(i)) revealed a significant correlation ($n = 34$, $r = 0.435$, $p = 0.0072$). The Bland-Altman plot (Figure 2.6C(ii)) indicates that the limits of agreement are ± 2.08 (z-scores). The measurement variability (grey shaded area) from the task itself is ± 0.59 (z-scores). The shaded area only represents a small fraction of the area within the limits, suggesting that most of the test-retest variability originates from external factors such as day-to-day variability in physiological mechanisms.

Lastly, the sampled correlation coefficients are plotted in a histogram (Figure 2.6C(iii)). As observed in Figure 2.6C(i), the correlation between the performance scores in both experimental sessions is robust. This is confirmed in Figure 2.6C(iii) where the correlation coefficient obtained from Figure 2.6C(i) resides in the outer edge of the histogram. This suggests there is much to be gained from using within-subject testing protocols.

4. Parallel-Oriented Dichoptic Masking

Pearson's correlation test revealed a significant correlation (n = 14, r = 0.56, p ¡ 0.05; Figure 2.6D(i)). A Bland-Altman plot (Figure 2.6D(ii)) shows that the limits of agreement are ± 1.83 (z-scores). The measurement variability (grey shaded area in Figure 2.6D(ii)) is ± 0.50 (z-scores). The shaded area only represents a small fraction of the area within the limits of agreement. This suggests that most of the test-retest variability originates from external factors such as day-to-day variability.

Lastly, the distribution of the sampled correlation coefficients is plotted (see Figure 2.6D(iii)). As we observed in Figure 2.6D(i), the correlation between the performance scores in both experimental sessions is robust. This is confirmed in Figure 2.6D(iii) where the correlation coefficient obtained from Figure 2.6D(i) seems to reside in the outer edge of the histogram. Therefore, there is an advantage from within-subject testing protocols.

5. Cross-Oriented Dichoptic Masking

Pearson's correlation test found a significant correlation (n = 14, r = 0.54, p ¡ 0.05; Figure 2.6E(i)). The Bland-Altman plot (Figure 2.6E(ii)) shows that the limits of agreement are ± 1.88 (z-scores). The measurement variability (grey shaded area in Figure 2.6E(ii)) is ± 1.10 (z-scores). It seems the larger portion of the areas within the limits of agreement are attributable to the measurement variability from the dichoptic masking task itself rather that from external factors such as day-to-day variability. However, it is notable that the additional area within the limits of agreement that is attributable to external factors is of a similar size.

Lastly, the distribution of the sampled correlation coefficients is plotted (Figure 2.6E(iii)). As we observed in Figure 2.6E(i), the correlation between the performance scores in both experimental sessions is strong. This is confirmed in Figure 2.6E(iii) where the correlation coefficient obtained from Figure 2.6E(i) resides in the outer edge of the histogram, suggesting that within-subject testing protocols are advantageous.

2.4.2 Magnitude of Changes in Sensory Eye Balance after Short-Term Patching

In this section, we analyze data that represent the magnitude of change in eye dominance as a result of short-term patching (i.e., patching effect). We follow the convention, where the differences between post-patching data and baseline data are used to quantify this effect.

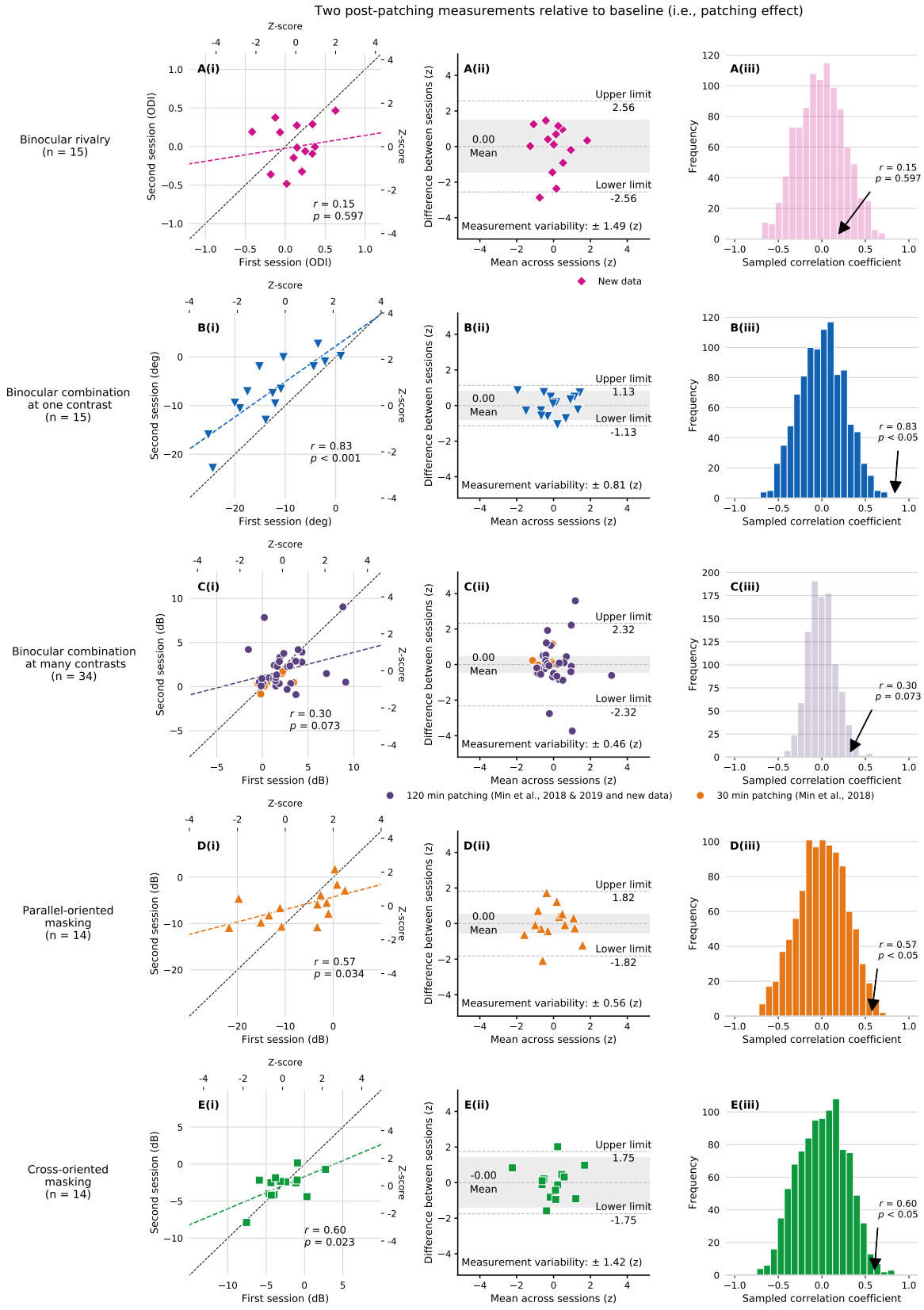

Figure 2.7: Evaluation of changes in ocular dominance after patching (i.e., patching effect) in the five psychophysical tasks.

Figure 2.7: **Repeatability of the patching effect as measured in the five psychophysical tasks.** This figure is divided into five rows (task) and three columns (data analyses). Row **(A) Binocular rivalry**. 15 subjects were patched for 120 minutes. Row **(B) Binocular phase combination at one contrast.** 15 subjects were patched for 120 minutes. Row **(C) Binocular phase combination at many contrasts.** 7 subjects were patched for 30 minutes. 27 subjects were patched for 120 minutes Row **(D) Parallel-oriented dichoptic masking.** 14 subjects were patched for 150 minutes. Row **(E) Cross-oriented dichoptic masking.** 14 subjects were patched for 150 minutes. Column **(i) Baseline reliability.** Column **(ii) Baseline measurement variability** in a Bland-Altman plot. Column (iii) **Baseline reliability** illustrated in a histogram. The columns present data in the same manner as in Figure 2.6.

1. Binocular rivalry

The patching effect is represented by the difference in ocular dominance index between baseline and post-patching measurements. The more positive the Δ ODI, the stronger the patching effect. A Pearson's correlation test revealed a non-significant correlation ($n = 15$, $r = 0.15$, $p = 0.597$) between the patching effects of the two repeated sessions.

The Bland-Altman plot in Figure 2.7A(ii) indicates that the limits of agreement are $\pm$ 2.56 (z-scores). The measurement variability from the binocular rivalry task itself (grey shaded area in Figure 7A(ii)) is $\pm$ 1.48 (z-scores). This corresponds to the median of the bootstrapped standard error for each testing block from both baseline and post-patching experiments. Unlike in the baseline measurements, the shaded area covers only half of the area within the limits of agreement. This suggests that half of the test-retest variability of the patching effect originates from the measurement error of the binocular rivalry task itself, rather than cognitive factors such as attention.

The weak correlation from Figure 2.7A(i) is confirmed in Figure 2.7A(iii) where the correlation coefficient obtained from Figure 2.7A(i) resides in the middle of the his-

togram, suggesting that it is not beneficial to use a within-subjects design.

2. Binocular Combination at One Contrast

The change in sensory eye dominance from patching is represented by the difference in perceived phase (deg) between baseline and post-patching measurements. The more negative the difference in perceived phase, the stronger the patching effect).

A Pearson's correlation test found a significant correlation (n = 15, r = 0.83, p ¡ 0.001) between the patching effects in both experimental sessions. The Bland-Altman plot in Figure 2.7B(ii) indicates that the limits of agreement are ± 1.13 (z-scores). The expected measurement variability from the binocular combination task itself (grey shaded area in Figure 2.7B(ii)) is ± 0.81 (z-scores).

The robust correlation from Figure 2.7B(iii) is corroborated in Figure 2.7B(iii) where the correlation coefficient obtained from Figure 2.7B(i) is located at the outer edge the histogram, suggesting that within-subjects designs are beneficial.

3. Binocular Combination at Many Contrasts

The change in sensory eye dominance from short-term patching is represented by the difference in contrast ratio (dB) between baseline and post-patching measurements. The more positive the difference in contrast ratio (Δ dB), the stronger the patching effect. The correlation was not significant (n = 34, r = 0.298, p = 0.073; Figure 2.7C(i)), probably due to some extreme points. However, these points are within 3 standard deviations and, therefore, were not categorized as outliers.

The Bland-Altman plot in Figure 2.7C(ii) indicates that the limits of agreement are ± 2.32 (z-scores). The expected measurement variability from the binocular combination task itself (grey shaded area in Figure 2.7C(ii)) is ± 0.46 (z-scores). Most of the area within the limits of agreement is not shaded in grey. That means most of the test-retest variability from the patching effect originates from factors other than the measurement

variability associated with binocular combination task itself.

The insignificant correlation from Figure 2.7C(i) surprisingly resides at the outer edge of the histogram, suggesting that within-subjects designs are more sensitive than between-subject designs

4. Parallel-Oriented Dichoptic Masking

The change in sensory eye dominance from patching is represented by the difference in contrast ratio (dB) between baseline and post-patching measurements. The more negative the difference in the contrast threshold for the test grating (Δ dB), the stronger the patching effect. This applies to both parallel- and cross-oriented dichoptic masking. A Pearson's correlation test revealed a significant correlation (n = 14, r = 0.57, p ¡ 0.05; Figure 2.7D(i)).

The Bland-Altman plot in Figure 2.7D(ii) indicates that the limits of agreement are $\pm$ 1.82 (z-scores). The expected measurement variability from the task (grey area in Figure 2.7D(ii)) is $\pm$ 0.56 (z-scores). Most of the area within the limits of agreement is not shaded in grey. This indicates that most of the test-retest variability of the patching effect originates from factors other than the task measurement error.

The strong correlation from Figure 2.7D(i) is confirmed in Figure 2.7D(iii) where the correlation coefficient resides at the outer edge of the histogram, suggesting that within-subject designs are superior to between-subject designs.

5. Cross-Oriented Dichoptic Masking

A Pearson's correlation test indicated a significant correlation (n = 14, r = 0.60, p ¡ 0.05; Figure 2.7E(i)). The Bland-Altman plot in Figure 2.7E(ii) indicates that the limits of agreement are $\pm$ 1.75 (z-scores). The expected measurement variability from the task itself (grey shaded area in Figure 2.7E(ii)) is $\pm$ 1.42 (z-scores). Most of the area within the limits of agreement is shaded in grey. This suggests that most of the test-retest

variability of the patching effect originates from the task measurement itself.

The robust correlation is confirmed in Figure 2.7E(iii) where the correlation coefficient resides at the outer edge of the histogram, indicating that there is an advantage of using a within-subject design for this task.

2.4.3 Summary of Results

In this task, four properties of the five psychophysical tasks are ranked. These properties are *baseline reliability, patching effect reliability, baseline measurement variability and patching effect measurement variability* (defined in the Introduction).

The correlations (i.e., test-retest reliabilities) for baseline measurements and for the magnitude of the patching effect are summarised as p-values from Pearson's correlation tests between the raw data from the first and second experimental sessions. P-values were used for ranking because they indicate whether a within-subject design is more advantageous than an unpaired-subject protocol (see column (iii) in Figures 6 and 7). For instance, column (iii) in Figures 6 and 7 shows that the lower the p-value, the more likely the correlation coefficient resides in the outer edge of the histogram. In short, if the correlation coefficient resides in the outer histogram, a within-subject design produces a stronger correlation than an unpaired design. On the other hand, if the correlation coefficient resides within the middle of the histogram, then there is no reason to implement a paired-subject design because the correlation coefficient will be similar between the two protocols.

The baseline and the patching effect measurement variabilities correspond to the width of the shaded gray regions in the Bland-Altman plots. They are the measurement error from the psychophysical task itself rather than extraneous errors such as day-to-day variability and attention levels. Baseline data can be used to compute the test-retest reliability and replicability of a task. The magnitude of the change in sensory eye dominance after patching relative to baseline was used to quantify the patching effect.

Therefore, the measurement of the patching effect includes variability from the baseline and the strength of the patching effect across days.

In order to rank the psychophysical tasks from best to worst, we normalised the statistical values (p-value from Pearson's correlation and z-scores from the measurement variability) that represent the four properties of all tasks using the equation:

$$normalisation = 1 - \frac{x_i - x_{min}}{x_{max} - x_{min}} \tag{2.7}$$

where x_i indicates a value that is to be normalised (e.g., binocular rivalry: p = 0.204 in baseline correlation, measurement variability = ± 1.69 z-scores), x_{min} the minimum value in the dataset, and x_{max} the maximum value in the dataset. If the normalised value is 1, it indicates that it is the best of all tasks; if the normalised value is 0, it indicates that it is the worst of all tasks. In the case of the reliabilities of baseline and the patching effect, the lowest p-value from Pearson's correlation tests across the tasks was converted to 1, and the highest p-value to 0. However, for the measurement variabilities of baseline and the patching effect, the smallest standard error within the limits of the agreement (grey areas from columns (ii) in Figures 2.6 and 2.7) was converted to 1, and the widest range to 0. Figure 2.8 shows the summary ranking of these four properties.

2.5 Discussion

2.5.1 Are Different Psychophysical Tasks Associated with Distinct Neural Sites and Mechanisms?

Studies using binocular rivalry and binocular combination at one contrast have revealed different magnitudes of the patching effect [1, 15, 33]. This supports that the patching effect takes place at multiple neural sites. For example, Baldwin and Hess (2018) interleaved two dichoptic masking tasks with different orientations of the mask grating within one experiment and repeated the experiment twice [2]. Their experimental de-

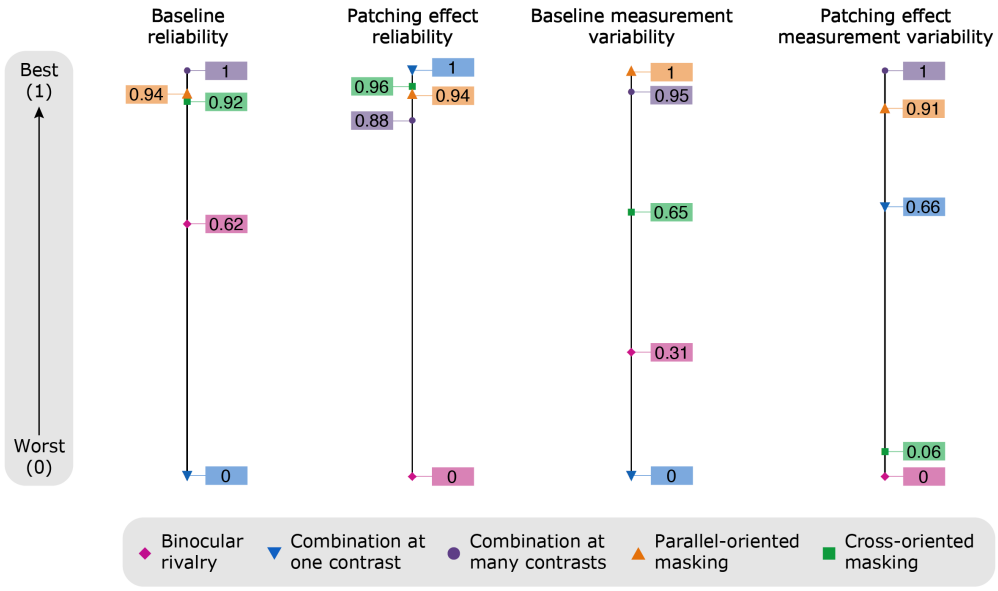

Figure 2.8: **Summary of results.** Baseline reliability refers to the p-values from correlation analysis of baseline data (column (i) in Fig. 2.6). Patching effect reliability indicates the p-values from correlation analysis of the difference between post-patching and pre-patching baseline data (column (ii) in Fig. 2.7). Baseline measurement variability refers to the median of the standard error for each testing block from baseline measurement; this is represented by the gray areas in column (ii) of Fig. 2.6. Patching effect measurement variability denotes the median of the standard error for each testing block from both post-patching and pre-patching baseline data; this is represented by the gray areas in column (ii) of Fig. 2.7. Each value was normalised in a scale where 1 represents best and 0 worst of all tasks.

sign minimized measurement variability between the two tasks. They reported that the orientation of the mask determines the magnitude of the patching effect. This finding reinforces the notion that the patching effect is multifaceted and that one psychophysical task might capture only one aspect of the change in neural plasticity. If this interpretation is true, different psychophysical tasks can be associated with different aspects/sites.

However, we show that this difference in results can also be attributed to a wide measurement variability of the patching effect due to the method itself, such as binocular rivalry (see Figure 2.8). Moreover, the measurement variability of the patching effect between the parallel- and cross-oriented masking tasks is different although the patching effect correlations are both robust. The measurement variability is much wider in the cross-oriented masking task (see Figure 2.8: Patching effect measurement variability). This suggests that when gratings of orthogonal orientations are presented dichoptically, the measurement variability of the patching effect can increase. This reasoning also applies to the obvious difference in the measurement variability of the patching effect between binocular rivalry and binocular combination tasks. Since the variability directly confounds the outcome of interest (i.e., magnitude of the patching effect), we cannot yet conclude that the results from different psychophysical tasks reflect separate neural sites. If our inference is true, it will be more beneficial to use a task, such as binocular combination and parallel-oriented masking, that presents gratings at a parallel orientation to both eyes to measure the patching effect.

2.5.2 How Reliable is Baseline Measurement for Each Task?

As Figure 2.8 shows, binocular rivalry and binocular combination at one contrast have poor reliability and measurement variability in baseline measurement. Conversely, binocular combination at multiple contrasts and parallel-oriented dichoptic masking seem to measure baseline in a consistent fashion. What can be the contributing factors for the poor reliability of binocular rivalry and binocular phase combination at one contrast?

