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

Tiong Peng Yap,<sup>1</sup> Chi D. Luu,<sup>2,3</sup> Catherine Suttle,<sup>1,4</sup> Audrey Chia,<sup>5,6</sup> and Mei Ying Boon<sup>1</sup>

<sup>1</sup>School of Optometry and Vision Science, University of New South Wales, Sydney, New South Wales, Australia

<sup>2</sup>Centre for Eye Research Australia; Royal Victorian Eye and Ear Hospital, East Melbourne, Victoria, Australia

<sup>3</sup>Department of Surgery (Ophthalmology), The University of Melbourne, Parkville, Victoria, Australia

<sup>4</sup>Division of Optometry and Visual Sciences, City, University of London, London, United Kingdom

<sup>5</sup>Pediatric Ophthalmology and Adult Strabismus Department, Singapore National Eye Centre (SNEC), Singapore

<sup>6</sup>Pediatric Ophthalmology and Strabismus Department, KK Women's and Children's Hospital (KKH), Singapore

Correspondence: Tiong Peng Yap, School of Optometry and Vision Science, University of New South Wales (UNSW), Barker Street, Rupert Myers Building, Sydney, New South Wales 2052, Australia; [tiongyap@igard.com.sg](mailto:tiongyap@igard.com.sg).

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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 sinewave 4 cycles per degree (cpd) grating stimuli oriented along each individual participants' 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 ( $\leq 1.50$  diopters [D]), moderate (1.75–2.75 D) and high ( $\geq 3.00$  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  $\mu\text{V}$  (monocular:  $P = 0.009$ ; binocular:  $P = 0.027$ ), respectively.

**CONCLUSIONS.** Deleterious effects of high astigmatism was 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 driver for amblyopia in some populations. For example, nearly 85% of amblyopia diagnoses in Singapore are attributed to uncorrected refractive errors, whereas only 15% of amblyopia can be attributed to strabismus.<sup>1–3</sup> The Singapore study found 30% of the amblyopic children had bilateral refractive amblyopia, whereas 70% had unilateral amblyopia.<sup>1</sup> Similar trends have been reported in other parts of Asia where strabismus accounts for only 12.8% of amblyopia in Korea<sup>4</sup> and 2.6% in Taiwan.<sup>5</sup> 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.<sup>6</sup>

Young children who have large magnitudes of refractive errors<sup>7,8</sup> are particularly at risk for developing amblyopia.<sup>9</sup> Red flags include hyperopia  $> +4.00$  diopters (D),<sup>10</sup> myopia  $> -8.00$  D,<sup>11</sup> astigmatism  $> 2.50$  D,<sup>11–13</sup> 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.<sup>11</sup> The severity of anisometric amblyopia tends to correlate with interocular difference in refractive errors.<sup>14–16</sup>

Based on a Singapore study, a large proportion of amblyopic children were found to have astigmatism—42% of amblyopes have aniso-astigmatism  $\geq 1.50$  D and 29% have

isometric astigmatism  $>2.50$  D.<sup>1</sup> Similarly, 19.2% of children with amblyopia in the Middle East were found to have astigmatism  $\geq 2.50$  dioptic cylinder (DC).<sup>17</sup> Even astigmatism as low as 1.00 D may be associated with unilateral amblyopia<sup>9</sup> and nearly 30% of the strabismic children were reported to have astigmatism  $\geq 1.00$  D on initial examination.<sup>18</sup> Hence, it is conceivable that astigmatism is an important amblyogenic factor and some of these astigmatic children may have *meridional amblyopia*<sup>19</sup> because the astigmatic meridian that has greater optical blur may chronically experience reduced vision.<sup>20,21</sup>

Astigmatism-related amblyopia may result in orientation-specific neural deficits in the astigmatic meridian,<sup>22</sup> as observed in studies of kittens<sup>23–25</sup> and human psychophysical studies of grating acuity<sup>20,21,26–29</sup> and visual electrophysiology<sup>28,30</sup> measures. In the 1970s, Freeman and Thibos<sup>28</sup> 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<sup>30</sup> 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;  $n = 16$ ).<sup>30</sup> 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.<sup>31–33</sup> This includes the *V4* cortical area, where neuron's orientation-tunings tend to be broader<sup>34</sup> even though only a small proportion of neurons in area *IT* are orientation-tuned.<sup>35</sup> 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<sup>31,36–38</sup> where orientation-tuned neurons compete in the presence of orthogonal rivaling 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.<sup>39</sup> 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).<sup>40</sup> 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.<sup>41</sup> In newborn infants, poorer sensitivity to horizontal than vertical square-wave gratings was observed psychophysically at very low spatial frequencies (0.06 to 0.10 cycles per degree [cpd]).<sup>42</sup> This type of meridional anisotropy differs from the oblique effect, which is a physiologically normal phenomenon in adults.<sup>43,44</sup> The oblique effect can be defined as more sensitive cardinal meridians compared with the oblique meridians, which is normally observed in adults; whereas the horizontal effect is defined by less sensitive horizontal meridians compared with the vertical and oblique meridians. Our previous study in children with normal vision found a horizontal effect,<sup>41</sup>

