

# Ocular Dominance Plasticity: A Mini-Review

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**Abstract:** Ocular dominance plasticity, the ability of the brain to change sensory eye balance, has traditionally been believed to be extremely limited in adult visual cortex. However, recent studies on short-term monocular deprivation (MD) demonstrate that its presence is prevalent in adult humans, as short-term MD is capable of significantly shifting ocular dominance in favor of the previously deprived eye. Thus, findings over the last 15 years highlight that short-term MD can be a promising alternative treatment for amblyopia, a neurodevelopmental disorder characterized by binocular imbalance. Conventionally, amblyopia has been treated with patching therapy, which shows limited effectiveness in restoring binocularity of adults and is associated with poor compliance rate and high psychosocial distress. Thus, it is an opportune time to explore how short-term MD can be utilized as an alternative treatment option for restoring amblyopic vision, especially individuals who do not respond robustly to standard treatment. This review provides an overview of foundational studies on ocular dominance plasticity in both visually intact and impaired observers. It also evaluates the potential of short-term MD as a treatment for amblyopia and suggests its future research directions, including the integration of multimodal therapeutic strategies that include short-term MD.

**Keywords:** ocular dominance plasticity, binocular vision, amblyopia

## Introduction

During early life, the visual system undergoes rapid development, driven by neural plasticity. Disruption of this process, such as through prolonged monocular deprivation (MD, artificial closure of one eye), can permanently impair binocular visual processing.<sup>1</sup> The effects of MD on the visual system can vary depending on its duration. Short-term MD, which lasts for a few hours in one day, induces small and reversible changes, whereas long-term MD, which spans consecutive days, months or years, elicits profound and long-lasting effects. For example, long-term MD introduced in early life can cause the deprived eye to stop functioning, as the brain ceases to process its signal, potentially leading to blindness.<sup>2</sup> Functional alterations following long-term MD are correlated with anatomical changes in the primary visual cortex (V1), particularly in the ocular dominance columns. Specifically, the number of cells responsive to the deprived eye decreases, while that responsive to the non-deprived eye increases, leading to an uneven distribution of neural population.<sup>3</sup> Put together, long-term MD reduces the cortical representation of the deprived eye in V1 without disrupting the anatomical integrity of the eye, possibly resulting in a permanent loss of vision for that eye.

The degree of MD's influence on the visual system not only depends on its nature of duration but also on when it is introduced. The brain is most sensitive to visual experience during early life, a phase termed the "critical period" by Hubel and Wiesel.<sup>2</sup> Disruptions during this period, such as MD, can severely damage visual function in animals like cats and monkeys,<sup>4-6</sup> whereas similar disruptions in adulthood have minimal effects. The cortical changes observed in MD experiments mirror those seen in amblyopia, a neurodevelopmental disorder characterized by imbalanced binocular vision.<sup>7-11</sup> Due to an abnormal visual development, the worse eye's input gets suppressed (ignored) in amblyopia, forcing affected individuals to rely mainly on the better eye for performing everyday tasks, such as hand-eye coordination and reading.<sup>12-14</sup> Nevertheless, in some individuals with binocular amblyopia condition, both eyes may show visual deficits, preventing them to interact with the world normally with either of the eyes.

Traditional therapies for amblyopia include patching the better (fellow) eye for 40–50% waking hours over several months. While they can improve visual acuity of the worse (amblyopic eye) if amblyopia is detected early and treatment

is introduced during childhood, they steeply lose their effectiveness after about 10 years of age.<sup>15–17</sup> Recently, there have been ongoing investigations in both laboratory and clinic settings demonstrating that other therapeutic approaches beside traditional patching therapy can be effective in restoring binocular vision in amblyopic adults whose level of neural plasticity is supposedly lower. In particular, short-term MD has emerged as a promising alternative, marked by its ability to significantly shift ocular dominance in favor of the deprived eye (rather than the non-deprived eye following long-term MD).<sup>18,19</sup> Understanding how short-term MD can induce a strong shift in ocular dominance, a phenomenon that has been believed to be unalterable after the critical period, and examining whether it can be used for amblyopia treatment are timely and relevant, especially when mainstream treatment protocols show a regression of amblyopia in 24% of the treated patients after patching treatment,<sup>20</sup> leaving them with no alternative solutions. Therefore, in this review, I aim to evaluate the potential of short-term MD as a treatment for amblyopia, focusing on its ability to restore binocular balance. Specifically, I provide an overview of foundational and modern studies on short-term MD, discussing its underlying mechanism and its interaction with strengthening factors such as attention and dark exposure. Also, I suggest potential routes for future amblyopia treatment that incorporate short-term MD and highlight the need for research on multimodal therapeutic strategies that combine different interventions.

