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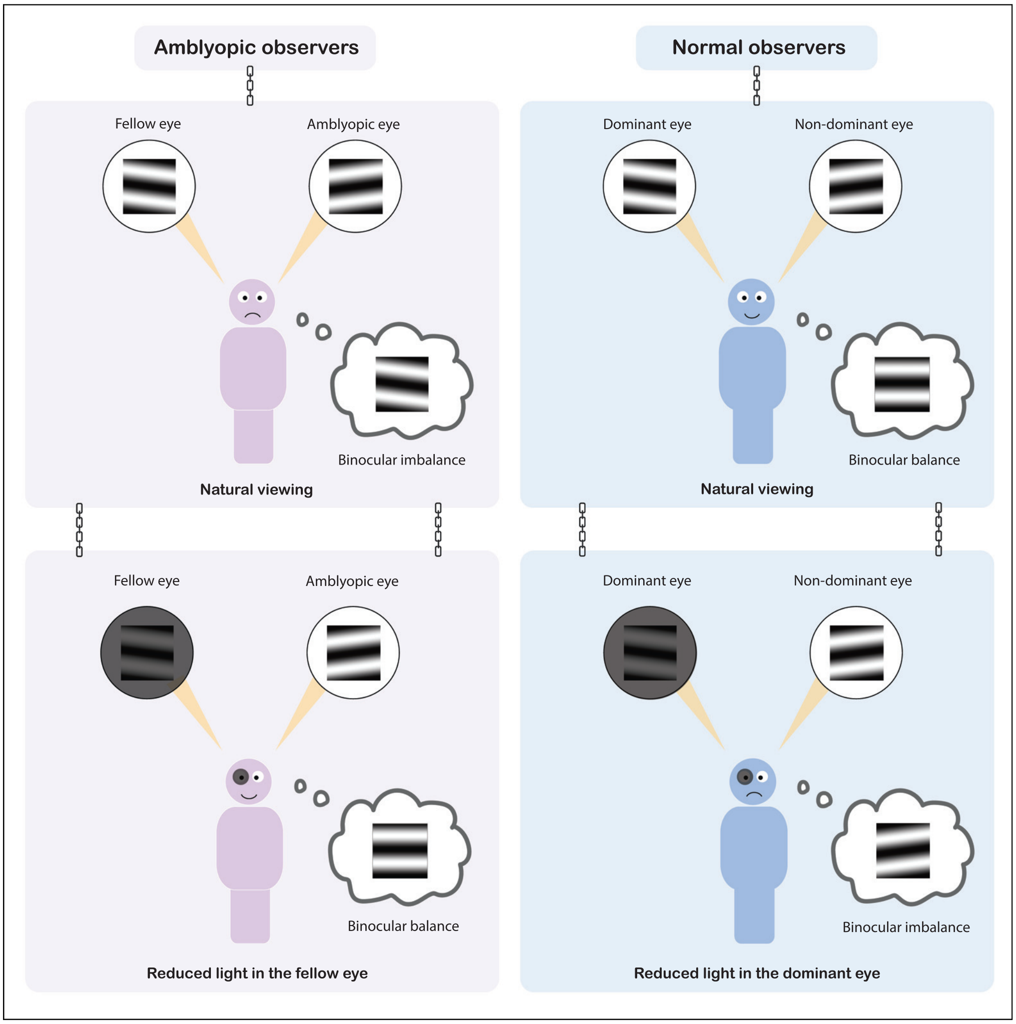

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Highlights

Binocular balance is impaired in amblyopia

Reduced luminance of the fellow eye can improve it across spatial frequencies in amblyopia

Reduced luminance of one eye from normal observers simulates amblyopic imbalance

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Modulation of mean luminance improves binocular balance across spatial frequencies in amblyopia

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SUMMARY

Amblyopia is a visual impairment that perturbs binocular balance at high spatial frequencies in favor of the fellow eye. Studies reveal that amblyopes who had been treated with monocular therapies still show imbalance. Binocular balance is achieved when both eyes' inputs are weighed equally. A reduced light can diminish the dimmed eye's weight in binocular combination. In this study, we examined if binocular balance across spatial frequencies could be improved by reducing the luminance of the fellow eye in adult amblyopes. By doing so, we relieved their binocular imbalance across spatial frequencies. Also, normal observers showed amblyopic binocular imbalance when the dominant eye's light level was dimmed. Therefore, reducing the luminance in the unaffected eye in amblyopia mitigated the binocular imbalance, whereas doing so in normal adults simulated the amblyopic imbalance across spatial frequencies.

INTRODUCTION

Amblyopia is a neural disorder that exhibits poor monocular and binocular vision. It arises from an abnormal visual development early in life during the critical period when neural plasticity peaks (Daw and Daw, 2006; Levi and Carkeet, 1993). A proper visual development ensues only after visual input to both eyes has remained balanced and unobstructed during childhood. Markers of normal visual development are both perceptual and physiological. Perceptual evidence for normal development is intact binocular vision. Physiological correlates reside in the primary visual cortex (Mendola et al., 2005), specifically in ocular dominance columns where inputs from both eyes get combined. However, when the visual input of one or both eyes gets deprived during the critical period (Hubel et al., 1977; Hubel and Wiesel, 1970), visual development halts, thereby bringing a string of perceptual and physiological consequences, such as amblyopia. These deprivations can occur naturally if an eye is blurred (anisometropia), misaligned (strabismus), or deprived of form information (congenital cataract) (Hess et al., 2014; Holopigian et al., 1986; Levi et al., 1980). Perceptual symptoms of amblyopia include a reduced visual acuity of the amblyopic eye (Levi and Klein, 1982) and significant suppression of its input by the fellow eye (Hess et al., 2014; Li et al., 2011). These impair binocular balance (Chen et al., 2021; Ding et al., 2013; Ding and Levi, 2014; Kwon et al., 2014, 2015; Mao et al., 2020; Zhou et al., 2013) and stereopsis (Levi et al., 2015). Also, the neural region at the columns corresponding to the unaffected eye is larger than that of the amblyopic eye (Goodyear et al., 2000). In short, amblyopia is a perceptual and physiological consequence of abnormal visual development during the critical period when neural plasticity peaks.

In clinical practice, monocular patching therapy for amblyopia, during which the fellow eye is patched, has been standard for the past 250 years (De Buffon, 1743). It improves the visual acuity of the amblyopic eye. Its improvement has been the main criteria for assessing the recovery of amblyopia. However, it often fails to ameliorate binocular balance and suppression (Hess et al., 2010a, 2010b; Hess and Thompson, 2015). For instance, amblyopic observers who have been fully treated with the standard patching therapy and have achieved normal monocular visual acuity can have a binocular imbalance that peaks at high spatial frequencies (Chen et al., 2021; Ding et al., 2013; Kwon et al., 2015; Mao et al., 2020). Psychophysical studies have examined binocular imbalance of amblyopes across spatial frequencies (0.5-4 c/deg) using a phase combination task (Ding et al., 2013; Ding and Levi, 2014; Ding and Sperling, 2006), a dichoptic letter chart (Kwon et al., 2015) and a binocular orientation task (Mao et al., 2020; Min et al., 2022). Moreover, studies report no correlation between the improvement of visual acuity and the depth of interocular suppression during monocular patching treatment (Chen et al., 2019; Kehrein et al., 2016). To summarize, an improved visual acuity of the amblyopic eye from the standard monocular therapy does not ensure an improvement

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of binocular visual functions, such as stereopsis, suppression, and binocular balance, all of which are pivotal in performing daily activities such as motor skills and driving (Birch, 2013; Molina et al., 2021; Vera et al., 2020). In addition, poor binocular vision, rather than the amblyopic eye's monocular visual acuity, has been shown to diminish children's self-perception of physical competence (Birch et al., 2019a; 2019b), hand-eye coordination (O'Connor et al., 2010; Suttle et al., 2011), and reading speed (Kelly et al., 2015, 2017). Therefore, correcting the binocular imbalance in amblyopes across the spatial frequency range—from coarse to fine image scales—might be necessary for the binocularly impaired population, such as those with amblyopia, to achieve a normal, everyday binocular vision leading to a better hand/eye coordination and psychosocial experience.