To begin with, binocular rivalry measures competition, rather than the combination, between the eyes by presenting two rivalrous images separately to both eyes. The interocular competition during rivalry causes a rapid and irregular fluctuation of sensory eye dominance over visual space and time [5, 4]. The random nature of binocular rivalry might widen the measurement variability. Moreover, attention can affect the temporal dynamics of rivalry [23], suggesting that this task is significantly influenced by cognitive factors [1]. The poor reliability of baseline measurement between the two separate days of testing might indicate that the level of attention throughout the task between the sessions differed. More importantly, binocular rivalry task is the only method that captures continuous time-series data of the subject, thereby adding one more dimension to the data (i.e., time). All other four tasks yielded discrete, rather than continuous, data. The discrete structure of the data might reduce the source of measurement error. Therefore, the random dynamic nature of binocular rivalry and the influence of top-down attentional factors might have increased the measurement variability of baseline measurement.

Our results are surprising given the fact that binocular rivalry has been used to study a wide range of visual phenomena [5], such as sensory eye dominance at a population level [8] and within the visual field [9] and its changes after short-term patching [22]. It has also been used as a golden standard when a novel test for measuring sensory eye dominance is developed [27]. A study has investigated the test-retest reliability of binocular rivalry measurement [9], reporting a robust correlation between two experimental sessions. The authors highlight the correlation as evidence to claim that binocular rivalry is a reliable test. However, the correlation coefficient is not indicative of test-retest replicability because two samples with significantly different means can still have a strong linear relationship. In our study, we also found a good correlation of binocular rivalry for the baseline measurement of our new data ($n = 15$, $r = 0.52$, $p = 0.043$; pink points in Figure 2.6A(i)). However, a large measurement variability was observed ($\pm$ 1.72 z-scores) in

the dataset.

In the case of binocular combination task at one contrast, as its name implies, only one contrast ratio between the eyes is used. We believe that using only one contrast ratio of the stimuli might have widened the measurement variability in baseline. Conversely, in binocular combination at many contrasts, the various contrast ratios were used to display the stimulus. Then the contrast ratio, where the perceived phase is 0, was estimated by fitting a contrast gain model [10] to the data across all contrast levels. Therefore, the version of the task in which data were collected across multiple contrast values, not surprisingly, had a much smaller measurement variability than the binocular combination task at one contrast.

Interestingly, we found a stark difference in the measurement variability (gray areas in the Bland Altman plots from Fig. 2.6) between parallel- and cross-oriented dichoptic masking tasks. The fourteen subjects in this experiment were identical as the two tasks were interleaved alternately (see Fig. 2.4 in Methods). The only difference in these methods was the orientation of the mask grating. Cross-oriented masking induces binocular competition between the eyes since the orientations of the mask and detection gratings are orthogonal. On the other hand, parallel-oriented masking does not induce any competition since both the mask and detection gratings are identically oriented. The orthgonal (i.e., non-fusible) orientations of the gratings might account for the large difference in the measurement variability between the two masking tasks. This explanation might also help explain the large measurement variability in the binocular rivalry task.

2.5.3 Is the Patching Effect Stable Across Days?

Studies using various tests have demonstrated the patching effect. However, the magnitude of the plasticity change has been reported to be not uniform across tasks. The stability of the patching effect can be figuratively shown by comparing the measure-

ment variability between the patching effect and baseline for each task. If the measurement variability of the patching effect is larger than baseline, then the patching effect can be interpreted as not stable because it does not introduce an additional source of variability. According to our results, all tasks except for cross-oriented masking have similar/narrower measurement variability (Fig. 2.7(ii)) compared to that from baseline. These tasks suggest that the patching effect is stable across days within the same subject.

2.5.4 Which psychophysical tasks should be used in the clinical setting to measure sensory eye dominance and the patching effect?

Recent clinical studies on amblyopes have incorporated training protocols that involve patching the dysfunctional eye [18, 31, 7], a design that is identical to the one used in short-term patching studies in normal observers. To ensure that the findings from preliminary studies are replicable in a wider population, the choice of test in clinical studies is important.

All tasks in this paper have short testing durations (3 to 5 minutes). In the clinic, the time for each patient is limited, so it is important to bear in mind that a task with a long task duration is not feasible. We do however understand that a long testing duration can potentially reduce the measurement variability of the task. To begin with, our findings show that binocular rivalry and binocular combination at only one contrast have poor test-retest replicability in baseline measurement. In addition, binocular rivalry exhibits a large test-retest variability and low detectability of the patching effect. This may limit its utility for clinical studies. Instead, psychophysical tasks that capture stable baseline performance and a repeatable patching effect and detect the patching effect easily will be most useful. According to our results, these tasks are binocular phase combination at multiple contrasts and parallel-oriented dichoptic masking.

2.5.5 Limitations of the study

In hindsight, we acknowledge that our experimental design for the next experiment was not ideal because we did not interleave two different binocular rivalry tasks (see Figure 2.1). As we previously mentioned, we first attempted to compare binocular rivalry and combination at many contrasts by interleaving them in a single design (see Fig. 2.1). However, due to the failure of the screen, we had to discard the data of binocular phase combination but keep those of binocular rivalry. To maintain a comparable design, we decided to recollect data of binocular phase combination at many contrasts by interleaving with another variation of binocular phase combination (at one contrast).

Moreover, the number of testing blocks and the duration of time for each block were not identical across the five psychophysical tasks. Furthermore, the subjects were not paired across the five tasks. Performing such a controlled comparison would require a large study designed from the outset for that purpose. In our case, the study we present is a meta-analysis across several published studies. We therefore do expect extraneous differences between those studies to account for a part of the differences we see between tasks.

2.5.6 Conclusion

There have been conflicting reports on the patching effect from short-term deprivation in adults and children. The magnitude of the patching effect has been found to be variable across different tests (binocular rivalry and combination) and within the identical test (binocular rivalry) across conditions. In the Introduction, three explanations for these discrepancies are introduced. First, the mechanism of the patching effect might be multifaceted and different tasks might reflect different processing sites. If this notion holds true, each psychophysical task might capture only one aspect of the entire plasticity change. Previous psychophysical studies have advocated this reasoning [1, 2]. Second, the measurement error associated with the tasks might be poorer with certain

tasks. In light of our findings, this claim is reasonable for some tasks. For instance, the presentation of orthogonal gratings (e.g., binocular rivalry and cross-oriented dichoptic masking tasks) appears to directly increase the measurement variability of the task, thereby making the baseline or the patching effect more variable. Third, the patching effect might be itself an unstable phenomenon. Our findings show that this is not the case, as we do not find evidence for any additional source of variability for the patching effect.

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Manuscript 2. The shift in Ocular Dominance from Short-Term Monocular Deprivation Exhibits No Dependence on Duration of Deprivation

Authors: Seung Hyun Min, Alex S. Baldwin, Alexandre Reynaud, and Robert F. Hess

3.1 Abstract

Deprivation of visual information from one eye for a 120-minute period in normal adults results in a temporary strengthening of the patched eye's contribution to binocular vision. This plasticity for ocular dominance in adults has been demonstrated by binocular rivalry as well as binocular fusion tasks. Here, we investigate how its dynamics depend on the duration of the monocular deprivation. Using a binocular combination task, we measure the magnitude and recovery of ocular dominance change after durations of monocular deprivation ranging from 15 to 300 minutes. Surprisingly, our results show that the dynamics are of an all-or-none form. There was virtually no significant dependence on the duration of the initial deprivation.

3.2 Introduction

The inputs from the two eyes are segregated into ocular dominance columns in the input layers of cortical area V1. They are only later combined in the more superficial layers. Any imbalance in the inputs from the two eyes can lead to competitive changes. These then affect the relative width of the ocular dominance column [12]. Neuroplastic changes after long-term monocular occlusion have been used as an index of ocular dominance plasticity in animals [26] and man [16, 28, 18]. These findings have helped define "the critical period" for visual development [13]. It is well-established that monocular deprivation during the critical period can permanently reduce the functioning of the deprived eye and shift ocular dominance in favour of the unpatched eye [13]. With this principle in mind, physicians for the past 250 years have recommended monocular occlusion of the fixing eye as treatment for children with amblyopia. Beyond the critical period, monocular occlusion of the fixing eye becomes ineffective for amblyopia treatment. However recent studies have shown that monocular deprivation for as little as 120 minutes in the adult strengthens the deprived eye's contribution to the binocular percept [28, 18, 29], an opposite finding to previous studies. This finding is surprising for two reasons. First, it shows that there is residual neural plasticity in the adult's primary visual cortex. Second, the effect of short-term monocular deprivation in adults strengthens the opposite eye to that of long-term monocular deprivation in early life. In adults, the contribution of the patched eye increases after a brief period (a few hours) of deprivation, whereas in young animals the patched eye loses function after long-term monocular deprivation (days) [26]. The results from studies of short-term monocular deprivation-induced ocular dominance changes show that the effect is transient in nature. The majority of the recovery occurs over a period of 30–90 minutes in adults [28, 18]. The return to baseline of this neuroplastic change suggests that there are homeostatic mechanisms [25] maintaining the balance of ocular dominance. Occluding one eye can only temporarily introduce an imbalance before the original balance is restored.

There are many approaches that can be used to quantify the contribution of each eye to binocular vision. Several of these have been used to measure the shift in ocular dominance in adults as the result of a short-term disruption to the input of one eye. The typical protocol is to measure the baseline balance between the two eyes (e.g. a ratio of each eye's influence) and then measure the balance following a period of monocular patching. The patching effect is quantified by taking the change in the balance between the two measurements. The tasks previously used include binocular combination tasks and binocular competition (e.g. rivalry) tasks [16, 18]. In terms of binocular combination, different stimuli have been used including interocular phase [28, 30], interocular perceived contrast [28], dichoptic global motion coherence [28] and an edge-detection task measuring both fusion and suppression [21].

In binocular rivalry, incompatible stimuli are presented to each eye which cause the inputs from each eye to compete rather than combine (fuse). Subjects are asked to report on the relative durations of each perceived stimulus. A change in eye dominance is indicated by a shift in the relative duration of each eye's percept. In binocular combination tasks, two fusible stimuli are shown to each eye. The influence of the two eyes in binocular vision is measured by obtaining information from the subject about the fused percept (where the input from each eye would bias the subject towards two different percepts). Although these two approaches (binocular rivalry and binocular combination) both support the view that short term monocular deprivation in the adult shifts ocular dominance in favour of the previously patched eye, the neural mechanisms involved in each task may be different. This is because binocular rivalry involves stimuli that are likely represented by separate neural populations (i.e. neurons with different preferred orientations), whereas combination tasks involve stimuli that are likely to activate a common neural population (i.e. neurons with the same orientation preferences). For example, co-oriented gratings seen by the two eyes would be expected to stimulate an overlapping population of simple cells in primary visual cortex. Recently, uncorrelated

individual differences have been shown for short-term monocular deprivation for cross-oriented and co-oriented dichoptic masking [1]. This is consistent with there being a different neural substrate for ocular dominance changes after monocular deprivation, as revealed by binocular rivalry and combination tasks.

Besides psychophysical techniques [28, 18, 30, 21] electrophysiological and neuroimaging techniques have also demonstrated the robust effect of monocular deprivation [4, 17, 27]. However, the majority of studies, be they psychophysical or electrophysiological, have only examined durations of monocular deprivation of between 120–150 minutes. So, although we have a good idea of the recovery of the effect (at least for this time scale of deprivation), we have no idea of how this varies with the duration of deprivation. In this study, we have examined the duration dependence of the effects of monocular deprivation-induced changes in ocular dominance. To do this we have measured changes in ocular dominance in adults across different time scales of monocular deprivation; a short-time scale from 15 to 30 minutes (first experiment) and a longer–time scale from 60 to 300 minutes (second experiment). In each of the experiments we measured the eye dominance using the phase combination task [28] (see methods), patched one eye for variable periods of time (15—300 min) and re-measured the eye balance at each of a number of time points (0, 3, 6, 12, 24, 48, 60 and 96 min) after monocular deprivation. We find that there is at best only a very weak relationship between patching duration and ocular dominance plasticity. A 20-fold increase in the deprivation duration results in the strength of the dominance change only increasing by a 25%. Also, the recovery of the patching effect seems to be quite similar across all deprivation durations, implying that there may not be duration dependence in the recovery. This finding implies that this homeostatic process has unusual dynamics being, to a first approximation, an all-or-none phenomenon.

3.3 Results

3.3.1 Short durations of monocular deprivation (15–30 minutes)

In the first experiment, we measured eye dominance using the binocular phase combination task [28] for two durations of monocular occlusion: 15 and 30 minutes. We plotted the data on semi-log coordinates and fitted them with a straight line (i.e. an exponential function) as this is consistent with the form of the recovery in previous studies using the phase combination procedure. The changes in eye dominance relative to baseline for the cohort of eight subjects are presented in Fig. 3.1b. If the patched eye became stronger, Δ contrast balance ratio would be positive. Since the effect of patching was plotted relative to baseline, Δ contrast balance ratio of 0 would represent the pre-patch baseline.

The averaged eye dominance change induced by patching durations of 15 and 30 minutes recovered back to baseline in 24minutes (shown by the recovery slopes in Fig. 3.1b). The Wilcoxon Signed Rank Test showed no significant difference between the recovery slopes of 15 and 30 minutes ($p = 0.95$). The patching effect peaked at between 0 and 7minutes after patch removal. The peak imbalance induced by the patching was 1.5 dB. When shown stimuli of the same contrast to their two eyes, the subjects responded as if there was a 19% difference in contrast.

Figure 3.1a shows the area under the curve (AUC) of Fig. 3.1b (summation of Δ contrast balance ratio from 0 to 96 minutes after monocular deprivation). To capture both the magnitude and duration of the effect we computed the AUC Δ contrast balance ratio. The higher the AUC, the stronger the patching effect for the patched eye. The Wilcoxon Signed Rank Test showed no significant difference between the calculated AUCs for the two patching durations ($p = 0.95$).

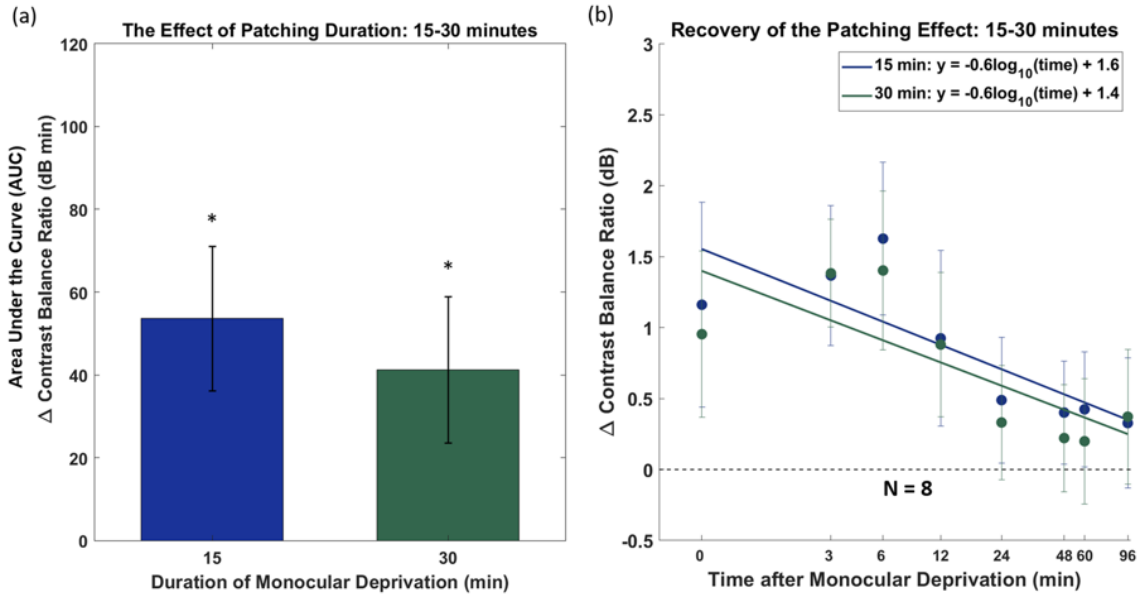

Figure 3.1: **Monocular deprivation for 15 and 30 minutes on eight subjects. (a)** Area under the curve calculated from (b). The error bars represent standard errors across the AUC Δ contrast balance ratio of subjects. Measurements that are significantly different (Wilcoxon Signed Rank test) from baseline are indicated; *p < 0.05. **(b)** Recovery of the patching effect over time after patch removal on log/log scaled axes. Each point represents the change in eye dominance as a function of the time after monocular deprivation. The x–axis values represent the time-points of post-patching measurement. The error bars represent standard errors.

3.3.2 Long durations of monocular deprivation (60–180 minutes)

In the second experiment, we measured ocular dominance changes on another cohort of eight subjects for a range of longer durations, namely 60, 120 and 180 minutes. In Fig. 3.2b, recovery curves are shown on log/log scaled axes and fitted with straight lines. The slopes of these fits are about 0.5 and 0.6 on log/log scaled axes (Fig. 3.2b). The Wilcoxon Signed Rank Test showed that the slopes are not statistically different between 60 and 120 minutes ($p = 0.84$), 60 and 180 minutes ($p = 0.95$) and 120 and 180 minutes ($p = 0.95$). Although there is a trend that longer durations of patching are associated with greater areal effects (AUC Δ contrast balance ratio), this was not statistically significant. The Wilcoxon Signed Rank Test showed no significant difference

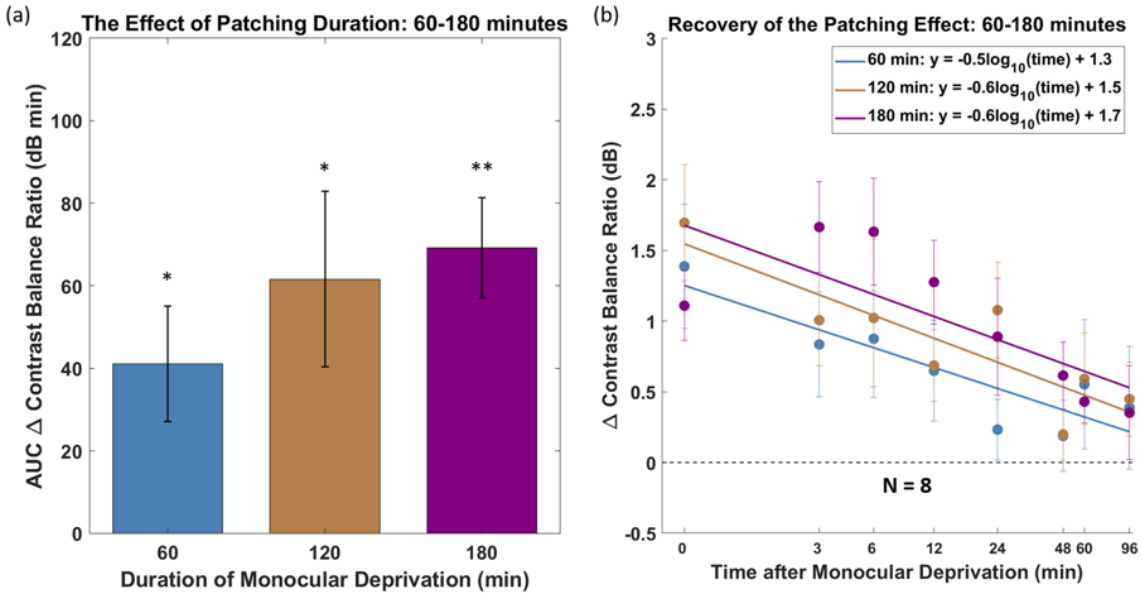

Figure 3.2: **Monocular deprivation for 60, 120 and 180 minutes on another cohort of eight subjects**. **(a)** Area under the curve calculated from **(b)**. The error bars represent standard errors across the AUC Δ contrast balance ratio of subjects. Measurements that are significantly different (Wilcoxon Signed Rank test) from baseline are indicated; **p $<$ 0.01, *p $<$ 0.05. (b) Recovery of the patching effect over time after patch removal on log/log scaled axes. Each point represents the change in eye dominance as a function of time after monocular deprivation. The x-axis values represent the time-points of post-patching measurement. The error bars represent standard errors.

between the AUCs of 60 and 120 minutes (p = 0.38), as well as between 120 and 180 minutes (p = 0.74). There was also no significant difference between the AUCs of 60 and 180 minutes (p = 0.25).

