

# Peripheral Binocular Imbalance in Anisometropic and Strabismic Amblyopia

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**Received:** October 25, 2023

**Accepted:** March 27, 2024

**Published:** April 23, 2024

Citation: Wiecek E, Kosovicheva A, Ahmed Z, et al. Peripheral binocular imbalance in anisometropic and strabismic amblyopia. *Invest Ophthalmol Vis Sci.* 2024;65(4):36. <https://doi.org/10.1167/iov.65.4.36>

**PURPOSE.** Individuals with amblyopia experience central vision deficits, including loss of visual acuity, binocular vision, and stereopsis. In this study, we examine the differences in peripheral binocular imbalance in children with anisometropic amblyopia, strabismic amblyopia, and typical binocular vision to determine if there are systematic patterns of deficits across the visual field.

**METHODS.** This prospective cohort study recruited 12 participants with anisometropic amblyopia, 10 with strabismic amblyopia, and 10 typically sighted controls (age range, 5–18 years). Binocular imbalance was tested at 0°, 4°, and 8° eccentricities (4 angular locations each) using band-pass filtered Auckland optotypes (5 cycles per optotype) dichoptically presented with differing contrast to each eye. The interocular contrast ratio was adjusted until the participant reported each optotype with equal frequency.

**RESULTS.** Participants with anisometropic and strabismic amblyopia had a more balanced contrast ratio, or decreased binocular imbalance, at 4° and 8° eccentricities as compared with central vision. Participants with strabismic amblyopia had significantly more binocular imbalance in the periphery as compared with individuals with anisometropic amblyopia or controls. A linear mixed effects model showed a main effect for strabismic amblyopia and eccentricity on binocular imbalance across the visual field.

**CONCLUSIONS.** There is evidence of decreased binocularity deficits, or interocular suppression, in the periphery in anisometropic and strabismic amblyopia as compared with controls. Notably, those with strabismic amblyopia exhibited more significant peripheral binocular imbalance. These variations in binocularity across the visual field among different amblyopia subtypes may necessitate tailored approaches for dichoptic treatment.

**Keywords:** amblyopia, binocular vision, psychophysics, pediatric vision

Amblyopia is a developmental disorder that affects the spatial vision of one or both eyes. It is associated with a history of abnormal visual experience during childhood and occurs in 1% to 4% of the population.<sup>1–5</sup> Amblyopia most commonly results from anisometropia (interocular difference in refractive error) or strabismus (ocular misalignment). The severity of amblyopia is often defined by loss of visual acuity, but with the introduction of dichoptic therapies, there is increased interest in quantifying the amblyopic deficit by measuring interocular suppression.<sup>6–9</sup> Dichoptic therapies rely on the understanding that binocular imbalance is correlated with depth of amblyopia, and improving this balance by awakening dormant binocular cortical connections may help to improve visual function in the amblyopic eye.<sup>6,10</sup>

Ocular dominance in amblyopia is an explicit representation of cortical integration of monocular images. Both clinicians and researchers have used various methods to characterize binocular combination and interocular suppression in amblyopia, including measures of binocular rivalry, binocular summation of contrast, and dichoptic global motion

coherence.<sup>11–14</sup> Although clinicians often use qualitative tools to assess interocular suppression, such as the Worth 4 dot test, more quantitative measures are often limited by long testing times and the inability to implement testing in a clinical environment with naive pediatric observers.