Investigations show that if the mean luminance in the fellow eye of amblyopes is reduced with a neutral density (ND) filter, the binocular balance can be improved at low spatial frequencies (Ding and Levi, 2014; Zhou et al., 2013). According to the mathematical definition of physical contrast, an ND filter reduces the mean luminance without changing the image's contrast (Hess, 1990, p. 199; Zhou and Hess, 2016). To illustrate, an ND filter decreases the maximum and minimum luminances by the same factor in both the numerator and denominator (ex. 90% for 1-ND filter). Therefore, the factor gets canceled, thereby allowing the overall contrast to be unaffected. However, even if the contrast of an image remains the same, the decreased luminance affects binocular perception because the contrast gain of the filtered eye is reduced (Ding and Levi, 2017; Zhou et al., 2013). This observation has also been made in animal studies. For example, reduced luminance diminishes the gain of M and P retinal ganglion cells in primates (Purpura et al., 1988) and simple and complex cells of the visual cortex in cats (Geisler et al., 2007; Hess, 1990). In sum, decreased luminance can lower the weight of the eye's visual input for binocular fusion. This has been described with a contrast gain control model at a low range of spatial frequency (Zhou et al., 2013; Ding and Levi, 2014; Ding and Levi, 2017). Based on this premise, it seems tenable that one could rectify the binocular imbalance in amblyopia by reducing luminance, and therefore its contrast gain, of the fellow eye.

The influence of luminance in binocular combination through a contrast gain mechanism has been modeled and examined in previous studies (Zhou et al., 2013; Ding and Levi, 2014; Ding and Levi, 2017). For example, Zhou et al. (2013) measured the balance of seven adult amblyopes using a phase combination task with visual stimuli at 0.29 c/deg while their fellow eyes were dimmed using 2ND and 3ND filters (Zhou et al., 2013). Moreover, Ding and Levi tested one adult amblyope with the same task using stimuli at 0.68 c/deg with a 1.5 ND filter (Ding and Levi, 2014). In light of the fact that amblyopes exhibit binocular balance at higher spatial frequencies (Ding et al., 2013; Kwon et al., 2015; Mao et al., 2020), we examined whether the binocular imbalance could be corrected by reducing the luminance of the fellow eye, and whether its beneficial effect would depend on spatial frequency. Moreover, we investigated whether amblyopic binocular imbalance could be reproduced in normal observers by dimming the luminance of one eye and whether this experimentally induced imbalance would also depend on spatial frequency. To do so, we measured the binocular balance across spatial frequencies with a binocular orientation combination task by reducing the mean luminance (0, 90, or 99%) of their fellow eye from amblyopic observers and that of the dominant eye from normal observers (see Figure 1).

RESULTS

Does dimming the dominant eye of normal observers simulate amblyopic binocular imbalance across spatial frequencies?

To see if |log BP| differed across spatial frequencies and across ND filters in normal observers, we performed two-way repeated measures ANOVA (within factors: spatial frequency and ND filters). We observed significant effects of both spatial frequency ($F(3,27) = 30.96$, $p < 0.001$, $\eta^2 = 0.28$) and ND filter ($F(2,18) = 130.61$, $p < 0.001$, $\eta^2 = 0.80$). Moreover, the interaction between spatial frequency and ND filter was significant ($F(2.25, 20.22) = 10.5$, $p < 0.001$, $\eta^2 = 0.18$). This interaction shows that |log BP| changes as a function of spatial frequency in a distinct fashion across distinct ND filters. The average values of |log BP| and their associated standard errors are displayed in Table S2.

As for the areas under a curve (AUCs; see Methods for details), we incorporated the data of 4 c/deg into our analysis so that the AUCs would encompass 0.5 to 4 c/deg. According to a one-way repeated measures ANOVA (within-subject factor: ND filter), normal observers experienced a more severe imbalance (as computed with the areal index) as the ND filter was denser ($F(2,27) = 69.17$, $p < 0.001$, $\eta^2 = 0.84$). Tukey HSD test was performed for post hoc analysis. The areal measures were significantly different between

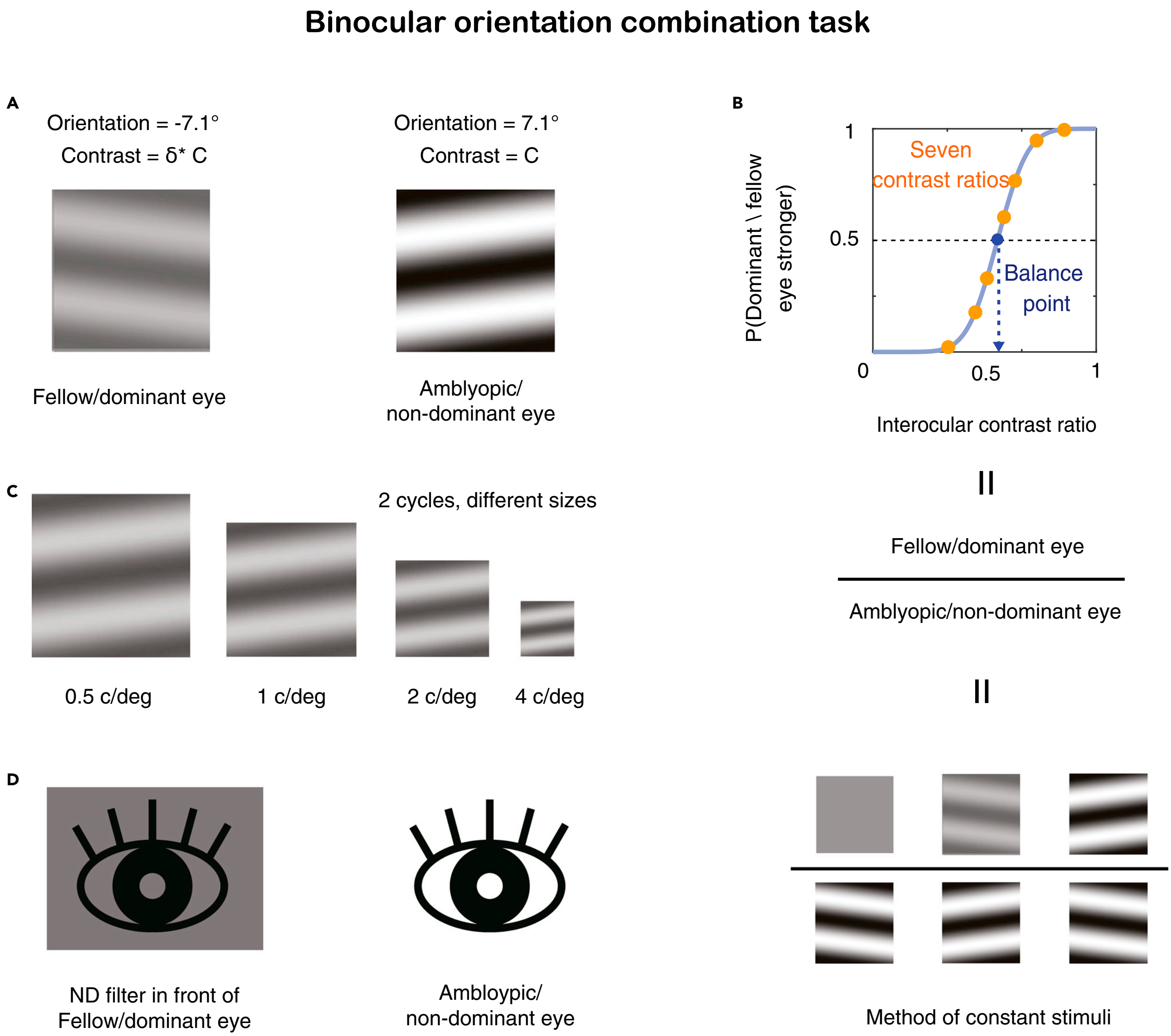

Figure 1. Stimuli and design

(A) Two horizontal sinusoidal gratings with a tilt of ±7.1 relative to the horizontal axis. Each grating was shown to each eye. The contrast of the grating shown to the fellow/dominant eye was lower than that shown to the amblyopic/non-dominant eye.