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.<sup>41</sup> This is thought to provide more efficient neural coding<sup>45,46</sup> and was found psychophysically in adults viewing natural scenes<sup>47–50</sup> 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 optically defocused 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.<sup>41</sup> 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

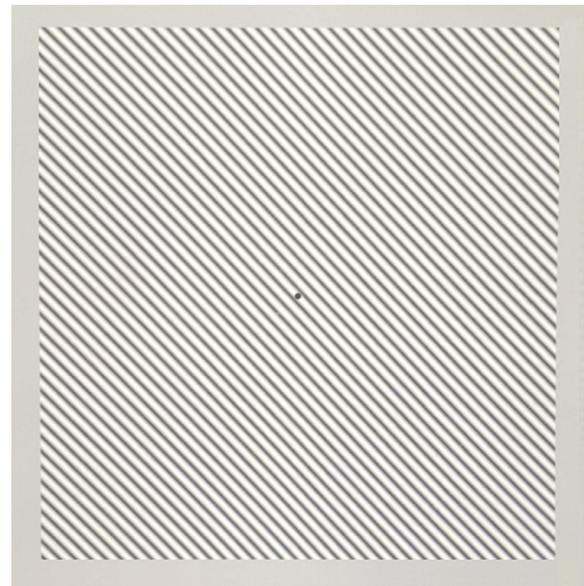
Preschool- and school-aged children with refractive amblyopia were included in the study, and cases of strabismus, ocular diseases, and/or abnormalities were excluded. Refractive amblyopes had VA of 0.3 logarithm of the minimum angle of resolution (logMAR; 20/40) or worse in at least one eye<sup>51</sup> 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 Frisby 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 amblyopes received cycloplegic refraction at the point of diagnosis. As the study was designed to understand the untreated amblyopic 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 spherominus 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 orientated 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,<sup>52</sup> 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,<sup>53</sup> but the participants in this present study were able to maintain vertical head posture throughout the entire testing period because the recording for each stimuli 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.



**FIGURE 1.** An illustration of the 12° field-size achromatic sinewave grating stimulus of 4 cycles per degree and a 2 mm diameter black dot in the center of the stimulus which was used as a fixation target. The grating was presented on a background of average luminance and chromaticity. The grating had a Michelson contrast of 54%. As shown in this example, the grating stimulus was oriented at meridian 135.

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,<sup>54</sup> 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 O<sub>z</sub> (occipital midline), C<sub>z</sub>, and F<sub>z</sub>, 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.<sup>55–57</sup>

TABLE 1. Refractive and Age Profiles of Children with Refractive Amblyopia

I.D.	Age, y	Right Eye					Left Eye					I.O.D.
		Sph	Cyl	Ax	SE	VA	Sph	Cyl	Ax	SE	VA	
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	-2.00	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	0.5	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
<b>Mean</b>		<b>-0.04</b>	<b>-2.37</b>	<b>N.A.</b>	<b>-1.23</b>	<b>0.30</b>	<b>+0.28</b>	<b>-2.57</b>	<b>N.A.</b>	<b>-1.01</b>	<b>0.32</b>	<b>N.A.</b>
<b>SD</b>		<b>2.40</b>	<b>1.34</b>	<b>N.A.</b>	<b>2.48</b>	<b>0.14</b>	<b>1.84</b>	<b>1.18</b>	<b>N.A.</b>	<b>1.95</b>	<b>0.14</b>	<b>N.A.</b>

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

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.

Participant No. 5 was excluded in the analysis.

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.