## Short-Term MD in Adult Humans

Short-term MD was first explored by Lunghi et al<sup>18</sup> who conducted a seminal study using psychophysics to measure ocular dominance in adult humans and provided important evidence that the adult brain still retained significant plasticity to drive functional visual changes. In their experiment, different stimuli were presented to each eye of normally sighted adults at the same contrast, inducing binocular rivalry. Since the stimuli were equally visible, the perception of the stimuli alternated randomly over time, and subjects reported which stimulus they perceived using a keyboard. Measurements of ocular dominance were taken before and after 150-min of MD. Before MD, as the stimuli were shown at an equal contrast, there were similar proportions of response in both eyes, indicating no ocular dominance. After MD, the response proportion for the previously deprived eye increased significantly, although the physical stimuli remained the same. This increase in the apparent contrast level of the deprived eye is opposite to the loss of function in the deprived eye observed in animal studies after long-term MD in early life. The authors suggested that the resulting dominance of the deprived eye reflects a change in contrast gain, which refers to the gain of function in contrast perception.

Zhou et al<sup>19</sup> expanded on this work, investigating the effect of short-term MD (150 minutes) on ocular dominance using different psychophysical approaches. They presented different but visually similar stimuli to both eyes at the same contrast, evoking fusion rather than rivalry. Like in the previous study by Lunghi et al, they observed that the previously deprived eye became more dominant. Importantly, Zhou et al also measured contrast detection thresholds for each eye before and after MD, as contrast perception is closely related to contrast gain. They observed that the non-deprived eye's threshold increased (worsened), while the deprived eye's threshold decreased (improved), showing an opposite pattern of change in contrast detection between the two eyes. Notably, they concluded that these functional changes appear to occur during,<sup>21</sup> rather than after, MD in beta-4 layer of V1.<sup>22</sup>

Beside psychophysics, studies using other methodologies have reported reciprocal changes in the cortical activity corresponding to both eyes after short-term MD. One of the goals of these studies was to confirm whether short-term MD effects were limited to changes in visual perception or whether it had neural correlates in visual areas of the brain. For instance, Lunghi et al used electroencephalogram (EEG) to measure cortical activity as visual evoked potentials (VEPs) in areas of V1 before and after short-term MD. They observed that the amplitude of VEP for deprived eye increased, while that paired with the non-deprived eye decreased following MD.<sup>23</sup> Similarly, Chadnova et al recorded VEP with magnetoencephalography (MEG),<sup>24</sup> characterized by a better spatial resolution (2–3 mm) than that of EEG (7–10 mm).<sup>25</sup> Their MEG recordings showed similar changes as in the previous study, with a boost in the cortical activity linked to the deprived eye and a decline in the activity paired with the non-deprived eye. Lastly, Binda et al performed a study using functional magnetic resonance imaging (fMRI), finding that areas of the ocular dominance columns in V1 previously linked to the non-deprived eye got reassigned to the deprived eye during MD. Their fMRI data indicated that the reciprocal pattern of change in the neural activity occurred during rather than after MD.<sup>26</sup> These shifts in ocular dominance following short-term MD were found to correlate with a decrease in the resting GABA concentration within

V1.<sup>27</sup> Together, psychophysical, physiological and neuroimaging studies report that shifts in ocular dominance following short-term MD involve multiple levels of neural functions, in which both eyes experience opposite perceptual changes in favor of the deprived eye.

## Relevance to Amblyopia

Zhou et al<sup>28</sup> observed that temporarily depriving the poor eye of amblyopic adults for 150 minutes increases its perceptual dominance relative to before MD. However, the shift in ocular dominance from one session of short-term MD did not restore balance in amblyopia entirely and was short-lived, lasting for only 30–90 minutes.<sup>29</sup> Nevertheless, this shows that the effects of short-term MD are observed in both normal and amblyopic adults, demonstrating its therapeutic potential for amblyopic adults.

