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ORIGINAL ARTICLE

Daily dose–response from short-term monocular deprivation in adult humans

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Abstract

Short-term monocular deprivation (MD) shifts sensory eye balance in favour of the previously deprived eye. The effect of MD on eye balance is significant but brief in adult humans. Recently, researchers and clinicians have attempted to implement MD in clinical settings for adults with impaired binocular vision. Although the effect of MD has been studied in detail in single-session protocols, what is not known is whether the effect of MD on eye balance deteriorates after repeated periods of MD (termed 'perceptual deterioration'). An answer to this question is relevant for two reasons. Firstly, the effect of MD (i.e., dose-response) should not decrease with repeated use if MD is to be used therapeutically (e.g., daily for weeks). Second, it bears upon the question of whether the neural basis of the effects of MD and contrast adaptation, a closely related phenomenon, is the same. The sensory change from contrast adaptation depends on recent experience. If the observer has recently experienced the same adaptation multiple times for consecutive days, then the adaptation effect will be smaller because contrast adaptation exhibits perceptual deterioration, so it is of interest to know if the effects of MD follow suit. This study measured the effect of 2-h MD for seven consecutive days on binocular balance of 15 normally sighted adults. We found that the shift in eye balance from MD stayed consistent, showing no signs of deterioration after subjects experienced multiple periods of MD. This finding shows no loss of effectiveness of repeated daily doses of MD if used therapeutically to rebalance binocular vision in otherwise normal individuals. Furthermore, ocular dominance plasticity, which is the basis of the effects of short-term MD, does not seem to share the property of 'perceptual deterioration' with contrast adaptation, suggesting different neural bases for these two related phenomena.

KEYWORDS
binocular balance, clinical application, dose-response, monocular deprivation, ocular dominance plasticity

INTRODUCTION

The critical period is a narrow time window after birth when the developing brain is most susceptible to visual influence from the environment. One extreme example is that removing the visual input to one eye (long-term monocular deprivation, LTMD) can significantly affect how the visual system processes information for a long period of time after early visual development. LTMD can be implemented by suturing one eye of animals; the eye whose input is removed is referred to as the deprived eye. Upon discovering the critical period in kittens and monkeys, Hubel and Wiesel[1–3] found that the response and population of neurons in the ocular dominance column of the primary visual cortex were significantly reduced in regions that were driven by the deprived eye if LTMD was introduced during the critical period, but not during adulthood.[2] These neural changes from LTMD during the critical period remain throughout life, even if the input to both eyes were to be restored during adulthood. Perceptual consequences from these physiological alterations following LTMD include diminished sensitivity of the deprived

eye and a decrease in its relative weight in binocular vision.[4] These perceptual changes are also referred to as ocular dominance plasticity because they are correlated with how the ocular dominance columns in the early visual cortex reorganised through plasticity.

More recently, human and primate studies have shown that a period of short-term MD (e.g., 2–3 h with an eye patch) can temporarily shift sensory eye dominance (i.e., relative weight in binocular vision) towards that of the deprived eye.[5–7] This change is in the opposite direction to that of LTMD during the critical period. The effect of short-term MD in humans for binocular vision has been demonstrated using various visual tests that measure sensory eye dominance in binocular combination and competition.[5,7,8] The effect of short-term MD has physiological correlates in the primary visual cortex of humans.[9–11] Recently, researchers have attempted to introduce repeated periods of short-term MD across days or months to restore the vision of young adults with binocular imbalance, which is a common feature of dissociative visual disorders that affect up to 18% of the population.[12] Amblyopia, a developmental visual disorder that affects 3%–5% of the population, is an extreme example of imbalanced binocular vision where there can be almost total reliance on one eye when both eyes are open.

However, the underlying mechanism of how short-term MD affects binocular balance remains to be clarified. Although short-term MD significantly shifts the binocular balance, the dynamic of the effect following short-term MD is transient, lasting for only 30–90 min.[5,7] Its dynamics are reminiscent of the dynamics of sensory changes following visual adaptation to a low-contrast input (i.e., contrast adaptation). Changes from a brief visual adaptation can disappear within a short timescale ranging from seconds to a few minutes.[13–17] With a longer duration of visual adaptation, the changes may last for more than 10 min,[18] displaying a similar dynamic to that of short-term MD. After adaptation to low contrast, the sensitivity of the adapted eye increases briefly.[19] Likewise, short-term MD using an eye patch removes all form information (i.e., contrast) from the deprived eye. So, it is reasonable to argue that the perceptual boost of the deprived eye could be attributed to a heightened sensitivity as a consequence of the eye being 'adapted' to zero contrast.[20]

After visual adaptation to a low-contrast stimulus, perceptual changes in that eye's processing can be of different magnitudes depending on recent prior experience. For example, they could be large if the eye had not recently experienced a single period of contrast adaptation. However, they are much smaller if the eye had previously experienced multiple periods of the same adaptation to the same stimulus for consecutive days.[21,22] The reduced sensitivity in producing perceptual changes after repeated periods of visual adaptation is referred to as perceptual deterioration.[21–26] Previous studies reported that perceptual deterioration is observed when six to eight (but not more) repetitions of adaptation are introduced in a cluster.[21,27–29] If perceptual deterioration is also present in the effect of short-term MD, its effect too should decrease after repeated periods of short-term MD, supporting that both contrast adaptation and the effect of short-term MD could share the same neural basis. In addition, if short-term MD is incorporated in clinical settings for adults with impaired binocular vision, it will be preferable if each session of short-term MD induces a maximal effect because the treatment protocol can involve consecutive periods of short-term MD across weeks or months and be more likely to restore long-term eye balance.