In the third experiment, four of the cohort above were also patched for 300 minutes
130 (Fig. 3.3). Although there is a trend that the patching effect from 60 minutes patching is less (i.e. Figure 3.3a–AUC Δ contrast balance ratio), the Wilcoxon Signed Rank test showed no significant difference between the AUCs in 60 and 300 minutes of patching (p = 0.13). The AUCs of the patching effect at 60 and 300 minutes duration were also similar.

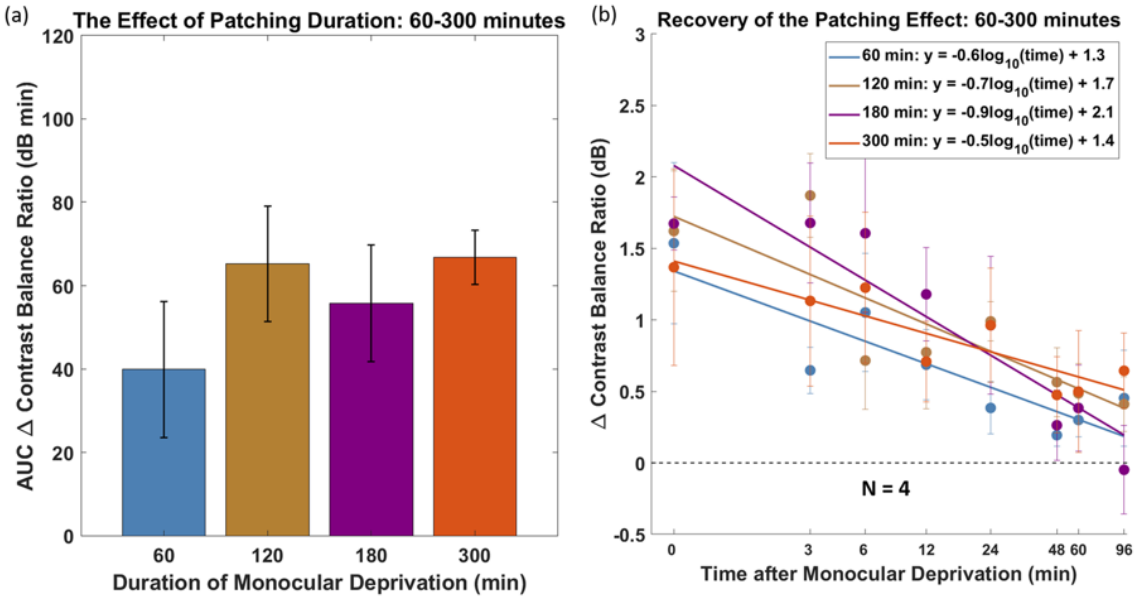

Figure 3.3: **Monocular deprivation for 60, 120, 180 and 300 minutes on four of the eight subjects in the second cohort**. **(a)** Area under the curve calculated from (b). The error bars represent standard errors across the AUC Δ contrast balance ratio of subjects. **(b)** Recovery of the patching effect over time after patch removal on log/log scaled axes. Each point represents the change in eye dominance as a function of the time after monocular deprivation. The x-axis values represent the time-points of post-patching measurement. The error bars represent standard errors.

The general summary of all results is shown in Fig. 3.4a. Although we found no significant effect of patching duration on the magnitude of the ocular dominance change, we are able to rule out the possibility of there being a relationship at all. When taking into account the data from all the patching durations examined in this study, there does seem to be a trend for longer durations to have slightly larger areal effects. To quantify this global trend, we derived bootstraps of the slope parameter (median = 0.1127) of the best fitting linear function (Fig. 3.4a- solid line) and found no overlap between the slope value of 0 and the 95% confidence interval (0.11 [95% CI 0.08, +0.08]) of the fitted slope. This suggests that there is a small but significant global trend when all patching durations are taken together. However, it is worth noting that a one-way analysis of variance (ANOVA) showed no significant difference (p = 0.75) between the areal effects

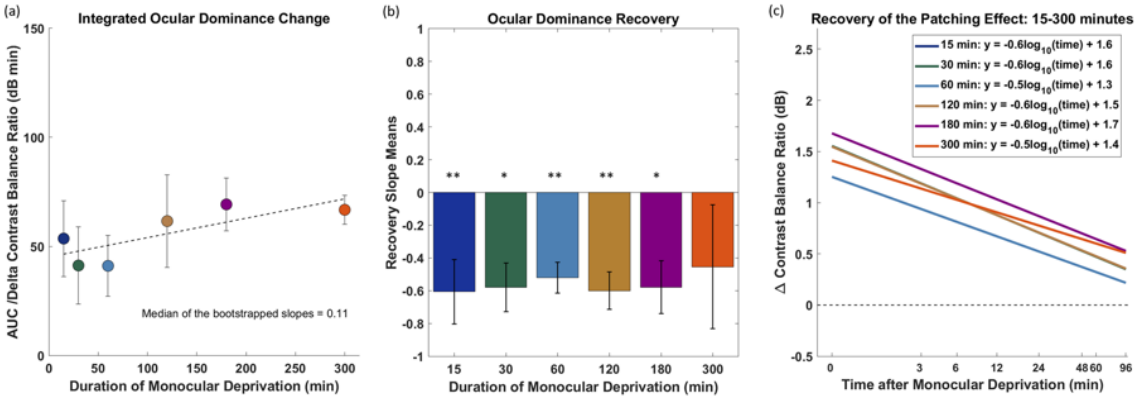

Figure 3.4: **Summary of integrated ocular dominance changes from monocular deprivation of varying durations** (a), their associated recovery times (b) and recovery of the patching effect (c). The first cohort of eight subjects performed 15 and 30 minutes of patching. The second cohort of eight subjects performed 60, 120, and 180 minutes of patching. Four of the second cohort performed 300 minutes of patching. (a) AUCs Δ contrast balance ratio of all subjects is summarized in this figure. The error bars represent standard errors across the AUC Δ contrast balance ratio of subjects. (b) Recovery slope means that are significantly different (Wilcoxon Signed Rank test) from 0 are indicated; **p $<$ 0.01, *p $<$ 0.05. The error bars represent standard errors of the recovery slopes across subjects. (c) Recovery of the patching effect on log/log scaled axes in all durations. The plots represent best fit lines to all data in each time point after monocular deprivation. The plots of 15 and 120 minutes are superimposed so only the plot of 120 minutes is visible.

of all patching durations.

It could be that for the sample size used here, the data we collected failed to represent a (small) real underlying effect (type II error). From looking at the statistical power of the Wilcoxon Signed Rank test and the standard deviation of the data we collected, we estimated the magnitude of the underlying effect size that would have to exist for us to be able to reliably detect it. For simplicity we only performed this analysis for the AUC comparisons. We determined that the difference between the effects for two patching durations would have to be around 45 dB*minutes. This is approximately the magnitude of the patching effect that we find for the shorter patching durations compared to baseline. This means that reliably finding a significant difference between

15 and 180 minutes would, for example, require that the patching effect for 180 minutes to be at least 90 dB*minutes. Another way of thinking about this, is to first assume that the small areal effect we find between 15 and 180 minutes is real. In this case we would need an excess of 300 participants for such an effect to reach statistical significance. Therefore, while we cannot conclude that there is no effect of patch duration on ocular dominance plasticity, we can conclude that any such effect is very small.

We were interested in whether there was a relationship between the patching duration and the rate of recovery in the patching effect. After calculating the recovery slope (linear fits in log/log scaled space) means of all subjects for each condition (Fig. 3.4b) we performed the Wilcoxon Signed Rank test across conditions. It showed no significant difference between the recovery slopes of 60 and 120 minutes of patching ($p = 0.55$), neither between 60 and 180 minutes of patching ($p = 0.84$) or between 120 and 180 minutes of patching ($p > 0.05$). We also performed a one-way ANOVA across all durations and found no statistically significant difference ($p > 0.05$). The lack of a significant difference across different patching durations implies that longer durations of monocular deprivation do not result in a slower recovery of ocular dominance to baseline.

3.4 Discussions

We used a binocular phase combination task to measure changes in eye dominance from different durations of monocular deprivation. We employed six different durations spanning 15 to 300 minutes. We tracked changes in visual recovery over 96 minutes following monocular deprivation. We had expected that there would be a strong relationship between both the magnitude and recovery duration of visual plasticity and the duration of monocular deprivation. However, we observed only a minimal increase in the magnitude of the ocular dominance change resulting from 15 to 300 minutes of monocular deprivation; a 20–fold increase in the duration of deprivation resulted in only a 25% difference in the ocular dominance effect. Also, we found that regardless of the patch-

ing duration, the neuroplastic recovery after monocular occlusion returned to baseline within 96 minutes. This implies that these changes reflect a homeostatic mechanism that responds instantaneously in an all-or-none fashion to a disrupted monocular input of variable duration.

The other end-point measure used to measure changes in ocular dominance occurring as the result of monocular deprivation has been binocular rivalry. Lunghi et al. used that task when they first demonstrated that monocular occlusion changed the sensory eye balance in favour of the patched eye. In their study, monocular deprivation of 150 minutes was employed. Several groups since then have corroborated the short-term monocular deprivation effect in adults using various psychophysical and neuroimaging techniques [28, 18, 30, 1, 21, 4, 17]. Although the bulk of literature has only examined durations of 120 to 150 minutes, some studies have provided information on shorter periods of monocular deprivation using continuous flash suppression. Kim et al., examined durations as short as 15 minutes and showed that monocular deprivation from continuous flash suppression could induce an effect comparable to that observed after the same duration of monocular deprivation using a diffuser [15]. They showed a significant change in dominance after only 3 minutes of monocular deprivation. However, no study has systematically investigated the relationship between the duration of monocular deprivation and either the magnitude or duration of subsequent ocular dominance changes.

This finding of a virtually all-or-none response of the binocular visual system to an imbalance in the input from the two eyes of variable duration is unexpected. Early in life there is a critical period of development during which the visual system is most plastic. During the critical period the duration of monocular deprivation affects both the magnitude and the recovery time of changes in ocular dominance [5]. Therefore, adult neuroplastic changes in ocular dominance measured here are not simply a reduced version of their counterparts in early life: not only is the effect in the opposite direction

(i.e. strengthening of the patched eye in adults, a weakening of the patched eye in children) but the dynamics are also fundamentally different. Furthermore, the difference here may not simply be between juvenile and adult forms of plasticity because "adaptation" in the adult which is also known to alter sensitivity in the short term through homeostatic mechanisms [25] also exhibits different properties to that of adult ocular dominance plasticity. Adaptation after-effects have been shown for a wide variety of visual attributes including, amongst others, contrast [2], orientation [9, 23] and motion [3, 24]. In all of these cases, it has been shown that both the magnitude of the after-effect and its longevity depends on the duration of adaptation both psychophysically [10] and neurophysiologically [14, 7, 8]. This is different from the deprivation-induced ocular dominance changes that we report here.

These findings may bear upon the clinical application of this form of plasticity in the adult for the restoration of balanced binocular function in amblyopia. Zhou et al.[30] first showed that ocular dominance shifts from short term monocular deprivation also occur in adults with amblyopia and that they can be of larger magnitude and of a more sustained form. They suggested that short term occlusion of the amblyopic eye could be used to restore a more normal binocular balance. Such an approach would be the opposite of what is currently used in children, where the fixing eye rather than the amblyopic eye is patched. There are clinical trials currently underway to assess this novel approach (J. Zhou et al. and C. Lunghi, personal communications). The findings presented here are relevant in that it appears that the ocular dominance changes, at least in normal adults, are of an all-or-none form and, if this is also the case in amblyopes, this approach may be less suited to therapeutic intervention where long lasting effects are required. This can be contrasted with the dose-response (duration of patching) effect from monocular patching that is known to occur in children [22]. However, the present experiments have only involved single "pulses" of deprivation of varying duration, it is yet to be determined whether greater and more long-lasting summation changes in ocular dominance can be

obtained from the interaction between double or indeed multiples "pulses" of monocular deprivation.

3.5 Materials and Methods

3.5.1 Participants

Fifteen Adults (age = 24 ± 3 years) with normal or corrected-to-normal vision participated in this study. Two subjects were the listed first and third authors. All other subjects were naïve to the purpose of this study. We obtained an informed consent from the subjects. The study is in line with the Declaration of Helinski and was approved by the Institutional Review Boards at McGill University.

One cohort of eight subjects was patched for 60, 120 and 180 minutes, another cohort of eight for 15 and 30 minutes. Four of the former cohort were also patched for 300 minutes. One of the authors participated in all experiments. All subjects completed two test sessions for every patching duration on different days.

3.5.2 Apparatus

On a Mac computer, we employed Matlab 2012a and PsychToolBox 3.0.9 extensions [20] to measure interocular sensory balance points of each subject in this study. We presented dichoptic stimuli using head mount goggles (eMagin Z800 pro, OLED) with a refresh rate of 60 Hz, resolution of 800 × 600 and mean luminance of 59 cd/m^2. The goggles provided a linear input vs. luminance curve within the range of luminances used in the experiment.

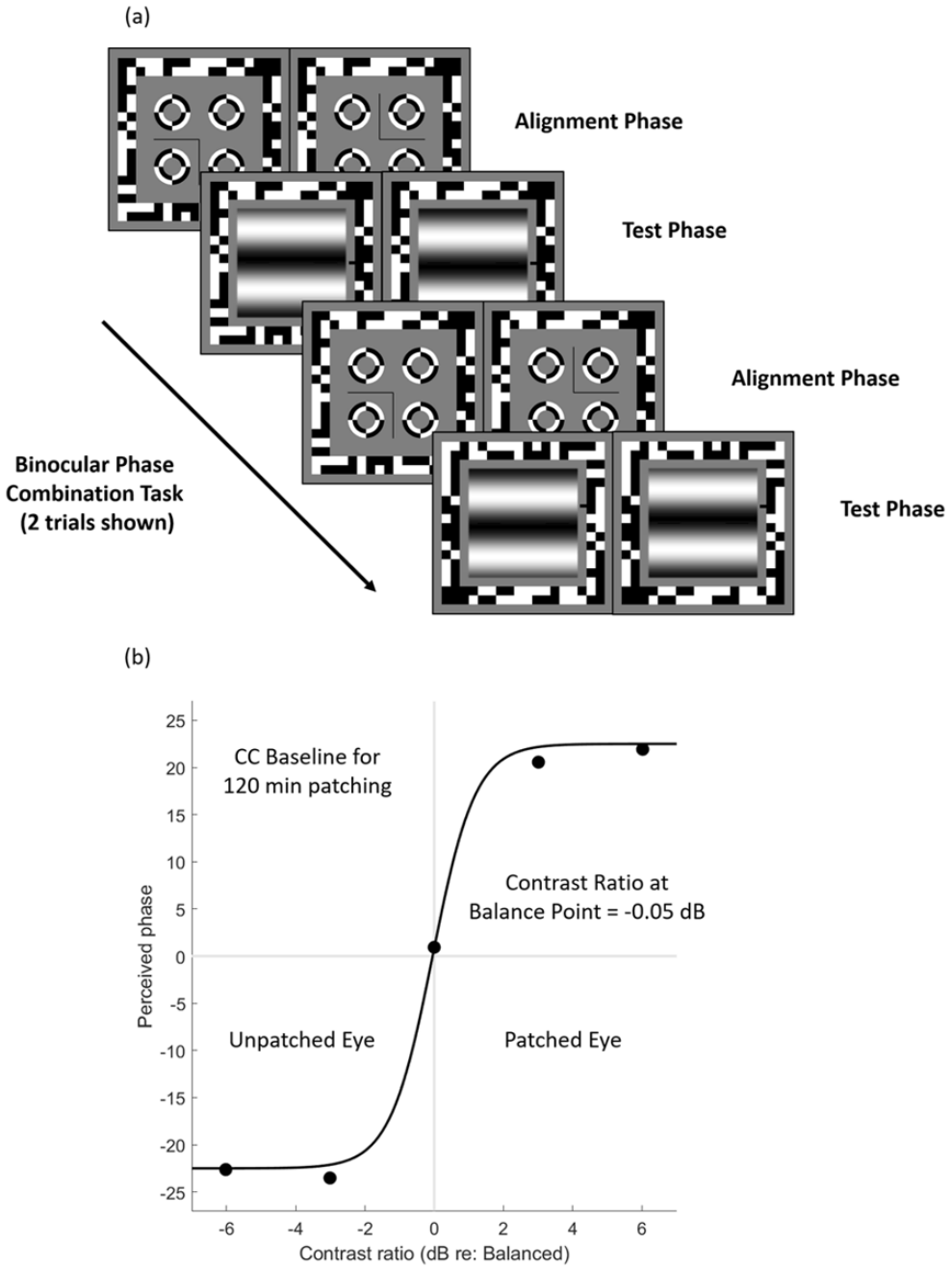

Figure 3.5: **The temporal sequence of the binocular phase combination task and an illustration of fitting data to a binocular combination model.** **(a)** Two trials of the binocular phase combination and two configurations are shown. There were 80 trials in the baseline test, and 30 trials in the post-patching test. The reference line was placed at the right side of the sinusoidal gratings. **(b)** Perceived phases from the binocular phase combination task during the baseline measurement of one subject were plotted as a function of contrast ratio. We fitted data from each measurement (baseline and post-patch) to a binocular combination model [11, 6].

3.5.3 General Rationale

We wanted to measure the contribution that each eye makes to the fused binocular percept. To do this each eye views a grating of each but opposite spatial phase $-22.5°$ for one eye and $+22.5°$ for the other eye). If the contribution from each eye is equal then the binocularly fused percept will be of a grating of zero phase. If the contributions are not equal then the perceived phase can be reset to zero by offsetting the contrasts in each eye (see Fig. 3.5). The interocular contrast ratio that produces equal contribution (i.e. zero phase) is our measure of the ocular dominance.

3.5.4 Stimuli

We used a binocular phase combination task as stimuli. A separate horizontal sine-wave grating ($6.6° \times 6.6°$ visual angle (°), 0.3 cycles/°) was presented to both dominant eye (DE) and non-dominant eye (NDE). The phases of the sinusoidal gratings were $+22.5°$ in one eye and $-22.5°$ in the other eye, both randomly assigned, relative to the center of the screen. Binocular presentation of these two gratings produced one fused grating percept. The phase difference between the gratings presented to both eyes ($\theta = |\theta_{DE} - \theta_{NDE}|$) was fixed at 45°. We measured the perceived phase of the fused grating at base contrast of 60%. In this study, we used the method of constant stimuli. The interocular contrast ratios between the eyes were $1/2$, $1/\sqrt{2}$, 1, $\sqrt{2}$, 2 in the baseline measurement test, and $1/\sqrt{2}$, 1, $\sqrt{2}$ in the post-patch measurement test. There were 8 repetitions for every interocular ratio in baseline measurement, and 5 in post-patching measurement. The baseline test lasted for about 10 minutes and consisted of 80 trials whereas post-patching measurements lasted for about 3 minutes and consisted of 30 trials.

Two configurations were used to remove any starting positional bias (see Fig. 3.5a). The first configuration showed $+22.5°$ to the dominant eye and $-22.5°$ to the non-dominant eye, the second configuration $-22.5°$ to the dominant eye and $+22.5°$ to the non-dominant eye. We presented each configuration the same number of times in the

task in a random order. Each configuration was repeated twice for every interocular ratio.