They 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

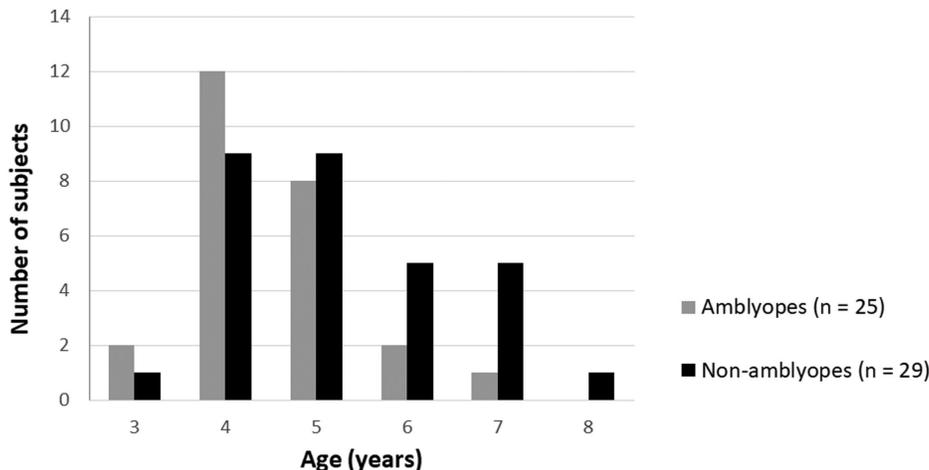
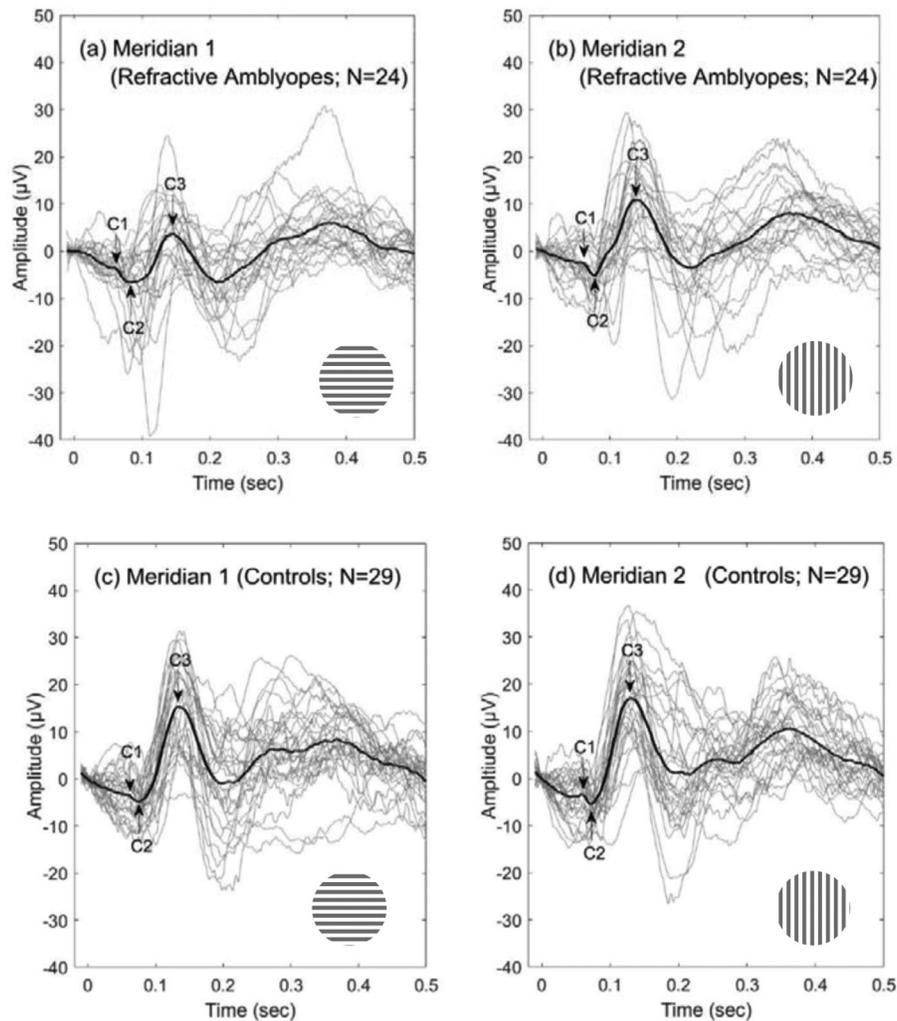


FIGURE 2. Frequency distribution of refractive amblyopes and non-amblyopic controls according to age.



**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).<sup>41</sup> Meridians 1 and 2 represents the two principal astigmatic meridians, which are approximately horizontal and vertical respectively for most participants. The averaged amplitude ( $\mu\text{V}$ ) 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.

the left or right side of the screen. The psychophysical staircase starting value was 2 cpd and its spatial frequency was increased in 3-decibel (dB) steps until the first error (reversal 1). This was then decreased in 3-dB steps until it was correct (reversal 2), then increased in 3-dB steps until an error was made (reversal 3), then decreased in 1.5-dB steps until it was correct (reversal 4), then increased in 0.75-dB steps until an error was made (reversal 5), and then decreased in 0.375-dB steps until it was correct (reversal 6). Psychophysical GAs were assessed along the same meridians using a 2-ANFC technique and threshold was estimated as the average of the last four reversals. This psychophysical protocol produced a convergence precision of 63%.