Clinically, the degree of perceptual change after a single period of short-term MD can be thought of as dose-response. In the standard patching therapy for children with amblyopia, the fellow eye is patched and the non-deprived eye's visual acuity is improved.[30] However, the recurrence rate of amblyopia after the therapy is high, and the compliance rate of the therapy is low because it forces the children to interact with their world solely through their worse eye during patching.[31–33] For this reason, the dose-response of amblyopic children to the patching therapy has been modelled by measuring the improvement rate of visual acuity over treatment duration to optimise the treatment regimen.[34,35] Recently, the dose-response to short-term MD of the non-dominant eye (i.e., the deprived eye), whose ocular dominance is increased in binocular vision, has been explored in amblyopic adults. The dose-response can be plotted as the magnitude of the binocular change as a function of repeated sessions of short-term MD.[36–38] For instance, anisometropic amblyopes' ocular dominance as measured from binocular rivalry was found to be more balanced after six sessions of short-term MD and physical exercise over 4 weeks.[37] In addition, Zhou et al.[38] observed an increase in visual acuity gain of the affected eye of amblyopic adults, as well as an improvement in eye balance

Key points

- A single session of 2-h short-term monocular deprivation can boost the previously deprived eye's relative contribution to binocular vision.
- Whether the effect of short-term monocular deprivation on ocular dominance is potent even after the observer experiences repeated doses of short-term monocular deprivation must be clarified to explore its potential application to long-term clinical therapy.
- These results indicate that the effect of short-term monocular deprivation produced equally potent shifts in binocular balance even after repeated exposures across consecutive days, providing support that short-term monocular deprivation and contrast adaptation may have different neural bases.

in binocular combination after 2-month short-term MD of the amblyopic eye. Together, psychophysical methods that measure binocular competition and combination have shown that depriving an amblyopic eye for months (2 h per day over 2 months) can bring out long-lasting benefits in monocular and binocular visual functions, possibly overcoming the issue of short-term MD effect's transience. However, dose-response to short-term MD on each day as a function of deprivation time has not been examined. Doing so would elucidate the therapeutic potential and whether its underlying mechanism involves visual adaptation to low-contrast stimuli or neural changes that involve ocular dominance plasticity.

The present study examined the dose-response to short-term monocular deprivation by conducting a perceptual test that measured binocular balance. Fifteen naive observers with normal vision who had not been exposed to MD previously were tested, and their non-dominant eye was occluded for 2 h across seven consecutive days. In this study, we specifically recruited normal observers to understand better how the interocular balance of the normal visual system changes to repeated periods of short-term MD.

METHODS

Participants

Fifteen adults (mean age ± SD: 25.1 ± 1.03 years; two males) with normal or corrected-to-normal vision (logMAR ≤ 0.00) from Wenzhou Medical University participated in our study. Their refractive range (spherical equivalent) was between −6.00 and +6.00 D and they had no history of ocular pathology or surgery. Subjects had not been exposed to MD prior to enrolment in the study and were naive to the purpose of the investigation. Written informed consent was obtained from each participant prior to their enrolment. This experiment was approved by the Ethics Committee of Wenzhou Medical University (NO. 2023-053-K-45-01) and in line with the Declaration of Helsinki.

Apparatus

The experiments were coded using MATLAB R2016b (mathworks.com) with PsychToolbox 3.0.14[39] on a MacBook Pro (13-in., 2017; apple.com). Stimuli were dichoptically presented with head-mount goggles that had undergone gamma correction (GOOVIS Pro, AMOLED display; NED Optics, goovis.net). The resolution of the organic light-emitting diode (OLED) goggles was 1920 × 1080 pixels and the pixels per degree of the screen was 41.6. The maximal luminance of the goggles was 150 cd/m^2 and the refresh rate was 60 Hz. Subjects were asked to perform the visual experiment in a dark room where there was no light source except for the computer screen and goggles.

Experimental design

The entire study involved seven consecutive days of short-term MD for 2 h each day. This design choice was based on previous psychophysical and neuroimaging studies on the deteriorated response after repeated rounds of visual adaptation, which has previously been assumed to underlie the effects of monocular deprivation.[21,23] Sighting dominance was used to establish the non-dominant eye for each subject using the hole-in-the-hand test.[40] The non-dominant eye of each subject was deprived of all pattern information (i.e., contrast) using a translucent patch (made of sulphuric acid paper) for 2 h at a similar time every day. The percentage light attenuation of the patch was 46%. A baseline measurement of the balance point (BP) before the short-term MD and post-deprivation measurement of the BP was performed on the first, third, fifth and seventh days. On the second, fourth and sixth days, subjects were asked to deprive their non-dominant eye for 2 h but not to perform the visual task for baseline and post-deprivation tests (see Figure 1). For baseline measurement, each subject completed two test sessions, from which the BP was extracted. Then, the BPs were averaged across the two tests. Subjects were familiarised with the task before they began

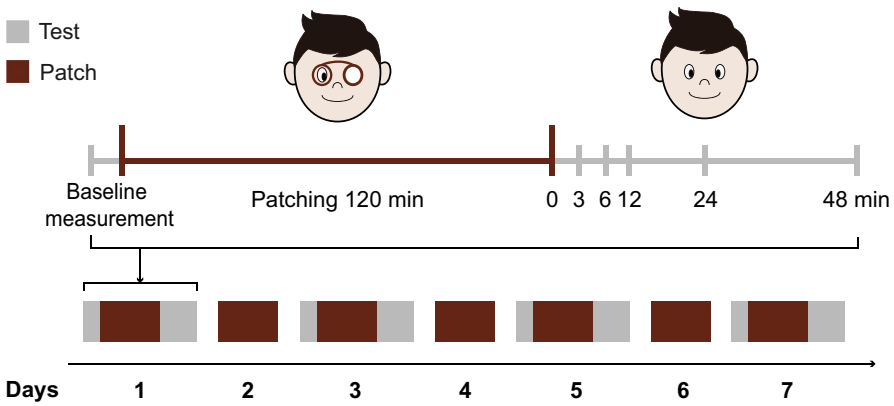

FIGURE 1 The experimental design. A translucent patch that was created using sulphuric acid paper was worn on the non-dominant eye of each subject for 2 h across seven consecutive days. Baselines and post-measurement were tested under normal viewing conditions where both eyes were open.