(B) A psychometric function of an amblyopic observer. The y-axis denotes the probability of the observer perceiving the tilt of the fused grating to be the same as that shown to the fellow/dominant eye. The x-axis denotes the interocular contrast ratio, which is the relative ratio of contrast between the gratings shown to the fellow/dominant eye and amblyopic//non-dominant eye. The data at seven interocular contrast ratios (the orange points) are presented here for illustration. Then, a psychometric function was fitted using a cumulative Gaussian distribution function to estimate the balance point (BP; the navy point), which is the contrast ratio where both eyes contribute equally to binocular vision. For the controls, the contrast of the gratings for the dominant eye was set at 0%-100%. The contrast for the non-dominant eye was set at 50%. For amblyopes, the contrast of the grating for the fellow eye was set at 0%-100%. The contrast for the amblyopic eye was fixed at 100%. Hence, the interocular contrast ratios ranged from 0 to 1 for the amblyopes, and 0 to 2 for the controls.

(C) For normal observers, the gratings were shown at 0.5, 1, 2, and 4 c/deg. For amblyopes, the gratings were set 0.5, 1, and 2 c/deg. 4 c/deg was not tested because some observers were not able to complete the test at this spatial frequency with one of the ND filers.

(D) An ND filter (0, 1, or 2-ND) was placed before the fellow/dominant eye throughout the experiment.

1- and 2-ND filters ($p < 0.001$, 95% CI = [0.98, 1.73]), and between 0- and 2-ND filters ($p < 0.001$, 95% CI = [1.35, 2.10]). Our results indicate that a similar form of binocular imbalance that peaks at higher spatial frequency can be recreated in normal observers, who have intact normal visual acuity.

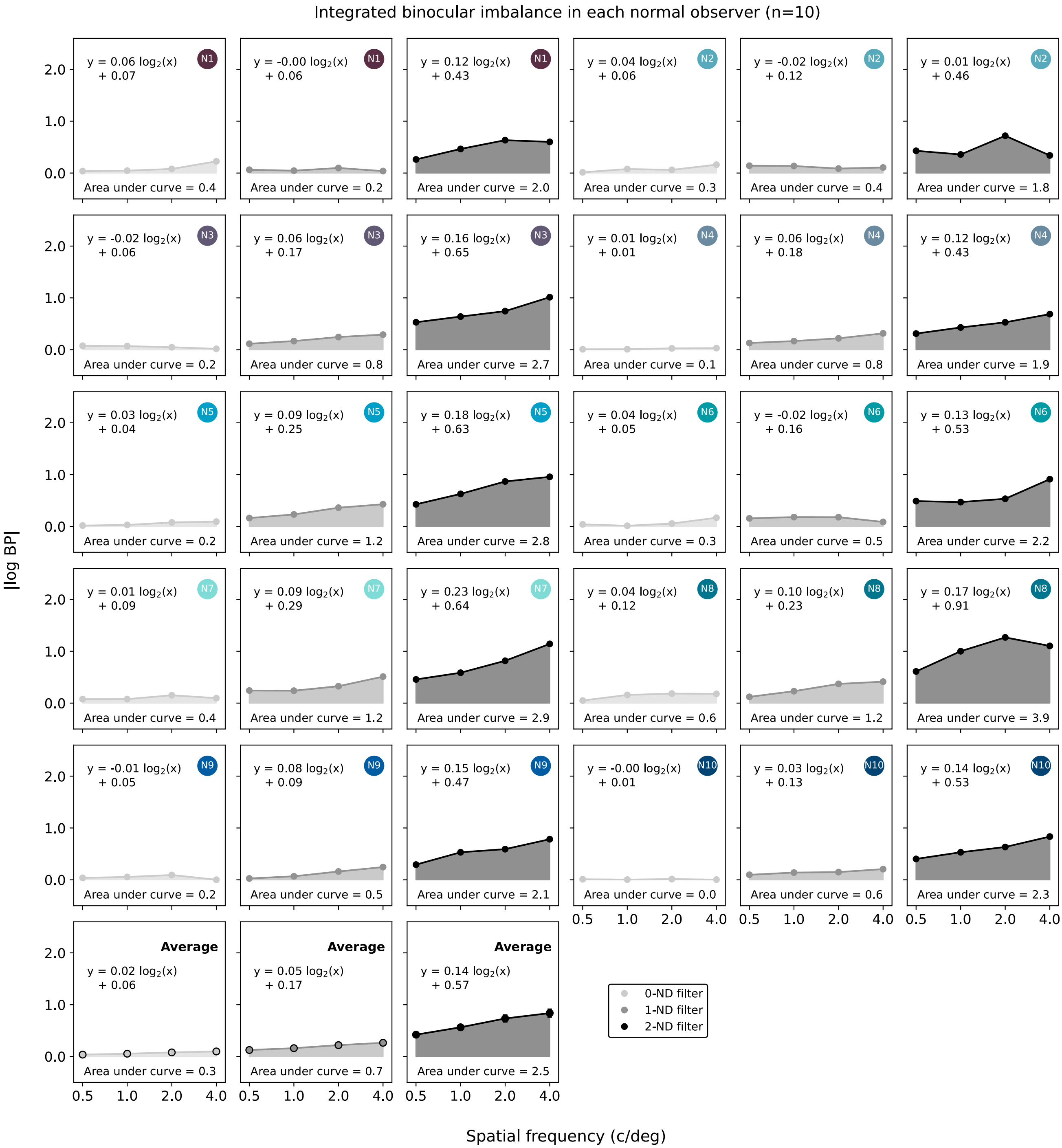

Figure 2. Binocular imbalance (|log BP|) as a function of spatial frequency from 10 normal observers

Each shade of gray represents each ND filter; the lightest one represents 0-ND, the darkest 2-ND. The data of each normal observer and the average of all normal observers are plotted. The average plots illustrate the average points of all subjects. The error bars in the average plots represent standard errors. Each panel shows the computed area under the curve from |log BP| as a function of spatial frequency.