Although many researchers have examined global ocular dominance in amblyopia, local measures of dominance across the retina have only been examined in a few small studies.<sup>15–17</sup> Importantly, how binocular information is combined across the entire visual field has become increasingly relevant as newly introduced dichoptic therapies differ on which parts of the visual field are manipulated in dichoptic presentation.<sup>18,19</sup> Furthermore, there are conflicting data on differences in binocular function between anisometropic and strabismic amblyopia.<sup>17</sup> Using a psychophysical adaptation paradigm, Sireteanu et al.<sup>17</sup> found notable differences in binocular adaptation that were dependent on the type of amblyopia, providing evidence that localized binocularity is preserved in the periphery of strabismic but not anisometropic amblyopia. Babu et al.<sup>15</sup> compared



ocular dominance, or suppression, at up to 30° eccentricity. Using a dichoptic contrast adjustment method, they found the strongest suppression centrally in amblyopic observers, with only strabismic observers showing more pronounced suppression in the periphery.<sup>15,20</sup>

In the present study, we use an adapted version of a previously established method to quantify interocular imbalance in children and adolescents with amblyopia.<sup>21</sup> In this method, the relative contrast of optotypes presented in each eye is adjusted until the participant reports each optotype with equal frequency. Although other researchers have successfully used this paradigm to assess foveal suppression in children and adults with amblyopia, our study focuses on investigating the variations in binocular imbalance across the visual field in pediatric individuals with strabismic and anisometropic amblyopia.<sup>7,21</sup>

## METHODS

### Clinical Characteristics

Participants were recruited at Boston Children's Hospital Department of Ophthalmology. Thirty-two participants, aged 5 to 18 years (56% females), were categorized into one of three comparison cohorts: anisometropic amblyopia ( $n = 12$ ), strabismic amblyopia ( $n = 10$ ), or typically sighted controls ( $n = 10$ ). Both anisometropic and strabismic amblyopes had at least a one-line difference in interocular visual acuity, with visual acuity corrected to 20/25 or better in their fellow eye. The strabismic amblyopia group included individuals before ( $n = 7$ ) and after surgical ( $n = 3$ ) correction. All strabismic amblyopes had a minimum of five prism diopter deviation by alternating prism cover test presurgical correction. Typically sighted controls had best corrected visual acuity of 20/25 or better in each eye, with no manifest strabismus. Snellen visual acuity, stereoacuity, and ocular alignment were measured during a clinic visit by either an ophthalmologist, optometrist, certified orthoptist, or ophthalmic technician before experimental testing (same day). Stereoacuity was tested using The Fly and the Randot Stereotest. Study group demographics are outlined in Table 1, and detailed information on study participants and treatment history can be found in Supplementary Table S1. All children who required refractive correction had been wearing glasses for at least 3 months before experimental testing. Written informed consent and assent were obtained from all participants before the experiment, and all experimental protocols and procedures were approved by the

institutional review board of Boston Children's Hospital and complied with the Declaration of Helsinki.

### Experimental Measures

All psychophysical testing was implemented using customized MatLab (Version R2018a) software and the Psychtoolbox<sup>22</sup> (Version 3.0.14.) interface on a gamma-corrected LG passive 42LM6200-UE 3D monitor (42.8° × 24.0°, refresh rate 60 Hz, resolution 1920 × 1080). Participants were positioned 90 cm from the display and wore corrective lenses as required for best-corrected visual acuity. Stimuli consisted of 10 unique Auckland Optotypes (Fig. 1C) and were displayed dichoptically in randomly selected pairs using polarized lenses.<sup>23</sup> The optotypes were spatially bandpass filtered with a raised cosine log filter with a peak object spatial frequency of 5 cycles per optotype, with a 1-octave (full width at half height) bandwidth using customized software in MatLab.<sup>7,21</sup> The retinal spatial frequency of letters were dependent on eccentricity and ranged from 0.5 to 2.0 cycles per degree (cpd).