3.5.5 Procedures

We patched subject's dominant eye. To determine the dominant eye, we used the test described by Miles [19]. The subjects formed a peephole with their hands, stretched their peephole at arm' length and located a target stimulus in the center of the peephole with both eyes open. They then alternately closed one eye and another and identified their dominant eye by determining when the object had most deviated from the center of the peephole.

Before patching each subject completed the baseline test of binocular balance. Subjects performed two rounds of baseline measurement per session. They were then patched for certain durations with a translucent patch, which removes form information from the visual input and blocks some light transmission (20%). During patching, subjects either read a book or used a computer. After patch removal subjects performed the post-patching test at 0, 3, 6, 12, 24, 48, 60, and 96 minutes with a shorter version of the binocular phase combination task that they had performed for the baseline measurement (see Fig. 3.6a).

Throughout the combination task a pixelated binary noise frame was presented around the stimuli to encourage proper convergence (Fig. 3.5a). Before each trial, subjects performed an alignment procedure where the screens displayed a dichoptic cross enclosed by high-contrast circles. Subjects aligned the two halves of the cross and the circles using a keyboard. They then pressed the spacebar to begin the trial. The horizontal gratings appear to both eyes. Subjects were asked to move a reference line (thickness of one pixel) using the up and down keys of the keyboard to indicate the perceived center of the dark strip in the fused grating percept. They then pressed the spacebar to continue. The dichoptic cross then reappeared followed by the next trial (Fig. 3.5a).

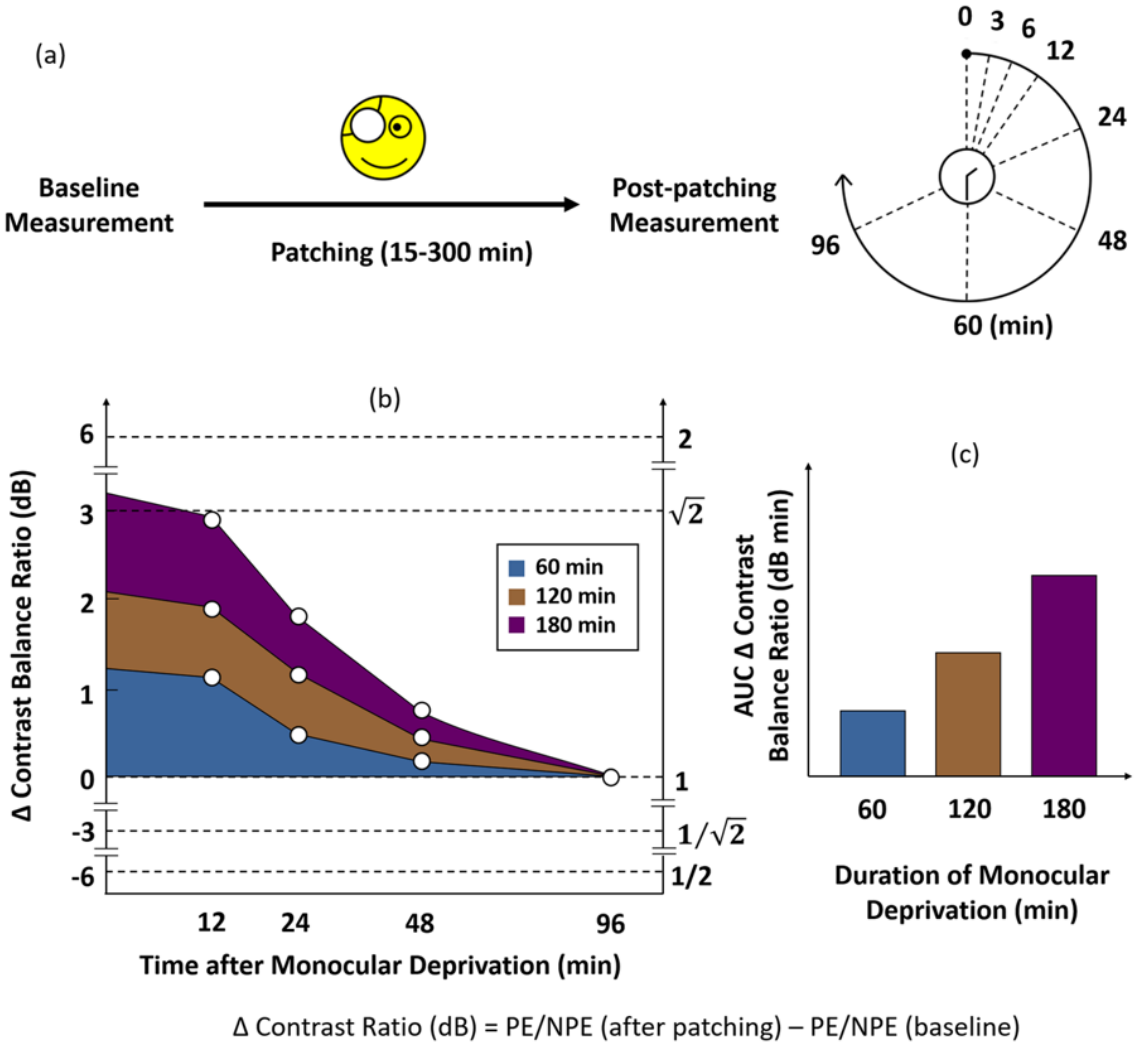

Figure 3.6: **The temporal order for the experiments (a) and data analysis (b,c). Contrast balance ratio is defined by the contrast in the patched eye (PE) over that in the unpatched eye (NPE). (a)** Time course of the experiment: Subjects performed a binocular phase combination task to measure their baseline eye balance. Their dominant eyes were patched for selected durations from 15 to 300 minutes. Finally, they performed the post-patching measurement with the same visual task at 0, 3, 6, 12, 24, 48, 60 and 96 minutes after patching. **(b)** Each point represents the difference in contrast balance ratios before and after monocular deprivation. 0 dB contrast balance ratio represents no difference between before and after monocular deprivation. Different colours represent different durations of monocular deprivation; the blue represents one hour, the brown two hours, and the purple three hours **(c)** After plotting the figure on the left we calculated the area under the curve (AUC) to quantity the overall effect of monocular deprivation; the higher the AUC, the greater the strengthening of the patched eye. The unit for AUC is dB*minutes because the AUC is a product of two units (dB and minutes).

3.5.6 Data Analysis

We averaged the perceived phases from the two configurations. We then fitted the values to psychometric curves defined by a binocular phase combination model [11, 6] (Fig. 3.5b):

$$\phi_A = 2\tan^{-1}\left[\frac{f(\alpha,\beta,\gamma)-\delta^{1+\gamma}}{f(\alpha,\beta,\gamma)+\delta^{1+\gamma}}\tan(\frac{\theta}{2})\right], \tag{3.8}$$

where

$$f(\alpha,\beta,\gamma) = \frac{1+\delta^{\gamma}}{1+\alpha\delta^{\gamma}}, \tag{3.9}$$

θ is the fixed phase difference between the gratings presented to both eyes (45°), ϕ_A is the perceived phase of the two gratings, δ is the interocular contrast balance ratio (of the stimuli shown on the screen), α is a gain factor giving the contrast balance ratio between the two eyes when they contribute equally to binocular vision, and γ controls the slope of the transition between the left and right eye percepts. The two free parameters α and γ are estimated from fitting our data with the function. In our analysis, we bootstrapped the trial-by-trial responses of each to generate a bootstrapped population of α values for each measurement.

We converted α into log units using this equation:

$$\alpha_{dB} = 20 \times log_{10}(\alpha_{ratio}), \tag{3.10}$$

where

$$\alpha_{ratio} = \frac{\alpha_{DE}}{\alpha_{NDE}}, \tag{3.11}$$

The estimated α_{ratio} represents contrast balance ratio when two eyes contribute equally to binocular vision on the linear scale. α_{dB} is the contrast balance ratio in log units. When ratio is 1, α_{dB} is 0, meaning that both eyes are equally balanced. If the patched eye is stronger than the unpatched eye, $\alpha_{dB} > 1$ and thus $\alpha_{dB} > 0$. If the unpatched eye

is stronger than the patched eye, $0 < \alpha_{ratio} < 1$ and thus $\alpha_{dB} > 0$. The higher the value of α_{dB}, the stronger the patched eye compared to the unpatched eye. We computed the difference between dB before and after monocular deprivation and plotted it as Δ con-
330 trast balance ratio (see Fig. 3.6b, left frame for illustration) over time after monocular deprivation. Summary areal measures (units of dB*minutes) were then derived (see Fig. 3.6c, right frame for illustration).

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Manuscript 3. Ocular Dominance Plasticity: A Binocular Combination Task Finds No Cumulative Effect with Repeated Patching

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4.1 Abstract

Short-term monocular deprivation strengthens the contribution of the deprived eye to binocular vision. This change has been observed in adults with normal vision or amblyopia. The change in ocular dominance is transient and recovers over approximately one hour. This shift has been measured with various visual tasks, including binocular rivalry and binocular combination. We investigated whether the ocular dominance shift could be accumulated across multiple periods of monocular deprivation over consecutive days. We used a binocular phase combination task to measure the shift in eye dominance. We patched the dominant eye of ten adults with normal vision for two hours across five consecutive days. Our results show no cumulative effect after repeated sessions of short-term monocular deprivation.

4.2 Introduction

Patching an eye for a few hours increases its contribution to binocular vision. This is observed in human adults after the critical period for visual development. Lunghi et al. [17] first showed this effect by patching adults with normal vision for two hours. This effect induces a shift in ocular dominance and lasts for 30 – 90 minutes after patching [17, 35]. Psychophysical [17, 35, 18, 37, 38], electrophysiological [16, 34] and brain imaging [7, 19, 4] studies in humans have also demonstrated this short-term patching effect. The contrast gain of the non-deprived eye is reduced and that of the deprived eye increased [35, 6] during short-term patching. These reciprocal changes occur possibly in layer 4 of the primary visual cortex (V1) [37, 27, 30] and involve binocular neurones tuned to high spatial frequencies [37, 20]. Intrinsic imaging and voltage-sensitive dye imaging in primate studies have shown these effects in V1 [27, 30]. Early work suggests that the effect does not show orientation tuning [37]. However a subsequent study shows that patching may have multiple effects and exhibit orientation tuning [3]. The patching effect is associated with reduced cortical GABA in V1 [19]. However later stages of visual processing may also be involved during patching [2, 26, 12]. This has been demonstrated with psychophysical studies. For example, Bai et al showed that short-term patching induces different effects in binocular rivalry and combination tasks [2]. Also kaleidoscope manipulation, which does not affect the properties of images, causes one eye to be weaker than the other eye [26]. Moreover continuous flash suppression, Kim et al showed that the patching effect can be induced solely by the suppression of one eye on the other eye without deprivation of visual input [12].

The short-term patching effect in normal adults shows that neural plasticity still exists after the critical period. This remaining plasticity can be exploited to potentially recover the binocular function in adults that had been previously lost in childhood. Amblyopia is a developmental disorder of the visual system. About 3 to 5% of children in the general population develop amblyopia and have poor binocular vision [13]. Several procedures

have been developed to harness any residual plasticity in adults. They may help recover function in the amblyopic pathway [14, 32, 1, 15] and restore binocular function [11].

Shifts in ocular dominance from short-term monocular deprivation could provide a therapeutic benefit. By rebalancing the eyes, short-term patching could restore binocular function. Psychophysical tools such as binocular competition (e.g. rivalry) and combination visual tasks have been used to measure this effect. In binocular rivalry incompatible stimuli are presented to each eye. Since the stimuli are incompatible to each other, these inputs from both eyes rather compete than fuse with each other. Changes in ocular dominance plasticity are measured by relative durations for which each stimulus is perceived. In binocular combination tasks, fusible stimuli are presented to each eye. This is a more typical input from an ecological perspective. Subjects perceive the fused percept based on each eye's level of contribution to binocular vision. Various combination tasks including phase combination, motion combination and contrast combination have been used to measure changes in ocular dominance from short-term patching [18]. Both binocular rivalry and combination tasks have been used to measure changes in sensory eye balance. However different neural mechanisms may be involved [3, 2]. Binocular rivalry represents an inhibitory rivalry of non-fusible monocular images. Binocular combination represents the excitatory combination of fusible images. Therefore they may measure different aspects of sensory eye dominance.

Zhou et al. [39] first showed that adults with amblyopia also exhibited the short-term patching effect with a phase combination task. Recent studies have shown sustained improvements in visual acuity and stereopsis from repeated short-term patching of the amblyopic eye in adults. Lunghi et al. demonstrated this with a binocular rivalry paradigm with physical exercise [22] and Zhou et al. [36] with a binocular combination paradigm. Also Zhou et al. reported marginal improvements in binocular balance [36]. As these studies indicate, when amblyopic eye is patched instead of the fellow eye – as seen in typical therapeutic patching - binocular function may recover. However, this

neuroplastic change will provide long-term benefits only if it can get integrated over time within a protocol. A recent study showed with a phase combination measure that there is little or no dependence of ocular dominance plasticity changes on the duration of the monocular deprivation in normal observers [24]. This suggests that the effects of the deprivation may rapidly saturate, at least for a single "pulse" of deprivation. In this study, we set out to determine whether effects can summate over multiple "pulses" of deprivation. This could be useful clinically, as several short periods of daily monocular occlusion across many weeks might lead to a longer-lasting accumulated benefit.

In this study we used a binocular phase combination paradigm to measure changes in eye balance from short-term patching. We patched normal observers for five consecutive days and found no accumulated changes in ocular dominance. We found no changes in baseline of sensory eye balance across days. This reinforces the notion that there may be no duration dependence in the patching effect [24], whether patching occurs within a single or across multiple days, in normal observers. This finding suggests that the dynamics of ocular dominance plasticity changes in normal observers induced by short-term monocular deprivation are of an all-or-none phenomenon.

4.3 Materials and Methods

4.3.1 Participants

Ten adults (average age = 23, range = 21–25) with normal or corrected-to-normal vision participated in this study. One subject was the listed first author. All other subjects were naïve to the purpose of this study and provided informed consent. This study conformed to the Declaration of Helinski and was approved by the Institutional Review Boards at McGill University.

4.3.2 Apparatus

We programmed the experiment in Matlab 2012a using PsychToolBox 3.0.9 [5, 25]. We presented dichoptic stimuli on head-mounted goggles with a refresh rate of 60 Hz, resolution of 800 × 600 pixels and a mean luminance of 59 cd/m^2. These had separate screens to present the dichoptic stimuli to each eye. For the first five subjects we used eMargin Z800 pro goggles. Due to equipment failure we replaced these with GOOVIS Cinego G2 for the remaining subjects.

4.3.3 Binocular Phase Combination Task

In this task, separate horizontal sine-wave gratings were presented to the two eyes in opposite phases: $-22.5°$ for one eye and $+22.5°$ for the other eye. The phase difference between the two eyes was 45°. The gratings were established at a visual angle of 6.6° × 6.6° degrees, spatial frequency of 0.3 cycles/deg, and base contrast of 60%. We used the method of constant stimuli. Subjects were asked to report the phase of the binocularly perceived grating. They located a flanking reference line to where they perceived the center of the dark strip from the fused percept. When two eyes contribute equally to binocular vision, the perceived phase will be zero (the sum of $+22.5°$ and $-22.5°$. However, when there is relatively stronger input from one eye, this imbalance will bias the fused percept in favour of that eye's stimulus phase.

We showed stimuli at different interocular contrast ratios by increasing the contrast in one eye and decreasing the contrast in the other eye. Modulating the interocular contrast ratio enabled us to find the contrast ratio when two eyes contributed equally (i.e. balance point). When the balance point is reached, the perceived phase is zero. We implemented five interocular contrast ratios ($1/2$, $1/\sqrt{2}$, 1, $\sqrt{2}$, 2) for measuring the baseline balance, and three interocular contrast ratios ($1/\sqrt{2}$, 1, $\sqrt{2}$) for post-patching balance. We determined how much the interocular contrast ratio had to be changed to reach the balance point before and after deprivation. The change in ocular dominance

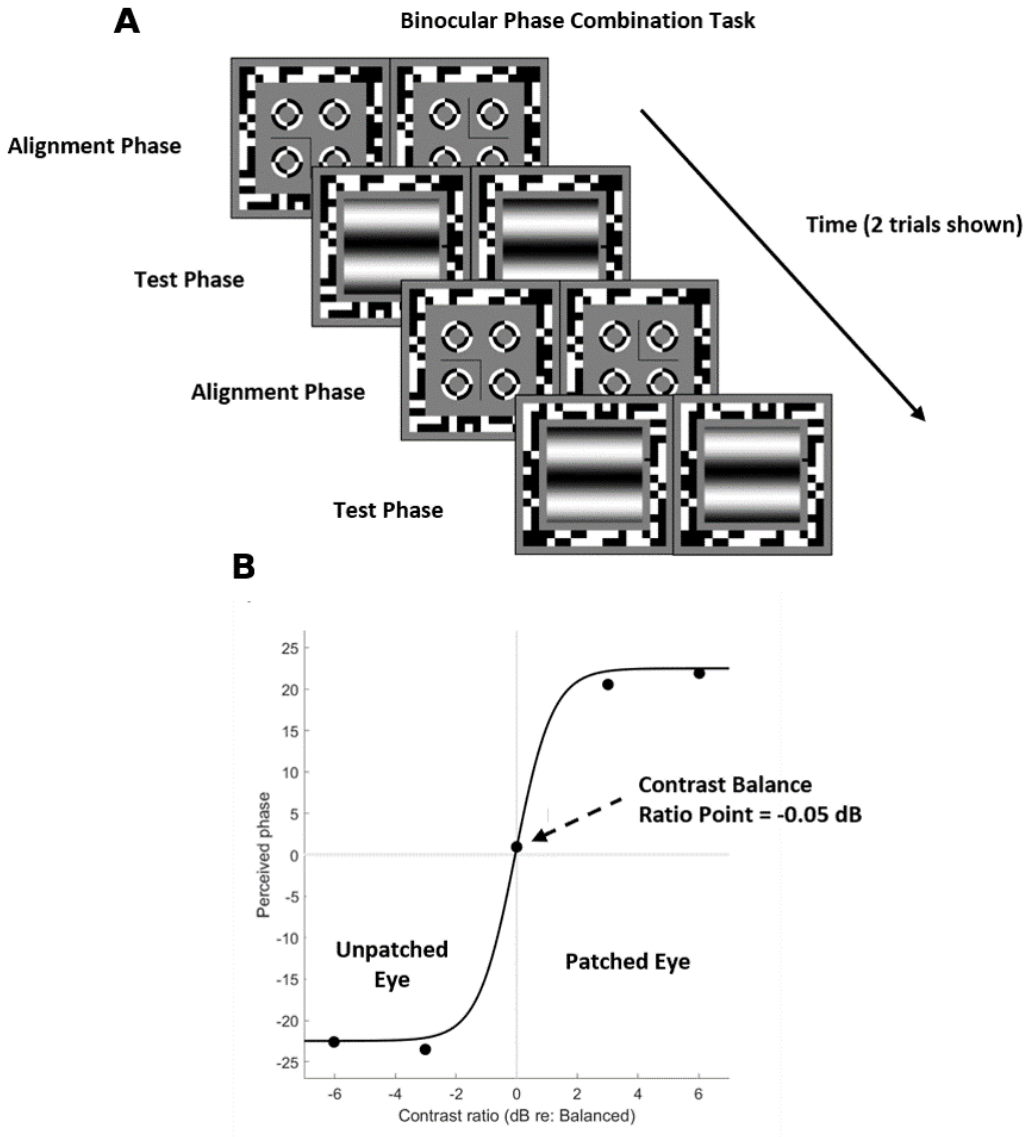

Figure 4.1: The binocular phase combination task and a curve fit of perceived phases to a binocular combination model. **(A)** One trial of the binocular phase combination task consisted of an alignment and test phase. There were eighty trials in baseline measurement and thirty in post-patching measurement. Subjects were asked to move the flanking reference line with a keyboard to where the perceived center of the darkest area in the fused grating was located. The horizontal sinusoidal gratings had a phase difference of 45°. Pixelated binary noise frames enabled subjects to maintain fusion throughout the task. **(B)** A curve fit of data to a contrast gain control model. We fitted perceived phases at different contrast ratios from the visual task to a contrast gain control model [9] to calculate the balance point. A balance point is when two eyes contribute equally to binocular vision (perceived phase = 0°). This figure has been modified from Min et al. [24].

after deprivation was quantified by the differences in the contrast balance ratio between before and after patching.