We also calculated the dependence of |log BP| on spatial frequency in the form of slopes from linear regression (see Figure 2). The slope is an index that describes the relationship between binocular imbalance and spatial frequency. If the slope is positively steep, then the binocular imbalance becomes more severe as spatial frequency increases. If the slope is near zero, it indicates an independent relationship where binocular imbalance does neither increase nor decrease as spatial frequency increases. A one-way repeated measures ANOVA (within-subject factor: ND filter) revealed that normal observers exhibited a significantly steeper slope as the ND filter's density increased ($F(2,18) = 15.6$, $p < 0.001$, $\eta^2 = 0.53$). A pairwise t-test with a Bonferroni correction for multiple comparisons indicated that there was a significant difference in the slopes between 0-ND and 1-ND, as well as between 0-ND and 2-ND. This illustrates that luminance attenuation in the dominant eye of normal observers can induce binocular imbalance that is dependent on spatial frequency. These results agree with Figure 2. For example, the reader will realize that |log BP| increases quickly as a function of spatial frequency when 2-ND filter is applied (see Figure 2). However, when no light is reduced, |log BP| remains consistent across spatial frequencies. These qualitative observations are backed by our statistical analysis on the slopes from linear regression; it indicates that the dependence of binocular imbalance on spatial frequency is noticeable when 2-ND, but not 0-ND, is on the dominant eye. Our findings confirm that an ND filter on an eye in the normal visual system simulates the amblyopic binocular imbalance, which is greater at higher spatial frequencies.

Does dimming the fellow eye of amblyopes reduce binocular imbalance across spatial frequencies?

We examined if |log BP| varied across spatial frequencies and different ND filters in amblyopic observers by conducting a two-way repeated measures ANOVA (within factors: spatial frequency and ND filters). We found significant effects of both spatial frequency ($F(2,14) = 52.40$, $p < 0.001$, $\eta^2 = 0.27$) and ND filter value ($F(2,14) = 191.71$, $p < 0.001$, $\eta^2 = 0.29$). Moreover, the interaction between spatial frequency and ND filter was significant ($F(4, 28) = 3.96$, $p = 0.011$, $\eta^2 = 0.020$). This indicates that the rate of |log BP| increase as a function of spatial frequency differs among ND filters. These results agree with Figure 3. For instance, |log BP| appears to increase as a function of spatial frequency. However, this rate of increase appears to be much higher at 0-ND than 2-ND filters; this qualitative observation is supported by a slope analysis later in the text. This finding shows that an ND filter on the fellow eye of the amblyopes can reduce binocular imbalance more at a high spatial frequency than at a low spatial frequency. The average values of |log BP| and their associated standard errors are displayed in Table S2.

We next examined the effect of the ND filter on the AUCs of the amblyopes. A one-way repeated measures ANOVA (within-subject factor: ND filter) indicated that the amblyopes experienced a much milder imbalance as the density of the filter increased ($F(2,21) = 4.39$, $p = 0.026$, $\eta^2 = 0.30$). Tukey HSD as post-hoc analysis indicated that the areal measures between 0- and 2-ND filters were significantly different ($p = 0.022$, 95% CI = [-1.64, -0.18]). This finding illustrates that a 2-ND filter on the fellow eye significantly reduces the binocular imbalance of amblyopes across spatial frequencies.

In addition, we also computed the dependence of |logBP| on spatial frequency by fitting linear regressions (see Figure 3). Results from a one-way repeated measures ANOVA (within-subject factor: ND filter) demonstrated that amblyopic observers exhibited a significantly flatter slope as the ND filter's density increased ($F(2,14) = 6.6$, $p = 0.010$, $\eta^2 = 0.26$). A pairwise t-test with a Bonferroni correction for multiple comparisons reported that there was a significant difference in the slopes between 0-ND and 2-ND. This illustrates that an appreciable attenuation of luminance in the fellow eye of amblyopic observers can mitigate the dependence of binocular imbalance on spatial frequency.

Comparison of binocular imbalance between normal and amblyopic observers

The areal index of binocular imbalance was also examined in detail. To allow a better comparison between the normal observers and amblyopes, we plotted and analyzed the areal measures by combining the data from 0.5, 1, and 2 c/deg only for both groups (see Figure 4). A two-way mixed ANOVA (within-subject factor: ND, between-subject factor: Subject groups) demonstrated a significant difference of AUC owing to subject groups ($F(1,16) = 17.98$, $p < 0.001$, $\eta^2 = 0.51$; normal versus amblyopes). The analysis also reported a significant effect of interaction between the subject groups and ND filters ($F(2,32) = 238.89$, $p < 0.001$, $\eta^2 = 0.50$). According to a one-sample t-test, the AUCs from amblyopes at 2-ND filter was still significantly different from 0 ($t(7) = 4.03$, $p < 0.01$). This indicates that the binocular imbalance across spatial frequencies was not completely nullified with the use of a 2-ND filter on the fellow eye of the amblyopic observers.

We also compared the slopes from the linear regression between the normal and amblyopic observers (see Figure 5) by using |log BP| data only from 0.5, 1, and 2 c/deg. A two-way mixed ANOVA (within-subject factor: ND filter, between-subject factor: group of observers) showed that there was a significant difference in

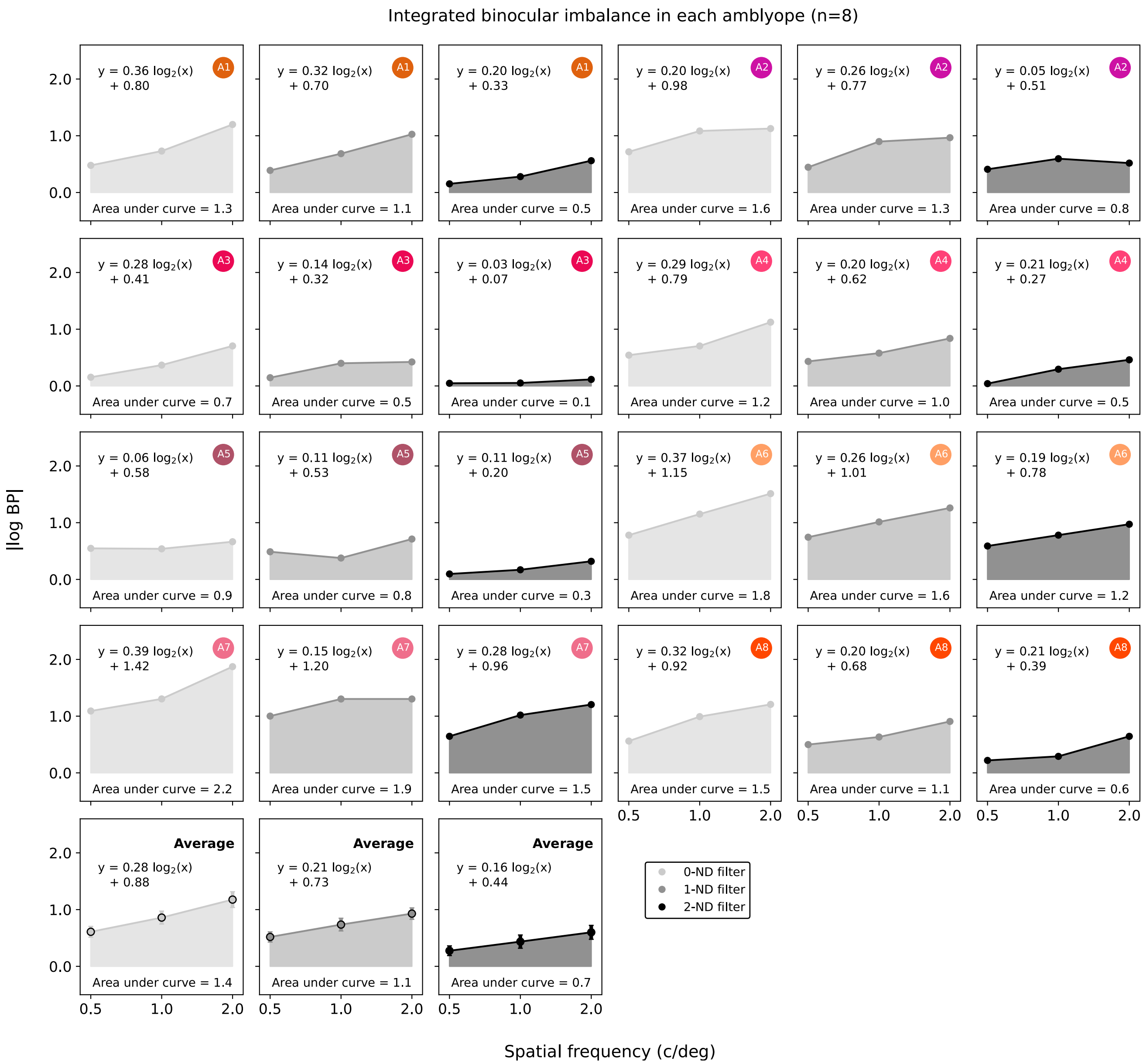

Figure 3. Binocular imbalance (|log BP|) as a function of spatial frequency from eight amblyopic observers