Optotypes were presented on a mean luminance background (65.6 cd/m<sup>2</sup>) centrally and at eight peripheral locations (four at each of 4° and 8° eccentricities). The size of the optotype was scaled with eccentricity, which resulted in optotypes increasing in size and decreasing in spatial frequency for more eccentric locations.<sup>24</sup> Optotypes were presented at 2 cpd (2.5°), 1 cpd (5°), and 0.5 cpd (10°) at 0°, 4°, and 8° eccentricities, respectively. These spatial frequencies were selected to produce comparable stimulus visibility across the visual field. The optotypes were gradually ramped on and off using a temporal Gaussian window ( $\sigma = 200$  ms) to vary their contrast. Location conditions were interleaved in a fixed sequence, such that participants completed the first trial of each sequence centrally, followed by one trial at each location in a clockwise sequence at each eccentricity (superior, right, inferior, and left of central fixation). This process was then repeated for a total of 12 sequences. This step was done to make the task easier for the pediatric participants, while minimizing the influence of practice effects. Participants were instructed to maintain fixation on a central white fixation dot (0.5°) before beginning the experiment and were reminded throughout testing. This instruction, along with the brief presentation time of the stimulus, were implemented to decrease the risk of making a saccade to peripheral targets. Testing took approximately 15 minutes to complete all trials. When a participant lost focus, the experimenter would praise them for their efforts and redi-

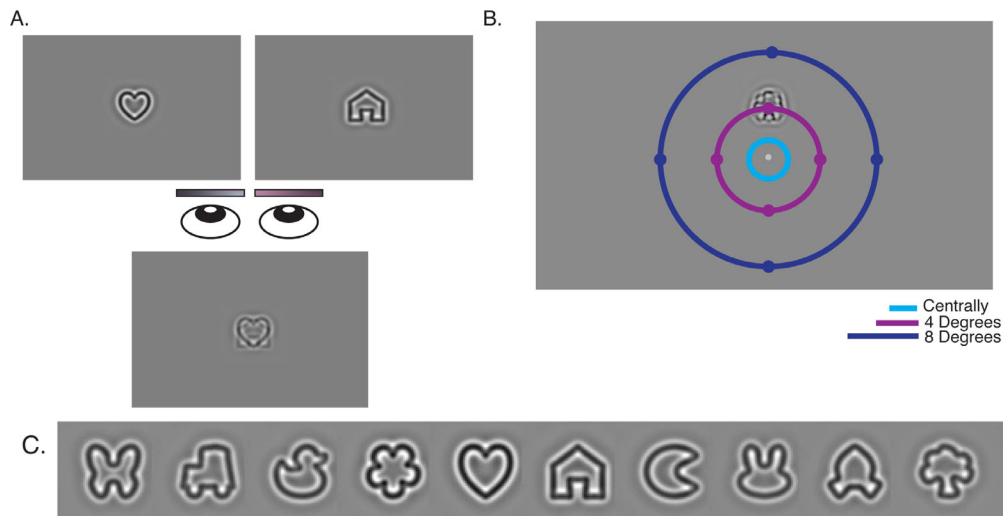
TABLE 1. Participant Demographic Summary

Group	Total	Female	Age (Years)	Mean Interocular	Mean LogMAR	Mean	Mean SER AE or OD	Mean SER FE or OS
				LogMAR Acuity Difference	Acuity Worse Eye	Stereoacuity (Arcsecs)		
Strabismic amblyopia	10	6 (60%)	8 (5–16)	0.19 (0.13)	0.26 (0.14–0.58)	88* (141.6)	3.35 D (–2.75 to 6.50)	2.55 D (–9.75 to 6.50)
Anisometropic amblyopia	12	6 (50%)	9.17 (5–18)	0.22 (0.13)	0.2167 (0.08–0.56)	79.17* (50.5)	2.65 D (–1.00 to 4.50)	1.07 D (–0.63 to 4.25)
Control	10	6 (60%)	10.9 (5–15)	0.00 (0.01)	0.024 (0–0.1)	60 (13.6)	–1.78 D (–8.50 to 0.50)	–1.58 D (–7.50 to 0.75)

AE, amblyopic eye; D, diopters; FE, fellow eye; OD, right eye; OS, left eye; SER, spherical equivalent refractive error.

\* Five strabismic participants and one anisometropic participant presented with no stereoacuity.

Note. SDs for mean interocular acuity difference and stereoacuity are presented in parentheses. Ranges for mean age, acuity in worse eye, and spherical equivalent are presented in parentheses.