A trial of the phase combination task had an alignment and test phase. During the alignment phase, subjects aligned the two halves of a dichoptic cross and four circles (Figure 4.1A) using a keyboard. Two circles and one half of the dichoptic cross was shown to each eye. A fused but unaligned percept would be a combinaiton of four circles and a misaligned dichoptic cross. After the align phase, a test phase ensued where a fused horizontal sinusoidal grating was shown. Subjects were asked to report their perceived center of the darkest area in the fused grating by moving a flanking black reference line. After the test phase, the alignment phase returned. Both the alignment and grating stimuli were displayed until each subject completed performing the task. Throughout the task a pixelated binary noise frame was presented around the stimuli to facilitate fusion. Moreover, there were two configurations of the sinusoidal gratings to eliminate positional bias. In the first configuration, the dominant eye was shown with a grating of $+22.5^\circ$ and the non-dominant eye with a grating of -22.5° relative to the center. In the second configuration, the dominant eye was shown with a grating of -22.5° and the non-dominant eye with a grating of $+22.5^\circ$ relative to the center. There were eight trials for every interocular contrast ratio for baseline measurement and five for post-patching measurement. This amounted to 80 trials in the baseline measurement (5 interocular contrast ratios $\times$ 8 repetitions $\times$ 2 configurations) and 30 in the post-patching measurement (3 interocular contrast ratios $\times$ 5 repetitions $\times$ 2 configurations). Subjects on average spent 10 minutes on the baseline task and 3 minutes on the post-patch task.

4.3.4 Procedures

Subjects began the study with baseline measurement. Then their dominant eye was deprived for 120 minutes with a translucent patch. The dominant eye was determined with the Miles test [23]. Post-patching tests were performed at 0, 3, 6, 12, 24 and 48

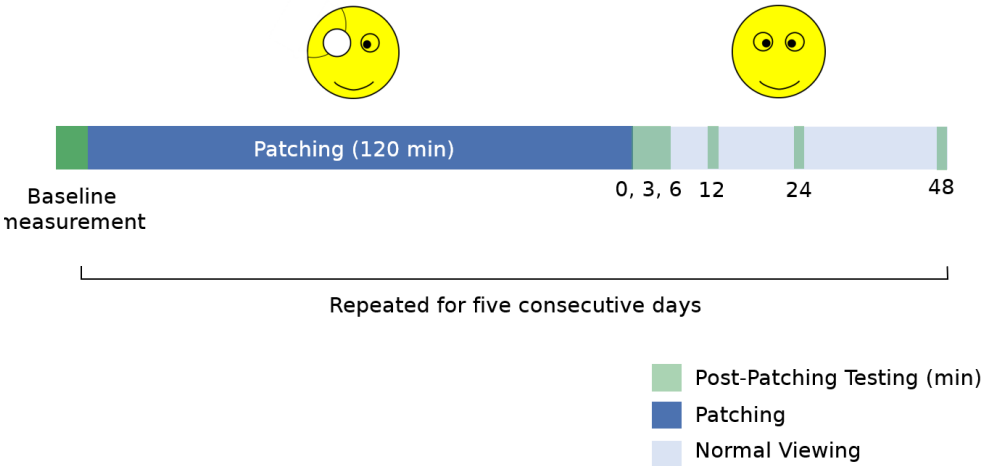

Figure 4.2: **The protocol for the experiment.**

minutes after patch removal. They repeated this sequence for the next four days at a similar time of the day (Figure 4.2).

4.3.5 Data Analysis

Perceived phases from two configurations were averaged. The averaged perceived phases were then fitted to a contrast gain control model ([9]; see Figure 4.1):

$$\phi_A = 2\tan^{-1}\left[\frac{f(\alpha,\beta,\gamma)-\delta^{1+\gamma}}{f(\alpha,\beta,\gamma)+\delta^{1+\gamma}}\tan(\frac{\theta}{2})\right], \tag{4.12}$$

where

$$f(\alpha,\beta,\gamma) = \frac{1+\delta^{\gamma}}{1+\alpha\delta^{\gamma}}, \tag{4.13}$$

θ denotes the fixed phase difference between the gratings that were presented to both eyes (45°), ϕ_A denotes the perceived phase from the two gratings, δ denotes the interocular contrast balance ratio (of the stimuli shown on the screen), α denotes the gain factor which determines the contrast balance ratio between the two eyes when they contribute

equally to binocular vision. γ is the parameter that controls the slope of the transition between the left and right eye percepts. We estimated the two free parameters α and γ by fitting our data of perceived phases to the contrast gain model function [9]. We bootstrapped responses from each trial to generate each measurement's bootstrapped population of α values.

We transformed α into log units with Equation 3:

$$\alpha_{dB} = 20 \times log_{10}(\alpha_{ratio}), \tag{4.14}$$

where

$$\alpha_{ratio} = \frac{\alpha_{DE}}{\alpha_{NDE}}, \tag{4.15}$$

The estimated α_{ratio} represents the contrast balance ratio of each eye's equal contribution to binocular vision in linear units. α_{dB} is the contrast balance ratio in log units. We transformed α_{ratio} into log units (α_{dB}) to avoid bias in favor of the dominant eye. For example, when the contribution of the non-dominant eye (α_{NDE}) is 2 and that of the dominant eye (α_{DE}) is 1, α_{ratio} is 0.5. However, when the contribution of the non-dominant eye (α_{NDE}) is 1 and that of the dominant eye (α_{DE}) is 2, α_{ratio} is 2. The differences between these balance ratios ($\alpha_{ratio} = 2$, $\alpha_{ratio} = 0.5$) and that when two eyes contribute equally ($\alpha_{ratio} = 1$) should be identical but they are not so in the linear scale. For this reason we transformed the contrast balance ratio into log units to avoid bias for the dominant eye. Log transformation of contrast balance ratio has been used in previous studies [3, 24]. We calculated differences in contrast balance ratios between baseline and after patch removal, and plotted them as Δ contrast balance ratio (units in dB). The y-axis (see Figure 4.3A, 4.3B and 4.3C) represents the difference in contrast balance ratios between baseline and after patch removal. The higher the y-axis, the stronger the contribution of the patched eye to binocular vision relative to that before patching. We quantified the patching effect over time (0 to 48 minutes post-patching) by

175 calculating the area under the curve between the linear units of time after deprivation (x-axis in minutes) and the log units of Δ contrast balance ratio (y-axis in dB). The areal measures were in the unit of dB*minutes (see Figure 4.3E and 4.3F).

4.4 Results

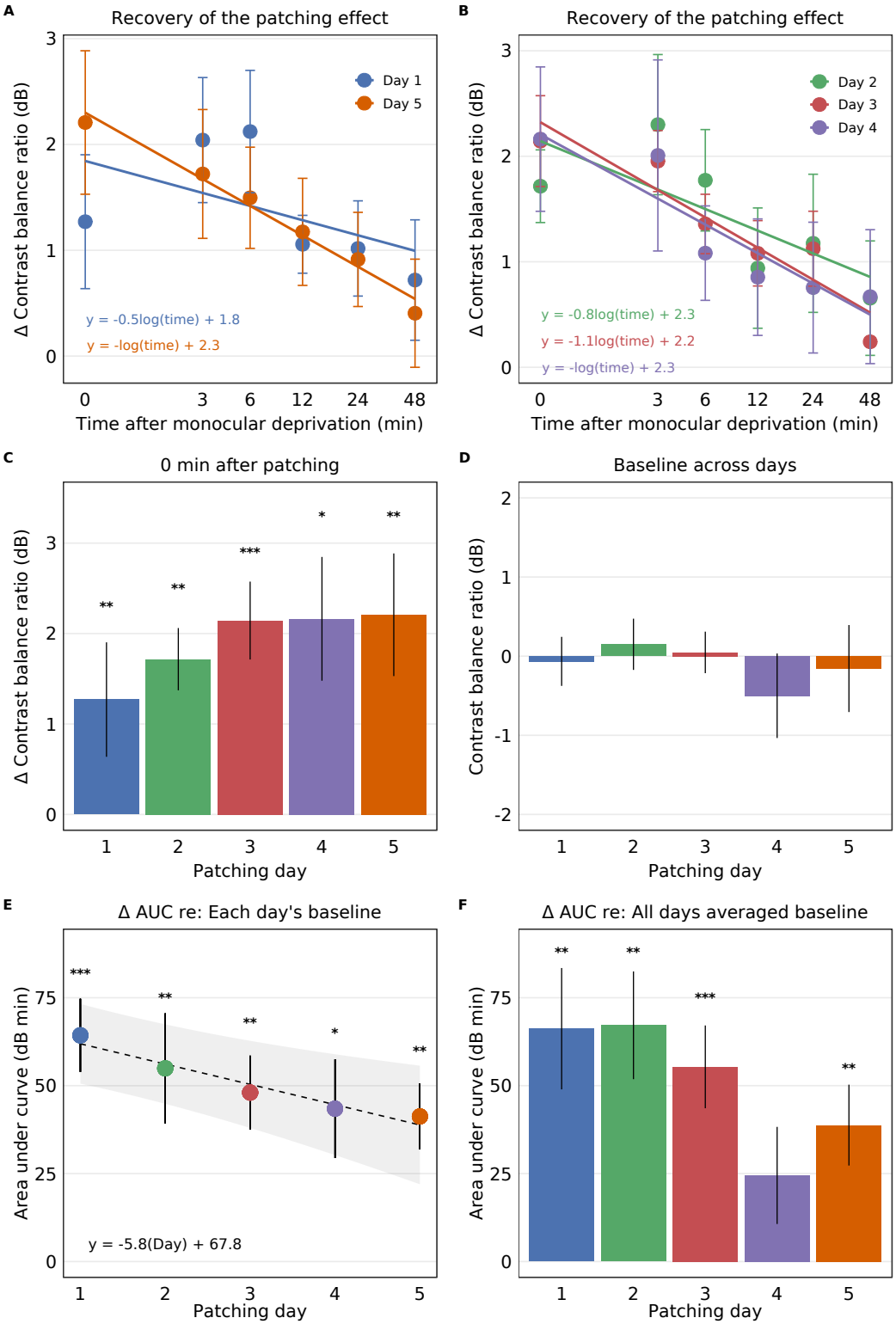
A
Recovery of the patching effect
Δ Contrast balance ratio (dB)
Day 1
Day 5
y = -0.5log(time) + 1.8
y = -log(time) + 2.3
Time after monocular deprivation (min)
B
Recovery of the patching effect
Δ Contrast balance ratio (dB)
Day 2
Day 3
Day 4
y = -0.8log(time) + 2.3
y = -1.1log(time) + 2.2
y = -log(time) + 2.3
Time after monocular deprivation (min)
C
0 min after patching
Δ Contrast balance ratio (dB)
Patching day
D
Baseline across days
Contrast balance ratio (dB)
Patching day
E
Δ AUC re: Each day's baseline
Area under curve (dB min)
y = -5.8(Day) + 67.8
Patching day
F
Δ AUC re: All days averaged baseline
Area under curve (dB min)
Patching day

Figure 4.3: **Averaged results across ten adults with normal vision. (A–B)** The averaged recovery rate of the patching effect on log/log scaled axes from day 1 to 5 of the study (individual recovery plots shown in the Appendix). Each point represents changes in sensory eye balance as a function of the time after monocular deprivation. The error bar shows standard errors. Each color represents different day of the study. **(C)** Averaged changes in contrast balance ratio relative to baseline from each day across all subjects. The error bars show standard errors. The changes in contrast balance ratio on all days are significantly different from baseline (*p $<$ 0.05, **p $<$ 0.01, ***p$<$0.001) according to a one-sample t-test. **(D)** The baseline of each day before each session. Each bar represents baseline from each day averaged across all subjects. The error bars represent standard errors. **(E)** Area under a curve (AUC) reflecting changes of ocular dominance relative to each day's baseline over the established timepoints after patching. This areal measure captures how sensory eye balances changes as a function of time after patch removal; it provides a single number to represent the ocular dominance effect from patching over time. AUC contrast balance ratio of 0 represents no change in eye dominance relative to the averaged baseline across all subjects over time. AUCs relative to each day's baseline is significant (*p $<$ 0.05, **p $<$ 0.01, ***p$<$0.001) according to a two-tailed one sample t-test. The error bars represent standard errors of the AUCs across all subjects. The dashed line represents the averaged linear slope and intercept across all subject over days; linear regression for each subject was performed across AUCs from five days of the study. The shaded error bar (in grey) indicates the range of standard errors from the slopes of best fitted lines for each subject. **(F)** AUC reflecting changes of ocular dominance relative to averaged baseline across all days. AUCs on all days except day 4 are significantly different the averaged baseline according to a two-tailed one sample t-test.

We were interested in whether the recovery rate of the patching effect would be similar between the first and later days after repeated sessions of patching (see Figure 4.3A-B). We linearly fitted the recovery slopes from all five days on log-log axes and quantified the slope and intercepts of the linear fits for every subject. We conducted a paired t-test using RStudio [28] between the recovery slopes on day 1 and 5 across all subjects and found no significant difference between both days, $t(9) = 0.72$, $p = 0.49$. We also conducted a two-way (factors: day of the study, patching) repeated measures ANOVA; we averaged Δ contrast balance ratio at 0, 3 and 6 minutes after patching to compute

the peak patching effect in the ANOVA. We found that the effect of patching itself was significant, $F(1,9) = 17.32$, $p = 0.002$ but the effect of day was not, $F(4, 36) = 1.542$, $p = 0.211$. Therefore, we found no significant difference in the peak patching effect across days. We were also interested in whether there would be a difference in the immediate effect of patching across days. Figure 4.3C shows the averaged changes in the contrast balance ratio relative to baseline across all subjects (individual data figure shown in the Appendix) at 0 minutes after patch removal. We performed a one-sample t-test and found that the patching effect itself was significant at 0 minutes after monocular deprivation (shown by the asterisks in figure 4.3C) on all days. However we found no significant difference in the immediate patching across days from a one-way repeated measures ANOVA ($p > 0.05$).

We wanted to investigate whether the baseline of binocular balance would vary across days after repeated patching. Figure 4.3D shows the averaged baselines across subjects (individual data figure shown in Appendix). We performed a one-way repeated measures ANOVA and found no significant difference in baseline across days, $F(4,36) = 0.88$, $p = 0.48$. We found no indication of accumulation. According to a two-tailed one sample t-test, we found that the averaged baseline across subjects from each day was not significantly different from zero (contrast balance ratio when each eye contributes equally to binocular vision), suggesting that no significant imbalance had been induced by repeated patching.

We quantified the patching effect over time by computing the area under a curve (AUC; units in dB minutes) between the log y-axis of the normalized contrast balance ratio (relative to baseline) and linear x-axis of the established timepoints after monocular deprivation (individual data figure shown in the Appendix (Figures 4.4-4.6; see Figure 4.3E for AUC). The areal measure would equal zero when patching had not induced a shift in sensory eye balance over time relative to baseline. We also wanted to assess whether the magnitude of the areal measure on each day was significantly different from

baseline. A two-tailed one sample t-test revealed a significant difference on all days (see Figure 4.3E). Moreover we examined whether the magnitude of AUC varied across days. A one way repeated measures ANOVA showed no significant difference in the the magnitude of each day's AUC across days, $F(4, 36) = 0.65$.

We observed that the magnitude of AUCs decreased across days (see Figure 4.3E). We wanted to investigate whether the decreasing trend was significantly different from the slope of zero. We linearly fitted the areal measures across days for every subject and calculated the slope and intercept for each linear fit (i.e. each subject). We then performed a two-tailed one sample t-test and found that the decreasing trend (averaged linear slope and intercept shown in Figure 4.3E) was not significantly different from zero, $t(9) = -1.87$, $p = 0.095$. The range of standard errors from the slopes of the linear fits is shown as a grey shade (see Figure 4.3E). We realized our sample size could have been too small to detect any significance. To avoid from making a type II error, we performed power analysis for one-sample t-test and found that we would need fifteen more subjects to reach statistical significance (power = 0.39). Figure 4.6B (in the Appendix) shows that seven subjects showed a decreasing trend of AUCs from day 1 to 5.

Since the baseline was not significantly different across days (see figure 4.3D), we averaged the baselines across all days for every subject and calculated AUCs relative to the averaged baseline across days (see Figure 4.3F; individual data figure in the Appendix). We wanted to investigate whether AUC on each day relative to the averaged baseline varied significantly from zero. So we performed a two-tailed one sample t-test and found that each day's AUC was significantly different from zero except the one from day 4. We were also interested in whether the AUCs relative to the averaged baseline differed across days. A repeated measures one-way ANOVA revealed no significant effect across days, $F(4, 36) = 1.69$, $p = 0.174$.

4.5 Discussions

We reported in a previous study that the patching duration (15 to 300 minutes) does not affect the magnitude and the recovery rate of the patching effect in adults with normal vision [24]. Therefore we suggested that the patching effect is an all-or-none phenomenon. In this study, we examined whether ocular dominance changes could be accumulated across repeated sessions of patching in normal adults. We found that the patching effect does not accumulate after five consecutive days of deprivation. This finding suggests that the patching effect from any one period of deprivation is not long lasting in normal adults. Furthermore, the baseline of eye balance was not different across days after repeated patching for five days. This is quite different from the plasticity effects produced by transcranial magnetic stimulation which, at least in terms of amblyopic observers, are short lived after a single period of stimulation [29] but do accumulate across separate periods of stimulation on five consecutive days [8].

Both this study and the aforementioned study on the effects of patching duration suggest that the patching effect is an instantaneous, all-or-none homeostatic mechanism with fast dynamics in normal adults [24, 31]. However it is important to note that both of these studies used a phase combination task as a primary measure for sensory eye balance. Findings reported in this and the previous study may not be observed in other measures such as binocular rivalry. A future work is necessary where other measures are used. Findings from one measure may not be generalized to others because different neural mechanisms may be involved during different psychophysical tasks [3]. For instance, binocular rivalry displays two incompatible stimuli to both eyes. Separate neuronal populations with different preference of orientation will get activated. Conversely, binocular combination shows compatible stimuli to both eyes and therefore activates a common neuronal population (i.e. same preference of orientation) in the primary visual cortex. A recent study found no correlation between parallel and cross-oriented masking after patching in adults with normal vision [3]. A parallel mask ensures that the spa-

tial properties of the visual stimulus are identical in both eyes, whereas a cross-oriented mask is orthogonally rotated to the visual target. The former represents binocular combination whereas the latter binocular rivalry. Likewise the levels of changes in ocular dominance after monocular deprivation may be task-specific [3]. Moreover, future studies should also investigate the test-retest reliability of various psychophysical tools for measuring sensory eye balance. Recent studies have shown opposite effects of exercise on the patching effect using binocular rivalry measures [21, 10].

