Effect of Stimulus Orientation on Visual Function in Children with Refractive Amblyopia

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PURPOSE. We investigated and characterized the patterns of meridional anisotropies in newly diagnosed refractive amblyopes using pattern onset–offset visual evoked potentials (POVEPs) and psychophysical grating acuity (GA).

METHODS. Twenty-five refractive amblyopes were recruited and compared with non-amblyopic controls from our previous study. Monocular POVEPs were recorded in response to sine-wave 4 cycles per degree (cpd) grating stimuli oriented along each individual participant’s principal astigmatic meridians, which were approximately horizontal (meridian 1) and vertical (meridian 2). Binocular POVEPs in response to the same stimuli, but oriented at 45°, 90°, 135°, and 180°, were recorded. Psychophysical GAs were assessed along the same meridians using a two-alternative non-forced-choice technique. The C3 amplitudes and peak latencies of the POVEPs and GAs were compared across meridians for both groups (refractive amblyopes and controls) using linear mixed models (monocular) and ANOVA (binocular), and post hoc analysis was conducted to determine if meridional anisotropies in this cohort of amblyopes were related to low (<1.50 diopters [D]), moderate (1.75–2.75 D) and high (>3.00 D) astigmatism.

RESULTS. In the newly diagnosed refractive amblyopes, there were no significant meridional anisotropies across all outcome measures, but the post hoc analysis demonstrated that C3 amplitude was significantly higher in those with low (P = 0.02) and moderate (P = 0.004) astigmatism compared to those with high astigmatism. Refractive amblyopes had poorer GA and C3 amplitudes compared to controls by approximately two lines on the logMAR chart (monocular: P = 0.013; binocular: P = 0.014) and approximately 6 μV (monocular: P = 0.009; binocular: P = 0.027), respectively.

CONCLUSIONS. Decorative effects of high astigmatism were evident in newly diagnosed refractive amblyopes, but the neural deficits do not seem to be orientation-specific for the stimulus parameters investigated.

Keywords: meridional anisotropy, children visual development, refractive amblyopia, oblique effect, horizontal effect

Refractive amblyopia may be defined as a loss of visual acuity (VA) that is primarily the result from the prolonged exposure to refractive blur during early childhood, but any structural ocular abnormalities and strabismus must be excluded at the point of diagnosis.

Uncorrected refractive errors seem to be the key error for amblyopia in some populations. For example, nearly 85% of amblyopic diagnoses in Singapore are attributed to uncorrected refractive errors, whereas only 15% of amblyopia can be attributed to strabismus.1–3 The Singapore study found 30% of the amblyopic children had bilateral refractive amblyopia, whereas 70% had unilateral strabismus.4 Similar trends have been reported in other parts of Asia where strabismus accounts for only 12.8% of amblyopia in Korea1 and 2.6% in Taiwan.5 In addition, only 19% of amblyopia in Hispanic/Latino and African American children could be partially attributed to strabismus, whereas 81% resulted from refractive errors alone.6

Young children who have large magnitudes of refractive errors,7,8 are particularly at risk for developing amblyopia.9 Red flags include hyperopia >+4.00 diopters (D), astigmatism >−8.00 D,11 astigmatism >2.50 D,11–13 and/or unequal refractive errors between the two eyes (i.e. anisometropia) by >1.00 D for hyperopia, >1.50 D for astigmatism, and >3.00 D for myopia.11 The severity of anisometropic amblyopia tends to correlate with interocular difference in refractive errors.14–16

Based on a Singapore study, a large proportion of amblyopic children were found to have astigmatism—42% of amblyopes have aniso-astigmatism ≥1.50 D and 29% have...
isometropic astigmatism $>2.50$ D. Similarly, 19.2% of children with amblyopia in the Middle East were found to have astigmatism $\geq 2.50$ dioptic cylinder (DC).37 Even astigmatism as low as 1.00 D may be associated with unilateral amblyopia$^6$ and nearly 30% of the strabismic children were reported to have astigmatism $\geq 1.00$ D on initial examination.38 Hence, it is conceivable that astigmatism is an important amblyogenic factor and some of these astigmatic children may have meridional amblyopia$^{22}$ because the astigmatic meridian that has greater optical blur may chronically experience reduced vision.$^{20,21}$

Astigmatism-related amblyopia may result in orientation-specific neural deficits in the astigmatic meridian,$^{22}$ as observed in studies of kittens$^{23–25}$ and human psychophysical studies of grating acuity.$^{20,21,26–29}$ and visual electrophysiology.$^{30,31}$ In the 1970s, Freeman and Thibos$^{28}$ carried out electrophysiological and psychophysical experiments on nine children and demonstrated that there was reduced sensitivity along the meridian, which experienced the greatest retinal blur. In another study, Fiorentini and Maffei demonstrated that the visual evoked potential (VEP) amplitudes tended to be greater in one of the two principal astigmatic meridians$^{50}$ in children with high astigmatism (3.00–4.00 D; $n = 7$), but not in those who had low astigmatism (0.50–1.50 D; $n = 16$).30 Although these studies demonstrated that the meridional anisotropies may correspond to the astigmatism, two of the five highly astigmatic participants in that study did not have any significant meridional anisotropy and it was not clear from the report if that participant had recovered from meridional amblyopia.

The main locus of neural deficit of amblyopia is at the visual cortex, $V1$, but deficits can be widespread and affect the extrastriate visual areas.$^{31–33}$ This includes the $V4$ cortical area, where neuron's orientation-tunings tend to be broader$^{34}$ even though only a small proportion of neurons in area $IT$ are orientation-tuned.$^{35}$ Although there is a possibility that orientation-tuned cortical neurons are defective, there is an alternative postulation that meridional anisotropies could be the result of orientation-based rivalry and suppression$^{36–38}$ where orientation-tuned neurons compete in the presence of orthogonal rivalry grating stimuli. In the case of the latter, each suppressed meridian may be systematically biasing the perception of the dominant meridian during rivalry of the competing meridians.$^{39}$ There is also a possibility that the suppression could be driven by attention, as found to affect orientation processing in the human lateral geniculate nucleus (LGN).$^{40}$ Hence, it is unclear whether newly diagnosed and untreated refractive amblyopes will demonstrate meridional anisotropies that are consistent with their astigmatic refractive error axes.