**FIGURE 1.** Stimuli. (A) Experimental setup for dichoptic display of Auckland optotypes using polarized lenses. (B) Nine retinal locations tested across the visual field. (C) Set of 10 Auckland Optotypes. Each optotype is bandpass filtered to five cycles per optotype.

rect their attention to the screen. The experimenter would confirm they were ready for the next trial before continuing and gave an estimated time to completion (e.g. “Only a few more minutes of testing left”). Head position was monitored throughout testing by the experimenter. There was no correction made for binocular image alignment or strabismus.

Ocular dominance was quantified using a previously established paradigm that uses contrast balancing of two unique dichoptically presented optotypes.<sup>21</sup> The peak contrast of each pair of optotypes summed to 100%; the peak contrast of the optotype in the left eye was equal to 100% minus the peak contrast of the optotype in the right eye. During testing, the relative contrast level of the two optotypes within a pair at each location was adjusted using an adaptive staircase through QUEST,<sup>25</sup> with one independent staircase per location. This algorithm considers the outcome of previous trials to determine the most informative contrast level that will maximize information gained for each trial to estimate the participants’ binocular balance point—the relative contrast level at which the participant is equally likely to identify either of the dichoptically presented optotypes.

Balance points ranged from 0 to 1, with values of 0.5 representing equal contrast in the two eyes. Balance points of greater than 0.5 indicated that the participant required a higher contrast in the left eye to report the two optotypes equally (right eye dominance). Conversely, values of less than 0.5 indicated higher contrast in the right eye (left eye dominance). This balance point was determined after 12 trials at each location tested (9 total locations) based on the mean of the QUEST posterior probability density function.

During each trial, a pair of dichoptic optotypes were presented overlapping one another at a single test location (Fig. 1). After presentation of the dichoptic test stimuli, each optotype within the pair was displayed adjacent to fixation at non-overlapping locations for the participant to record their response. Participants were instructed to use a computer mouse to select which of the two optotypes visually appeared the strongest. In the case that a child was unable to maneuver the computer mouse independently, the

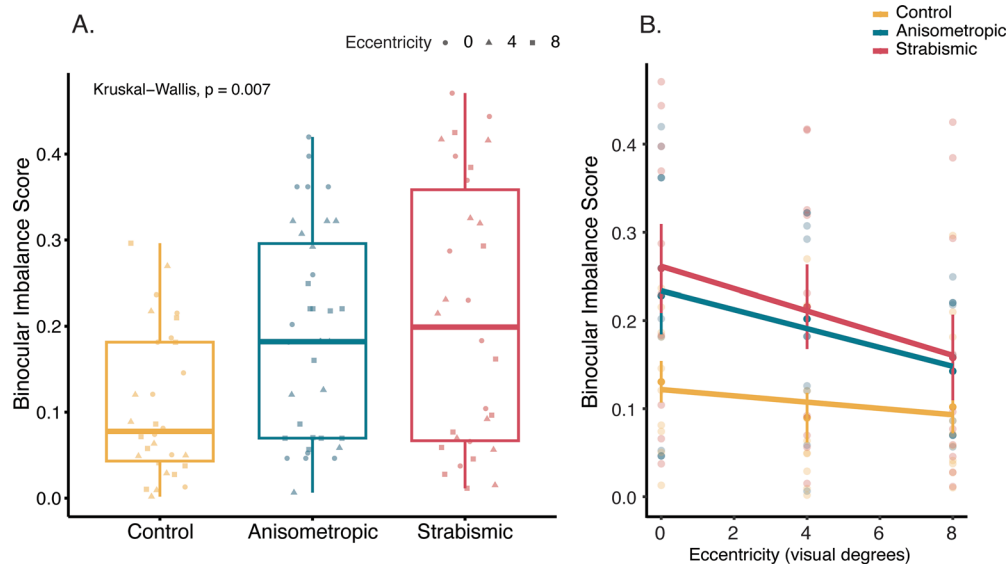
experimenter selected the chosen optotype after a verbal response from the participant.