### 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.<sup>41</sup> 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

**TABLE 2.** Comparison of Refractive Profile of Refractive Amblyopes in this Present Study (Left Column) with Non-Amblyopic Control Group from a Previous Study<sup>41</sup> (Right Column)

	Refractive Amblyopes	Non-Amblyopic Controls*
<b>N</b>	24 (18 bilateral; 64 anisometropic)	29 (9/29 astigmats; 20/29 non-astigmats)
<b>VA (mean ±SD)</b>	OD 0.30 ± 0.14 logMAR OS 0.32 ± 0.14 logMAR	OD 0.00 ± 0.01 logMAR OS 0.00 ± 0.01 logMAR
<b>Mean refractive error</b>	<u>Anisometropic amblyopes:</u> OD -1.45 DS/-2.30 DC OS -0.10 DS/-1.95 DC <u>Bilateral amblyopes:</u> OD +0.31 DS/-2.39 DC OS +0.38 DS/-2.73 DC	<u>Astigmats:</u> OD +0.83 DS/-1.59 DC OS -0.92 DS/-1.66 DC <u>Non-astigmats:</u> OD -0.09 DS/0.00 DC OS -0.09 DS/0.00 DC
<b>Power range</b>	<u>Anisometropic amblyopes:</u> OD +4.00 to -7.00 DS/0.00 to -4.50 DC OS +3.25 to -3.50 DS/-0.75 to -2.75 DC <u>Bilateral amblyopes:</u> OD +4.00 to -4.00 DS/ -0.75 to -5.00 DC OS +4.25 to -5.00 DS/-0.75 to -5.00 DC	<u>Astigmats:</u> OD +2.50 to -3.50 DS/-0.50 to -3.00 DC OS +3.00 to -3.75 DS/-0.50 to -3.50 DC <u>Non-astigmats:</u> OD +0.25 to -1.75 DS/N.A. OS +0.75 to -1.75 DS/N.A.
<b>Spherical equivalent (mean ±SD)</b>	<u>Anisometropic amblyopes:</u> OD -2.6 ±4.73 D OS -1.08 ±2.67 D <u>Bilateral amblyopes:</u> OD -0.88 ±1.56 D OS -0.99 ±1.82 D	<u>Astigmats:</u> OD -1.54 ±1.31 D OS -1.65 ±1.40 D <u>Non-astigmats:</u> OD -0.09 ±0.40 D OS -0.09 ±0.40 D

D, diopters; DC, diopters cylinder; DS, diopters sphere; N, number; N.A., not applicable; OD, right eye; OS, left eye.  
\* Controls were non-amblyopic children from a previous study<sup>41</sup> for comparison.

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 terms of octaves (representing the doubling or halving of a spatial frequency) and its equivalent logMAR acuities for the ease of comparison. Bonferroni correction was applied to multiple paired comparisons to correct for family-wise error. As there was a wide range of astigmatic refractive errors, a post hoc LMM analysis was conducted to check the outcome measures for any significant differences among low ( $\leq 1.50$  D), moderate (1.75–2.75 D), and high ( $\geq 3.00$  D) degrees of astigmatism, similar to a previous study.<sup>58</sup> A post hoc analysis was also conducted, where normalization of the binocular data was undertaken by dividing the raw amplitudes by the horizontal meridian amplitude.

**RESULTS**

Twenty-five amblyopic ( $n = 19$  bilateral and  $n = 6$  anisometropic amblyopia; median age 4.9 years; range, 3.8–7.1 years) were recruited. The VAs (mean ±SD) were OD  $0.30 \pm 0.14$  OS  $0.32 \pm 0.14$  logMAR and their average refractive errors (sphero-minus cylinder form) were mostly with-the-rule astigmatism (Table 1). Stereopsis was  $38 \pm 11$  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 age distribution profiles and Figure 3 shows the averaged monocular POVEP recordings for each meridian in each group. As the refractive amblyopes in this present study are compared with a non-amblyopic control group from a previous study,<sup>41</sup> their refractive profiles are presented in Table 2 for comparison.