Normally developing non-amblyopic children aged 3 to 9 years with normal 20/20 VA have been found to produce a horizontal effect under electrophysiological testing, regardless of their astigmatism status.31 In newborn infants, poorer years with normal 20/20 VA have been found to produce a consistent with their astigmatic refractive error axes.41 Hence, it is conceivable that astigmatism is an important amblyogenic factor and some of these astigmatic children may have meridional amblyopia$^{22}$ because the astigmatic meridian that has greater optical blur may chronically experience reduced vision.$^{20,21}$

where electrophysiological signals in response to binocular stimulation using horizontal gratings of 4 cpd were significantly poorer than the vertical and oblique gratings. This type of meridional anisotropy has been postulated to be an adaptive strategy for the visual system to optimize the perception of orientations that are less naturally encountered.$^{31}$ This is thought to provide more efficient neural coding$^{45,46}$ and was found psychophysically in adults viewing natural scenes$^{47–50}$ containing both broad spatial frequencies and orientation content.

The purpose of this study is to investigate whether young children newly diagnosed with amblyopia have meridional differences in visual function that are related to their refractive error, which might be suggestive of meridional amblyopia, and whether this differs from children without amblyopia. As there is a wide spread of astigmatic refractive errors among refractive amblyopes, it was also of interest to determine if there would be any relationship between the magnitude of meridional anisotropies and the magnitude of astigmatism in children who have not yet received any amblyopia treatment, including the use of spectacles, which is also known as optical treatment. To date, no previous electrophysiological studies have systematically investigated meridional anisotropies of children with newly diagnosed and untreated refractive amblyopia. It was hypothesized that grating stimuli presented along the more optimally defocussed of the principal astigmatic meridians would produce lower pattern onset-offset visual evoked potential (POVEP) amplitudes, longer peak latencies, and poorer grating acuity (GA) in the amblyopic children.

**METHODS**

Newly diagnosed (untreated) refractive amblyopic children were recruited from an outpatient ophthalmology clinic at KK Women’s and Children’s Hospital. Their visual processing in response to orientation-specific grating stimuli was evaluated using electrophysiological and psychophysical techniques, as published previously for non-amblyopic children.$^{31}$ The research study adhered to the tenets of Helsinki and ethical approval was obtained from the Centralized Institutional Review Board (CIRB) (Registration number: R1083/98/2013) at SingHealth and ratified by the human research ethics committees at the University of New South Wales, Sydney, New South Wales, Australia (Approval number: 09364). Parents and guardians gave their informed consent and children six years of age and above provided assent.

**Participants**

Preschool- and school-aged children with refractive amblyopia were included in the study, and cases of strabismus, ocular diseases, and/or abnormalities were excluded. Refractive amblyopes had VA of 0.3 logarithm of the minimum angle of resolution (logMAR; 20/40) or worse in at least one eye$^{31}$ in the presence of significant myopia/hyperopia ($\geq 2.00$ D) or astigmatism ($\geq 1.50$ D), or a combination of both spherical and astigmatic ametropias. Spectacles were prescribed by the participants’ own attending clinicians, where required, and all of them underwent ocular health examination, logMAR VA (HOTV chart; Good-Lite Company, Elgin, IL, USA), stereopsis (Near 3-plates Frisy Stereotest; Stereotest Ltd., Fulwood, Sheffield, UK), binocular...
vision, retinoscopy, autorefraction, and manifest subjective refraction assessments using age-appropriate refraction techniques. All participants were able to fluently read the English alphabet. Being an observational study, clinical procedures and decisions were made independently by the participant’s own clinician and were not influenced by the researchers. All ambylopies received cycloplegic refraction at the point of diagnosis. As the study was designed to understand the untreated ambylopia visual system, spectacles were dispensed by the researcher only on their first research visit in order to ensure that optical treatment did not commence prior to the study. However, the children were allowed about 10 minutes to adapt with the spectacles before electrophysiological and psychophysical tests were conducted.

Orientation-Specific POVEP

Electrophysiological testing was customized to evaluate refractive amblyopia by assessing each refractive meridian independently in order to determine if meridional anisotropies were induced by astigmatic refractive errors. Single channel transient POVEPs were measured monocularly in response to a 12° field-size achromatic sinewave grating stimulus of 4 cpd oriented along the principal astigmatic meridians of each eye. The principal astigmatic meridians of the refractive errors were considered in spherical cylinder form, with meridians 1 and 2 representing the astigmatic axes that were closest to the horizontal and vertical orientations, respectively. In addition, POVEPs were recorded binocularly with the same stimuli oriented in four meridians (45, 90, 135, and 180) in order to investigate the presence or absence of the oblique effect and/or the horizontal effect. A representation of the sinewave grating stimulus and the participant’s fixation target is presented in Figure 1.

Each stimulus condition was tested through two successive averages of 30 sweeps of one second duration, under an onset/offset duration of 100 msec and 400 msec, respectively, and the order of stimulus presentation was randomized. The two sets of 30-sweep averaged POVEP waveforms were then averaged to form one single 60-sweep average. The stimuli had a Michelson contrast of 54%, which was designed to reduce luminance artifacts from the monitor, and at a temporal frequency of 2 hertz (Hz) against a background of the same space-averaged luminance at a viewing distance of one meter. Participants were required to view a central fixation target (black dot with a 2 mm diameter) at 1 meter, or at the center of the screen if they were unable to see the fixation target. Their fixation, seating posture, and head position were monitored visually by the examiner. To maximize the comfort of the children, the study did not utilize any additional head stabilization equipment. Instead, the participants were regularly reminded to lean against the seat’s backrest in order to maintain the test viewing distance and head position. Errors to the measurement of astigmatic axes is known to be introduced by lateral head tilts during refraction procedures, but the participants in this present study were able to maintain vertical head posture throughout the entire testing period because the recording for each stimulus orientation was only ~2 minutes each. Recordings were paused and repeated if the participants were excessively fidgeting or nonattentive and sweeps that were contaminated by artifacts were removed manually offline.