The binocular balance point was characterized as the contrast level ratio after 12 trials at each location. The absolute difference of this balance point from 0.5 was then used to calculate a binocular imbalance score. Scores ranged from 0 to 0.5, with higher scores corresponding with greater binocular imbalance. All statistical analyses were completed in RStudio 2021.09.0+351 “Ghost Orchid” Release with the following R packages: R.matlab, ggplot2, ggpubr, pracma, dplyr, ggsci, nlme, lme4, BayesFactor, tidyr, and sjPlot. The Kruskal–Wallis test was used to compare binocular imbalance scores across groups and post hoc pairwise comparisons were made using the Wilcoxon rank-sum test with Bonferroni adjustment. A linear mixed effects model was used to analyze the relationship between retinal location, cohort, and binocular imbalance score. Pearson correlation was used to compare the relationship between visual acuity and binocular imbalance and Bayes factor was reported to further characterize this relationship.

## RESULTS

When collapsed across all eccentricities, binocular imbalance was significantly greater in both amblyopic groups compared with controls (Kruskal–Wallis  $\chi^2 = 10.08$ ;  $P = 0.006$ ) (Fig. 2A). Controls had the lowest amount of imbalance, followed by anisometric and strabismic amblyopes. The difference in binocular imbalance across groups was strongest at central vision and decreased with increasing eccentricity. Individual psychometric functions to determine the binocular balance point are included in Supplementary Figure S1.

A linear mixed effects model was used to better characterize the continuous relationship between binocular imbalance, eccentricity, and type of amblyopia. The model included a random effect for individual, with fixed effects for group and eccentricity. There was a significant main effect for eccentricity ( $P = 0.001$ ), where binocular imbalance decreased with increasing eccentricity. Participants with both anisometric and strabismic amblyopia had increased binocular imbalance compared with controls; however, only



**FIGURE 2.** Binocular imbalance across cohort and eccentricity. **(A)** Box plots show the distribution of binocular imbalance scores across nine retinal locations for all participants. **(B)** Estimated binocular imbalance scores at 0°, 4°, and 8° eccentricities. Regression lines are fit to the mean score at each eccentricity for each cohort, individual data points for each retinal location are shown, and error bars represent the standard error of the mean across participants.

**TABLE 2.** Binocular Imbalance Score Linear Mixed Effects Model Parameters

Predictors	Coefficient Estimate	Confidence Interval for Estimate	P Value
Intercept	0.14	0.08 to 0.22	<b>&lt;0.001</b>
Eccentricity	−0.01	−0.01 to 0.00	<b>0.001</b>
Anisometropic	0.08	−0.01 to 0.17	0.068
Strabismic	0.10	0.01 to 0.20	<b>0.032</b>
Random effects			
$\sigma^2_{\text{Participant}}$	0.01		
ICC	0.57		
Observations		96	
Marginal $R^2$ /conditional $R^2$		0.159/0.638	

Coefficient estimates for linear mixed effects model along with  $P$  values estimated from the  $t$ -statistic. ICC- intraclass correlation coefficient is calculated by dividing the variance of the random effect by the total random variance, to depict how much variance is explained by the random effect. The marginal  $R^2$  considers only the variance of the fixed effects, while the conditional  $R^2$  accounts for both the fixed and random effects.

Boldface entries indicate statistical significance.