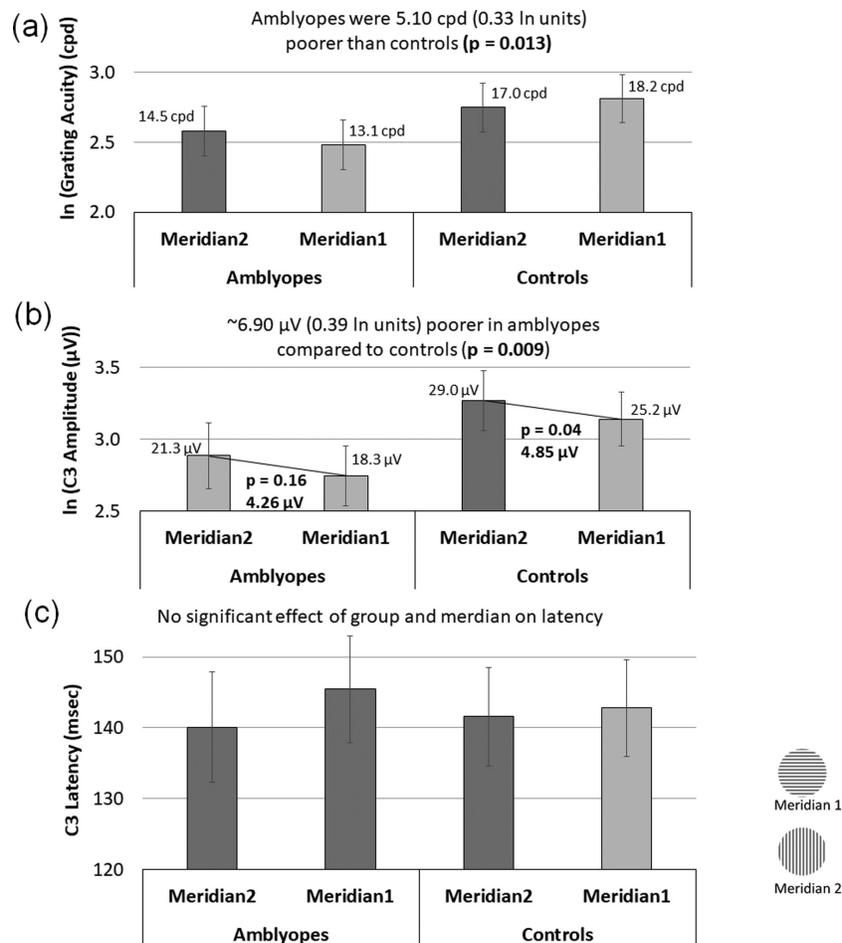
**Meridional Anisotropies in Refractive Amblyopes**

In this cohort of refractive amblyopes, there were no significant meridional anisotropies for monocular (Fig. 4) and binocular (Fig. 5) assessments of GAs, 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  $1.30 \pm 0.20$ ,  $1.50 \pm 0.19$ , and  $1.30 \pm 0.17$  for meridians 45, 90, and 135, 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 amplitude 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 (Fig. 7) and selected POVEP waveforms were also presented (Fig. 8).

**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



**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).<sup>41</sup> The GA and POVEP C3 amplitude in non-amblyopic controls were  $0.42$  octaves ( $P = 0.013$ ;  $0.33 \pm 0.13$  ln units; 95% confidence interval [CI]:  $0.07$ – $0.59$ ; Figure 4a; binocular:  $0.58$  octaves;  $P = 0.014$ ;  $6.66$  cpd or  $0.32 \pm 0.13$  ln units; 95% CI:  $0.07$ – $0.58$ ; Fig. 5a) and approximately  $6 \mu\text{V}$  (monocular:  $6.90 \pm 3.00 \mu\text{V}$ ;  $P = 0.009$ ;  $0.39 \pm 0.15$  ln units; 95% CI:  $0.10$ – $0.69$ ; Fig. 4b; binocular:  $6.65 \mu\text{V}$ ;  $P = 0.027$ ;  $0.45 \pm 0.20$  ln units; 95% CI:  $0.05$ – $0.85$ ; Fig. 5b) compared with non-amblyopic controls. However, there were no significant differences between the two groups in terms of C3 latencies (monocular: Fig. 4c; binocular: Fig. 5c).

octaves;  $P = 0.013$ ;  $0.33 \pm 0.13$  ln units; 95% confidence interval [CI]:  $0.07$ – $0.59$ ; Figure 4a; binocular:  $0.58$  octaves;  $P = 0.014$ ;  $6.66$  cpd or  $0.32 \pm 0.13$  ln units; 95% CI:  $0.07$ – $0.58$ ; Fig. 5a) and approximately  $6 \mu\text{V}$  (monocular:  $6.90 \pm 3.00 \mu\text{V}$ ;  $P = 0.009$ ;  $0.39 \pm 0.15$  ln units; 95% CI:  $0.10$ – $0.69$ ; Fig. 4b; binocular:  $6.65 \mu\text{V}$ ;  $P = 0.027$ ;  $0.45 \pm 0.20$  ln units; 95% CI:  $0.05$ – $0.85$ ; Fig. 5b) compared with non-amblyopic controls. However, there were no significant differences between the two groups in terms of C3 latencies (monocular: Fig. 4c; binocular: Fig. 5c).