the formal test by completing one or two test blocks; the data from the practice blocks were not used in data analysis. If the difference between the two baselines was inappropriately large, they were asked to perform another set of two baseline tests to make sure all subjects had stable performance before the deprivation (i.e., ≤1 dB). Subjects were allowed to do any office work, such as reading and web browsing when patched except sleeping, but they were not permitted to engage in strenuous exercise[37,41] or close their eyes for a sustained period during patching.[42] In fact, all subjects were allowed to sit in the laboratory but not leave the hospital building where the lab was located. After the deprivation, BP was tested at six different time-points after deprivation; specifically, these were at 0, 3, 6, 12, 24 and 48 minutes after the deprivation (see Figure 1).

Psychophysical procedure

An alignment trial and a test phase were included in the binocular orientation combination task (see Figure 2). Throughout the whole process, the surrounding frame, composed of pixelated binary noise, was shown to facilitate fusion and maintain convergence. In this procedure, since we used head-mounted goggles to dichoptically display the stimulus separately to the two eyes, we were able to show different stimuli to each eye. In the alignment trial, subjects were presented with half of a cross in each eye (see Figure 2a). They were instructed to press the arrow keys to adjust the two halves so that they could be joined into a complete cross. The purpose of the trial was to align the two dichoptic screens to facilitate fusion throughout the psychophysical measurement. Then, during the test phase (see Figure 2b), the gratings (more details in the subsection below) were dichoptically displayed for 750 ms to both eyes. The stimulus duration was set to 0.75 s to prevent the onset of rivalry, from which the observer could see one orientation in one instance and then another over time if the stimulus presentation was indefinitely long. First, the contrast increased from zero to its peak contrast level as a function of a half-period sinewave. The exact value of the peak contrast level was calculated as shown in Figure 2b. Then, the peak contrast level was fixed for 250 ms; next, its contrast level decreased to zero as a function of a half-period sinewave for 250 ms. Participants were asked to report the relative orientation of the fused grating with

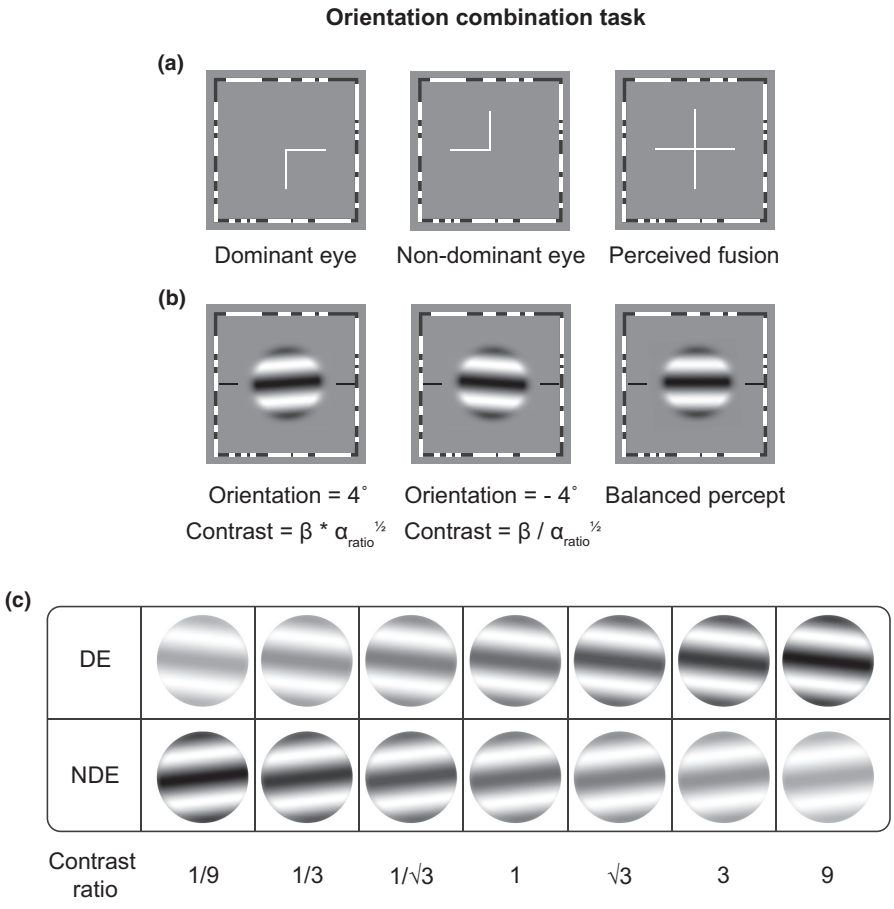

FIGURE 2 Binocular orientation combination task at multiple contrast ratios. (a) An alignment trial. Subjects were asked to align the right angle images to get a complete cross at the beginning of the task. (b) One trial in the test phase. Two sinusoidal gratings with different tilt orientations (±4°) were dichoptically shown to each eye. Subjects saw a horizontal grating when they had a binocular balance. (c) Seven contrast ratios were used in both baseline and post-test. DE, dominant eye; NDE, non-dominant eye. α_{ratio} is the interocular contrast ratio while β represents the base contrast.

the keyboard. The contrast ratio is the ratio between the dominant eye's peak contrast level to the non-dominant eye's peak contrast level. If the contrast ratio is 1, then the contrast levels of the two gratings are equal. If the contrast ratio is greater than 1, then the contrast of the dominant eye's grating is higher during the stimulus presentation. Specifically, depending on the contrast ratio and the sensory eye balance of the observer, the fused grating could be tilted in a clockwise or counter-clockwise direction; subjects were asked to report their perceived orientation by pressing the left key (for clockwise) or the right key (counterclockwise) after the stimulus presentation. So, the visual task had two alternative forced choices (AFC) for each response (i.e., 2-AFC task). After the onset of the response, the next trial of the test phase would follow. Throughout the task, there was pixelated binary noise in the periphery to facilitate fusion. There were 140 trials per test block, during which each of the seven contrast ratios was repeated 20 times. The method of constant stimuli was used to obtain psychophysical data. The test block would take 3 min to complete and yielded a robust psychometric function and stable balance points (see Figure 4).