Occluding the amblyopic eye to improve its function is in contrary to the standard patching therapy's procedure, which blocks the better eye of children with amblyopia. Also, the standard protocol targets monocular visual acuity, while short-term MD targets on mitigating binocular imbalance. Hence, short-term MD is commonly referred as inverse patching. It has recently been tested in children and young adults with amblyopia in clinical settings.<sup>30,31</sup> Zhou et al<sup>31</sup> deprived the amblyopic eye for 120-min daily for two months, resulting in significant improvement in binocular balance, visual acuity of the amblyopic (deprived) eye (0.13 logMAR improvement) and stereoacuity. Lunghi et al,<sup>30</sup> who introduced short-term MD for six sessions in four weeks, also found significant improvement in the visual acuity of the amblyopic eye (0.15 logMAR improvement) but not in stereoacuity. Based on these studies, a two-month MD regimen appears to be more effective than one month, as it also benefits stereopsis and binocular balance. Together, repeated sessions of short-term MD seem effective in rebalancing the amblyopic visual system, benefiting both monocular and binocular visual functions.

This idea of depriving the poor eye for amblyopia treatment is not new. In fact, Bangerter proposed it in the 1950s, though his approach did not gain wide acceptance. This is because blocking the better eye typically improved the visual acuity of the amblyopic eye more.<sup>32–35</sup> However, contemporary studies indicate that occluding the better eye, as in the standard patching therapy, reduces the compliance rate and causes psychosocial issues in amblyopic children.<sup>15,36,37</sup> Therefore, inverse patching therapy appears to be an appropriate and reliable addition to the array of treatments for amblyopia.

## Mechanisms of Short-Term MD Effect

First introduced by Lunghi et al,<sup>18</sup> the prevailing explanation for why previously deprived eye's dominance increases after short-term MD is that it experiences an increase in its "contrast gain." However, contrast gain refers to the sensitivity to a range of contrasts rather than the state of perceptual dominance.<sup>38</sup> The visual system constantly adjusts the contrast gain of both eyes, as the visibility of the surrounding environment can change over time.

According to a recent review by Hess and Min,<sup>39</sup> this perpetual process of modulating contrast gain to enable us to better distinguish one visual element from another across different levels of background visibility does not regulate ocular dominance plasticity. In other words, perceptual changes driven by short-term MD might not be the same as that from contrast adaptation,<sup>39</sup> which essentially is a homeostatic control of contrast gain in V1.<sup>40</sup> Hess and Min argue that after short-term MD, the non-deprived eye also experiences a perceptual change, mainly by its decreased contribution to binocular vision, even though its overall contrast level does not change. If contrast adaptation and ocular dominance shift are regulated by the same process that continuously regulates contrast gain based on the background visibility, the non-deprived eye's dominance should also increase due to interocular transfer of the dominance boost in the deprived eye. Instead, studies indicate that both perceptual and neural changes are reciprocal,<sup>21,24</sup> such that non-deprived eye's gain is reduced, while the deprived eye's gain is enhanced. Therefore, it seems that contrast adaptation and short-term patching are fundamentally different and might have separate neural bases.<sup>39,41</sup> Hence, contrast gain from visual adaptation might not account for the patching effect.

Instead, the gain-control model by Ding and Sperling could potentially explain how the contrast gain of each eye shifts after short-term MD in opposite directions, where the non-deprived eye's gain decreases, and the deprived eye's gain increases.<sup>42</sup> According to their model of binocular combination, when the contrast gain of the deprived eye

increases, the contrast gain of the non-deprived eye is reciprocally reduced. This interocular inhibition can account for the decreased predominance of the non-deprived eye and the increased predominance of the deprived eye following short-term MD.

In the 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.<sup>42</sup> When a stimulus shown to one eye has high contrast, it can significantly inhibit the other eye's weight in binocular combination, reducing the signal and gain of the eye. The change in gain in one eye by the other eye is referred to as gain control. This interocular inhibition between the eyes, as explained by the gain control model, can account for why the sensitivity of the non-deprived eye worsens, while that of the deprived eye improves following short-term MD. The equation of the model is shown below.

$$\delta = \frac{1 + \left(\frac{m_R}{g_c}\right)^\gamma}{1 + \left(\frac{m_L}{g_c}\right)^\gamma} \times \frac{m_R}{m_L}$$

$\delta$  denotes the contrast ratio to achieve binocular balance;  $g_c$  is the minimum contrast level for the gain-control inhibition to exert its effect,  $m_R$  and  $m_L$  are contrast levels of the stimuli shown to right and left eyes, respectively, and  $\gamma$  refers to the gain-control parameter. The gain-control parameter  $\gamma$  affects both eyes' input by controlling the degree of the reciprocal inhibition between both eyes.