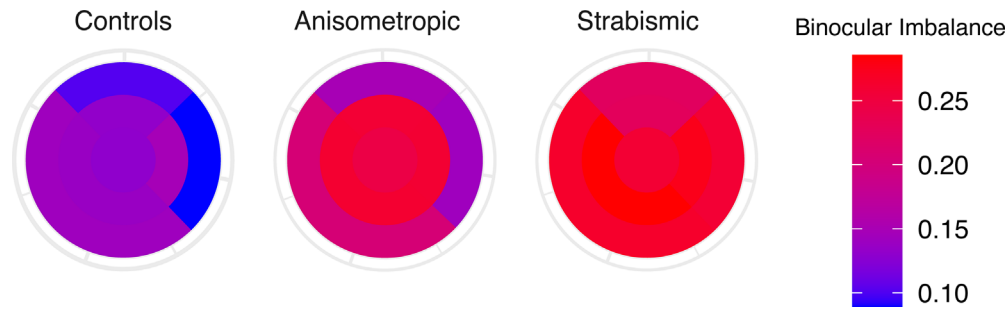
the strabismic group showed a significant main effect compared with controls. An interaction term between eccentricity and group did not show a significant main effect ( $P > 0.1$ ) and was removed from the final model. The random effect for individual participant explained 57% of the remaining variance in binocular imbalance not explained by eccentricity or cohort. Model parameters are displayed in [Table 2](#).

A Kruskal–Wallis test for direction (superior, right, left, and inferior visual fields) found no significant effect of direction on binocular imbalance across all groups (Kruskal–Wallis  $\chi^2 = 2.35$ ;  $P = 0.50$ ) ([Fig. 3](#)). To directly compare the peripheral binocular imbalance across groups, we averaged peripheral binocular imbalance scores for each participant at 4° and 8° eccentricities (8 locations total) to calculate a single peripheral imbalance score for each participant. We found a significant difference in the mean peripheral binocular imbalance score across groups (Kruskal–Wallis  $\chi^2 = 20.05$ ;  $P < 0.001$ ) ([Fig. 3](#)). Post hoc pairwise comparisons using the Wilcoxon rank-sum test with Bonferroni adjustment

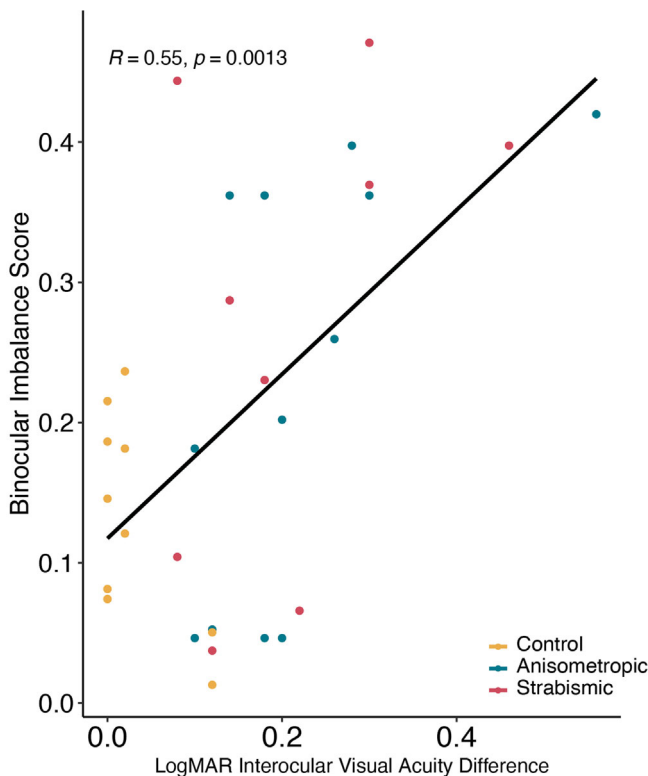
revealed the strabismic cohort had significantly more peripheral binocular imbalance (mean binocular imbalance score at 4° and 8° eccentricities) compared with typically sighted controls ( $P < 0.001$ ) and participants with anisometropic amblyopia ( $P = 0.001$ ). There was no correlation with age or binocular imbalance score for all eccentricities ( $P > 0.5$ ). A supplementary analysis of participants under the age of 8 years ( $n = 15$ ) found the same trend as the larger cohort ([Supplementary Fig. S2](#)).