Stimuli

We used a binocular orientation combination task to assess the BP at a constant spatial frequency (i.e., 0.5 c/d). Two sinusoidal gratings with different orientations (8° difference between the two gratings) along the horizontal axis were shown dichoptically; the size of the whole stimulus was 4.2°×4.2°; and the visible stimulus was a circle with a diameter of 2.8° through the mask of a Gaussian filter function (see Figure 2b). For configuration of the stimuli, the grating shown to one eye had an orientation of +4°, whereas that to the other eye had an orientation of −4° relative to the horizontal axis. In the other configuration, it was flipped. So, the orientation difference between the two gratings was 8°, which was set to promote fusion but prevent mixed perception. For example, when both eyes were balanced, there would be fusion, enabling the observer to perceive a horizontal grating rather than a superimposition of the two gratings shown to both eyes. The usage of two configurations enabled us to remove the bias of specific key or positional responses from the subjects. They were randomly set across different trials. We set the base contrast (β) at 0.28 and incorporated seven interocular contrast ratios (α_{ratio}) in both the baseline and post-deprivation measurements; the ratios were 1/9, 1/3, 1/√3, 1, √3/1, 3/1 and 9/1 (see Figure 2c). Prior to collecting data, we made sure that the stimulus was shown clearly at all ratios from the goggles.

Data and Statistical Analysis

The purpose of the data analysis was to translate the key responses from the subjects to a BP, where both eyes would contribute equally to binocular vision at a certain contrast ratio. To do so, we converted the contrast ratios into a log scale to assume symmetry between eyes:

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

where the contrast ratio is

$$\alpha_{ratio} = \frac{\alpha_{DE}}{\alpha_{NDE}}.$$

DE and NDE refer to the dominant and non-dominant eye, respectively.

Next, we fitted a psychometric function with a cumulative logistic function, whose *y*-axis was the probability of the dominant eye's response from the subjects and the *x*-axis was a series of contrast ratios in log units (see Figure 3a). Using the Palamedes toolbox (Psychophysics Toolbox Version 3, psychtoolbox.org),[43] we estimated the BP, which is the contrast ratio that yielded a perfect binocular balance. If the sensory eye balance tilts towards the non-dominant eye (i.e., patched eye), then BP will be positive. Conversely, if the BP is negative, the eye balance is in favour of the dominant eye. To capture the effect of changes in ocular dominance after short-term monocular deprivation, we subtracted the post-deprivation measures from the average of the two baseline results for each subject on each day. Positive differences indicate that the non-dominant eye's dominance had increased after the deprivation. Using the differences, we computed the area under the curve (AUC in units dB×min; see Figure 3b) from a function that showed the difference of ocular dominance over the six timepoints after the deprivation. AUC captures both the size and duration of the changes in eye dominance after patching the non-dominant eye.

We used the Shapiro–Wilk test to examine whether the data set was normally distributed and the Spearman test to perform correlation analysis of a non-normally distributed data set. A Bland–Altman plot was used to test the consistency and repeatability of two quantitative data sets. We also performed a one-way, repeated measures analysis of variance (ANOVA) with the effect size calculated as η^2 to compare the changes in dose-response across days. The above statistical analytic procedures relied on the *rstatix* package in R software[44] (r-project.org). To further verify the results, we used a Bayesian approach to perform a one-way repeated measures ANOVA using JASP 0.17.1 (jasp-stats.org). The test reported a Bayes factor (BF_{01}), which is the ratio of marginal likelihoods between the null and alternative hypotheses. The higher the BF_{01}, the more robust the evidence for the null hypothesis.

RESULTS

In this study, we used an orientation combination task with seven contrast ratios to quantify binocular balance. We examined the test–retest reliability and repeatability

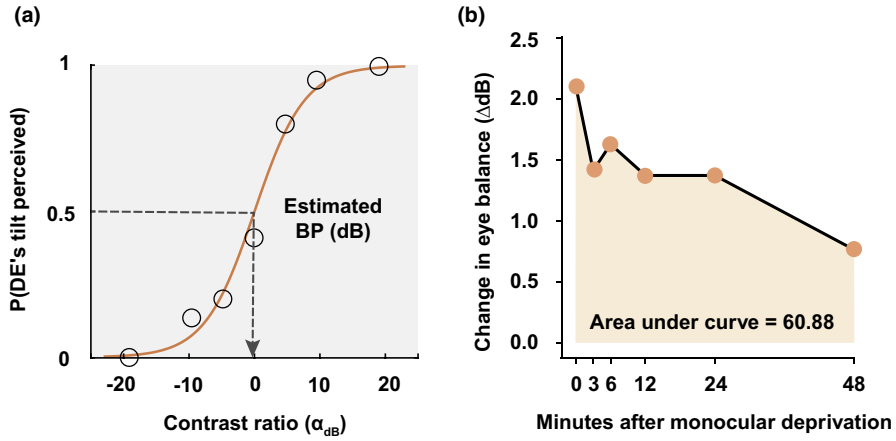

FIGURE 3 Illustration of data analysis using data of one representative subject. (a) A psychometric function. A cumulative logistic distribution function was used to fit this psychometric curve. The *y*-axis represents the probability (P) of the binocular percept to be the dominant eye's (DE) percept. The *x*-axis represents the contrast ratio of stimuli shown to both eyes. The balance point (BP) indicates the point where the two eyes had equal contribution in binocular combination. (b) Area under the curve (AUC). Each point represented the change in BP value at different timepoints after patching. The curve referred to the connection of six points. The specific AUC value was calculated by the sum of five divisible trapezoidal areas under the curve. The *y*-axis refers to the magnitude of changes in eye balance (dB) after patching normalised to baseline. The larger the AUC, the greater the perceptual change within 48 min.