So, what does “contrast gain” mean in the context of short-term MD and binocular balance? As described in the Ding and Sperling's model, contrast gain might refer to the ability of the eye to dynamically inhibit the other eye's input rather than contrast sensitivity of the eye per se. This inhibitory control – also known as *gain* – depends on the relative contrast of the stimuli shown to both eyes. Depending on the contrast of visual information that passes through each eye, the *gain* of one eye can be controlled by another eye; this is known as *gain-control*. Mathematically, this *gain* can be summarized as the gain-control exponent parameter ( $\gamma$ ) in the Ding-Sperling model.<sup>43</sup> As contrast regulates the degree of gain, its modulation is referred as contrast gain-control, where the word “contrast” is used as adjective to describe its dependency.<sup>42</sup> The gain-control ( $\gamma$ ) parameter ensures that there is inhibitory interaction between both eyes. Ding and Sperling claimed that the model could be extended to other stimuli types, such as those that trigger binocular rivalry.<sup>42</sup> If there is no gain-control parameter in the model of binocular combination, then there will be a linear combination of two eyes' input because one eye's input will not affect the weight of the other eye's input.

In normal observers, the gain-control exponent parameter ( $\gamma$ ) can be assumed to be equal in both eyes,<sup>43</sup> but not in amblyopia.<sup>44</sup> If one eye has a higher  $\gamma$  value than the other eye, its inhibition on the other eye will be greater. After short-term MD, previously deprived eye becomes more perceptually dominant as its  $\gamma$  (gain) increases (Figure 1), thereby inhibiting the other eye more. In amblyopia, however, the shift in perceptual dominance might be inadequate to restore binocular balance (Figure 1D), as demonstrated in previous studies.<sup>28,44–46</sup>

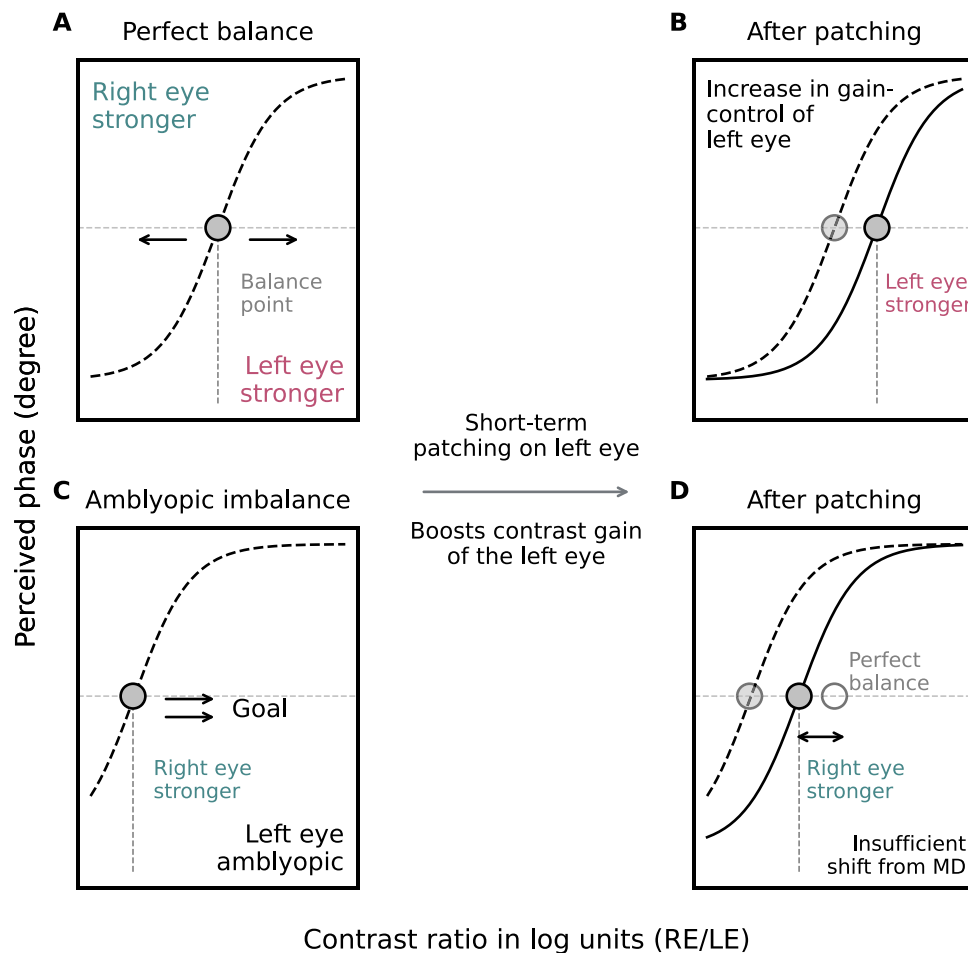
## Metaplasticity: Efforts to Boost Ocular Dominance Plasticity in Adults