## DISCUSSIONS

Newly diagnosed amblyopic children were examined for meridional anisotropies that may be related to their refractive error. As the amblyopic children in this cohort have not started wearing spectacles, the results from this present study represents the baseline electrophysiological findings prior to optical treatment. If electrophysiological signals were reduced in the blurred astigmatic meridian, it would indicate a selective dysfunction of orientation-specific cells,

as demonstrated previously in animals, assuming normal retinal function.

Although meridional anisotropies can be induced by astigmatism,<sup>30</sup> the main analysis in this present study suggests that neurophysiological deficits in newly diagnosed refractive amblyopes may be confined to the diminished POVEP C3 amplitude and poorer GA throughout all assessed meridians, hence the neural deficits were not orientation-specific. However, this study agrees with the postulation that high magnitude of astigmatism can have deleterious effects on early vision development.

In the post hoc analysis, it was of interest to investigate if there would be any relationship between the magnitude of meridional anisotropies and the magnitude of astigmatism. However, all three groups of astigmatic amblyopes failed to yield any significant anisotropies. Instead, it was found that refractive amblyopes with high astigmatism had significantly lower POVEP C3 amplitude compared with refractive amblyopes with low to moderate magnitudes of astigmatism.

Other studies have reported that non-amblyopic astigmatic children can also suffer from poorer optical quality<sup>58</sup>

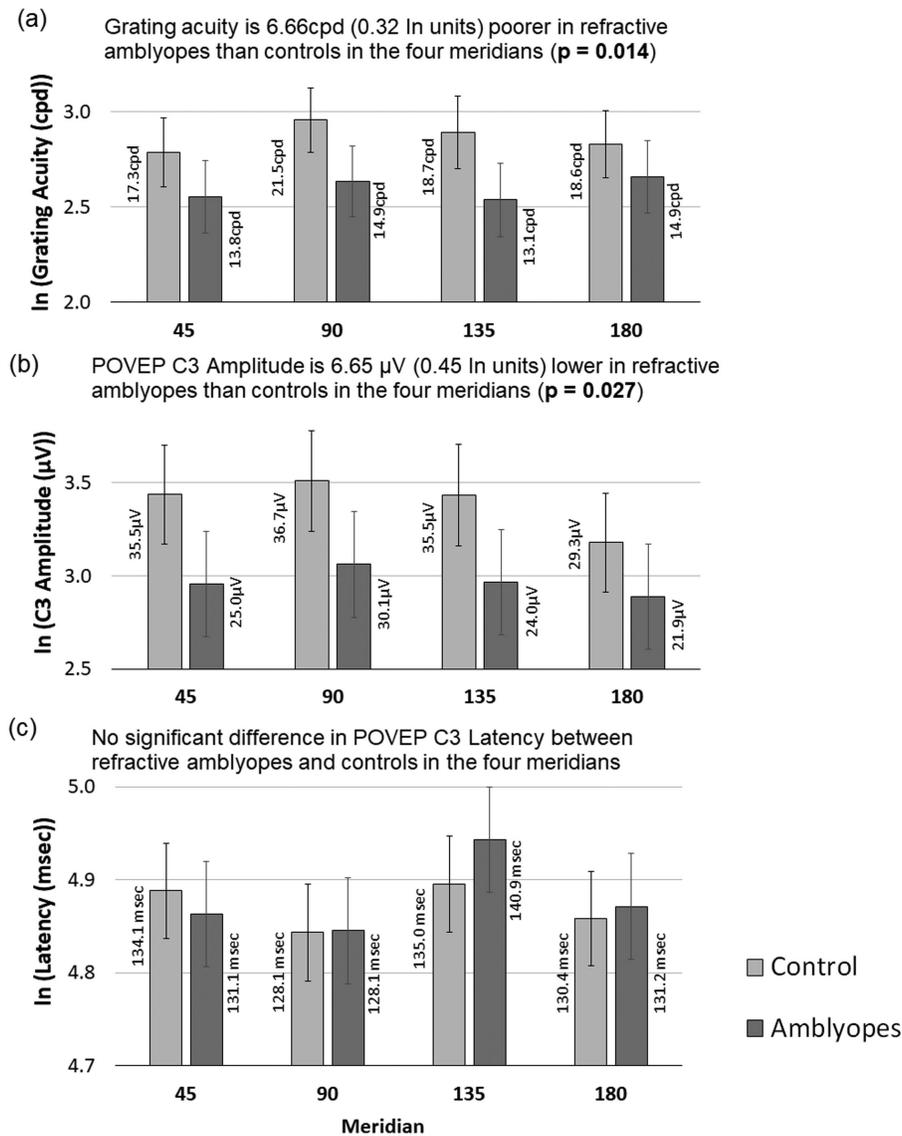


FIGURE 5. Binocular assessment of (a) psychophysical grating acuity (GA), (b) C3 amplitudes, and (c) C3 latencies for orientation-specific pattern onset-offset visual evoked potentials (POVEP) in refractive amblyopes ( $n = 24$ ) in meridians 45, 90, 135, and 180. For comparison, the data of non-amblyopic controls ( $n = 29$ ) were adapted from Yap et al. (2019).<sup>41</sup> Error bars indicate the 95% confidence intervals.