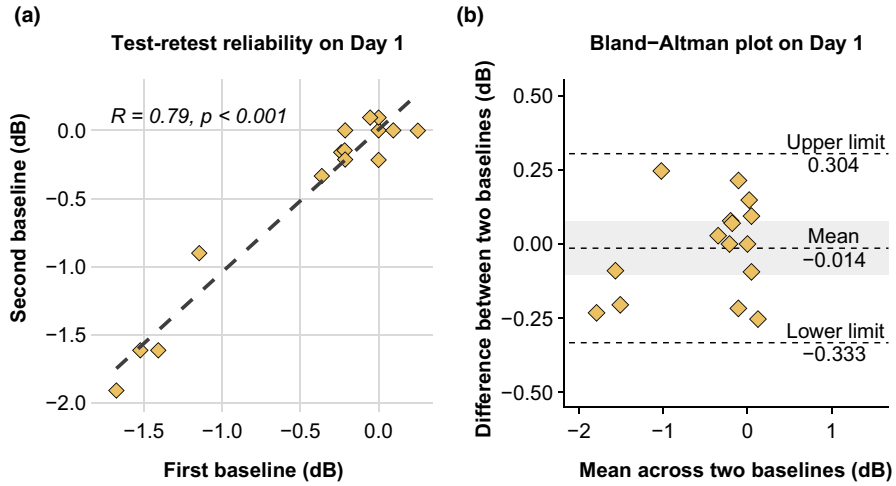

FIGURE 4 Test–retest reliability and repeatability of the task. (a) The correlation plot from Day 1's baseline data. The *R*-value measured the strength and direction of the correlation, which showed a strong and positive correlation between the two baselines using Spearman correlation analysis. (b) The Bland–Altman plot from Day 1's baseline data. The upper and lower dashed lines represent the range of variability between the two baselines. The middle-dashed line represents the mean difference between the two baselines and the grey-shaded area shows the 95% confidence interval of the difference based on a one-sample *t*-test from zero.

of the binocular orientation combination task using the baseline data from Day 1. To examine the test–retest reliability, we conducted a Spearman correlation analysis because our preliminary statistical procedures, such as the Shapiro–Wilk test, revealed that the two baseline data sets on Day 1 were not normally distributed (all *p*-values < 0.05). The Spearman test revealed a strong correlation between the two baseline measurements ($R = 0.79$, $p < 0.001$; see Figure 4a). This indicates that the baseline measurement from the first session was able to predict that from the second session, highlighting the reliability of the behavioural task. To address the test–retest repeatability of the task, we performed an analysis that involved a Bland–Altman plot, which shows the mean difference between the two baseline data sets (middle dashed line; −0.014 dB) in the form of a horizontal dashed line (see Figure 4b) and the 95% confidence interval of the mean differences (i.e., limits of agreement) between the two sessions. The upper and lower limits were obtained by calculating the mean difference ± 1.96 × standard deviation of the difference. The larger the limits, the wider the measurement variability. Our analyses indicated that the range was small (between −0.333 and 0.304 dB), demonstrating that the task was reliable for baseline measurement. The shaded grey region was calculated from the 95% confidence interval derived from a *t* distribution for

the given sample size and alpha value.[44] In other words, if 0 and the shaded region overlap, as shown in Figure 4b, there was no systemic bias between the two baseline sessions. However, despite the reliability of the task as shown by the data from the two baseline sessions, it is important to point out that this reliability would not be generalised to the measurement of the short-term MD effect because only one test session was performed for each timepoint after patch removal.

Next, we wanted to examine whether the dose-response, which is defined as the change in binocular balance after short-term MD in this study, was repeatable across days. The binocular change on each day was computed as the difference in eye balance before and after each day's short-term MD (see Figure 5). The change in eye balance was calculated at six different timepoints using a log scale. Figure 5 shows that the change in eye balance reached about 2 dB immediately (i.e., 0 min) after patch removal and then gradually decreased to the near baseline over time. A change of 2 dB means that the previously deprived eye became more perceptually dominant by a linear factor of 1.26 to binocular combination. Also, we investigated whether the baseline before each short-term MD was significantly different across 4 days (see Figure 6a) using a one-way repeated measures ANOVA, which revealed no significant difference ($F_{3,56} = 1.16$, $p = 0.34$, $\eta^2 = 0.06$). The baseline values remained stable over the 7 days of daily deprivation. Interestingly, baseline data on Day 5 were very close to 0 dB compared to those on other days, indicating that most subjects showed a stable binocular balance before short-term monocular deprivation. There was an increasing trend of the baseline from Day 1 to 5, showing a tendency for the baseline balance to improve across days. However, the baseline became more imbalanced on Day 7.