Increasing ocular dominance plasticity in adults is important because the effects of short-term MD are short-lived and not sufficient to permanently restore balance in amblyopia (see Figure 1). So, considerable effort has been undertaken to increase plasticity using modulators of metaplasticity. These modulators can be simple, such as increasing the duration or sessions of MD, or complex, involving environmental changes that adjust the physiology of the brain and body.

### Duration

Functional changes in both eyes occur during short-term MD,<sup>21</sup> becoming larger throughout the course of MD. So, a longer duration of MD could perhaps drive more significant alterations in functions of both eyes, such as a larger shift in binocular balance.

Min et al tested this possibility in normal adults, observing only a weak relationship between the duration of MD and their following changes in binocular balance.<sup>47</sup> They reported that the shift from 300-min MD was only 25% larger than that from 15-min MD, despite a difference of 200% in the duration of MD. No statistically significant effect of MD



**Figure 1** Illustration of how short-term monocular deprivation affects normal and amblyopic eye balance using simulated data. The gain-control parameter ( $\gamma$ ) in the Ding-Sperling model is assumed as equal in the normal observer (**A** and **B**) but unequal in the amblyopic observer (**C** and **D**) between two eyes. Short-term MD might increase the value of the  $\gamma$  parameter of the deprived eye, increasing its perceptual dominance and inhibition on the other eye. The horizontal dashed grey line denotes 50% response rate of one eye. (**A**) A simulated normal observer's data before short-term MD, having a perfect balance between two eyes (solid grey point). (**B**) The simulated normal observer's data after short-term MD, with perceptual dominance shifted in favor of the previously deprived (left) eye. (**C**) A simulated amblyopic observer's data before short-term MD, with the right eye significantly more dominant. (**D**) The simulated amblyopic observer's data after short-term MD, which caused a slight but insufficient increase of the previously deprived (left) eye's perceptual dominance, making the right eye still more dominant.

**Abbreviations:** RE, right eye; LE, left eye.

duration was found, possibly due to their limited sample size of four participants in the 300-min MD condition. So, the authors repeated the study using a more sensitive measurement method,<sup>48</sup> with more trials and larger sample sizes of normal and amblyopic adults.<sup>29</sup> This time, they reached a statistical significance from the effect of duration of MD. Nevertheless, they observed no significant difference in perceptual shifts between 120-min and 300-min MD durations in both controls and amblyopic observers. Even if their second study showed a statistical significance and the first study did not, their conclusions were still aligned: the perceptual changes following short-term MD could be enhanced with a longer duration of MD, but only to a very limited extent. Then, other studies also reported that a longer duration of MD could increasingly alter perception,<sup>49,50</sup> though their longest duration of MD was 120-min.