During the POVEP recordings, participants wore their full prescribed refractive correction, either using spectacles or trial lenses within a trial frame, but their accommodation was not controlled with any additional lenses as they were expected to have sufficient accommodation for the test viewing distance. The electrode montage was based on the International 10-20 configuration, where three gold-cup surface electrodes (9 mm) were attached using electroencephalogram (EEG) conductance paste and micropore tape, with active, reference, and ground electrodes located at O2 (occipital midline), C3, and Fp1, respectively. Impedance was verified to be below 8 kΩ prior to each recording.

Equipment

The POVEP recording was produced using the Espion system (Diagnosys, Cambridge, UK), which has a recording window of 1 second per sweep and a sampling rate of 5 kHz and a band-pass filter of 0.312 to 100 Hz. The stimuli were generated using the ViSaGe Mk II (Cambridge Research Systems, Kent, UK) and presented on a calibrated gamma-corrected high-performance cathode ray tube (CRT) monitor (Sony CPD-G500 21-inch Trinitron; Maximum Resolution 2048 × 1536 @ 75Hz; Horizontal and Vertical Scan Range 30–121 kHz and 48–160 Hz, respectively). The stimulus generator was a 14-bit system, which was capable of presenting up to 35.2 cpd gratings at a viewing distance of 2.2 meter (m) without aliasing.

Grating Acuity

Psychophysical GAs were assessed using a two-alternative non-forced-choice (2-ANFC) preferential-looking design with a modified 1 down 1 up staircase technique.
Table 1. Refractive and Age Profiles of Children with Refractive Amblyopia

| I.O.D. | Age, y | Sph | Cyl | Ax, axis of astigmatism in degrees; Cyl, cylindrical power of astigmatism in diopters; I.D., participant's identifier number; I.O.D., interocular difference; N.A., not applicable; SD, standard deviation; SE, spherical equivalent power of refractive errors in diopters; Sph, spherical power of ametropia in diopters; VA, visual acuity in logMAR units. | Right Eye | Left Eye | I.O.D. |
|-------|--------|-----|-----|--------|--------|--------|--------|--------|
| 1     | 4.4    | +2.25 | −3.00 | 170 | +0.75 | 0.40 | +2.25 | −4.00 | 170 | +0.25 | 0.52 | 0.50 |
| 2     | 5.2    | 0.00 | 0.00 | NA  | 0.00 | 0.00 | +0.50 | −2.50 | 180 | −0.75 | 0.34 | 0.75 |
| 3     | 4.6    | 0.00 | −3.50 | 180 | −1.75 | 0.16 | 0.00 | −4.00 | 175 | 2.00 | 0.26 | 0.25 |
| 4     | 4.4    | 0.00 | −1.50 | 5   | −0.75 | 0.14 | +0.50 | −3.00 | 165 | −1.00 | 0.34 | 0.25 |
| 5     | 4.8    | 0.00 | −1.50 | 175 | −0.75 | 0.14 | 0.00 | −1.25 | 175 | −0.63 | 0.16 | 0.13 |
| 6     | 4.3    | 0.00 | −1.50 | 5   | −0.75 | 0.12 | +0.50 | −2.75 | 5   | −0.88 | 0.32 | 0.13 |
| 7     | 7.1    | +0.25 | −3.50 | 5   | −1.50 | 0.14 | +0.50 | −5.00 | 175 | −2.00 | 0.24 | 0.50 |
| 8     | 4.4    | +1.25 | −3.00 | 180 | −0.25 | 0.50 | +1.75 | −4.00 | 170 | −0.25 | 0.52 | 0.00 |
| 9     | 6.0    | −7.00 | −4.00 | 5   | −9.00 | 0.50 | −3.50 | −2.75 | 175 | −4.88 | 0.44 | 4.13 |
| 10    | 5.2    | 0.00 | −5.00 | 5   | −2.50 | 0.40 | 0.00 | −3.25 | 5   | −1.63 | 0.38 | 0.88 |
| 11    | 4.8    | −5.50 | −1.50 | 10  | −6.25 | 0.42 | −1.75 | −1.25 | 165 | −2.38 | 0.20 | 3.88 |
| 12    | 5.4    | +4.00 | −4.50 | 15  | +1.75 | 0.44 | +1.00 | −0.75 | 165 | +0.63 | 0.02 | 1.13 |
| 13    | 5.5    | +0.25 | −1.25 | 165 | −0.38 | 0.30 | 0.00 | −2.50 | 180 | −1.00 | 0.32 | 0.63 |
| 14    | 6.6    | +1.00 | −2.00 | 5   | 0.00 | 0.30 | +1.50 | −2.75 | 180 | 0.13 | 0.32 | 0.13 |
| 15    | 5.7    | −4.00 | −0.75 | 180 | −4.38 | 0.58 | −5.00 | −2.50 | 170 | −6.25 | 0.70 | 1.88 |
| 16    | 3.3    | +0.50 | −2.00 | 170 | −0.50 | 0.32 | 0.00 | −1.75 | 175 | −0.88 | 0.32 | 0.38 |
| 17    | 4.3    | +1.25 | −1.50 | 10  | +0.50 | 0.22 | +3.25 | −2.50 | 170 | +2.00 | 0.34 | 1.50 |
| 18    | 5.5    | +4.00 | −0.50 | 110 | 3.75 | 0.32 | +4.25 | −0.50 | 30  | +4.00 | 0.32 | 0.25 |
| 19    | 4.9    | 0.00 | −3.50 | 170 | −1.75 | 0.50 | 0.00 | −3.50 | 175 | −1.75 | 0.50 | 0.00 |
| 20    | 4.9    | −0.50 | −1.25 | 180 | −1.13 | 0.22 | 0.00 | −2.00 | 175 | −1.00 | 0.24 | 0.13 |
| 21    | 5.7    | 0.00 | −4.00 | 180 | −2.00 | 0.22 | 0.00 | −3.00 | 180 | −1.50 | 0.20 | 0.50 |
| 22    | 4.7    | +1.25 | −2.25 | 160 | −0.13 | 0.32 | +1.25 | −1.75 | 160 | +0.38 | 0.32 | 0.25 |
| 23    | 3.9    | 0.00 | −1.75 | 30  | −0.88 | 0.24 | 0.00 | −1.00 | 170 | −0.50 | 0.12 | 0.38 |
| 24    | 4.9    | 0.00 | −4.00 | 5   | −2.00 | 0.30 | 0.00 | −4.50 | 175 | −2.25 | 0.30 | 0.25 |
| 25    | 5.2    | 0.00 | −2.00 | 170 | −1.00 | 0.30 | 0.00 | −2.00 | 180 | −1.00 | 0.28 | 0.00 |

Mean: −0.04 −2.37 N.A. −1.23 0.30 +0.28 −2.57 N.A. −1.01 0.32 N.A.