One way to characterise the dose-response is the immediate deprivation effect, which is the degree of perceptual change immediately (i.e., 0 min) after patch removal (the first point on each day in Figure 5). According to a one-sample *t*-test, we observed that there was a significant shift in eye balance relative to zero, that is, instantly after the deprivation (all p's < 0.05; see Figure 6b). Moreover, a one-way repeated measures ANOVA did not show a significant difference in the degree of immediate shift in eye balance across days ($F_{3,56} = 1.07$, $p = 0.37$, $\eta^2 = 0.05$). This finding shows that there was no deterioration in the immediate perceptual response after repeated short-term MD. We also showed the absolute eye balance immediately (i.e., 0 min) after patch removal (coloured points in Figure 6b). Another way to identify the dose-response is to monitor the rate at which the perceptual change dissipates after patch removal; we refer to this as the recovery rate.[45–47] In our analysis, the recovery rate was captured using simple linear regression between changes in sensory eye balance (dB) and time points in log scale (dashed lines in Figure 5). The goodness of fit of linear regression on the averaged data is shown for each day in Figure 5. The recovery rate was entirely negative and significantly different from zero based on a one-sample *t*-test (all p's < 0.05; see Figure 6c). However, we found that the recovery rate remained consistent across days based on a one-way repeated measures ANOVA ($F_{3,56} = 0.82$, $p = 0.49$, $\eta^2 = 0.04$). Together, both the immediate perceptual shift after deprivation and the rate of recovery remained similar across days. If there was perceptual deterioration in the dose-response, we would have observed a decrease in the immediate effect and an increasingly faster recovery rate as a function of days.

Finally, we performed a trapezoidal integration using values (dB) that represent perceptual changes after the deprivation across time on each day to capture both the degree and duration of the deprivation effect on each day (i.e., area under the recovery curve on each day; see Figure 6d). This area measure could also be referred to as dose-response with the dimensions of magnitude and time. An AUC of 0 would indicate no change in eye balance

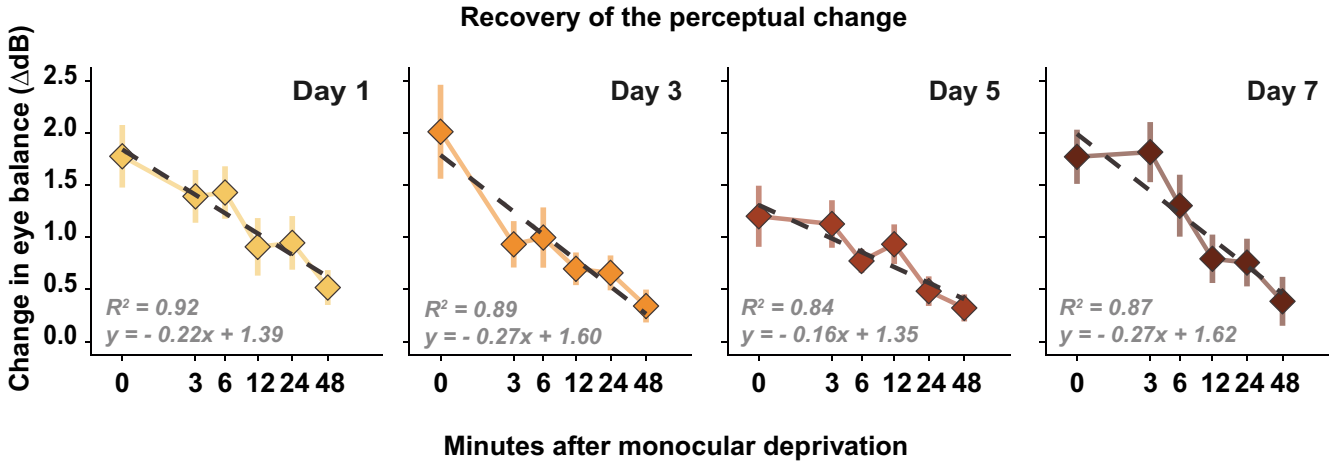

FIGURE 5 Averaged results of 15 observers. The points represent the perceptual change at different time points in log scale after short-term monocular deprivation on each test day. When the *y*-axis is 0, this represents no change in eye balance after the deprivation. The black dashed lines represent the linear regression for the averaged data from each day. The error bars indicate standard errors.