Intriguingly, Ramamurthy and Blaser reported that changes driven by patching occur on multiple timescales: shorter durations of MD (up to 5 hrs) strengthened the dominance of the deprived eye, while longer durations boosted the dominance of the non-deprived eye.<sup>51</sup> Interestingly, beyond 5 hrs, ocular dominance shift after MD was found to be reduced relative to shorter durations.<sup>51</sup> Their finding could partially explain why Min et al observed a significantly larger shift in 2-hr MD compared to 30-min MD but not between 2-hr and 5-hr MD.<sup>29</sup> This relationship between patching duration and ocular dominance shift could have plateaued reaching 5-hr MD, later to be decreased, in a biphasic fashion. Indeed, while short-term MD (eg, 15 min to 5 hrs) increases the perceptual contribution of the previously deprived eye,<sup>47</sup>



long-term MD (beyond 5 hrs) decreases the deprived eye's dominance and its cortical response. For example, Tyler and Katz observed from EEG measurement that, during 9-hr MD, VEP's amplitude decreased in the occipital lobe associated with the previously deprived eye, while it increased in regions associated with the non-deprived eye.<sup>52</sup> Next, a transcranial magnetic stimulation (TMS) study reported that the level of excitability from TMS pulses decreased in both hemispheres of the occipital cortex that receive input from the deprived eye, indicating a loss of signal power from the deprived eye.<sup>53</sup> However, before the study of Ramamurthy and Blaser got published, there had been no single study that systematically observed the effects of short- and long-term MD, showing reversed shifts in sensory eye balance within one sample of subjects. The finding that MD could shift ocular dominance in a biphasic fashion could have important clinical implications, especially on targeting which eye to strengthen in binocular vision.

## Exercise

Physical exercise can benefit adult rodents with amblyopia by reinstating plasticity,<sup>54</sup> leading to a complete recovery of ocular dominance and visual acuity.<sup>55</sup> Inspired by these animal studies, Lunghi and Sale examined whether exercise could influence changes in balance following short-term MD in adult humans.<sup>56</sup> They observed that the previously deprived eye's dominance became more prominent from exercise and MD together than that from MD alone. Then, other researchers attempted to reproduce their findings using the same method (binocular rivalry)<sup>57–59</sup> or different psychophysical methods, such as those that elicit binocular combination<sup>60</sup> and surround-suppression.<sup>61</sup> Unfortunately, only the original study has reported that exercise increases perceptual changes following MD, suggesting its limited utility for boosting ocular dominance plasticity.

## Repetitions

Effects of short-term MD in adult humans have been reported to be transient and inadequate to fully restore balance in amblyopia. Perceptual learning studies show that the adult brain can process visual inputs more effectively after sufficient training and repetitions.<sup>62–64</sup> This opens up the possibility that the effects of short-term MD could have a longer lifespan and potency with repeated sessions. However, there have been mixed findings. Some studies report that daily short-term MD (2 hrs) over consecutive 5–7 days does not lead to more permanent changes in binocular balance.<sup>65,66</sup> They also indicate that the effect's potency remains similar even after prior exposure to short-term MD, suggesting that the brain may not adapt to the effects of short-term MD and reduce its impact. Clinical studies in amblyopia show more promise, demonstrating that the visual benefit from repeated rounds of short-term MD for months can last for months after the treatment ends.<sup>30,31</sup>

Although studies on short-term MD have been inconclusive on whether it can induce accumulative shifts in ocular dominance, binocular training methods have demonstrated greater potential in normally sighted adults. For instance, Du et al evaluated the effects of six-day complementary-patchwork adaptation training, a binocular approach first introduced by Bao et al,<sup>67</sup> in adults with amblyopia.<sup>68</sup> During the patchwork training, each eye was viewed as half of the image's content, while the other half of the image was hidden as scattered, mosaic patches. They observed that the trained individuals exhibited long-lasting perceptual changes after the training, with binocular balance improving in an accumulative fashion over time. The benefit from six sessions of visual training was also observed after one month following its cessation in amblyopic observers.<sup>68</sup> This contrasts with some short-term MD studies, which have shown no accumulation of effects on ocular dominance in normally sighted adults.<sup>65,66</sup> These findings suggest that binocular approaches may be more effective than monocular methods like short-term MD for inducing and consolidating changes in ocular dominance through multiple sessions. Together, these results highlight the strong potential of repeated training sessions, particularly in binocular paradigms, in enhancing ocular dominance plasticity in amblyopia.