Each shade of gray represents each ND filter; the lightest one represents 0-ND, the darkest 2-ND. The data of each amblyopic observer and the average of all amblyopes are shown. The average plots illustrate the average points of all subjects. The error bars in the average plots represent standard errors.

the slopes between the groups ($F(1,16) = 16.2$, $p < 0.001$, $\eta^2 = 0.39$) and a significant interaction between the effect of groups and the ND-filter ($F(2,32) = 28.2$, $p < 0.001$, $\eta^2 = 0.40$). However, according to a one-sample t-test, the slope from amblyopes at 2-ND filter was still significantly different from 0 ($t(7) = 5.34$, $p < 0.01$). This indicates that the dependence of |log BP| on spatial frequency was not completely abolished with the use of a 2-ND filter on the fellow eye of the amblyopic observers. The results suggest that the relationship between the increase in the linear regression slope and the ND filter's density in normal observers differs from that between the slope and the ND filter's density in amblyopic observers.

Normalization of AUCs at 1, 2 neutral density filters relative to AUCs at 0 neutral density filter

As our results indicate, the areal measures increase as a function of the ND filter's density in the normal observers. Conversely, the integrated binocular imbalance reduces as the density of the filter increases

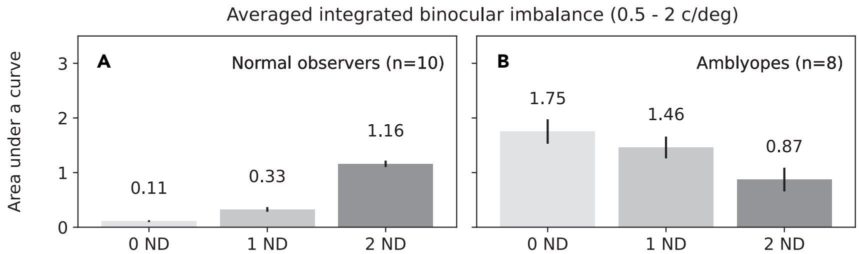

Figure 4. Averaged area under a curve (AUC) as an index for integrated binocular imbalance from all subjects shown in bar plots

Each shade of gray represents each ND filter; the lightest one represents 0-ND, the darkest 2-ND. The error bars represent standard errors. The averaged AUC reported in this figure might be different than those in Figures 2 and 3 because the earlier figures show the AUCs that were computed from the averaged |log BP| across all subjects. Also, Figure 2 shows the AUC of normal observers' |log BP| from 0.5 to 4 c/deg, but AUCs shown in this figure were computed with |log BP| from 0.5 to 2 c/deg.

(A) Averaged AUCs from normal observers.

(B) Averaged AUCs from amblyopic observers.

in the amblyopes. However, we see that the rate of the increase of AUC as a function of the ND filter's density is not exactly equal to the rate of the decrease of AUC as a function of the filter's density in amblyopes (see Figure 4). As a matter of fact, these two can directly be compared against one another. To do so, we normalized the areal measures of binocular imbalance at 1- and 2-ND relative to that at baseline (i.e., the 0-ND). By calculating the linear regression using the normalized scores at each ND level using the AUCs, we computed the rate of increase or decrease of overall binocular imbalance across spatial frequencies (i.e., AUC) in normal (Figure 6) and amblyopic (Figure 7) observers, respectively, when they were viewing through ND filters.

Normalizations of AUCs in normal observers at 1- and 2-ND relative to those at 0-ND are shown in Figure 6. We see that the relationship between binocular imbalance and the density of the filter is positive and steep (one-sample t-test from 0: $t(9) = 11.98$, $p < 0.001$). Notice that both x and y axes are in non-linear scale (ND filter itself is in log units). If one instead plots these functions as the normalization of AUCs as a function of light attenuation, the linear fits in Figure 6 can be described as power functions, where the slope of the linear fits in Figure 6 is the exponent of the function. The relationship in Figure 6 indicates that the binocular balance of controls can be severely disrupted when a ND filter is applied, and that binocular imbalance as indexed by AUCs could continuously increase as a function of the ND filter's density in the normal visual system.

Normalizations of AUCs in amblyopes at 1- and 2-ND relative to those at 0-ND are shown in Figure 7. We see that the relationship between binocular imbalance and the density of the filter is negative (one-sample t-test from 0: $t(7) = -5.50$, $p < 0.001$). With the aid of a 2-ND filter placed in front of the fellow eye in

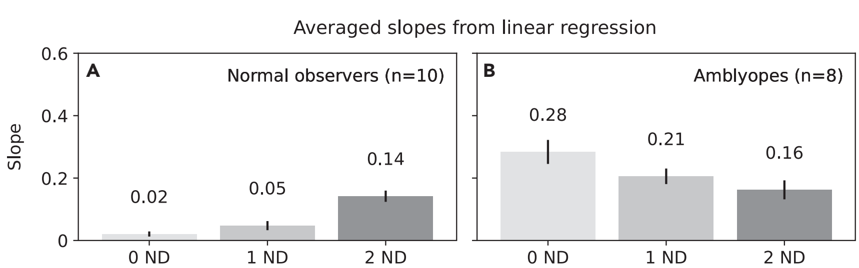

Figure 5. Averaged slopes from linear regression as an index for the dependence of binocular imbalance (|logBP|) on spatial frequency (in log2 units) from all subjects shown in bar plots

Each shade of gray represents each ND filter; the lightest one represents 0-ND, the darkest 2-ND. The error bars represent standard errors.

(A) Averaged slopes from normal observers.

(B) Averaged slopes from amblyopic observers.