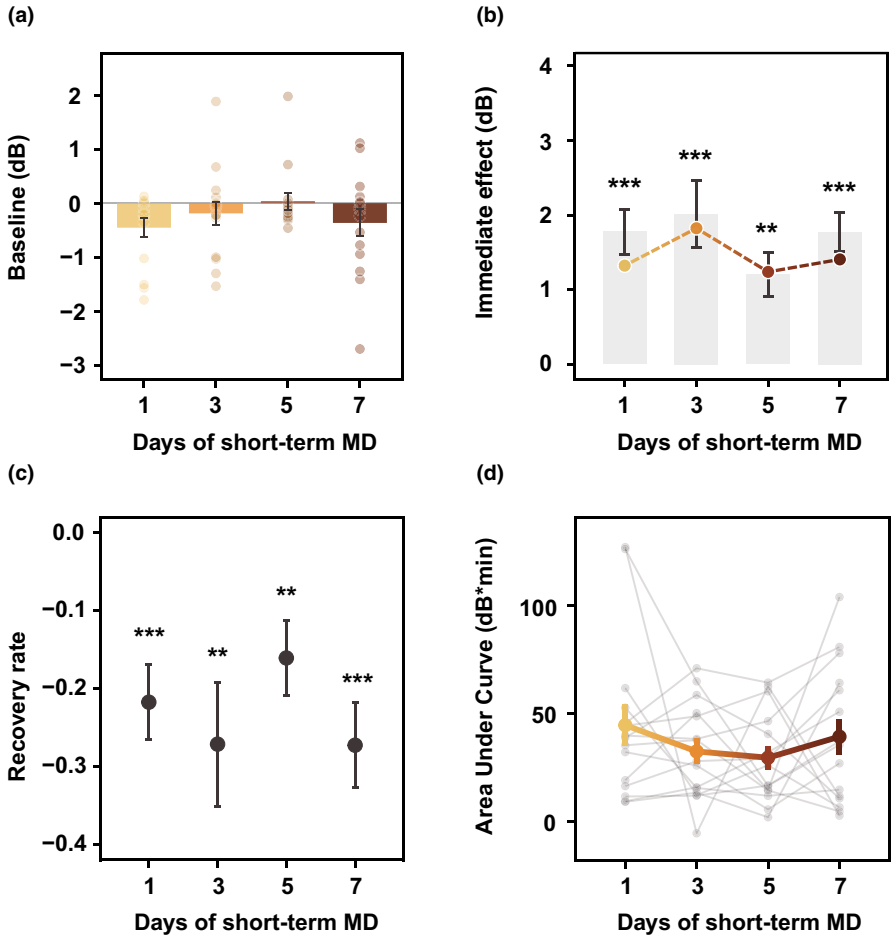

FIGURE 6 The baseline and dose-response from short-term monocular deprivation (MD) across days. The panels represent three different ways to show the dose-response. (a) The baselines before short-term monocular deprivation across days. The points represent the individual's data. The grey line with a *y*-axis of 0 indicates binocular balance. The negative balance points mean that the eye balance is in favour of the dominant eye. (b) Immediate effect in sensory eye balance after patching in a graph. The coloured points represent the absolute immediate eye balance point 0 min after patching. The bars represent the averaged shift in sensory eye balance at 0 min after patching across subjects. (c) The rate of decay of changes in sensory eye balance after short-term monocular deprivation (i.e., recovery rate). The points represent the averaged slopes of the changes in eye balance after deprivation across participants on different test days. (d) Area under the curve (AUC). The coloured points represent the average AUC across all subjects. The grey plots represent each individual's AUC. Error bars indicate standard errors. The *x*-axis of each figure represents the number of total patching days. $*p<0.05$, $**p<0.01$, $***p<0.001$.

after the deprivation across the six different time points (0–48 min), relative to the baseline balance that was measured before patching. To begin with, we performed a one-sample *t*-test to examine statistically whether each day's AUC was significantly larger than zero; the test revealed that all AUCs were significantly different from zero (all *p*'s < 0.05). Subsequently, we conducted a one-way repeated measures ANOVA to see if the AUCs were significantly different across days; it revealed no significant difference ($F_{3,56}=0.83$, $p=0.49$, $\eta^2=0.04$; see Figure 6d). In the Bayesian method, the larger the Bayes Factor (BF_{01}), which represents the ratio of the probability between the null and alternative hypotheses, the greater the likelihood that the null hypothesis is correct. Therefore, unlike the frequentist method that reports a *p*-value, which does not support the null hypothesis by its own definition, the Bayesian counterpart can statistically support the null hypothesis rather than merely rejecting it. The test revealed that $BF_{01}=4.31$, which provides robust evidence for the null hypothesis.[48] Using the AUCs, we also performed a post-hoc power analysis, which revealed that a sample size of 337 would be required between Day 1 and Day 7 to show a statistically significant difference (power = 80%, $\alpha=0.05$) based on the two-tailed significance level.[49] This in turn suggested that the likelihood of showing significant differences between the AUCs across days was small. In sum, the dose-response in the form of AUC remained stable and consistent as a function of the deprivation sessions.

DISCUSSION

We explored the features of the dose-response to repeated periods of short-term MD in normal-sighted adults. Previously, we indicated that the short-term MD effect has been thought of as either ocular dominance plasticity

or visual adaptation to a low-contrast visual stimulus. Some have categorised it as the latter[14] because there are similarities between short-term MD and contrast adaptation: the dynamics of the effect after a single period of short-term MD and removal of contrast during short-term MD. A key characteristic of contrast adaptation is perceptual deterioration, causing different magnitudes of sensory changes after adaptation depending on recent prior experience of the observer. For instance, if the observer had experienced a cluster of repeated adaptation periods to the same stimulus for consecutive days, then the adaptation effect could gradually diminish.[22] Resolving whether the effect of short-term MD shows perceptual deterioration is important for two reasons. First, doing so clarifies its therapeutic potential because administering short-term MD in the clinic for visually imbalanced populations, such as those with amblyopia, inevitably results in prescribing daily episodes of short-term MD across weeks or months. Whether its efficacy decreases after repeated periods of short-term MD should be known before short-term MD is incorporated into clinical settings. Second, it bears upon whether ocular dominance plasticity is simply a class of contrast adaptation or something unique. The former has been shown to exhibit perceptual deterioration in the form of reduced responses.[21,23] We show that there is a comparable dose-response to short-term MD across the 7 days of this study, suggesting that the effect of short-term MD is most likely a unique phenomenon due to ocular dominance plasticity rather than a reflection of contrast adaptation.

There has been some controversy as to whether the effect of short-term MD (i.e., ocular dominance plasticity) and contrast adaptation from long-term exposure to a high- or low-contrast environment involve the same underlying neural substrate.[20] If they do, then perceptual responses after repeated episodes of short-term MD should wane over time in line with what is known about contrast adaptation.[21–23] As previously mentioned, similarities are their dynamics from single sessions and the fact that they both involve the removal of contrast to one eye. Also, there are some differences between the two phenomena.[20] First, the effect of short-term MD has lowpass spatial dependence; this means that the removal of low-spatial frequency information does not drive the effect of short-term MD.[50] However, contrast adaptation shows tuning for spatial frequency; if contrast adaptation is performed using a stimulus at a low spatial frequency, then the change in detection threshold will be observed at low but not high spatial frequencies. They also have mechanistic differences. Contrast adaptation is a binocular process, whereas the effect of short-term MD is a reciprocal process that affects the eyes differently; if one eye is adapted to a low-contrast stimulus, then its boost in sensitivity will also be seen to a lesser extent in the other, unadapted eye.[51] This is known as interocular transfer because the adaptation effect transfers to the non-adapted eye, and it reflects a binocular mechanism. Electrophysiological and psychophysical evidence shows that there is a reciprocal change between the eyes after short-term MD.[8,11,52] The deprived eye's sensitivity, weight in binocular vision and neural signal become stronger, whereas those of the non-deprived eye get weaker after short-term MD. Furthermore, unlike contrast adaptation, the effect of short-term MD does not show orientation selectivity. For example, deprivation in the vertical orientation also boosts the deprived eye's contribution when measured with stimuli in other orientations.[53] However, after visual adaptation to a low-contrast stimulus with a vertical orientation, the sensitivity for vertical orientation will increase but not in the horizontal orientation.[19] Our results show that the dose-response in ocular dominance plasticity is stable across time, further demonstrating that ocular dominance plasticity and contrast adaptation are different, and likely have different underlying neural bases.