SD: 2.40 1.34 N.A. 2.48 0.14 1.84 1.18 N.A. 1.95 0.14 N.A.

* I.O.D. of >0.75 diopter spherical equivalent refractive errors to indicate anisometropia.

Custom-designed software (School of Optometry and Visual Science (SOVS) – Centre For Eye Health (CFEH) Psychophysical Testing Suite, Sydney, Australia) was used to generate the stimulus (Matlab, version R2017a; MathWorks Inc., Natick, MA, USA). The psychophysical stimuli were also sine wave grating stimuli were presented pattern onset-offset (100 msec on and 400 msec off) but stopping after 2500 msec.

The had 54% contrast stimuli with room lights turned off. The grating stimulus subtended a field size of 3° and a test distance of 2.2 meters allowed high spatial frequency gratings to be presented without aliasing by the monitor. Participants viewed the grating stimuli with their central vision by checking either side of the screen (2° from the center of the screen) to identify whether the stimulus appeared on

**Figure 2.** Frequency distribution of refractive amblyopes and non-amblyopic controls according to age.
FIGURE 3. Orientation-specific monocular pattern onset-offset visual evoked potential (POVEP) recordings for (a) meridian 1, (b) meridian 2 of refractive amblyopes ($n = 24$) in this present study, in comparison with (c) meridian 1 and (d) meridian 2 of non-amblyopic controls ($n = 29$) from a previous study by Yap et al. (2019).41 Meridians 1 and 2 represents the two principal astigmatic meridians, which are approximately horizontal and vertical respectively for most participants. The averaged amplitude (μV) waveform is plotted (thick line) against time (seconds) together with the individual waveforms (thin lines) for each eye of each participant. The main POVEP components (C1, C2 and C3) are indicated on the group averaged waveforms. The stimulus representations within a circle are symbolic and do not reflect the actual stimulus appearance, which is presented in Figure 1.

Analysis
Electrophysiological and psychophysical data from this cohort of newly diagnosed refractive amblyopes were analyzed in comparison with a non-amblyopic control group from a previous study.41 The main outcome measures in this present study are POVEP C3 amplitude, C3 latency, and psychophysical GA for the two participant groups (refractive amblyopes and controls). The C3 component of the POVEP waveform was chosen for analysis because it was the most repeatable component as it had the best intra-session repeatability as compared with the other components. Linear mixed models (LMMs) analysis was used on the monocular dataset to investigate the effect of stimulus meridian (meridians 1 and 2) and group on the outcome measures. The binocular dataset was analyzed using repeated measures analysis of covariance (ANCOVA) to examine for within-participant differences across the four meridians (45, 90, 135, and 180°) and between participant differences by group with age as a covariate. Planned analysis for the monocular data was linear mixed modeling, which takes into account the linkages of data between the same subjects. The data were not categorized based on the better or poorer eye because most amblyopes in this present study were bilateral with very
similar VAs in both eyes. Logarithmic (natural log) transformation was applied, where necessary, in order to satisfy normality assumptions of LMM and the power law function of visual perception. Psychophysical GA was expressed in arc seconds. The data of one bilateral refractive amblyope (participant no. 5) was excluded from the analysis as the participant was inattentive during POVEP recording despite encouragement to maintain fixation. Figure 2 shows the meridional anisotropies for monocular (Fig. 4) and binocular (Fig. 5) recordings of GA, POVEP C3 amplitudes, and C3 latencies. Analysis of both normalized and raw data produced the same results. The normalized values of the binocular C3 amplitudes were 1.30 ± 0.20, 1.50 ± 0.19, and 1.30 ± 0.17 for meridians 1, 2, and 3, respectively, which were all expressed as a ratio by taking reference to meridian 180. In view that the finding of a lack of meridional anisotropy in the amblyopic children did not support the original hypothesis, a post hoc analysis was conducted to determine if the lack of astigmatism-associated anisotropies may have been related to the magnitude of astigmatism of individuals within this cohort.

The post hoc analysis demonstrated that POVEP C3 amplitudes were significantly higher in refractive amblyopes who had low (n = 12 eyes in 10 participants; P = 0.02) and moderate (n = 16 eyes in 12 participants; P = 0.004) magnitudes of astigmatism compared with those participants who had high astigmatism (n = 19 eyes in 11 participants), but there were still no significant meridional anisotropies in all three astigmatic groups (Fig. 6). One eye from one participant was not analyzed as there was no astigmatism in that eye (right eye of participant no. 2). The absolute difference of meridians 1 and 2 of each participant were plotted to illustrate the wide spread of anisotropies that do not seem to be related to the magnitude of astigmatism in this cohort.

Comparison of Refractive Amblyopes and Non-Amblyopic Controls

Refractive amblyopes had poorer GA and POVEP C3 amplitudes compared with non-amblyopic controls by approximately two lines on the logMAR chart (monocular: 0.42

| Refractive Amblyopes | Non-Amblyopic Controls* |
|----------------------|-------------------------|
| N 24 (18 bilateral; 64 anisometric) | 29 (9/29 astigmat; 20/29 non-astigmat) |
| VA (mean ±SD) | |
| OD 0.30 ± 0.14 logMAR | OD 0.00 ± 0.01 logMAR |
| OS 0.32 ± 0.14 logMAR | OS 0.00 ± 0.01 logMAR |
| Mean refractive error | |
| Anisometropic amblyopes: | |
| OD −1.45 DS/−2.30 DC | OD +0.83 DS/−1.59 DC |
| OS −0.10 DS/−1.95 DC | OS −0.92 DS/−1.66 DC |
| Bilateral amblyopes: | |
| OD +0.31 DS/−2.39 DC | OD −0.09 DS/0.00 DC |
| OS +0.38 DS/−2.73 DC | OS −0.09 DS/0.00 DC |
| Power range | |
| Anisometropic amblyopes: | |
| OD +3.25 to −1.56 DS | OD +3.00 to −1.75 DS |
| OS −3.50 to 2.75 DS | OS −1.50 to 1.31 D |
| Spherical equivalent (mean ±SD) | |
| Anisometropic amblyopes: | |
| OD −2.6 ±4.75 D | OD −1.34 ±3.11 D |
| OS −1.08 ±2.67 D | OS −1.65 ±1.40 D |
| Bilateral amblyopes: | |
| OD −0.88 ±1.56 D | OD −0.09 ±0.40 D |
| OS −0.99 ±1.82 D | OS −0.09 ±0.40 D |

* Controls were non-amblyopic children from a previous study41 for comparison.