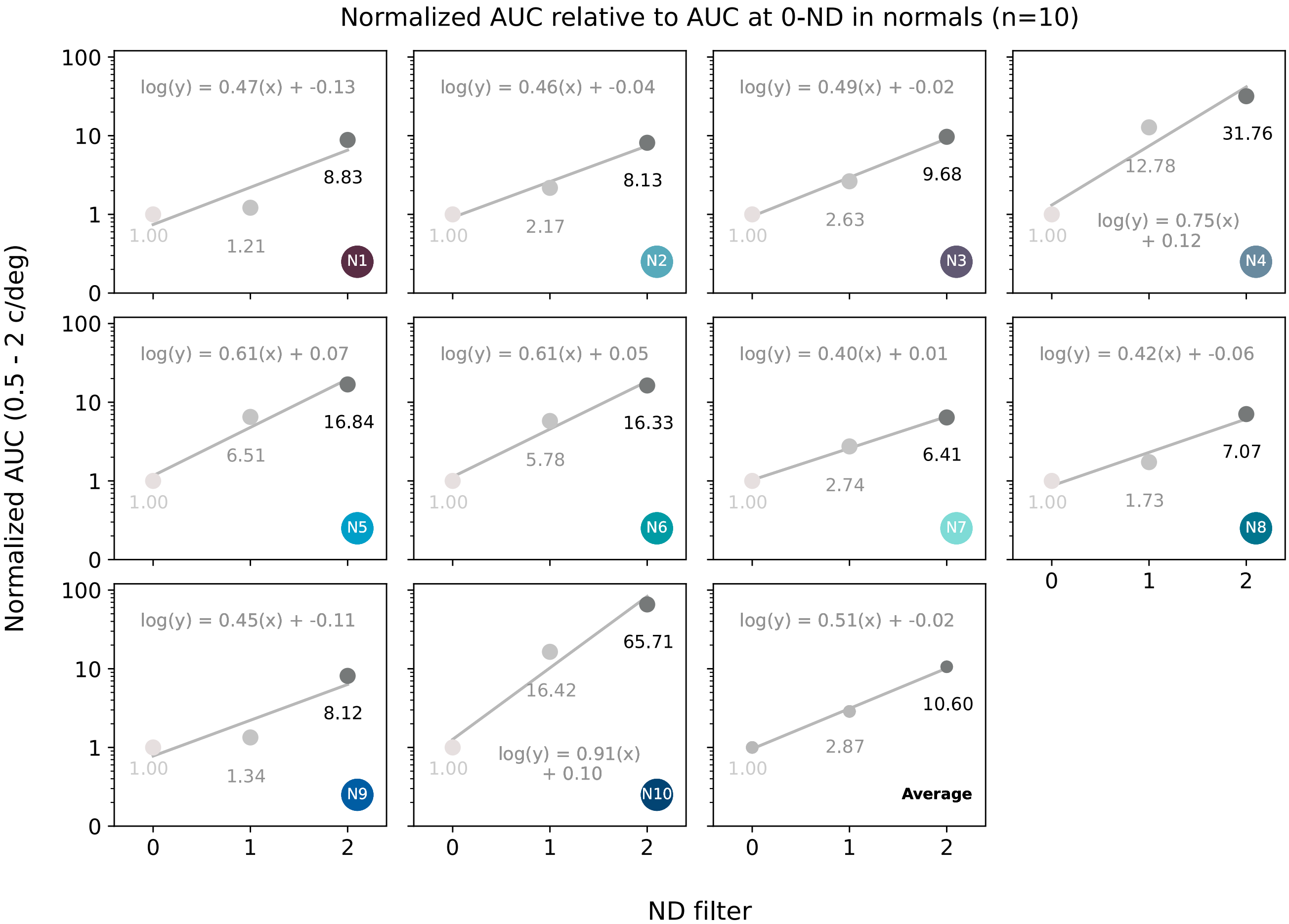

Figure 6. Normalizations of AUCs in normal observers at 1- and 2-ND filters relative to those at 0-ND filter from 10 normal observers

Points at each shade of gray represent each ND filter; the lightest one represents 0-ND, the darkest 2-ND. The ratio between AUC at 2-ND and AUC at 0-ND is defined as normalized AUC at 2-ND relative to 0-ND. The higher the normalized AUC, the more severe the imbalance at 2-ND relative to at 0-ND. The average plot illustrates the normalization score obtained from the averaged AUCs (shown in Figure 4A).

amblyopes, their binocular imbalance was reduced by 50% (as shown in the average plot in Figure 4). We also compared the slopes of regression from controls and amblyopes. A Welch's two-sample unpaired t-test showed a significant difference between the slopes ($t(15.15) = 12.88$, $p < 0.001$) from amblyopes and controls. This result indicates that both the sensitivity of binocular balance to the ND-filter (ex. steep or mild) and the relationship between it and the ND-filter (ex. positive or negative) are significantly different between the normal observers and the amblyopes.

DISCUSSION

Binocular imbalance worsens as a function of spatial frequency in amblyopia (Chen et al., 2021; Ding et al., 2013; Kwon et al., 2015; Mao et al., 2020). Kwon et al., states that suppression from the fellow eye, rather than the deficit in acuity in the amblyopic eye, drives the imbalance at high spatial frequencies (Kwon et al., 2015). Along with the perceptual evidence, neurophysiological studies support this. For instance, a recent neuroimaging study shows that amblyopia is associated with a reduced response in the parvocellular layers of the lateral geniculate nucleus (Wen et al., 2021), which is a region that is crucial for processing high spatial frequency achromatic information. Fortunately, changing the mean luminance of one eye could mitigate the binocular imbalance. Light reduction reduces the weight of the eye's visual input for binocular combination. This has been described with a contrast gain control model in the low spatial frequency range (Zhou et al., 2013; Ding and Levi, 2014; Ding et al., 2017). In this study, we examined whether binocular

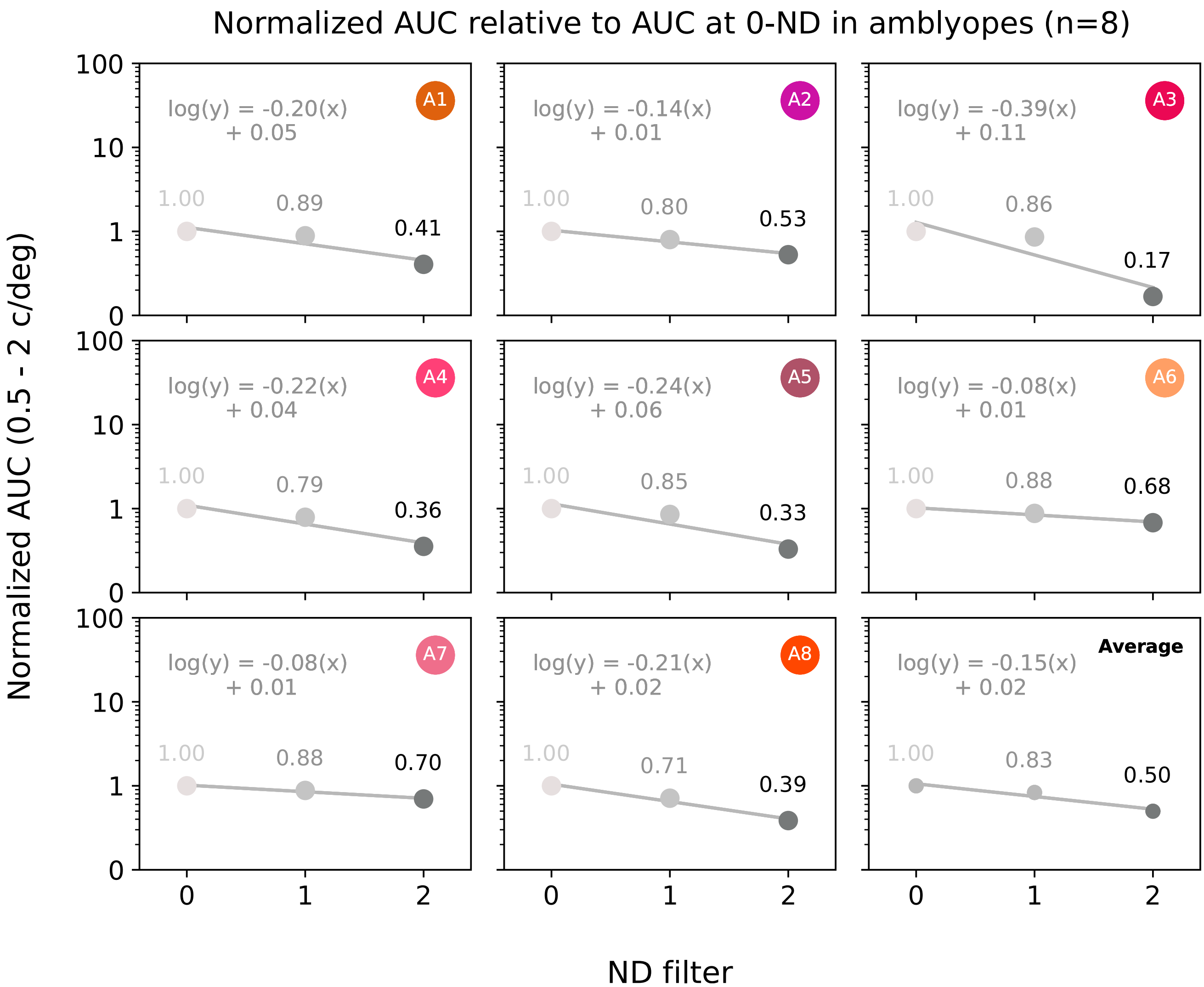

Figure 7. Normalizations of AUCs in amblyopic observers at 1- and 2-ND filters relative to those at 0-ND filter from 8 amblyopic observers
Points at each shade of gray represent each ND filter; the lightest one represents 0-ND, the darkest 2-ND. The average plot illustrates the normalization score obtained from the averaged AUCs (shown in Figure 4B).