## Brain Stimulation

Non-invasive brain stimulation methods, such as transcranial random noise stimulation (tRNS) and transcranial direct current stimulation (tDCS), enhance plasticity and improve the effectiveness of visual training in adult humans by increasing the cortex's excitability, altering the regulation of plasticity.<sup>69–73</sup> Interestingly, changes in the excitatory/inhibitory balance in V1 are also related to perceptual changes that follow short-term MD. For example, reduced

concentrations of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, in V1 areas associated with the previously deprived eye are correlated with an increase in the eye's perceptual dominance after MD.<sup>27</sup> To explore this topic further, Chen et al examined whether tRNS and tDCS could increase the perceptual alterations that follow short-term MD, possibly by reducing inhibition in V1.<sup>49,71</sup> However, they observed that neither stimulation method heightened the MD effect. Future studies should explore whether these brain stimulation methods can enable the adult brain to better consolidate perceptual changes after repeated doses of short-term MD.

## Attention

Attention modulates ocular dominance in an eye-specific fashion, with the eye, with a visual cue becoming more perceptually dominant.<sup>74–77</sup> Action-video gaming, which increases attention, improves visual performance and enhances functional plasticity.<sup>78</sup> Since attention and short-term MD can both cause changes in binocular balance, they can possibly interact. Interestingly, Wang et al reported that an increased attentional load during a few hours of MD can heighten the patching effect.<sup>75</sup> Conversely, Chen et al observed no positive effect of action-video gaming on the patching effect;<sup>79</sup> it is possible that the certain game in the study did not provide enough attentional load to significantly enhance the MD effect. In fact, if the deprived eye is open behind the patch during short-term MD, the resulting shift in eye dominance can be larger<sup>80</sup> than when the deprived eye is closed behind the patch, indicating that the attentional demand due to the open state of the eye during MD can enhance the patching effect.

However, these previous studies have not systematically controlled for the degree of attentional load across different attentional conditions or between the two eyes.<sup>81</sup> To address this limitation, Song et al developed a dichoptic-backward-movie adaptation paradigm, in which one eye views a regular movie, while the other eye views a reversed movie, to carefully ensure that both eyes received rich visual information while allowing researchers to manipulate eye-specific attention.<sup>82</sup> They observed that eye-specific attention plays a critical role in inducing changes in ocular dominance, with larger shifts occurring when more attentional load is allocated to the attended eye. Importantly, the effect of short-term MD depends on the presence of attention.<sup>41,83</sup> The crucial role of attention was further corroborated by studies using electroencephalography, neuroimaging and brain stimulation methods.<sup>74,76,82</sup> The fact that attention is important factor in driving ocular dominance plasticity is in contrast to how contrast adaptation can be induced without attention.

## Dark Exposure

Animal studies have revealed that a brief period of dark exposure heightens cortical plasticity.<sup>84,85</sup> For instance, dark rearing from birth can extend the length of the critical period<sup>86</sup> and reactivate juvenile plasticity in adult animals.<sup>87</sup> Inspired by these foundational studies, Min et al studied whether a brief interlude of dark exposure (60-min) could boost ocular dominance plasticity in adults following short-term MD.<sup>88</sup> They reported that it could enhance changes in binocular balance following MD in normal adults but not in amblyopes. While dark exposure seems to be potentially useful, future research should explore the safety and feasibility of incorporating dark exposure into therapeutic strategy in clinical settings.

## Pharmacology

Acetylcholine is a neurotransmitter that regulates plasticity,<sup>89</sup> specifically by modulating excitatory/inhibitory balance in the cortex.<sup>90</sup> Limiting the expression of Lynx1, a protein that regulates neural plasticity, enhances the level of signaling through acetylcholine (cholinergic signaling), resulting in the reactivation of juvenile plasticity in adult mice.<sup>91</sup> Cholinergic signaling can facilitate the recovery of visual performance of individuals who experienced brain injury, demonstrating that it heightens functional plasticity.<sup>92,93</sup> Based on its positive effect on visual plasticity reported in these studies, Sheynin et al tested whether increasing cholinergic signaling enhances perceptual changes following short-term MD in adults with healthy vision. However, they observed that it decreases the perceptual alterations, indicating that donepezil's utility might be limited.<sup>94</sup>

## Future Directions: Short-Term MD as a Potential Treatment for Amblyopia

Short-term MD has emerged as a promising treatment for amblyopia, as it directly addresses binocular imbalance – a core feature of the disorder – while also improving monocular visual acuity as a secondary outcome.<sup>30,31</sup> However, its

effects are transient, typically lasting only 30–90 minutes in adult humans. This limitation is attributed to homeostatic regulation of the human visual system, which reverts ocular dominance to its baseline perceptual state.<sup>26,27</sup> To unlock the full potential of short-term MD, researchers must find ways to amplify and prolong its effects by exploring key factors such as optimal duration and frequency of short-term MD and the use of complementary interventions such as dark exposure and eye-specific attention. The longevity and magnitude of the short-term MD effect on ocular dominance will ultimately determine its viability as a clinical treatment for amblyopia.