**Table 2.** Comparison of Refractive Profile of Refractive Amblyopes in this Present Study (Left Column) with Non-Amblyopic Control Group from a Previous Study41 (Right Column)
FIGURE 4. Monocular assessment of (a) psychophysical grating acuity (GA), (b) C3 amplitude, and (c) C3 latency for orientation-specific pattern onset-offset visual evoked potentials (POVEP) in refractive amblyopes (n = 24). For comparison, the data of non-amblyopic controls (n = 29) were adapted from Yap et al. (2019). The GA and POVEP C3 amplitude in non-amblyopic controls were 0.42 octaves (P = 0.013; 0.33 ± 0.13 ln units) and 6.90 ± 3.00 μV (P = 0.009; 0.39 ± 0.15 ln units) greater than refractive amblyopes, respectively. Error bars indicate the 95% confidence intervals. The stimulus representations within a circle are symbolic and do not reflect the actual stimulus appearance, which is presented in Figure 1.

dis尽早诊断的弱视儿童被评估为可能与他们的屈光误差有关的经线性异构。由于这些弱视儿童在这组尚未开始佩戴眼镜，因此本研究的结果代表了在光学治疗前的基线电生理学发现。如果电生理信号在模糊的散光经线时减弱，这将表明存在特定于经线性视觉细胞的选择性功能障碍，正如在动物中以前所示的，假设正常视网膜功能。

虽然经线性异构可以由散光引起，但在本研究的主要分析中，神经生理学缺陷在新诊断的屈光性弱视儿童可能限于降低了POVEP C3幅度和更差的经线性视觉细胞。然而，这些神经生理学缺陷并非特定于经线性视觉细胞，尽管本研究与上述假设一致，即高散光程度可以对早期视觉发育产生不利影响。

在事后分析中，我们感兴趣的是在可能与经线性异构程度和散光程度相关的经线性异构程度。然而，所有三组散光弱视儿童未能达到显著性异构。相反，它被发现为散光高散光的屈光性弱视儿童有显著低于POVEP C3幅度与更低的POVEP C3幅度与低到中等程度的散光相比。

其他研究已经报告，非弱视的散光儿童也可能会遭受更差的光学质量。
and poorer POVEP C3 amplitudes.\textsuperscript{41} Thus, it may be that astigmatism’s deleterious effects can be experienced not only in amblyopes but also non-amblyopic astigmatic children. Examples of the POVEP waveforms were presented for refractive amblyopes with high (Fig. 8a) and moderate bilateral astigmatism (Fig. 8b) and a non-amblyopic child (Fig. 8c).

Even though the majority of amblyopes with >10.0 μV of meridional anisotropies (12/18 eyes) had high astigmatism (≥3.00 D), the types and magnitudes of meridional anisotropies were idiosyncratic for each individual and such variability may explain the group statistical observation that amblyopia deficits were not orientation-specific. Of the 18 amblyopes with >10.0 μV of meridional anisotropies, five had moderate astigmatism (1.75–2.75 D) and one did not have any astigmatism. As the children in this present study were closely monitored by the examiner, it is not likely that the results were affected by off-axis stimuli presentation during POVEP recording. Similarly, Fiorentini and Maffei\textsuperscript{30} reported that five of seven children with high astigmatism (3.00–4.00 D) developed meridional anisotropies and two did not, although the magnitude of difference they accepted as anisotropy was unstated in their study.

However, the stimuli of Freeman and Thibos\textsuperscript{28} and Fiorentini and Maffei\textsuperscript{30} differed from the present study, which may also account for differences in findings. For example, Fiorentini and Maffei used 3.0 cpd, 5 × 4° field-size sinusoidal gratings that alternated at a frequency of 8 cycles per second, which elicits a sinusoidal steady-state VEP rather than a transient VEP, as in the present study. Freeman and Thibos used sinusoidal gratings of 7° field-size with varying spatial frequencies that alternated at a temporal frequency of 9 or 12 Hz, which also elicits sinusoidal VEPs.

In monkeys, pattern reversing stimuli were thought to produce VEPs that originate from areas V1 and MT/V5,\textsuperscript{32} but it is likely that this present study may be recording signals...
Figure 6. Monocular orientation-specific pattern onset-offset visual evoked potential (POVEP) C3 amplitude of refractive amblyopes with different magnitudes of astigmatism. The C3 amplitudes of each eye were significantly higher in refractive amblyopes with low (≤1.50 dioptic cylinder [DC]; n = 12 eyes; P = 0.02) and moderate (1.75 to 2.75 DC; n = 16 eyes; P = 0.004) degrees of astigmatism compared to refractive amblyopes with high astigmatism (≥3.00 DC; n = 19 eyes) regardless of the meridians (meridians 1 and 2) tested. One eye from one participant was not analyzed as there was no astigmatism in that eye. Error bars indicate the 95% confidence intervals.

Cases of Astigmatism-Induced Meridional Anisotropies

While inspecting individual cases of refractive amblyopia, it was observed that the magnitudes of meridional anisotropies tended to be greater in one eye than the other eye. There is a possibility that the eyes that had higher magnitude of astigmatism was too blurred for meridional anisotropy to develop, such that both astigmatic meridians became suppressed. For example, a bilateral refractive amblyope with 3.50 D of astigmatism had 21.04 μV of meridional anisotropy in one eye whereas the other eye with 4.50 D of astigmatism had only 4.84 μV of meridional anisotropy (Fig. 8a). It is, however, unclear whether the meridional anisotropies reported by Fiorentini and Maffei\textsuperscript{30} and Freeman and Thibos\textsuperscript{28} were for one eye or both eyes.