imbalance from amblyopes could be reproduced in normal observers by reducing the light level of one of their eyes. Also, we investigated whether dimming the fellow eye of an amblyope could improve binocular balance across spatial frequencies.

Our results from the normal observers show that an ND filter (ex. 2-ND) on the dominant eye of a binocularly normal individual reproduces amblyopic binocular imbalance (see Figure 2). This observation confirms the role of luminance in binocular combination across spatial frequencies. Light reduction reduces the weight of the affected eye's input in binocular combination. Conversely, binocular balance was improved in amblyopia when the fellow eye's luminance was reduced with an ND filter (Figure 3). However, although the binocular imbalance (AUC) and the dependence of |log BP| on spatial frequency (slopes from linear regression) were both reduced with the aid of a 2-ND filter, they were still significantly different from 0. To illustrate, even with the aid of ND-filters, the imbalance still peaked at the highest spatial frequency that was measured (i.e., 2 c/deg). Furthermore, the overall imbalance across spatial frequencies in amblyopes with a 2-ND filter was slightly higher than that of normal observers who had a 1-ND filter placed before one of their eyes. Our analyses indicate that a 2-ND filter is not enough to fully correct binocular balance in more severe amblyopes and abolish the relationship between spatial frequency and balance.

Binocular combinations in both the normal and amblyopic visual systems have been modeled (Ding et al., 2013; Huang et al., 2009; Zhou et al., 2013). The contrasts of inputs (suprathreshold) in both eyes determine their weights in binocular combination. A contrast gain control model describes this process (Ding and Sperling, 2006; Richard et al., 2018; Zhou et al., 2013). If the contrast of one eye's input is sufficiently high, it exerts a gain control that weakens the weight of the other eye's input. The visual input from the eye with a larger weight contributes more to the binocular fused image. In addition, luminance can affect gain control in binocular combination (Ding and Levi, 2017). For example, if luminance is reduced in one eye, the affected eye's input gets weighed less in binocular combination. It reduces the contrast energy of the dimmed eye, thereby reducing the gain control over the other eye's input (Zhou et al., 2013). This has been modeled at a low spatial frequency (Ding and Levi, 2014; Zhou et al., 2013). Our study shows that this phenomenon can be generalized across spatial frequencies in amblyopes with statistical support. In amblyopia, when the ND filter is on the fellow eye, its gain control over the amblyopic eye reduces. Then, the weight of the amblyopic eye's input is enhanced. Therefore, if reduced luminance weakens the gain control of the fellow eye's influence on the amblyopic eye, binocular imbalance in amblyopia can be rectified across spatial frequencies.

Our findings have clinical relevance. Binocular imbalance in amblyopia can be greatly reduced across spatial frequencies with an ND filter on the fellow eye. We speculate that this phenomenon can be described with the contrast gain control model. At present, dichoptic treatment has been used to improve binocular balance and reduce suppression in amblyopia (Baker et al., 2008; Gambacorta et al., 2018; Hess et al., 2014; Hess and Thompson, 2015). During this treatment, the dichoptic display, which presents the stimuli to the fellow eye at a lower contrast, encourages both eyes to achieve a better binocular fusion. Also, dichoptic treatment with movies and games have been used by displaying the visual stimuli at a lower luminance to the fellow eye and higher luminance to the amblyopic eye (Mezad-Koursh et al., 2018; Vedamurthy et al., 2015). These different forms of dichoptic training therapies (dichoptically different contrasts and luminances) have been shown to improve both the visual acuity of the amblyopic eye and the balance between the two eyes. Our results also demonstrate that a neutral density filter might be promising in achieving the same benefit. However, it is important to note that the ND filter should be applied in a controlled viewing environment because the absolute luminance difference between the eyes can vary depending on the surrounding light level (Zhou and Hess, 2016). In fact, both the interocular luminance ratio and the absolute luminance difference seem to affect binocular balance (Zhou and Hess, 2016). A future study should be conducted to assess the therapeutic potential of the ND filter in both environments with controlled and uncontrolled natural light levels.

Limitations of the study

There are a few limitations to the study. First, we were not able to successfully measure the balance point at higher spatial frequencies using the same ND filters in the amblyopic observers. Second, we did not apply ND filters with a higher density (i.e., 3-ND) because the observers failed to perform the visual task. Third, most amblyopic observers were anisometropic (A2-A8).

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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- QUANTIFICATION AND STATISTICAL ANALYSIS
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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2022.104598.

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AUTHOR CONTRIBUTIONS

S.M., Y.M., R.H., and J.Z. conceived the experiments. Y.M. and S.C. performed the experiments. S.M., Y.M., S.C., R.H., and J.Z. analyzed and interpreted the data, and wrote the article. All authors contributed to article revision, read, and approved the submitted version.

DECLARATION OF INTERESTS

There is no conflict of interest.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Experimental models: Organisms/strains		
10 normal observers (age: 22.6 ± 2.3 years, mean ± SD; 6 females)	Recruited at Wenzhou Medical University	N/A
8 amblyopes (age: 23.5 ± 5.6 years; 1 female; see Table S1 for details)	Recruited at Wenzhou Medical University	N/A
Software and algorithms		
MATLAB R2016b v9.1.0	MathWorks	https://www.mathworks.com/products/matlab.html
Psychtoolbox extension v3.0.14	Brainard and Vision, 1997	http://psychtoolbox.org/
RStudio	RStudio	https://www.rstudio.com/
Python	Python	https://www.python.org/
Other		
MacBook Pro 2017	Apple, Inc	https://www.apple.com/mac/
ASUS monitor (PG279Q)	AsusTek Computer Inc	https://www.asus.com/Displays-Desktops/Monitors/All-series/
GOOVIS (AMOLED display)	NED Optics	https://goovis.en.alibaba.com/company_profile.html

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Jiawei Zhou (zhoujw@mail.eye.ac.cn)

Materials availability

No new unique reagents were developed by this study.

Data and code availability

All data reported in this study will be available from the lead contact author (Jiawei Zhou: zhoujw@mail.eye.ac.cn) upon request.

The paper does not report original code.

Any additional information required to reanalyze the data reported in this paper is available from the lead contact (Jiawei Zhou: zhoujw@mail.eye.ac.cn) upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Participants

10 normally sighted observers (22.6 ± 2.3 years, six females) and eight observers with amblyopia (23.5 ± 5.6 years, one female) participated in the study. All subjects were blind to the goal of the study. Clinical details of the patients are provided in Table S1. All participants provided written informed consent prior to the study, which was approved by the international review boards at Wenzhou Medical University and agrees with the Declaration of Helsinki.