We also considered how binocular imbalance varied with depth of amblyopia. We compared participants' central binocular imbalance scores with their interocular visual acuity difference and found a significant, moderate correlation across all participants ( $R = 0.55$ ;  $P = 0.001$ ; BF [Bayes factor] = 38.64) ([Fig. 4](#)). The relationship between visual acuity and binocular imbalance weakened slightly at the 4° and 8° eccentricities ( $R = 0.47$ ;  $P = 0.01$ ; BF = 9.07;  $R = 0.49$ ;  $P = 0.003$ ; BF = 14.12, respectively). When we compared interocular acuity difference and central binocular imbalance within each cohort, the trend persisted but





**FIGURE 3.** Binocular imbalance heat maps. Heat maps indicate the average degree of binocular imbalance scores across nine retinal locations for all participants.



**FIGURE 4.** Binocular imbalance and visual acuity. Individual points represent individual participant data for the central binocular imbalance measure. The *black line* represents linear regression line of best fit with data collapsed across all participants.

weakened ( $R = 0.6$ ;  $P = 0.03$ ,  $BF = 2.54$  for anisometric;  $R = 0.48$ ;  $P = 0.16$ ,  $BF = 1.18$  for strabismic). There was no significant correlation between stereoacuity and central binocular imbalance across all participants. Five individuals with strabismus had no measurable stereoacuity and were removed from this analysis ( $R = 0.14$ ;  $P = 0.47$ ;  $BF = 0.52$ ) (Supplementary Fig. S3).

## DISCUSSION

Individuals with both strabismic and anisometric amblyopia show increased binocular imbalance compared with typically sighted controls. This study successfully applied a previously established method for quantifying interocu-

lar suppression in pediatric observers.<sup>21</sup> To our knowledge, this study is the first to quantify interocular balance across the visual field in a younger cohort, many of whom were concurrently undergoing amblyopia treatment.

Our data align with previous studies on adults with amblyopia, demonstrating variations in the degree of interocular suppression between anisometric and strabismic observers.<sup>15,17</sup> We found significantly more peripheral binocular imbalance in individuals with strabismic compared with anisometric amblyopia. Our data show less pronounced differences in binocularity between amblyopia subtypes as compared with prior studies.<sup>15,17</sup> This finding may be secondary to the younger age of our participants and the fact that a substantial number of our participants with strabismic amblyopia were still within the critical period for visual development. We speculate that plasticity in the visual system may contribute to lower binocular imbalance across the visual field. Additionally, three of our strabismic participants had a history of strabismic surgery. This factor may also contribute to differences in remapping of retinal locations resulting in less suppression, or binocular imbalance, in the periphery. Our strabismus cohort included a mix of both esotropic and exotropic participants, but this sample was not powered to examine localized deficits in binocular combination based on angle of deviation.

In addition to evaluating a younger cohort, our study also differed from previous work in that our peripheral stimuli were scaled for size and spatial frequency to optimize visual function at more eccentric retinal locations. This scaling attempted to equate visual function across the visual field and help to ensure that any differences in binocular imbalance across eccentricity would be due to a difference in binocular representation rather than decreased acuity or contrast sensitivity. Alternatively, if we had tested a binocular combination (i.e., contrast balancing) at the same spatial frequency at all peripheral locations, it would be difficult to rule out whether changes in the binocular combination were secondary to differences in interocular suppression or differences in contrast sensitivity. The decision to scale spatial frequency with eccentricity does, however, make it difficult to rule out the impact of spatial frequency on interocular balance. Although amblyopic observers have been shown to have deficits in binocular combination at high spatial frequencies, this hypothesis has only been tested with foveal vision.<sup>21,26</sup> Measuring contrast thresholds at multiple spatial frequencies across nine different retinal locations was not feasible in this cohort owing to the limited attention span of pediatric participants. Future work that quantifies binocular balance using multiple spatial frequencies across

the visual field would help to better characterize peripheral visual function in amblyopic subjects.