Although the sample size for the post hoc analysis is too small to be conclusive, it suggests an avenue for further research to investigate anisometropic amblyopia, whether the eye that had lesser magnitude of astigmatism would tend to develop meridional anisotropy. For the eye that has astigmatism-induced meridional anisotropy, there could be two possible reasons for their orientation-specific neural deficits: (1) there was a retraction of neurons within the orientation columns in the V1, as was observed in animal studies\textsuperscript{60–61} or (2) there was orientation-specific suppression\textsuperscript{36,37} that may be similar to orientation-tuning properties in the V1,\textsuperscript{37} which could possibly be modulated by higher-order attention.\textsuperscript{62–65}

Could the Horizontal Effect be an Indicator of Normality in Children?

The recordings of the POVEP in refractive amblyopia did not yield any significant meridional anisotropies that resembles either the horizontal effect or the oblique effect, which are normally expected in non-amblyopic children\textsuperscript{41} and adults,\textsuperscript{66} respectively. Because young children have more limited visual experiences than adults, they would naturally have less opportunity to develop biases against oblique meridians, as in the case of an oblique effect. Hence, it is possible that the horizontal effect in children could be in a continuum of visual development in normally developing children until the onset of an oblique effect. The absence of either of these two types of meridional anisotropies would suggest that the visual system is abnormal and it is possible for refractive amblyopia to have stalled the normal development of meridional anisotropies due to the chronic optical blur during early childhood.

In consideration of the horizontal effect in non-amblyopic children, it must be noted that this type of meridional anisotropy was found electrophysiologically under mid-level contrast stimulation of a specific spatial frequency (4 cpd).\textsuperscript{31} However, the types and magnitudes of meridional anisotropies are expected to vary under other choices of spatial frequency,\textsuperscript{67,68} contrast,\textsuperscript{45} types of stimuli (e.g. texture,\textsuperscript{69} Gabor,\textsuperscript{70} grating,\textsuperscript{44,71–74} or broadband natural images),\textsuperscript{46,75} mode of stimuli presentations...
FIGURE 8. Case comparison to demonstrate the wide range of meridional anisotropies. The stimulus representations within a circle are symbolic and do not reflect the actual stimulus appearance, which is presented in Figure 1. Orientation-specific pattern onset-offset visual evoked potential (POVEP) recordings from each principal astigmatic meridians (meridians 1 and 2) of the right (OD) and left eyes (OS) of (a) refractive amblyope with high bilateral astigmatism (aged 7.1 years; OD +0.25 -3.50 × 5VA 0.14 OS +0.50 −5.00 × 175 VA 0.24), (b) refractive amblyope with moderate bilateral astigmatism (aged 4.7 years; OD +1.25 −2.25 × 10 VA 0.32 OS +1.25 −1.75 × 160 0.32), and (c) non-amblyopic control with low-moderate bilateral astigmatism (aged 5.3 years; OD +0.25 −0.75 × 180 VA 0.02 OS plano −1.75 × 180 VA 0.02) from a previous study by Yap et al. (2019). Meridional anisotropy (MA) refers to the absolute difference between POVEP C3 amplitudes of meridians 1 (dotted lines) and 2 (solid lines). Visual acuity (VA) were recorded in logMAR.

The results of the absence of horizontal effect in this present study mainly relies on binocular POVEP as the recordings entails four meridians. However, only two meridians were assessed monocularly in consideration of the children’s limited attention span. Hence, it is not possible for this present study to conclusively negate the presence of oblique effect under monocular conditions. This could be a research question for future studies because this present study was primarily designed to examine astigmatism-induced meridional anisotropies. As amblyopes are variable in presentation and characteristics, these results are particular to this sample and the stimuli used. For this reason, it is possible that a different sample or stimulus may have yielded different results. Hence, the findings in this present study may not be generalizable to amblyopes with different characteristics or other stimuli.

CONCLUSIONS

Chronic optical blur during early childhood can have detrimental effects on visual development. Deleterious effects of high astigmatism on POVEP C3 amplitudes was evident in children with newly diagnosed refractive amblyopia, but the neural deficits do not seem to be orientation-specific for the stimulus parameters investigated. The POVEP testing protocols in this present study were able to distinguish between refractive amblyopic and non-amblyopic control participants, thus allowing future work to assess the effect of spectacle optical treatment.

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References

1. Chia A, Dirani M, Chan YH, et al. Prevalence of amblyopia and strabismus in young Singaporean Chinese children. Invest Ophthalmol Vis Sci. 2010;51:3411–3417.

2. Chia A, Lin X, Dirani M, et al. Risk factors for strabismus and amblyopia in young Singaporean Chinese children. Ophthalmic Epidemiol. 2013;20:138–147.

3. Dirani M, Chan YH, Gazzard G, et al. Prevalence of refractive error in Singaporean Chinese children: the strabismus, amblyopia, and refractive error in young Singaporean Children (STARS) study. Invest Ophthalmol Vis Sci. 2010;51:1348–1355.

4. Lim HT, Yu YS, Park SH, et al. The Seoul Metropolitan Preschool Vision Screening Programme: results from South Korea. Br J Ophthalmol. 2004;88:929–933.

5. Chang CH, Tsai RK, Sheu MM. Screening amblyopia of preschool children with uncorrected vision and stereopsis tests in Eastern Taiwan. Eye (Lond). 2007;21:1482–1488.

6. Prevalence of amblyopia and strabismus in African American and Hispanic children ages 6 to 72 months the multi-ethnic pediatric eye disease study. Ophthalmology. 2008;115:1229–1236. e1221.

7. Ziyian S, Yabas O, Zorlutuna N, Serin D. Isoametric amblyopia in highly hypermetropic children. Acta Ophthalmol Scand. 2007;85:111–113.

8. Leat SJ. To prescribe or not to prescribe? Guidelines for spectacle prescribing in infants and children. Clin Exp Optom. 2011;94:514–527.