Apparatus

We conducted the experiments on a 13-inch MacBook Pro (Apple, Inc., Cupertino, CA, USA) using MATLAB R2016b (v9.1.0 MathWorks, Inc., Natick, MA, USA) with the PsychToolBox extension (Brainard and Vision, 1997; Kleiner et al., 2007). The stimuli were displayed with gamma-corrected head-mounted goggles (GOOVIS Pro; NED Optics, Shenzhen, China) with a refresh rate of 60 Hz and a resolution of 1600 × 900 pixels (corresponding to 46 × 26°). The mean luminance was about 75 cd/m^2. The stimuli were shown dichoptically; one eye was shown with a slightly different stimulus (a grating with a different orientation) than the other eye.

Due to the design of the goggles, which had an extra layer of glass that encapsulates the display screens, we were not able to directly measure the luminance level with the photometer. To obtain the mean and minimum luminance, we contacted the manufacturer. Nevertheless, we were able to confirm the actual transmission of our ND filters. The measured density of 1-ND filter is 0.999-ND; the measured density of 2-ND filter is 1.998-ND. Based on our calculation, the mean luminance for 1-ND would be 7.48 cd/m^2 and that for 2-ND would be 0.753 cd/m^2.

METHOD DETAILS

Visual stimuli: binocular orientation combination task

A binocular orientation combination task has been developed on the premise that humans can perceive a fusion of two stimuli that slightly differ in their orientations by 20–30° (Braddick, 1979; Campbell et al., 1973; Wang et al., 2019; Yehezkel et al., 2016). During the test, two sinusoidal gratings were displayed to both eyes in two configurations. In the first configuration, the dominant (or the fellow) eye was shown with a grating that was tilted by +7.1° relative to the horizontal axis, whereas the non-dominant (or the amblyopic) eye was shown with a grating that was tilted by -7.1° relative to the horizontal axis. In the second configuration, the orientation of the grating shown to the dominant (or the fellow) eye was -7.1°, and that of the non-dominant (or amblyopic) eye was +7.1°. The usage of two configurations removed a positional bias, which could be manifested when the observer only responded with one orientation, during the measurement of binocular balance. In both configurations, the net difference of the grating orientations was 14.2°.

The contrasts of the gratings differed depending on who the test subject was for our study. For example, the base contrast was set at 100% to the poorer eye of the amblyopic observers. The grating was shown at a full contrast to the amblyopic eye because the overall balance of these observers significantly favored their unaffected, fellow eye. The grating was shown to the fellow eye at seven different contrasts. Hence, there were seven interocular (between the eyes) contrast ratios (fellow eye's contrast/amblyopic eye's contrast, ranged from 0 to 1) that were used to estimate the balance point of the observer. When the contrast ratio was 1, the contrast of the fellow eye's grating would be 100%.

On the other hand, the base contrast was set to 50% in the non-dominant eye of the normal observers because their eyes are balanced. The eye dominance of the normal observers was established using the Miles test (Miles, 1930). The participants used their hands to form a peephole with their index finger and the thumb. They were asked to alternatively close each eye and report which eye was closed when the visual target behind the peephole shifted the most; the eye would be the dominant eye. During the test, we presented the grating shown to the fellow eye at seven different contrasts, thereby creating seven interocular contrast ratios (dominant eye's contrast/non-dominant eye's contrast, ranged from 0 to 2). When their contrast ratio was set to 1, the contrast of the dominant eye's grating would be 50% (Figure 1B). The base contrast was set at 50% to the dominant eye because that the dominant eye tested from the Miles test might not be exactly dominant during the binocular orientation combination test. As a result, the interocular contrast ratio (dominant eye/non-dominant eye) could be larger than 1 in some occasions. If a base contrast of 100% was used, as it was so for the amblyopic observers, we might not have been able to get proper balance points for all normal observers.

In both groups, the observers underwent an extensive training period with practice trials so that we could determine their seven interocular contrast ratios properly. For instance, if the contrast ratios yielded points mostly resided in the segments of the fitted psychometric function near 0 and 1, we readjusted their contrast ratios so that their data were also in the steepest section of the fit (see Figure 1B). Each ratio and configuration were repeated 20 times, amounting to 280 trials (two orientation configurations × seven interocular contrast ratios × 20 repetitions) for one measurement of balance point at a given spatial frequency. The orders of the interocular contrast ratio and configuration were randomized.

Balance points were obtained at four spatial frequencies (0.5, 1, 2, and 4 c/deg) for normal observers and some amblyopic observers. However, the balance points of amblyopic observers at only 0.5, 1, and 2 c/deg are reported here because five of the recruited amblyopes were not able to perform the task as intended at

4 c/deg with a 2-ND filter on their fellow eye. They always perceived the tilt from their amblyopic eye because the fellow eye did not perceive the grating clearly. Despite their ease in aligning the two dichoptic screens during our test, their performance yielded a flat, rather than a sigmoidal, psychometric function. However, they were able to perform the task with 1.5 or 1.7ND filters (data not presented here). The sinusoidal gratings were presented with two cycles across all spatial frequencies. Therefore, the gratings at different spatial frequencies were shown at different sizes (in degrees); as the spatial frequency of the gratings increased, the perceived size of the gratings decreased. A grating at 0.5 c/deg had a size of 4 deg in visual angle, 1 c/deg a size of 2 deg, and 2 c/deg a size of 1 deg. The ordering of the testing conditions (i.e., spatial frequency and ND filters) was randomized. Subjects were allowed to perform more than one testing condition in a day.

Procedure

There were two parts in the task. Each trial began with an alignment phase. Subjects were asked to align dichoptic crosses into a cross proper by using the keyboard. This enabled the dichoptic display of the screen to be properly fused for each observer. To facilitate fusion throughout the task, a fusion frame was presented at all times. Then, during the test phase, the subjects were dichoptically shown with two tilted gratings (as described in *Visual Stimuli*). They were asked to report whether the fused grating had a perceived positive or negative tilt (+/− 7.1 deg) relative to the horizontal axis (see Figure 1). The alignment and test phases formed a single trial. The ordering of the testing conditions (i.e., spatial frequency and ND filters) was randomized. Subjects were allowed to perform more than one testing condition in a day.

QUANTIFICATION AND STATISTICAL ANALYSIS

A psychometric function of the probability of perceiving the tilt shown to the dominant/fellow eye (y-axis) as a function of interocular contrast ratio (x-axis) was fit with a cumulative Gaussian distribution function. The balance point (BP) was estimated as the value of interocular contrast ratio that yields 50% in the y-axis. It is the contrast ratio where both eyes contribute equally to binocular combination and, therefore, the fused percept. As an index of binocular imbalance, BP was transformed into its absolute log10 units (|log BP|). If BP deviates from 0 in positive or negative direction, |log BP| increases. The higher the |log BP|, the more severe the binocular imbalance.

We computed the area under a curve (AUC) using data of |log BP| as a function of spatial frequencies (y-axis:|log BP|, x-axis: linear units of spatial frequency). The higher the AUC, the higher the overall binocular imbalance across spatial frequencies. In addition, the relationship between |log BP| and spatial frequency has been shown to be causative (Mao et al., 2020). |log BP| increases as a function of spatial frequency in amblyopia. The dependence of |log BP| on spatial frequency was quantified by slopes from linear regression (y-axis: |log BP|, x-axis: log2 of spatial frequency). The more impactful the dependence, the steeper the rise of |log BP| as a function of spatial frequency. R and Python were used for statistical analysis and data visualization.

ADDITIONAL RESOURCES

There is no additional forum that provides additional information about this study, which is not part of a clinical trial.