In adults with normal vision, a fast-homeostatic mechanism after visual disruption is expected. For example, if changes from visual disruption such as patching is accumulated in normals, their binocular balance can be lost. Therefore, a homeostatic mechanism that returns eye balance back to baseline soon after abnormal visual experience will be beneficial in normals. If a similar hemostatic mechanism occurs in adult amblyopes as observed in normals, short-term patching may be an unsuitable therapeutic intervention. Long-lasting neuroplastic changes are necessary to recover their binocular function. Thus the nature of the homeostatic mechanism can be different. Both Lunghi et al and Zhou et al [22, 36] demonstrated with binocular rivalry (coupled with physical exercise) and binocular combination respectively that the visual acuity and stereopsis improvements could be sustained after repeated patching. This result suggests that changes in ocular dominance may be longer lasting after visual disruption in adult amblyopes than normals. However it should be noted that the changes in ocular dominance that we report here for normals are for a stimulus of low spatial frequency where we have sufficient spatial resolution to make accurate phase measurements. The spatial loss in amblyopia is limited to high spatial frequencies, so future studies of the cumulative effect of monocular patching in amblyopia should target high spatial frequencies. To do this another approach whose accuracy is not compromised at high spatial frequencies will have to be undertaken, such as the recently developed orientation combination task [33].

4.6 Appendix

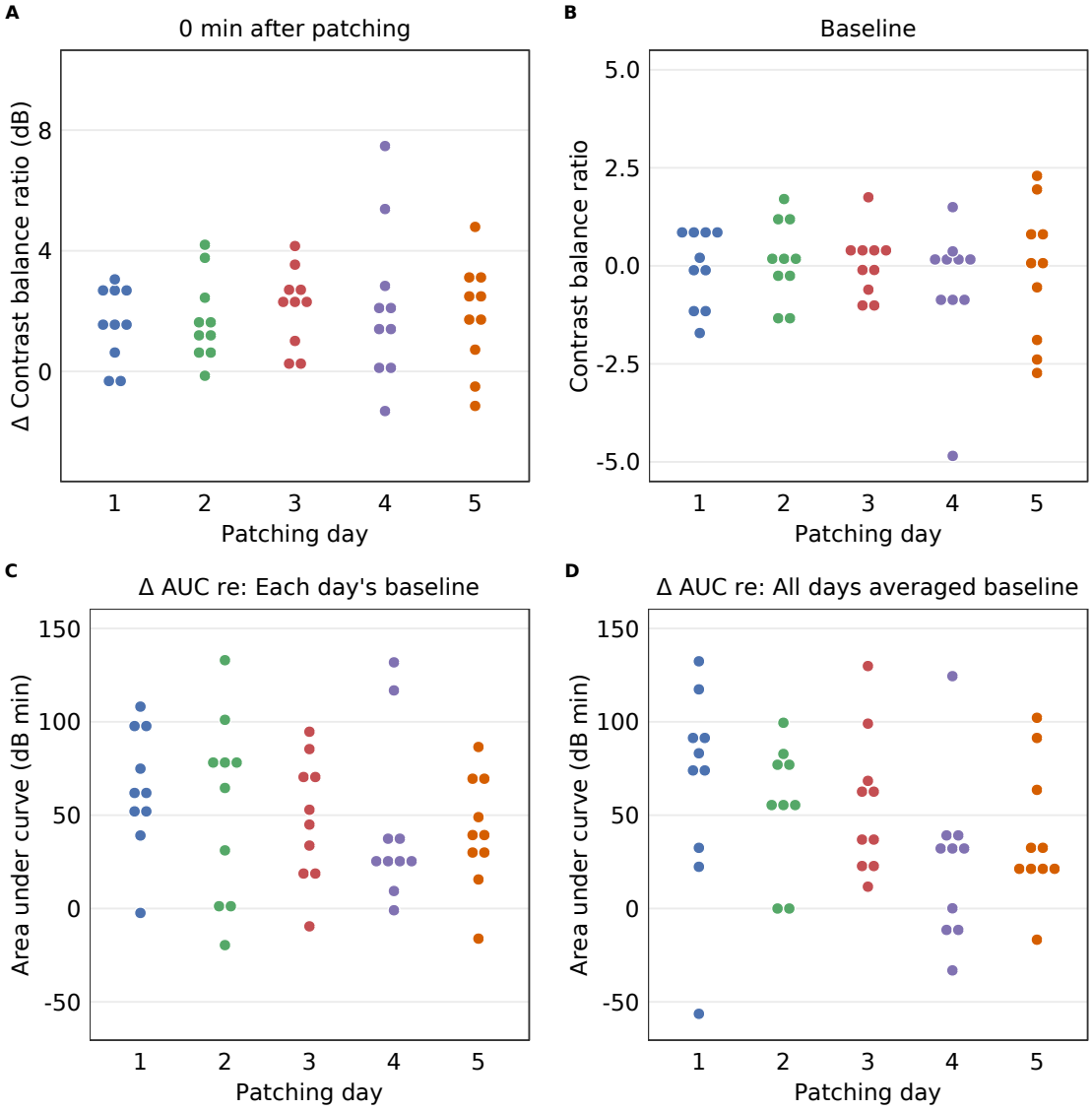

Figure 4.4: **Dot plots of individual data.** **(A)**Each subject's differences in contrast balance ratios between 0 minutes after patching and baseline across five days. **(B)** Each subject's baseline of contrast balance ratio across five days. **(C)** Each subject's area under the curve relative to each day's baseline. **(D)** Each subject's area under the curve relative to the averaged baseline of all days.

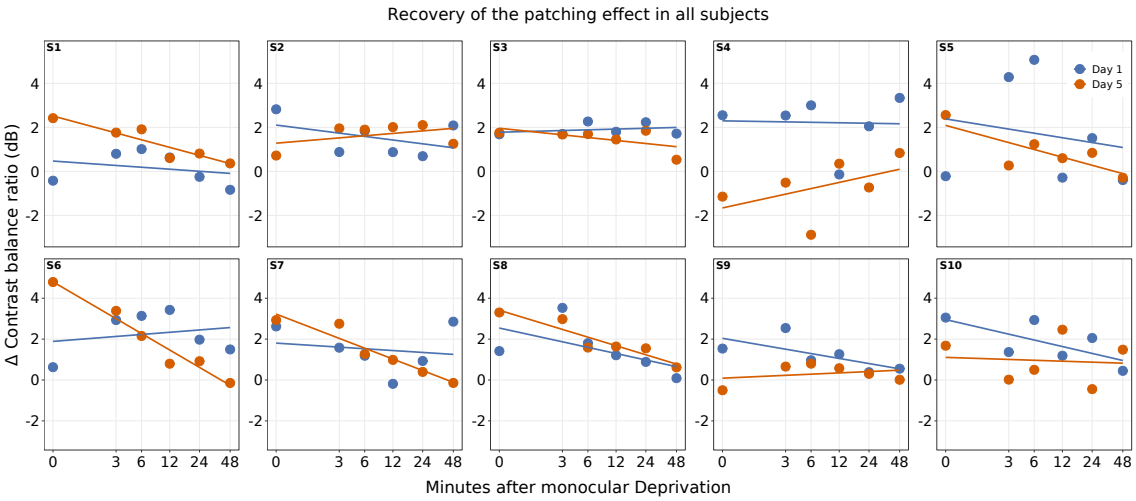

Figure 4.5: **Each subject's recovery slope after monocular deprivation on day 1 and 5.**

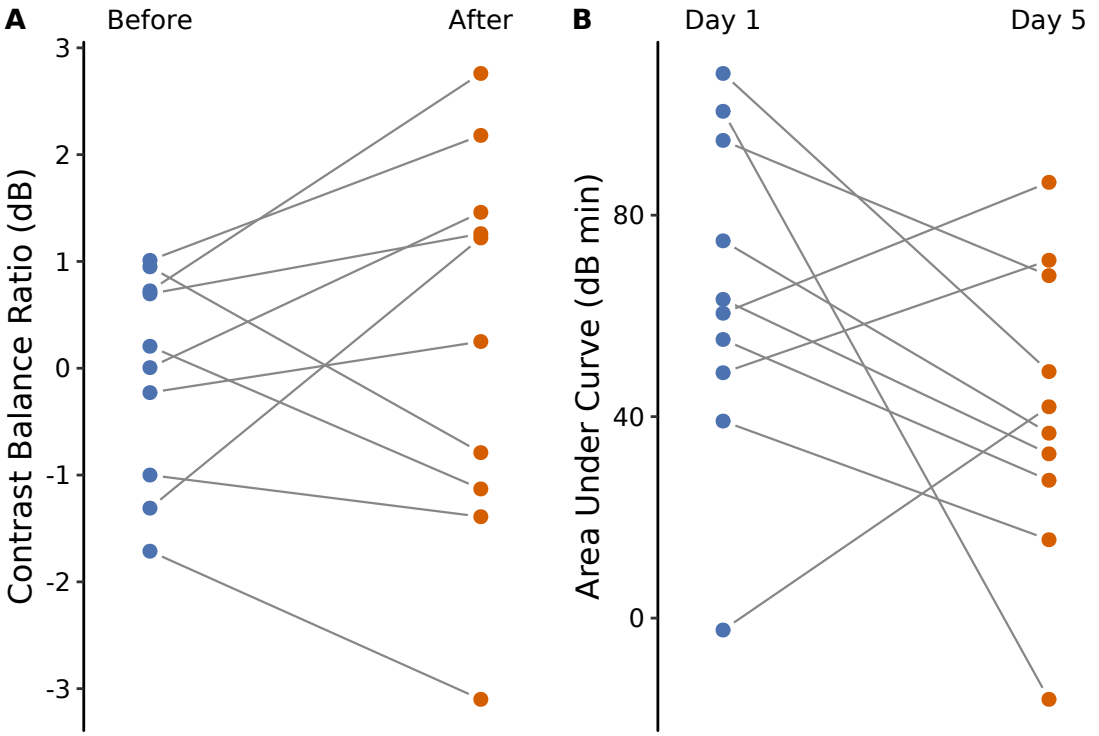

Figure 4.6: **Each subject's changes in eye balance between day 1 and 5. (A)** Contrast balance ratio of each subject from before (i.e. baseline on day 1) to after the study (48 minutes after patching on day 5). **(B)** Area under the curve for each subject on day 1 and 5.

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Manuscript 4. The shift in ocular dominance depends on the duration of deprivation in amblyopia

Authors: Seung Hyun Min, Yiya Chen, Zhifen He, Jiawei Zhou and Robert F. Hess

5.1 Abstract

Recent studies have shown that short-term monocular deprivation (as short as 15 minutes) strengthens the deprived eye's contribution to binocular vision in both normal and amblyopic adults. In this study, we investigate whether changes in ocular dominance plasticity in amblyopia depend on the duration of deprivation. We recruited 9 adults with amblyopia and patched their amblyopic eye for 30, 120 and 300 minutes across separate days. We tested their sensory eye balance before and after deprivation using a binocular phase combination task. We observed that the magnitude of the amblyopic eye's contribution in binocular phase combination strengthened significantly for all deprivation durations. Moreover, we found a significantly larger change in ocular dominance from 30 minutes to either 120 or 300 minutes of deprivation. However, we found no difference in the change of ocular dominance between 120 and 300 minutes. Our findings indicate that a longer duration of deprivation brings about a larger change in ocular dominance balance in amblyopia, but in a non-linear fashion. These results are

pertinent to any future protocol using patching of the amblyopic eye as an adjunct to binocular treatment.

5.2 Introduction

Although amblyopia therapy over the last 200 hundred years has concentrated on improving monocular acuity [17], there is a growing realization that restoration of binocular vision would be much more beneficial for real-world tasks. In the best-case scenario of 20/20 vision being recovered in the amblyopic eye, the binocular benefit would be only a 40% gain in binocular acuity. That assumes a full recovery of binocular vision (i.e., perfect binocular combination). If, for example, binocular vision was not fully restored, then the functional binocular benefit would be zero. On the other hand, restoration of binocular vision would result in a number of real-word benefits which have important functional consequences; reading speed [10], postural stability [35], prehension [16], driving performance [1] and sport performance [5]. This is why there is a current interest in approaches to therapy in amblyopia that are aimed at restoration of binocular vision (for review see, Hess and Thompson [8]) rather than what has been done in the past with patching therapy, which only focussed on improving the vision in the amblyopic eye.

Relatedly, it has been shown that short-term occlusion of an eye in a normal subject can strengthen that eye's contribution to binocular vision [18, 31]. This is thought to be due to homeostatic mechanisms, reflecting a residual neuroplasticity [26]. Although this benefit is short-lived, a similar effect has been demonstrated in patients with amblyopia [34]. The clinical relevance of this finding is that, if the amblyopic eye is patched, the subsequent strengthening of the amblyopic eye's contribution to binocular vision could represent an important new type of binocular therapy. An added attraction is that, unlike the current patching of the sighted eye, this would not be met with such resistance by amblyopic kids [27]. Two recent laboratory trials have demonstrated the

effectiveness of amblyopic eye patching in children over a two-month period [19, 32]. Both trials showed long-term binocular benefits and associated monocular benefits in acuity.

One fundamental consideration in the development of a new patching treatment is the duration of patching that should be used each day. Although normal and amblyopic observers both display a change in their binocular balance after 1-2 hrs of monocular deprivation that lasts between 30-60 minutes, it is not known how the magnitude of this binocular imbalance changes with the duration of monocular deprivation. In normal observers, there is a surprisingly small dependence of the change in either the magnitude or the longevity of the binocular effect with duration of deprivation between 15 min to 5 hrs [22]. For any clinical application of this approach to amblyopia, one needs to know how the rebalancing of binocular vision (amblyopic eye being patched) depended on the duration of patching, as we cannot assume it would the same as for normal vision. We set out to answer this question.

In 9 amblyopic patients we studied the dependence of patching duration of the amblyopic eye on the subsequent rebalancing of binocular function. We examined three durations of patching, 30, 120 and 300 minutes for each patient. We observed a significant change in binocular balance between 30 and 120 minutes, as well as between 30 and 300 minutes of patching. However, we found no difference between 120 and 300 minutes. Therefore, our findings indicate that the response to short-term patching exhibits a non-linear relationship with patching duration.

5.3 Material and methods

5.3.1 Participants

Nine patients (aged 23.8 $\pm$ 2.3, 5 females) with anisometropic amblyopia participated in this study. The clinical details of the patients are provided in Table 1. All subjects were

naïve to the purpose of the experiment and provided written informed consent. This study is in line with the Declaration of Helsinki and was approved by the Institutional Review Boards at McGill University and Wenzhou Medical University.

Table 5.1: Clinical details of the participants

ID	**Age/Sex**	**Cycloplegic refractive errors (OD/OS)**	**logMAR visual acuity (OD/OS)**	**Patient history**
S1	26/M	-0.50 +5.00/- 3.00×180	0.00 0.70	Glasses since 18 yrs old, patched for 3 months since 18 yrs old
S2	21/M	-4.50 +5.50	-0.10 0.60	Glasses since 11 yrs, patched for 6 months since 11 yrs old
S3	22/M	-4.00 +5.00	-0.10 0.60	Glasses since 8 yrs, patched for 1 yr since 8 yrs old
S4	23/F	-6.00/-3.00 ×75 -6.00	0.20 -0.10	Glasses since 13 yrs old, patched for 1 yr since 18 yrs old
S5	21/F	+0.50/-0.50 ×180 -2.75/-0.50×180	0.20 0.00	Glasses since 10 yrs old, patched for 1 yr since 10 yrs old
S6	27/M	-4.00/-1.25 ×180 +0.25	0.00 0.40	Glasses since 13 yrs old, patched for 1 month since 13 yrs old
S7	27/F	Plano +1.50/-0.50×180	-0.10 0.15	No glasses, no patching
S8	23/F	-1.00 +1.50	0.00 0.30	No glasses, no patching
S9	25/F	Plano +4.50/-0.75×15	0.00 0.50	No glasses, no patching

5.3.2 Apparatus

70 We programmed the experiment with MATLAB 2015a with PsychToolBox 3.0.9 extensions [24]. We measured sensory eye balance of all subjects on a Mac computer by presenting dichoptic stimuli with gamma-corrected head mount goggles (NED Optics Groove pro, OLED) with a refresh rate of 60 Hz and resolution of 1920 x 1080 to each

eye. The maximal luminance of the goggles was 150 cd/m^2.

5.3.3 Binocular Phase Combination Task

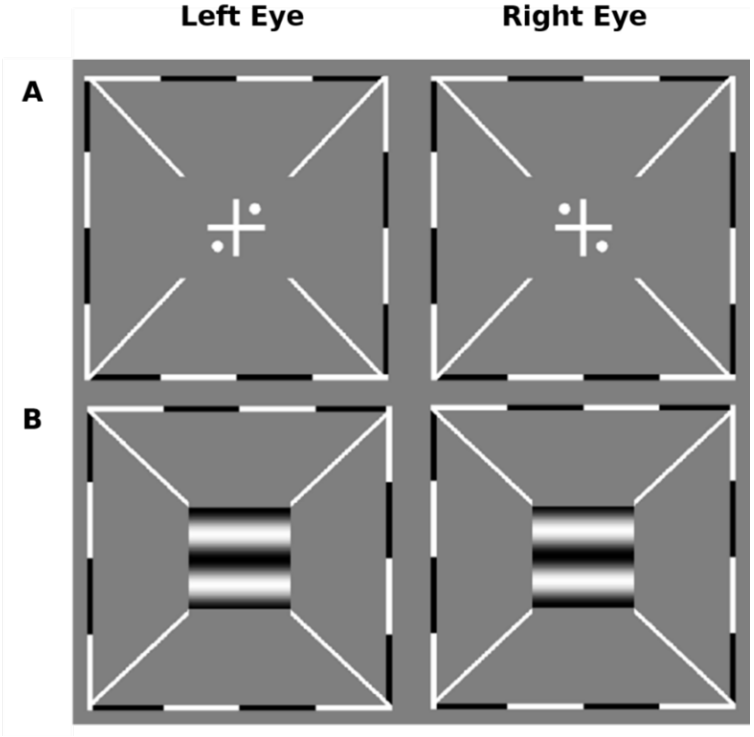

Figure 5.1: **An illustration of the binocular phase combination task. (A)** The alignment task facilitates fusion between the two screens. The subject was asked to align the dots within the crosses so that the distance between neighboring dots were equal. **(B)** During the test task subjects were shown with two similar but oppositely phase-shifted sinusoidal gratings.

In this study we used a binocular phase combination task to measure the patching effect. Two separate horizontal sine-wave gratings (0.46 cycle/°, 4.33°× 4.33°) with equal and opposite phase shifts (+22.5° and -22.5°) relative to the center of the screen were presented to both eyes. The perceived phase of fused stimuli was 0° when the two eyes contributed equally to binocular fusion. A trial of the combination task consisted of two tasks: alignment and test tasks. During the alignment task, subjects were asked to align two pairs of dots both eyes so that the distance between the neighboring dots were

equal. This task ensured proper fusion throughout the measure. Then subjects began the test task where the two sinusoidal gratings were presented (see Figure 5.1), one to each eye. The subjects located their perceived middle portion of the dark patch in the fused grating by placing a flanking 1-pixel reference line. The stimuli were displayed until subjects completed the task in each trial. Observer's binocular perceived phase was then calculated based on the position of the reference line.

Throughout the task the amblyopic eye was displayed with stimuli at a fixed contrast of 100%, whereas the normal eye was shown with stimuli at a fixed contrast 100% $\times$ balance point (δ). The balance point is the value of the interocular contrast ratio between the non-patched eye and the patched eye when they contribute equally to binocular vision in the baseline test (see Figure 5.2). Two configurations of the stimuli were used to account for positional bias. For example, For example, the fellow eye was once shown with a phase of -22.5° and the amblyopic eye with a phase of +22.5° (configuration 1), and then those of +22.5° and -22.5° respectively (configuration 2). We randomized the order of the configurations. We quantified the perceived phase of the fused grating by dividing the difference between the perceived phases in the two configurations by two (i.e., 0.5 x ($\text{Phase}_{configuration2}$ - $\text{Phase}_{configuration1}$).