9. Pascual M, Huang J, Maguire MG, et al. Risk factors for amblyopia in the vision in preschoolers study. Ophthalmology. 2011;118:622–629 e621.

10. Edelman PM, Borchert MS. Visual outcome in high hypermetropia. J APOS. 1997;1:147–150.

11. Rouse MW, Cooper J.S., Cotter S.A., Press L.J., Tannen B.M. Care of the patient with amblyopia. Optometric Clinical Practice Guidelines. St. Louis: American Optometric Association; 1997:6341–67881.

12. Pai AS, Rose KA, Leone JF, et al. Amblyopia prevalence and risk factors in Australian preschool children. Ophthalmology. 2012;119:138–144.

13. Cotter SA, Varma R, Tarczy-Hornoch K, et al. Risk factors associated with childhood strabismus: the multi-ethnic pediatric eye disease and Baltimore pediatric eye disease studies. Ophthalmology. 2011;118:2251–2261.

14. Tanlamai T, Goss DA. Prevalence of monocular amblyopia among anisometropes. Am J Optom Physiol Opt. 1979;56:704–715.

15. Hardman Lea SJ, Loades J, Rubinstein MP. The sensitive period for anisometric amblyopia. Eye (Lond). 1989;3(Pt 6):783–790.

16. Townshend AM, Holmes JM, Evans IS. Depth of anisometropic amblyopia and difference in refraction. Am J Ophthalmol. 1993;116:431–436.

17. Al-Tamimi ER, Shakeel A, Yassin SA, Ali SI, Khan UA. A clinic-based study of refractive errors, strabismus, and amblyopia in pediatric age-group. J Family Community Med. 2015;22:158–162.

18. Abrahamsson M, Fabian G, Sjöstrand J. Refraction changes in children developing convergent or divergent strabismus. Br J Ophthalmol. 1992;76:723–727.

19. Harvey EM. Development and treatment of astigmatism-related amblyopia. Optom Vis Sci. 2009;86:634–639.

20. Dobson V, Miller JM, Harvey EM, Mohan KM. Amblyopia in astigmatic preschool children. Vision Res. 2003;43:1081–1090.

21. Mitchell DE, Freeman RD, Millodot M, Haegerstrom G. Meridional amblyopia: evidence for modification of the human visual system by early visual experience. Vision Res. 1973;13:535–558.

22. Charman WN, Voisin L. Optical aspects of tolerances to uncorrected ocular astigmatism. Optom Vis Sci. 1993;70:111–117.

23. Hirsch HV, Spinelli DN. Visual experience modifies distribution of horizontally and vertically oriented receptive fields in cats. Science. 1976;186:869–871.

24. Muir DW, Mitchell DE. Visual resolution and experience: acuity deficits in cats following early selective visual deprivation. Science. 1973;180:420–422.

25. Ferster D, Miller KD. Neural mechanisms of orientation selectivity in the visual cortex. Annu Rev Neurosci. 2000;23:441–471.

26. Mitchell DE, Wilkinson F. The effect of early astigmatism on the visual resolution of gratings. J Physiol. 1974;243:739–756.

27. Hess RF, Malin SA. Threshold vision in amblyopia: orientation and phase. Invest Ophthalmol Vis Sci. 2003;44:4762–4771.

28. Freeman RD, Thibos LN. Visual evoked responses in humans with abnormal visual experience. J Physiol. 1975;247:711–724.

29. Harvey EM, Dobson V, Miller JM, Clifford-Donaldson CE. Changes in visual function following optical treatment of astigmatism-related amblyopia. Vision Res. 2008;48:775–787.

30. Fiorentini A, Maffei L. Evoked potentials in astigmatic subjects. Vision Res. 1973;13:1781–1783.

31. Nguyen VA, Freeman AW, Alais D. Increasing depth of binocular rivalry suppression along two visual pathways. Vision Res. 2003;43:2003–2008.

32. Wilson HR. Computational evidence for a rivalry hierarchy in vision. Proc Natl Acad Sci U S A. 2003;100:14499–14503.

33. Freeman AW. Multistage model for binocular rivalry. J Neurophysiol. 2005;94:4412–4420.

34. Desimone R, Schein SJ, Moran J, Ungerleider LG. Contour, color and shape analysis beyond the striate cortex. Vision Res. 1985;25:441–452.

35. Desimone R, Albright TD, Gross CG, Bruce C. Stimulus-selective properties of inferior temporal neurons in the macaque. J Neurosci. 1983;4:2051–2062.

36. Nguyen VA, Freeman AW, Wenderoth P. The depth and selectivity of suppression in binocular rivalry. Percept Psychophys. 2001;63:348–360.

37. Stuit SM, Cass J, Paffen CI, Alais D. Orientation-tuned suppression in binocular rivalry reveals general and specific components of rivalry suppression. J Vis. 2009;9(17):11–15.

38. O’Shea RP, Crassini B. The sensitivity of binocular rivalry suppression to changes in orientation assessed by reaction-time and forced-choice techniques. Perception. 1981;10:283–293.

39. Pearson J, Clifford CW. When your brain decides what you see: grouping across monocular, binocular, and stimulus rivalry. Psychol Sci. 2005;16:516–519.

40. Ling S, Pratte MS, Tong F. Attention alters orientation processing in the human lateral geniculate nucleus. Nat Neurosci. 2015;18:496–498.

41. Yap TP, Luu CD, Suttle CM, Chia A, Boon MY. Electro-physiological and psychophysical studies of meridional
anisotropies in children with and without astigmatism. *Invest Ophtalmol Vis Sci.* 2019;60:1906–1913.

42. Brown AM, Lindsey DT, Cammenga JG, Giannone PJ, Stenger MR. The contrast sensitivity of the newborn human infant. *Invest Ophtalmol Vis Sci.* 2015;56:625–632.

43. Murray IJ, Elliott SL, Pallikaris A, Werner JS, Choi S, Tahir HJ. The oblique effect has an optical component: orientation-specific contrast thresholds after correction of high-order aberrations. *J Vis.* 2010;10(11):10.