A limitation of the study was that the locations of testing were not randomized, although our conditions were interleaved to minimize learning effects. This was done intentionally to make the task easier for our pediatric participants. Testing was completed sequentially so the central location was tested once, and then in a clockwise fashion and 4° and 8° (once per location), and the process repeated. We did not observe any effect of quadrant, and it is unlikely that the eccentricity effect reported across cohorts would differentially affect subtypes of amblyopia. Furthermore, the task was limited to 8° eccentricity testing for peripheral vision and four-degree parafoveal vision. Future work that assesses binocular balance in both the mid and far periphery would be informative for mapping the full extent of binocular imbalance across the visual field.

Although we found that participants with strabismic amblyopia had more peripheral suppression compared with individuals with anisometropic amblyopia, this difference may be attributed partly to a difference in testing. We did not align stimuli on corresponding retinal points in individuals with strabismic amblyopia, although it is presumed that dichoptic stimuli in the periphery of anisometropic participants would have been overlapping. We made this decision to better evaluate what peripheral vision would be like under real-world viewing conditions, rather than in a simulated environment. We were also limited on the ability to subjectively align dichoptic stimuli in the periphery in children, because this task would require reliable subjective feedback from pediatric participants as well as the presence of suppression in amblyopic participants.

Participants with amblyopia showed significantly greater binocular imbalance compared with typically sighted participants. However, it is important to note that the control group still exhibited a variety of binocular imbalances across all retinal locations. This finding is in alignment with prior work on normally sighted adults that showed sensory eye dominance varied across the binocular visual field in sign and magnitude.<sup>27</sup> Similar to that study, we found that foveal binocular imbalance predicted peripheral binocular imbalance (Supplementary Fig. S4) ( $R = 0.62$ ;  $P = 0.004$ ).

Our study used contrast to dichoptically balance the signal between the amblyopic and fellow eye, but little is known about monocular contrast perception in the peripheral vision of individuals with amblyopia. Future work that quantifies sensitivity to contrast across different spatial frequencies at more eccentric retinal locations will help to inform the nature of binocular combination in an amblyopic visual system. This knowledge, in combination with binocular balance measures described in the current study, will help in the development of customized therapies that target the most impacted locations of the visual field.

Finally, with the emergence of new dichoptic binocular therapies, the integration of binocular perception across the visual field in the pediatric population is of the utmost importance. Specifically, therapies differ in the region of treatment/binocular combination; some therapies implement antisuppression therapy only in central vision, whereas others require the participant to integrate binocular information across the entire visual field.<sup>18,19</sup> In the context of our findings, it may be more important to dichoptically balance binocular information in central vision, whereas unaltered peripheral eccentric visual stimuli for individ-

uals with anisometropic amblyopia. This strategy would have the advantage of treating the retinotopic location most impacted in anisometropic amblyopia while promoting binocular fusion with peripheral stimuli. Alternatively, individuals with strabismic amblyopia may benefit from stimuli that require binocular balancing across the entire visual field.

In summary, our data suggest decreased peripheral binocular imbalance compared with central vision in both anisometropic and strabismic observers. Nonetheless, the higher peripheral binocular imbalance observed in strabismic individuals may necessitate the exploration of distinct treatment approaches for different subtypes of amblyopia.

### Acknowledgments

Supported by funding from the Knights Templar Eye Foundation Career Starter Grant and a Children's Hospital Ophthalmology Foundation Discovery Award (E.W.) and National Institutes of Health (R01EY032162 to P.J.B., F32 EY028814 to A.K., and 5K23EY034212 to E.W.).

Disclosure: **E. Wiecek**, None; **A. Kosovicheva**, None; **Z. Ahmed**, None; **A. Nabasaliza**, None; **M. Kazlas**, None; **K. Chan**, None; **D.G. Hunter**, I Rebion, Inc. (I, O, P), Luminopia, Inc. (I, C), OHP Technologies, Inc. (I); **P.J. Bex**, AST (I, O), PerZeption (I, O), quickCSF, FInD and AIM methodologies (P)

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