Two separate sinusoidal gratings were presented to the two eyes. These gratings had opposite phase shifts ($\pm$ 22.5°) relative to the center of the screen. In this example, the phase shift is negative for the fellow (non-patched) eye and positive for the amblyopic eye (patched). If the fellow (non-patched) eye gets stronger, the perceived phase in the fused stimuli will become negative. Conversely if the amblyopic (patched) gets stronger, it will become positive.

We first obtained each subject's balance point with the binocular phase combination task (see Figure 5.1). This balance point was defined as the interocular contrast ratio, where the two eyes were equally effective in binocular phase combination; and the perceived phase was 0 degrees (Figure 5.2). The balance point was unique for each subject

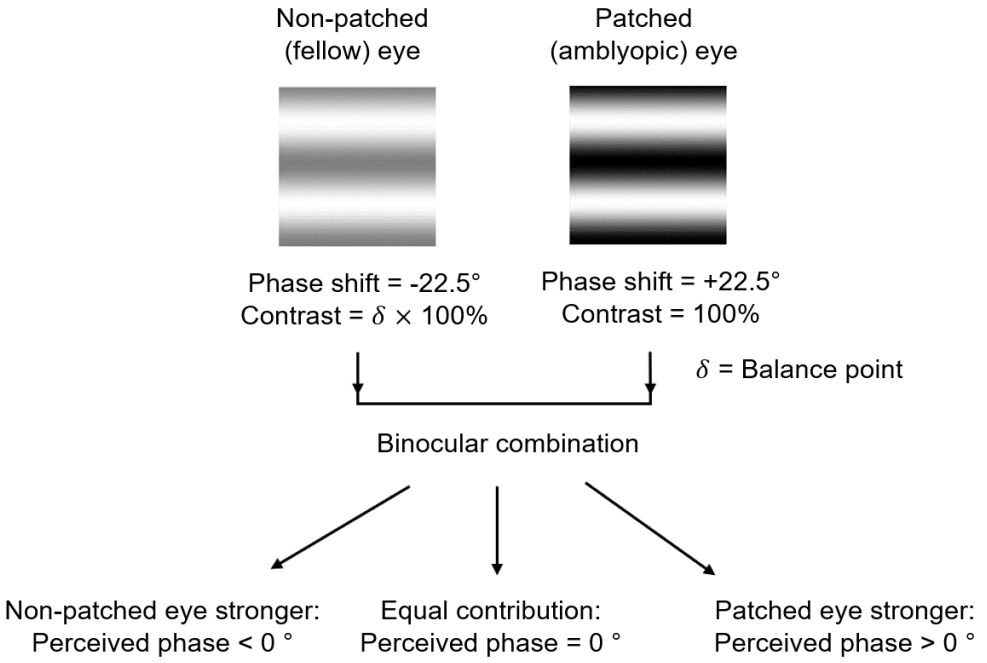

Figure 5.2: **Ocular dominance plasticity was quantified with values from the change in binocular perceived phase.** Two separate sinusoidal gratings were presented to the two eyes. These gratings had opposite phase shifts (22.5°) relative to the center of the screen. In this example, the phase shift is negative for the fellow (non-patched) eye and positive for the amblyopic eye (patched). If the fellow (non-patched) eye gets stronger, the perceived phase in the fused stimuli will become negative. Conversely if the amblyopic (patched) gets stronger, it will become positive.

depending on their eye balance. In all subjects, the relative contrast of the grating shown to the unpatched eye (i.e., fellow eye) is less than that to the patched eye (i.e., amblyopic eye; see Figure 5.2) at the balance point. We selected this interocular contrast ratio at balance point for the patching study for each observer.

Before patching, the subjects were asked to perform three blocks of baseline experiment, each of which lasted for about three minutes (see Figure 5.3). This enabled us to measure their binocular perceived phase before patching. After completing the baseline test, participants were asked to occlude their amblyopic eye with a translucent patch for either 30, 120 or 300 minutes. We randomized the order of the three conditions (patch-

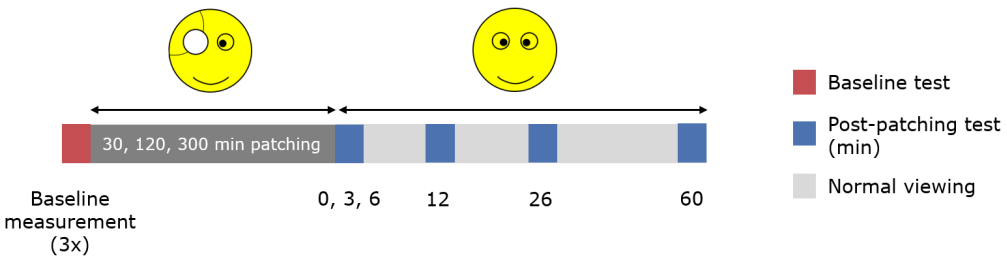

Figure 5.3: **The procedure of the experiment** Three sessions of baseline test were conducted. Then the patients were patched for either 30, 120 or 300 minutes (completed in a randomized order). Next, they performed post-patching test at 0, 3, 6, 12, 26 and 60 minutes after patching.

ing durations). Each condition was performed on a separate day. During patching, the subjects performed ordinary office tasks such as using a computer or reading a book. After patching, we re-measured observers' binocular perceived phase at 0, 3, 6, 12, 26 and 60 minutes after patching (see Figure 5.3). These timepoints were chosen so that the space in log units would be approximately identical; they are not exactly uniform because the task usually takes about 3 minutes to complete, and some intervals were smaller than 3. The experimental conditions were separated by at least 24 hours.

5.3.4 Data Analysis

We used R software to perform statistical analysis and data visualization. We performed a two-way, repeated measures analysis of variance (ANOVA) with two within-subject factors as patching duration and timepoint after patching. The alpha was established at 0.05 for statistical significance. Then, we computed area under the curve as a unit that represents the longevity of the patching effect. Using the areal measures, we then performed a pairwise t-test (with Bonferroni correction) with the alpha level at 0.05. We also calculated effect size as Cohen's d and its 95% confidence intervals between the areal measures. If the confidence interval of the effect size does not overlap 0, it indicates statistical significance. Data from normal observers were extracted from Min et al. [22] and were analyzed in a similar fashion as above.

5.4 Results

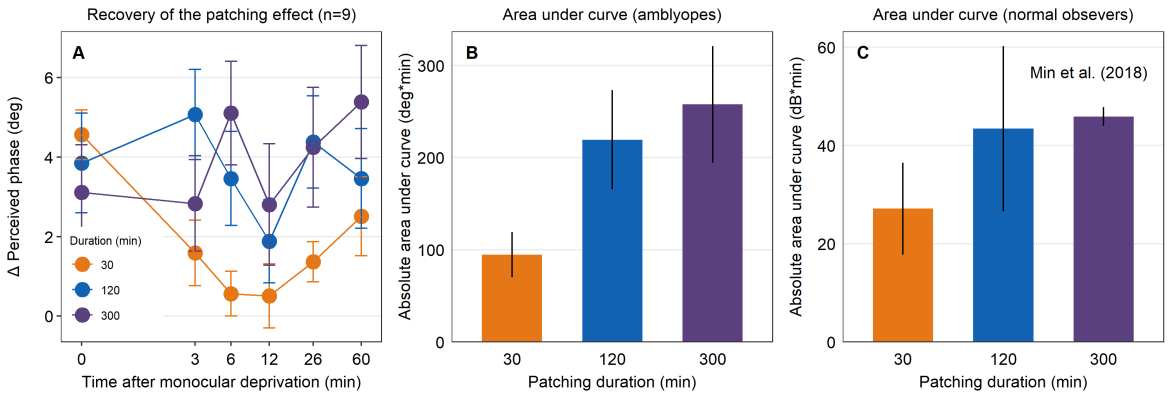

Figure 5.4: **Results.** **(A)** The data show the mean changes (y-axis) in sensory eye balance (post-patching – baseline), which is represented by perceived phase (degrees), over time (x-axis). Different colors denote different durations. Nine amblyopes were tested. **(B)** The bar graph shows the area under curve of panel A for each patching duration. **(C)** The bar graph shows the area under curve using data of normal observers in the three identical patching durations extracted from Min et al. [22]. The unit in the y-axis (sensory eye balance) is different from those of panels A and B because a slightly different binocular phase combination task was used. The subjects are not paired.

To begin with, we wanted to compare the changes in binocular perceived phase relative to baseline (i.e., the patching effect) across different patching durations at each timepoint. As shown in Figure 5.4A, 0 at y-axis represents baseline; any point above 0 in the y-axis represents an increase in the contribution of the deprived (amblyopic) eye in binocular phase combination. We performed a two-way repeated measures analysis of variance (ANOVA; two within-subject factors: timepoint after patching and patching duration). The effect of patching duration was found to be not significant ($F(2,16) = 3.24$, $p = 0.066$, partial eta squared $= 0.078$); the effect of time was not significant ($F(5,30) = 1.584$, $p = 0.187$, partial eta squared $= 0.046$); the interaction between patching duration and time was also not significant ($F(10,60) = 1.85$, $p = 0.065$, partial eta squared $= 0.077$). It is clear from the ANOVA result and quantitative assessment of Figure 5.4A that the effect of time is not significant; hence, the null hypothesis for

the effect of time cannot be rejected. However, we can observe (see Figure 5.4A) that the time course of the patching effect is different depending on the patching duration. For instance, the orange plot (30 minutes patching) descends to near 0 (baseline) at 6 and 12 minutes after patching, whereas the blue and purple (120- and 300-minutes patching) plots hover at around 2-5 degrees. Therefore, it seems reasonable to consider the possibility that there is a notable difference in the magnitude of the patching effect (ANOVA factor: patching duration) and its time course (interaction between patching duration and time). One reason that our ANOVA reported a non-significant effect of patching duration and the interaction is that there is a direct relationship between the p-value and the sample size regardless of the effect size of treatment (which in this case is either the patching duration or interaction). Hence, when the sample size is small, one can fall into the trap of not rejecting the null hypothesis when the effect of treatment truly exists (type II error: false negative). On the other hand, when the sample size is excessively large, even a minor treatment effect can lower the p-value below 0.05 (type I error: false positive). In our case, the p-values are slightly above the alpha level (0.05). There are two explanations as to why they exceed the alpha level: 1) there is no effect of patching duration and the interaction, 2) our sample size is inadequate to properly detect a statistical significance even if the effects are truly large. Therefore, we will also use effect size (Cohen's d).

We quantified the longevity of the patching effect by calculating the area under curve from the plots shown in Figure 5.4A. Longevity is clinically relevant because the patching effect must be long-lived to provide long-term benefit. A difference in area under curve across the conditions can indicate either that the magnitude of the patching effect across durations is different or that the time course of the patching effect recovery (long-lived vs. short-lived) is different across durations. Therefore, it represents both the effect of patching and interaction between patching duration and timepoint in the context of our ANOVA analysis. To compare the means of the areal measure across the patching

durations, we performed a pairwise t-test (with Bonferroni correction) and computed Cohen's d as effect size. We observed a significant difference between 30 and 120 minutes of patching ($t(8) = 2.91$, $p = 0.058$, Cohen's $d = 0.995$, 95% CI for Cohen's d = [0.0157, 1.9746]) and between 30 and 300 minutes of patching ($t(8) = 3.14$, $p = 0.042$, Cohen's d = 1.13, 95% CI for Cohen's d = [0.138, 2.1289]). However, we did not find a significant difference between 120 and 300 minutes of patching ($t(8) = 0.461$, $p = 0.657$, Cohen's d = 0.219, 95% CI for Cohen's d = [-0.708, 1.145]). Note that for the comparison between 30 and 120 minutes of patching, the p-value remained above the alpha level but the confidence interval of Cohen's did not overlap with 0. This indicates that our sample size is not large enough to reject the null hypothesis based on the p-value alone, but the effects of patching duration and interaction seem to be significantly large for our findings to be replicated across laboratories. Therefore, we cannot simply fail to reject the null hypothesis even if the p-values are above 0.05 because the effect size of the patching duration and interaction is significantly large. In short, there is a significant difference in the areal measures between 30 and 120 minutes of patching, and 30 and 300 minutes of patching, but not between 120 and 300 minutes of patching.

To compare our results from amblyopic observers to those from normal observers (Min et al., 2018), we replotted the areal measures (changes in eye balance across 0 to 60 minutes after patching) for the same patching durations: 30, 120 and 300 minutes (Min et al., 2018). There are three differences between the current study and the one of Min et al (2018). First, in the study of Min et al. (2018) subjects were not paired except one for 30 (n=7) and 120 (n=8) minutes conditions. Also, only three subjects from the 120-minute duration participated in the 300-minute duration. Second, the y-axes in Figure 5.4B and 5.4C are different because the tasks are slightly different although they both measure binocular combination with phase stimuli. Third, the timepoints after patching are slightly different although both designs span from 0 to 60 minutes. To compare the means of the areal measure between patching durations, we performed

a Welch Two Sample t-test and computed Cohen's d as effect size. We did not find a significant difference between 30 and 120 minutes of patching (t(11.2) = -0.629, p = 0.54, Cohen's d = 0.314, 95% CI for Cohen's d = [-0.707, 1.133]). Also, we did not find a significant difference between 30 and 300 minutes of patching (t(7) = -1.356, p = 0.22, Cohen's d = 0.615, 95% CI for Cohen's d = [-0.423, 1.653]). Therefore, in normal observers, there seems to be no effect of patching duration on the magnitude of the changes in eye balance.

5.5 Discussion

A previous study showed that there was no significant relationship between the magnitude of eye balance changes and the patching duration in normal adults [22]. Furthermore, it has been shown that repeated patching for 150 minutes for five consecutive days does not result in the accumulation of the effect in normal adults [21]. These results raise the possibility that the change in sensory eye balance from short-term patching is not a typical visual adaptation, which typically exhibits a dependence on the duration of adaptation [4, 30] and a storing of effects across days [29, 25]. Instead, it appears that the dynamics of the patching effect in normal observers is an instantaneous, all-or-none phenomenon, having little or no storage.

On the other hand, the capacity for the sensory eye balance changes in normal adults is limited to begin with. This might explain why a significant effect did not carry across patching durations. In amblyopes however, the capacity for change is greater than adults with normal vision because their visual system is already very imbalanced [9, 31]. Therefore, a significant effect of patching duration in amblyopia may occur. Our findings suggest that the duration of deprivation may matter when it comes to comparing short (30 minutes) and long durations (120 minutes or above) in adults with amblyopia. However, the patching effect seems to saturate at around 120 minutes, as we found no significant difference between 120 and 300 minutes of deprivation. In summary,

the duration of patching and the subsequent changes in eye dominance show a non-linear saturating relationship (see Figure 5.4B).

5.5.1 Strengths and weaknesses of our approach

There have been various methods used to measure changes in ocular dominance after short-term monocular deprivation, one of which is binocular rivalry [18, 11]. A recent study compared the test-retest reliability and the range of measurement error [23] in all the different methods that have been used to measure sensory eye balance after patching. It showed that the binocular combination task that we used here is a superior choice when measuring the change in eye dominance after patching. Therefore, one strength of this study is that we used a binocular phase combination task.

Furthermore, we used a binocular combination task at a low spatial frequency (0.46 cpd) and a high suprathreshold contrast. This choice of stimulus has a number of strengths. These stimuli are very visible to the amblyopic eye as the contrast sensitivity deficit is almost exclusively restricted to high spatial frequencies [6]. Moreover, measurement error is reduced if a low spatial frequency is used in a phase combination task for amblyopes [12]. Also, amblyopic phase discrimination is normal in this spatial range [2, 7, 14, 15]. Finally, it has recently been shown that interocular suppression in amblyopia is maximal at lower spatial frequencies for stimuli of the same suprathreshold contrast [33].

For these reasons, we used a low spatial frequency stimulus [2, 7, 14, 15]. On the other hand, one weakness of this approach is that the results that we report here at low spatial frequencies may not be generalized to high spatial frequency stimuli, where it would be problematic to use the current measurement approach. Recent studies have argued that binocular imbalance is more severely disrupted at high spatial frequencies in amblyopes [3, 13, 20], however the role of the threshold loss has been neglected. Nevertheless, it is not to be assumed that short term occlusion will affect balance at all spatial frequencies

equally. Future studies might be able to answer this question at high spatial frequencies using a different measurement approach, for example the recently developed orientation combination approach [28]. The use of stimuli of comparable suprathreshold contrast would be needed to be able to gauge the contribution of the threshold loss per se.

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Discussion

6.1 Summary

Studies over the past decade have shown that short-term monocular deprivation strengthens the patched eye's contribution in binocular vision. My thesis addresses the following questions:

1. Which test is most reliable and shows least measurement variability when sensory eye dominance and its changes after short-term monocular deprivation are measured? (Manuscript 1)

2. Does a longer duration of short-term deprivation induce a larger change in sensory eye dominance in adults, be they normal or amblyopic? (Manuscripts 2 and 4 respectively)

3. Can changes in eye dominance from short-term deprivation be maintained across days in adults with normal vision? (Manuscript 3)

My first study (Manuscript 1) evaluates which test is most reliable and accurate to measure sensory eye dominance and the patching effect. Numerous studies have been able to replicate the finding of Lunghi et al., who first reported the effect of short-term monocular deprivation in adults [14]. However, there have been conflicting reports between studies using different experimental methods [2, 15, 16, 30, 31] and also between studies that have used the same experimental method [10]. For instance, randomization

of phase information via Fourier transform has been shown to increase the mean phase duration of the deprived eye when measured with a binocular rivalry task [2]. However, it does not seem to strengthen the contribution of deprived eye when measured with a binocular combination task [2, 30]. Furthermore, Lunghi et al. reported that the patching effect, which was measured with binocular rivalry, could be potentiated if the subjects exercised during patching [16]. However, Finn et al. was not able to replicate the finding using the same method (i.e. binocular rivalry) [10]. In our first study, we examined the test-retest reliability and measurement error associated with psychophysical tasks such as binocular rivalry, binocular combination, and dichoptic masking. Surprisingly, binocular rivalry which was used to first report this change in eye balance in normal adults was the least reliable method. Also, the test-retest reliability of parallel-oriented dichoptic masking was better than that of its cross-oriented counterpart. We discussed the possibility that psychophysical tasks that show rivalrous images might raise the difficulty of the task for participants and diminish the reliability. Moreover, the binocular rivalry task was the only one that collected continuous, rather than discrete, data, thereby creating another dimension of the data (i.e., time). This extra dimension of time might have contributed to the increased measurement variability of the task.

My second study (Manuscript 2) explores the relationship between patching duration and changes in eye dominance in adults with normal vision. We used psychophysics, namely binocular phase combination task, which utilizes the binocular fusion of visual stimuli into a single coherent percept. We found that that a 20-fold increase in the duration induced a change in eye balance no larger than 25%. This finding indicates that there is a very weak relationship between patching duration and changes in ocular dominance plasticity in normal adults.

Next, my third study (Manuscript 3) investigates whether the neuroplastic changes induced by short-term monocular deprivation can accumulate if observers are patched

on consecutive days. In other words, we tested the capacity of the brain to retain the neuroplastic changes from visual manipulation. We found that the eye sensory balance changes did not accumulate across days even if normal adults were patched for 150 minutes each day for five consecutive days. The first two studies therefore suggest that, at least in normal adults, ocular dominance plasticity (i.e., the patching effect) can be characterized as an instantaneous all-or-none homeostatic mechanism with fast dynamics.