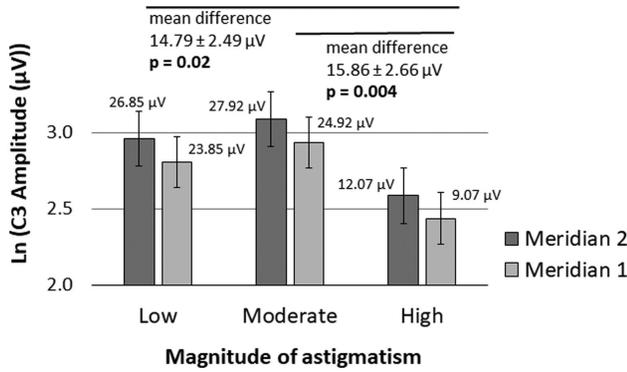
and poorer POVEP C3 amplitudes.<sup>41</sup> Thus, it may be that astigmatism's deleterious effects can be experienced not only in amblyopes but also non-amblyopic astigmatic children. Examples of the POVEP waveforms were presented for refractive amblyopes with high (Fig. 8a) and moderate bilateral astigmatism (Fig. 8b) and a non-amblyopic child (Fig. 8c).

Even though the majority of amblyopes with  $>10.0$   $\mu$ V of meridional anisotropies (12/18 eyes) had high astigmatism ( $\geq 3.00$  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  $>10.0$   $\mu$ V 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<sup>30</sup> 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<sup>28</sup> and Fiorentini and Maffei<sup>30</sup> differed from the present study, which may also account for differences in findings. For example, Fiorentini and Maffei used 3.0 cpd,  $5 \times 4^\circ$  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  $7^\circ$  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,<sup>59</sup> 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 ( $\leq 1.50$  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 ( $\geq 3.00$  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.

from slightly different sets of neurons than Fiorentini and Maffei<sup>30</sup> and Freeman and Thibos<sup>28</sup> when using a pattern onset-offset stimulus.<sup>28,30</sup>

**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

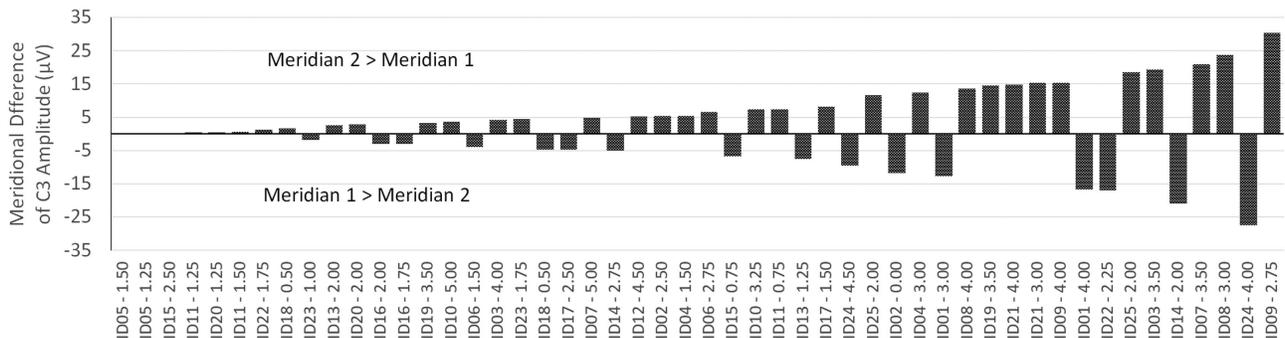
anisotropies reported by Fiorentini and Maffei<sup>30</sup> and Freeman and Thibos<sup>28</sup> were for one eye or both eyes.