44. Furmanski CS, Engel SA. An oblique effect in human visual cortex. *J Neurophysiol.* 2010;103:3465–3471.

45. Maloney RT, Clifford CW. Orientation anisotropies in human visual cortex. *NeuroImage.* 2015;119:129–145.

46. Mansion DJ, McDonald JS, Clifford CGW. Orientation anisotropies in human visual cortex. *J Neurophysiol.* 2010;103:3465–3471.

47. Essock EA, DeFord JK, Hansen BC, Sinai MJ. Oblique stimuli are seen best (not worst!) in naturalistic broad-band stimuli: a horizontal effect. *Vision Res.* 2003;43:1329–1335.

48. Hansen BC, Essock EA. A horizontal bias in human visual processing of orientation and its correspondence to the structural components of natural scenes. *J Vis.* 2004;4:1044–1060.

49. Haun AM, Essock EA. Contrast sensitivity for oriented patterns in 1/f noise: contrast response and the horizontal effect. *J Vis.* 2010;10:1.

50. Ahmed A, Watson TL. Assessing the functional significance of the horizontal effect. *Australasian Cognitive Neuroscience Conference: Frontiers in Human Neuroscience; University of Brisbane, Australia, November 29 to December 2, 2012.*

51. Wallace DK, Chandler DJ, Beck RW, et al. Treatment of bilateral refractive amblyopia in children three to less than 10 years of age. *Am J Ophtalmol.* 2007;144:487–496.

52. Brigell M, Bach M, Barber C, Moskowitz A, Robson J. Calibration Standard Committee of the International Society for Clinical Electrophysiology of Vision. Guidelines for calibration of stimulus and recording parameters used in clinical electro-physiology of vision. *Doc Ophtalmol.* 2003;107:185–193.

53. Fesharaki H, Azizzadeh A, Ghoreishi SM, Fasihni M, Badiei S, Rezaei L. The effects of lateral head tilt on ocular astigmatic axis. *Adv Biomed Res.* 2014;3:10.

54. Odom JV, Bach M, Barber C, et al. Visual evoked potentials standard (2004). *Doc Ophtalmol.* 2004;108:115–123.

55. Cornsweet TN. The staircase-method in psychophysics. *Am J Psychol.* 1962;75:485–491.

56. Jones FN. A forced-choice method of limits. *Am J Psychol.* 1956;69:672–673.

57. Blackwell HR. Psychophysical thresholds: experimental studies of methods of measurement (Rep. No. 36). *Bulletin of the Engineering Research Institute.* Ann Arbor, MI: University of Michigan; 1953.

58. Gao J, Wang X-X, Wang L, Sun Y, Liu R-F, Zhao Q. The effect of the degree of astigmatism on optical quality in children. *J Ophtalmol.* 2017;2017:5786265–5786265.

59. Xu X, Collins CE, Khatiyn I, Kaas JH, Casagrande VA. Unequal representation of cardinal vs. oblique orientations in the middle temporal visual area. *Proc Natl Acad Sci U S A.* 2006;103:17490–17495.

60. Hubel DH, Wiesel TN. Receptive fields and functional architecture in two nonstriate visual areas (18 and 19) of the cat. *J Neurophysiol.* 1965;28:229–289.

61. Hubel DH, Wiesel TN. The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J Physiol.* 1970;206:419–436.

62. Popple AV, Levi DM. The attentional blink in amblyopia. *J Vis.* 2008;8:12.

63. Sharma V, Levi DM, Klein SA. Undercounting features and missing features: evidence for a high-level deficit in strabismic amblyopia. *Nat Neurosci.* 2000;3:496–501.

64. Whitney D, Levi DM. Visual crowding: a fundamental limit on conscious perception and object recognition. *Trends Cogn Sci.* 2011;15:160–168.

65. Levi DM, Klein SA, Chen I. What limits performance in the amblyopic visual system: seeing signals in noise with an amblyopic brain. *J Vis.* 2008;8:1–23.

66. Moskowitz A, Sokol S. Effect of stimulus orientation on the latency and amplitude of the VEP. *Invest Ophtalmol Vis Sci.* 1985;20:246–248.

67. Arakawa K, Tobiimatsu S, Kurita-Tashima S, Nakayama M, Kira JI, Kato M. Effects of stimulus orientation on spatial frequency function of the visual evoked potential. *Exp Brain Res.* 2000;131:121–125.

68. Leehey SC, Moskowitz-Cook A, Brill S, Held R. Orientational anisotropy in infant vision. *Science.* 1975;190:900–902.

69. Westheimer G. Meridional anisotropy in visual processing: implications for the neural site of the oblique effect. *Vision Res.* 2003;43:2281–2289.

70. Westheimer G. Lines and gabor functions compared as spatial visual stimuli. *Vision Res.* 1998;38:487–491.

71. Swisher JD, Gatenby JC, Gore JC, et al. Multiscale pattern analysis of orientation-selective activity in the primary visual cortex. *J Neurosci.* 2010;30:325–330.

72. Furmanski CS, Schluppeck D, Engel SA. Learning strengthens the response of primary visual cortex to simple patterns. *Curr Biol.* 2004;14:573–578.

73. Sun M, Huang J, Wang F, et al. Quantitative comparison of the hemodynamic activation elicited by cardinal and oblique gratings with functional near-infrared spectroscopy. *Neuroreport.* 2013;24:354–358.

74. Freeman J, Brouwer GJ, Heeger DJ, Merriam EP. Orientation decoding depends on maps, not columns. *J Neurosci.* 2011;31:4792–4804.

75. McDonald JS, Mansion DJ, Clifford CGW. Gain control in the response of human visual cortex to plaids. *J Neurophysiol.* 2012;107:2570–2580.

76. Heeley DW, Buchanan-Smith HM. Orientation acuity estimated with simultaneous and successive procedures. *Spat Vis.* 1992;6:1.

77. Murasugi CM, Cavanagh P. Anisotropy in the chromatic channel: a horizontal-vertical effect. *Spat Vis.* 1988;3:281–291.

78. Koelewijn L, Dumont JR, Muthukumaraswamy SD, Rich AN, Singh KD. Induced and evoked neural correlates of orientation selectivity in human visual cortex. *NeuroImage.* 2011;54:2983–2993.

79. Sloper J. The other side of amblyopia. *J AAPOS.* 2016;20:e1–e13.