The finding that there is a consistent and comparable change in ocular dominance across 7 days of short-term MD provides a basis on which it could be used clinically for patients with imbalanced ocular dominance. A significant degree of binocular imbalance can impair hand–eye coordination,[54] reading[55,56] and depth perception.[57] There are multiple visual conditions that exhibit binocular imbalance, such as those associated with asthenopic symptoms (i.e., the dissociative visual disorders),[12,58] as well as sensorymotor imbalance associated with symptoms of sore eyes, eye strain and headaches with a prevalence rate of 70%.[59] A less common condition where this approach would have a more direct application is in amblyopia (4%), where the ocular dominance is so imbalanced that vision only occurs through one eye when both eyes are open.[60–62] Some preliminary attempts have been made at using daily short-term MD as a new therapeutic intervention to alleviate binocular imbalance in these visual conditions, specifically amblyopia because it has the most severe imbalance.[36–38] This is of particular interest because it is directly opposite to the presently accepted therapy for amblyopic children, which has been in common practice for over 200 years.[63] In fact, standard patching therapy is still associated with high recurrence (24%)[32] and low compliance rates[33] because it forces the amblyopic children to interact with their visual world through their poorer eyes, potentially increasing the associated discomfort[64] and psychosocial distress.[65] Short-term MD, however, involves depriving the worse eye, to boost its contribution to binocular vision, while keeping the fellow eye open. Previous studies have demonstrated that monocular and binocular visual benefits from short-term MD (i.e., depriving the worse eye) over 2 months can be long-lasting[37,38] in adult amblyopes, demonstrating long-term benefits in rebalancing the eyes via ocular dominance plasticity. If short-term MD is introduced for binocularly imbalanced individuals with amblyopia and other visual conditions, it would be helpful to know the pattern of the short-term MD effect after each period of deprivation. This study provides, at least in the case for normal human observers, evidence that each daily dose of short-term MD has no less potency across time.

In a previous study,[45] we reported a weak but insignificant deterioration in normally sighted observers over 5 days of short-term monocular deprivation using a phase combination task. However, in light of the present results, we feel that this previously small effect could have been artefactual. First, most participants in the previous study had already been subjected to short-term monocular deprivation on multiple occasions. Hence, whether they had the same starting point in the dose-response curve could not be resolved based on the experimental design. Second, the number of short-term MD sessions was different between the previous and current studies. In the former, 2 h of MD was introduced for 5 days, whereas 2 h of MD was completed for 7 days in the current study. Third, the non-dominant eye, rather than the dominant eye, was deprived in this study. This design of depriving the non-dominant eye ensured less saturation of the perceptual response to short-term MD. Since it is widely believed that homeostatic plasticity underlies ocular dominance plasticity by dynamically promoting stability,[66] it seems reasonable to assume that the extent to which ocular re-balancing occurs will be less affected by a ceiling limitation using the present design (deprivation of the non-dominant eye). Although ocular dominance was determined qualitatively using the hole in the hand test (i.e., sighting dominance rather than sensory eye dominance), their state of ocular dominance was consistent across the qualitative and quantitative orientation tests in 11 out of 15 subjects. As for the four remaining subjects, the orientation task revealed that their sensory eye balance was very close to zero, indicating a near-perfect binocular balance.

Although not statistically significant, we did find that the effect of short-term MD on Day 5 was slightly lower than that from other days. For instance, the immediate short-term MD effect was lowest on Day 5 (Figure 6b), whereas the recovery rate was highest on Day 5 (Figure 6c), indicating that the rate of decay was the slowest. Finally, the integrated short-term MD effect over time (Figure 6d) was the lowest on Day 5. According to our baseline data (Figure 6a), the binocular balance was close to zero (i.e., perfect balance) on Day 5. The effect of short-term MD has been thought to drive neural changes in the primary visual cortex through homeostatic plasticity,[66–68] which limits perturbation of the homeostatic status. It could be that the magnitude of changes in ocular dominance was smallest when there was a near-perfect binocular balance before short-term MD.

To summarise, we measured the daily dose-response from short-term monocular deprivation in normally sighted observers across 1 week. We observed that the dose-response was sustained after repeated short-term MD. We found no evidence of any perceptual deterioration unlike that previously shown for contrast adaptation. Therefore, these findings, in terms of clinical translation, warrant a future study that will measure the daily dose-response of visually impaired patients for short-term MD. An examination of the dose-response to short-term MD in a clinical population over a longer period of time (i.e., months) is needed for binocular balance, fusion and stereopsis.

AUTHOR CONTRIBUTIONS

Liying Zou: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Chenyan Zhou:** Data curation (equal); formal analysis (equal); methodology (equal); writing – review and editing (equal). **Robert F. Hess:** Conceptualization (equal); funding acquisition (equal); investigation (equal); project administration (equal); writing – original draft (equal); writing – review and editing (equal). **Jiawei Zhou:** Conceptualization (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (equal); validation (equal); writing – review and editing (equal). **Seung Hyun Min:** Conceptualization (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); software (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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