Although the sample size for the post hoc analysis is too small to be conclusive, it suggests an avenue for further research to investigate anisometric 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,<sup>60,61</sup> or (2) there was orientation-specific suppression<sup>36,37</sup> that may be similar to orientation-tuning properties in the V1,<sup>37</sup> which could possibly be modulated by higher-order attention.<sup>62-65</sup>

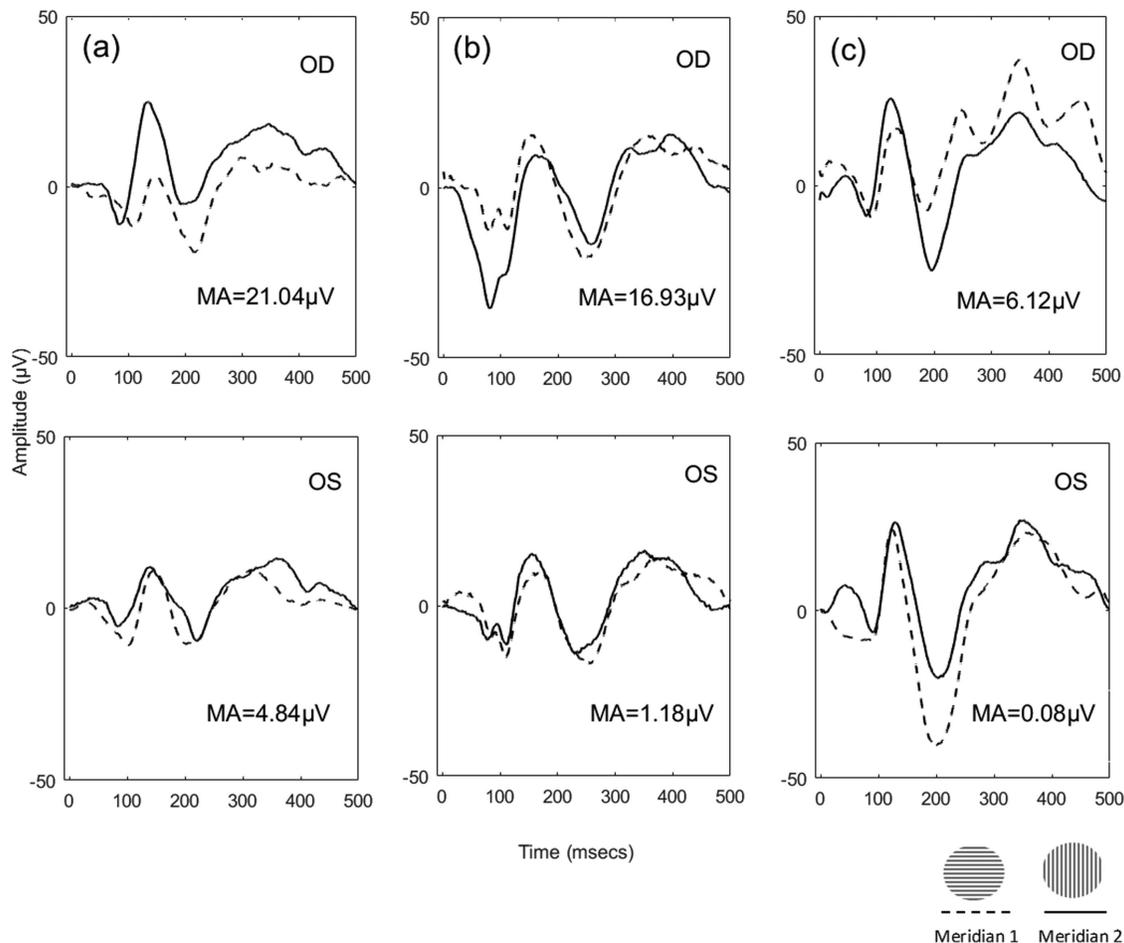
**Could the Horizontal Effect be an Indicator of Normality in Children?**

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<sup>41</sup> and adults,<sup>66</sup> 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).<sup>41</sup> However, the types and magnitudes of meridional anisotropies are expected to vary under other choices of spatial frequency,<sup>67,68</sup> contrast,<sup>45</sup> types of stimuli (e.g. texture,<sup>69</sup> Gabor,<sup>70</sup> grating,<sup>44,71-74</sup> or broadband natural images),<sup>46,75</sup> mode of stimuli presentations



**FIGURE 7.** Meridional anisotropies in children with refractive amblyopia. Meridional anisotropy (as defined by the absolute difference between meridians 1 and 2) of the monocular orientation-specific pattern onset-offset visual evoked potential (POVEP) C3 amplitude (μV) for each eye was arranged in ascending order against the magnitude of astigmatism in dioptic cylinder (DC) for each participant's identifier number (ID). There was wide variability in terms of the type and magnitude of the meridional anisotropy, with positive values indicating that vertical meridians had higher C3 amplitude than horizontal meridians and vice versa for negative values.



**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 × 5 VA 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).<sup>41</sup> 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.

(e.g. simultaneously or successively),<sup>76</sup> color (e.g. chromatic versus non-chromatic luminance),<sup>77</sup> and the electrophysiological component of interest (i.e. response timing; e.g. earlier versus later electrophysiological components, which may derive from different visual areas).<sup>78</sup>

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,<sup>79</sup> 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.<sup>67</sup>

## 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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