Clinical studies show that the effect of short-term MD can persist in adult humans even after treatment cessation.<sup>30,31</sup> However, binocular approaches, which modulate inputs of both eyes to rebalance binocular vision, have demonstrated a greater potential for inducing long-lasting change in ocular dominance compared to monocular approach like short-term MD. For example, studies on normally sighted adults found that shifts in ocular dominance could accumulate with binocular approaches<sup>67</sup> but not with monocular approaches.<sup>65,66</sup> Despite their promise, binocular approaches are more technologically sophisticated than simple monocular patching, which may reduce compliance rates and limit accessibility for individuals from diverse socioeconomic backgrounds.<sup>12</sup> However, future studies should also investigate if binocular approaches, such as complementary-patchwork adaptation training using an altered-reality system<sup>67,68,95</sup> or dichoptic training through contrast-rebalanced movies or games<sup>96–100</sup> are more effective in amblyopic adults. These approaches could be evaluated using reliable and precise quantitative tests, such as binocular orientation combination task<sup>29,101</sup> or dichoptic letter charts,<sup>102</sup> across various spatial frequencies.

Dark exposure has been proposed as a method to enhance the effects of short-term MD, as it can amplify changes in binocular balance in normally sighted adults.<sup>88</sup> These effects are correlated with the magnitude of absolute changes in E/I balance, where larger changes in E/I balance predict greater shifts in ocular dominance following short-term MD. However, in amblyopic adults, the effect of dark exposure appears to be negligible.<sup>88</sup> This difference may stem from altered neural responses in amblyopes to dark exposure. Studies have shown that spontaneous neural activity and functional connectivity differ between controls and amblyopes,<sup>95,103</sup> and these differences can be partially mitigated through visual training using augmented reality tools.<sup>95</sup> Such neural differences may also explain why the duration of patching has a more pronounced effect in normally sighted adults than in amblyopic individuals.<sup>29</sup> The relationship between neural activity in the visual cortex – such as changes in E/I balance – and ocular dominance plasticity in both normal and clinical populations can be studied in the future. This research could help explain why interventions like dark exposure, and increasing the duration of patching are more potent in normally sighted individuals than in amblyopes.

Given the wide variety of amblyopia treatments available, future research could explore the potential of combining short-term MD, binocular approaches (eg, dichoptic movies and games) and metaplastic facilitators – such as eye-specific attention and dark exposure – to create a more robust and long-lasting therapeutic strategy for restoring binocular balance. However, the effectiveness of these multimodal interventions may vary significantly across individuals due to factors such as age, severity of amblyopia, and neural characteristics. This variability underscores the need for a personalized approach to treatment. To enable clinicians to adopt personalized protocols, it will be essential to incorporate a range of clinical tests that can serve as both start- and end-point measures for assessing treatment efficacy.<sup>104</sup> For example, concise tests have been developed to quantitatively measure stereopsis detection and discrimination thresholds<sup>105</sup> as well as binocular imbalance.<sup>106,107</sup> These tools could help tailor interventions to individual patient needs and improve overall treatment outcomes.

## Conclusion

The conventional view that neural plasticity is highly limited in the adult visual cortex has been challenged by a surge of studies over the past 15 years, which collectively demonstrate the strong existence of ocular dominance plasticity. This effect can easily be induced using short-term MD, which involves depriving one eye's input for a few hours. In this review, I argue that short-term MD can be a promising alternative to standard amblyopia therapy because of its ability to directly target binocular imbalance, which is the core deficit in amblyopia, especially for those who might not respond effectively to standard patching therapies. Also, I describe the underlying mechanism of short-term MD in eliciting reciprocal perceptual changes in the two eyes using the Ding-Sperling model of binocular combination. Lastly, I outline future research directions on the application of short-term MD on amblyopia treatment, with an emphasis on multimodal



therapeutic regimens that incorporate short-term MD but also other treatment methods, such as binocular methods, to account for varying age groups and treatment response in the amblyopic population.

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## Disclosure

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