Lastly, because of its obvious clinical potential, we tested whether an increased patching duration would induce a larger change in sensory eye balance in adults with amblyopia (Manuscript 4). To begin with, Zhou et al. observed that the capacity for neuroplastic change in amblyopia was larger than in normal adults [29]. This finding points to the possibility that an increased duration of patching could induce a larger effect. Also, we were interested in finding the optimal duration of patching to bring about the maximal change in the contrast or response gain of the amblyopic eye to facilitate rebalancing binocular vision. We found a non-linear relationship between patching duration and its effect. There was a significant difference between 30 and 120 minutes, and 30 and 300 minutes of patching, but not between 120 and 300 minutes. This suggests that the patching effect saturated after 120 minutes.

6.2 Relationship between Contrast Adaptation and Ocular Dominance Plasticity

It has been widely known that neurons in both the retina and visual cortex can adapt to the prevailing levels of mean contrast of an image. For instance, after an exposure to a high-contrast environment, the sensitivity of the adapted eye can decrease [7, 8, 12, 20]. Conversely, an exposure of low-contrast stimulus can increase the sensitivity of the adapted eye [28]. This mechanism ensures that the apparent contrast of our

perceptual world remains relatively constant even if the mean contrast of the immediate environment changes over time [11]. It could be argued that the effect of short-term monocular deprivation could be thought of as a severe form of contrast adaptation where the prevailing mean contrast falls to zero (opaque patch) or close to zero (translucent patch). After the contrast condition of one eye changes, the contribution of said eye will be automatically adjusted and, as a result, its contribution to binocular vision will increase. Therefore, ocular dominance plasticity changes could simply be explained as the consequence of contrast adaptation. However, a closer look at the literature suggests that there are numerous differences between contrast adaptation and ocular dominance plasticity to warrant a separate explanation for each phenomenon.

6.3 Comparison between Contrast Adaptation and Ocular Dominance Plasticity

Table 6.1: Contrast Adaptation and Ocular Dominance Plasticity

Parameter	**Contrast adaptation**	**Ocular dominance plasticity**
1. Physiology	Sub-cortical and cortical regions	Primary visual cortex
2. Interocular transfer	Same direction of adaptation in both eyes	Opposite direction of change between eyes
3. Spatial frequency	Bandpass for spatial frequency	Only by removal of high spatial frequency
4. Orientation	Bandpass for orientation	Untuned for orientation
5. Duration	Strong linear dependence	Weak/no dependence
6. Storage	Storage of adaptation in the dark	No storage of changes in eye dominance in the dark
7. Spacing effect	Spacing effect exists	No spacing effect

The usual viewing condition of **contrast adaptation**: while one eye is adapted, the other eye is occluded. The usual viewing condition in studies of **ocular dominance plasticity**: while one eye is deprived, the other eye remains open.

Although it is not the main focus of my thesis, the relationship between contrast adaptation and ocular dominance plasticity is discussed here because both reflect the changes in visual sensitivity of the adapted (i.e., deprived) eye.

The most obvious difference between the classical studies on contrast adaptation and the more recent studies on ocular dominance plasticity is the duration of induction of the effect. Typically, contrast adaptation is induced by just a few minutes of adaptation, whereas ocular dominance plasticity has involved hours or more of deprivation. However, the recent studies from Engel's lab [3, 4] have shown that contrast adaptation can work over extended timescales. So, this factor is no longer an important difference between the two effects.

In a typical adaptation experiment, either both eyes are adapted, or one eye is adapted and the other is occluded. After adaptation, the visual effect is tested either under binocular viewing (if adaptation was binocular) or monocular viewing (if adaptation was monocular). However, in studies of changes in ocular dominance plasticity resulting from short-term monocular deprivation, the eye that is not deprived (equivalent to unadapted eye in contrast adaptation) remains open and the subsequent measurement is in terms of the eye balance between the eyes. Therefore, there is a fundamental difference in the way contrast adaptation and ocular dominance plasticity effects are induced and measured. Contrast adaptation can be a monocular phenomenon, whereas ocular dominance plasticity has to be a binocular phenomenon.

The physiological sites where contrast adaptation and changes in ocular dominance plasticity from short-term monocular deprivation take place seem to be different. First, contrast adaptation can occur at subcortical levels, including the retinal ganglion cells [1, 23] and magnocellular cells [24] in the lateral geniculate nucleus, where visual processing is strictly monocular. Contrast adaptation can also occur at the primary visual

cortex, where binocular visual processing takes place. Changes in ocular dominance resulting from the patching effect must, by their very nature, be cortical in origin because short-term monocular deprivation affects both eyes in a reciprocal fashion. This has been confirmed by three different optical images approaches: intrinsic, voltage-sensitive dyes and FUS [5, 22, 26]. For contrast adaptation, the direction of adaptation for each eye is the same (i.e., the interocular transfer) [6, 7]. If one eye is adapted to a stimulus, the unadapted eye also displays a smaller form of adaptation in the same direction to that of the adapted eye. On the other hand, the sensitivity changes that occur as a result of short-term monocular deprivation display a reciprocal change in the two eyes; the deprived eye becomes more sensitive after patching, whereas the nondeprived eye becomes less sensitive. This has been verified by psychophysics [21, 29], MEG [9] and optical imaging [5, 22]. Therefore, the direction of interocular transfer is the opposite between contrast adaptation and short-term monocular deprivation. The threshold changes after contrast adaptation seem to be of a binocular nature because adaptation in one eye is transferred directly to the other eye. On the other hand, changes in ocular dominance after short-term monocular deprivation reflect an interocular reciprocal inhibition, by which the deprived eye's ocular dominance gets strengthened and that of the non-deprived eye weakens.

Another parameter that indicates a difference between contrast adaptation and monocular deprivation is spatial frequency tuning. Contrast adaptation shows a bandpass property by demonstrating a selectivity for spatial frequency [7, 20]. On the other hand, monocular deprivation seems to be not tuned to spatial frequency. Zhou, Reynaud and Hess used a suprathreshold task at a low spatial frequency to measure ocular dominance before and after short-term monocular deprivation [30]. After they removed the low spatial frequency content, they found no change in ocular dominance. However, after they removed high spatial frequency content and found a clear change in ocular dominance. These findings show that monocular deprivation effect has a lowpass dependence on

spatial frequency (i.e., removal of low SF does not induce changes in ocular dominance plasticity), not the bandpass dependence as shown by contrast adaptation.

Orientation selectivity is a feature of contrast adaptation [7]. On the other hand, patching studies have shown that there is no selectivity for orientation [27, 30].

In addition, the effect of duration seems to be uniquely different between contrast adaptation and the patching effect. Studies [4, 28, 13] have shown that the duration of contrast adaptation linearly increases the magnitude of adaptation. It is interesting that both short (seconds) and long (hours) durations of contrast adaptation affect the degree of adaptation. This applies to both high- [13] and low-contrast adaptations [4, 28]. On the other hand, Manuscript 2 shows only a very weak dependence of monocular deprivation on duration of deprivation [19]. A 20-fold increase in the deprivation length resulted in increasing the patching effect by merely 25%. However, there seems to be a similarity in the relationship between duration and the recovery of sensitivity (i.e., the decaying rate) from either contrast adaptation or monocular deprivation. The recovery of the contrast adaptation and monocular deprivation seems to be independent of the duration [13, 19].

Contrast adaptation and ocular dominance plasticity differ in the storage of the effect. For instance, Thompson and Movshon measured the contrast threshold to orientation before and after adaptation [25]. They observed an increase in the threshold immediately after the adaptation. It has been shown that changes from adaptation decay over time. However, they also noted that the adaptation effect remained even after a period in the dark following adaptation. Their study shows that the increase in contrast threshold after adaptation was stored in the dark and could be revealed later upon testing. On the other hand, our preliminary study (Min, Baldwin and Hess, unpublished; data plotted in Figure 6.1A above) shows that changes in eye dominance after short term monocular deprivation are not maintained in the dark. In our preliminary study, six subjects were tested in two conditions. In the first condition, the dominant eye of the subjects was

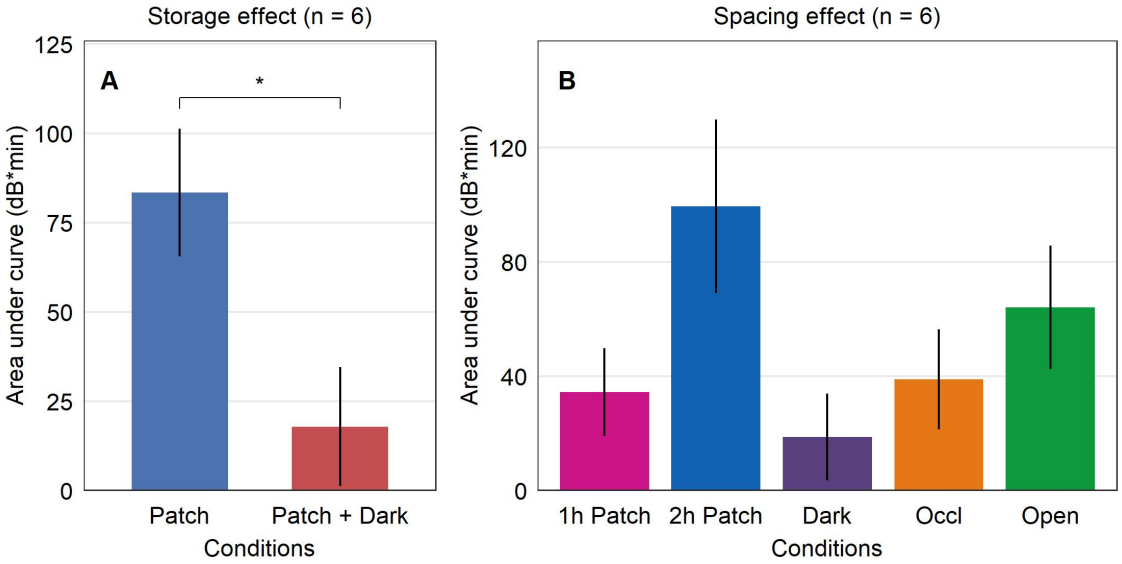

Figure 6.1: **Preliminary data on the storage and spacing effects. (A)** Storage effect for OD plasticity (unpublished data). Comparison between 2h Patching and 2h Patching followed by 1h in the dark. There is a significant difference ($t(5) = -3.74$, $p = 0.014$) between the two groups, suggesting that the changes in eye dominance over time dissipated in the dark (i.e., no storage effect in the dark). **(B)** The spacing effect for OD plasticity (unpublished data). A cyan block represents 1h patching. Blue represents 2h patching. Purple represents 1h patching + 30 min binocular deprivation in the dark (i.e., space) + 1h patching. Orange represents 1h patching + 30 min binocular occlusion from contrast (i.e., space) + 1h patching. Green represents 1h patching + 30 min in normal viewing (i.e., space) + 1h patching. According to a Kruskal-Wallis test, there is no statistical significance between groups $\chi^2(4) = 5.65$, $p = 0.23$). If there was a spacing effect, orange, green and purple bars (conditions with 'space') would have induced a larger patching effect than 2h patching. Thus, there is no evidence for a spacing effect.

patched for 2 hours. In the second condition, the subjects were also patched for 2 hrs and then put in a dark room for 1 hr. As for our measurement, we used a binocular phase combination task. We measured eye balance before patching (i.e., baseline) and at 0, 3, 6, 12, 24, 48 and 96 minutes after patching. We computed changes in sensory eye balance by computing the difference in eye balance between after patching and baseline. The data shown in Figure 6.1A is the area under curve (changes in eye balance over 96 minutes); the higher the value, the larger the change in eye balance over time. We used a paired t-test to compare the areal measure between the two conditions and found a significant difference: $t(5) = -3.74$, $p = 0.014$. Therefore, our results show that the patching effect does not demonstrate storage in darkness. Instead, it decays in the darkness over time. In sum, it seems that the changes in adaptation and eye dominance could also differ in how they interact with subsequent testing.

Lastly, studies have shown that short-term contrast adaptation exhibit what is called, a spacing effect [17, 18]. For example, five sessions of adaptation (each 2 minutes), separated by 1-min recovery (i.e., interrupted adaptation), induce a larger and more long-lasting aftereffect than 10-minute of continuous adaptation. This finding suggests that the 'space' between the adaptation periods potentiated the magnitude of the adaptation. However, our preliminary (Min, Baldwin, Hess, unpublished- data plotted in Figure 6.1B above) study shows no evidence for a spacing effect for the patching effect. In this study, the experimental procedure was similar to that in previous spacing effect studies [17, 18]. Subjects were patched for 1 hour, then spent 30 min without a patch (i.e., space), then they were patched for 1 hr again. There were three different conditions for the 'space.' In the first condition, subjects spent the 30 min 'space' in the dark (both eyes were deprived of light and contrast; this is labelled as 'Dark' in Figure 6.1B). In the second condition, both eyes of the subjects were occluded of contrast but not luminance with translucent patches (labelled as 'Occl' in Figure 6.1B). In the third condition, the subjects were allowed to view normally without a patch during the 30-min 'space' (labelled as 'Open'

in Figure 6.1B). As for controls, we patched the same subjects for 1 and 2 hrs (cyan and blue bars in Figure 6.1B). For our measurement, we used a binocular phase combination task. Eye balance was measured before patching (i.e., baseline) and at 0, 3, 6, 12, 24, 48 and 96 minutes after patching. We computed changes in sensory eye balance by computing the difference in eye balance after patching with respect to baseline. The data shown in Figure 6.1B is the area under curve (changes in eye balance over 96 minutes). We observed that the patching effect from 2h of deprivation was slightly larger than that for conditions with 30-min 'space' (Figure 6.1B) although there was no significant difference between the groups (Kruskal-Wallis test, $\chi^2(4) = 5.65$, $p = 0.23$). If there was a spacing effect, we would have observed a larger shift in eye dominance from the three conditions with the 'space.' Therefore, it seems that the 'space' between the patching sessions does not magnify the changes in eye balance, as it does for contrast deprivation [17, 18].

In summary, there are numerous fundamental differences between contrast adaptation and short-term monocular deprivation to suggest that the underlying mechanism are different. We cannot support the proposal that ocular dominance plasticity resulting from short-term monocular deprivation is simply contrast adaptation by another name.

6.4 Future Directions

I only used psychophysics to study ocular dominance plasticity. However, electrophysiological methods such as MEG and EEG could also be used. One could measure the cortical excitability in the visual cortex that corresponds to the deprived and nondeprived eyes and see whether the findings in my thesis are generalizable beyond psychophysics. In fact, Chadnova et al. used neuroimaging (i.e., MEG) to study the patching effect and observed that the cortical excitability increased for the deprived eye and decreased for the non-deprived eye [9]. It would be interesting to find electrophysiological evidence for my psychophysical conclusion that an increased duration of patching induces a large

cortical excitability for the deprived eye in amblyopes.

Several methodologies have been used to measure sensory eye balance. Some report conflicting results. For instance, phase scrambling has been reported to induce the patching effect if the eye balance is measured with binocular rivalry but not with binocular combination [2, 30]. There are three possible explanations to describe this discrepancy. First, the method of choice might not be reliable. Second, different methods might probe separate neural sites. Third, the patching effect could fluctuate across days. To address the issue of reliability and repeatability, my thesis compares different methodologies that have been used to measure sensory eye balance and examined whether the patching effect is consistent across days (Manuscript 1). We found that some methods are more reliable than others. For instance, binocular phase combination (suprathreshold measure) and dichoptic masking (threshold measure) methods seem to be superior to a binocular rivalry task. The patching effect also seems to show small variability across days within same subjects if the psychophysical test itself is reliable. Therefore, researchers who are planning to conduct a study about short-term monocular deprivation should be selective when choosing a particular method. This same issue could be assessed in amblyopes in future studies.

In addition, my thesis investigates the effect of patching duration on changes in ocular dominance plasticity. I found that there is a dependence on the patching duration in amblyopes (Manuscript 4) but not in adults with normal vision (Manuscript 2). These findings replicate the original study of Lunghi et al., who suggested that short-term monocular deprivation increases the mean phase duration of the deprived eye in a binocular rivalry test [14]. This study shows that neural plasticity exists even in the adult brain. Some might argue that the phenomenon from short-term monocular deprivation is simply that of visual adaptation. Deprivation of visual input has been shown to increase the sensitivity after adaptation. However, an interesting point to note is that the other eye (i.e., non-deprived eye) also exhibits a reciprocal change in sensitivity. This

contralateral reciprocal effect supports the argument that short-term monocular adaptation is different from that of a typical visual adaptation such as tilt after-effect, during which both eyes experience an increase in sensitivity after adaptation even if only one eye undergoes adaptation. However, the patching effect has been shown to induce a contralateral reciprocal change in the eyes of human observers. Hence, the interaction between the eye seems to be different during short-term patching from during visual adaptation. Moreover, there is a need for a future study to investigate the physiological basis within the visual cortex of short-term monocular deprivation in animals. Whether short-term monocular deprivation changes the width or just the strength of the ocular dominance column is an important question that needs to be addressed in future.

6.5 Limitations

As previously mentioned, since the findings in my thesis are based on psychophysical methods, they might not be generalized to electrophysiology. I have chosen psychophysics for my thesis because it is non-invasive, and it has allowed me to directly measure sensory eye balance in humans before and after patching.

The first limitation of my thesis is the small sample size in some studies. For instance, Manuscript 2 investigates the effect of patching duration in normal adults [19]. To answer this question, we tested six different patching durations: 15, 30, 60, 120, 180 and 300 minutes. However, since there were too many conditions, I was not able to recruit the same subjects for all conditions. Instead, the subjects were identical in 15 and 30 minutes of deprivation. Then there another set of subjects was recruited for 60, 120, 180 minutes. Lastly, three individuals from the subject pool completed 300 minutes of patching. Since the subjects were not entirely paired across all durations, I was not able to perform statistical analysis for paired sample pools. Also, since my subject pools were not identical, there could have been additional variability not only between patching durations but also between the subject pools (inter-subject variability). As

previously mentioned, we found that an increased patching duration does not induce a significantly larger shift in sensory eye dominance. To determine significance, we used a nonparametric Wilcoxon signed rank test and set the alpha as 0.05. However, since a p-value is directly related to the sample size, our large p-value might not have been due to the null effect. Instead, it could have been large due to the sample size. For this reason, my data are reanalyzed in Manuscript 4, which investigates the effect of patching duration in adult amblyopes, using effect size. However, I found a small effect size between different patching durations in data from Manuscript 2. This result suggests that an increased patching duration does not increase the patching effect in normal observers. In retrospect, I could have reduced the number of conditions to 15, 120 and 300 minutes and recruited the same subjects across all conditions. However, Manuscript 1, which evaluates the test-retest reliability of five psychophysical tasks, shows that the psychophysical method itself – binocular phase combination at multiple contrasts – is very reliable and has a narrow measurement variability. For this reason, although we recruited a small sample, I am still confident that my findings can be replicated across laboratories and groups.

Recruiting amblyopic observers was definitely a challenge, even more so during the pandemic. Therefore, we had to resort to recruiting a small sample of amblyopes (n = 9) in Manuscript 4. In this study, we examined whether an increased patching duration induces a larger change in eye dominance in amblyopes. With my experience from Manuscript 2, I decided to reduce the number of conditions and recruit the same subjects across all conditions so that I could perform pairwise statistical analysis. However, the problem with this approach was that it was extremely hard to recruit patients because each had to spend 12 hours in total. Despite the small sample size, we were able to report convincing statistical results and show that an increased patching duration brought about a larger change in sensory eye balance in amblyopic patients. In addition, it was also unfortunate that we were able to recruit only patients with anisometropic

amblyopia. We might have found differences between different types of amblyopia, such as strabismic, anisometropic or deprivation amblyopia.

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