Vision Research 222 (2024) 108439

Contents lists available at ScienceDirect

Vision Research

journal homepage: www.elsevier.com/locate/visres

# The development of meridional anisotropies in neurotypical children with and without astigmatism: Electrophysiological and psychophysical findings

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ARTICLE INFO

*Keywords:*
Refractive error
Astigmatism
Children visual development
Meridional anisotropies
Amblyopia
Visual evoked potentials
Myopia
Olique effect
Horizontal effect

ABSTRACT

It is important to understand the development of meridional anisotropies in neurotypical children since those with poor visual development, such as amblyopia, can have different patterns of meridional anisotropies. While the oblique effect is usually observed in adults, neurotypical children who have normal 20/20 visual acuity tend to demonstrate a horizontal effect electrophysiologically. In this longitudinal study, orientation-specific visual evoked potentials (osVEPs) and psychophysical grating acuity were used to investigate the changes in the meridional anisotropies in children aged 3.8 to 9.2 years over two visits averaging four months apart. While it was hypothesized that the electrophysiological horizontal effect may shift towards an oblique effect, it was found that the electrophysiological horizontal effect persisted to be present in response to the suprathreshold moderate contrast 4 cycles-per-degree grating stimuli. Psychophysical grating acuity, however, demonstrated an oblique effect when assessed binocularly. In addition, a significant effect of visit, representing an increase in the average age over this period, was observed in the average osVEP C3 amplitudes (4.5 μV) and psychophysical grating acuity (0.28 octaves or approximately 1-line on the logMAR chart). These findings are relevant when evaluating amblyopia treatments and interventions, as it confirms the necessity to take into account of the effect of normal maturation and learning effects when evaluating young children. Special attention should also be given to children with early-onset myopia and high astigmatism even when their visual acuity is 20/20 as the electrophysiological findings are suggestive of poor visual development, which warrants further investigation.

## 1. Introduction

### 1.1. Meridional anisotropies in children's vision

Meridional anisotropies may be defined as orientation-specific biases in human visual processing, (Mitchell, Freeman, Millodot, & Haegerstrom, 1973) where there is greater sensitivity in one orientation than another. The underlying neurophysiological mechanism is thought to derive from a larger number of cortical neurons in the primary visual cortex that are tuned to a certain orientation as compared to other orientations. The phenomenon of meridional anisotropy may confer an ecological advantage in terms of visual information processing and provide more efficient neural coding as the visual system may adapt towards the more dominant features of the environment and/or emphasize any irregularities in the visual scene. (Essock, DeFord, Hansen, & Sinai, 2003; Gwiazda, Brill, Mohindra, & Held, 1978).

There are two main types of meridional anisotropies that are of particular interest in the human visual system: (1) the oblique effect, and (2) the horizontal effect. The oblique effect is the most commonly reported type of meridional anisotropy, where the processing of visual information, such as gratings in the cardinal orientations (vertical and horizontal) are superior to those that are oriented obliquely. In contrast, horizontal effect is characterized by poorer processing of horizontal lines in comparison to vertical or oblique lines.

The oblique effect, typically observed in adults, is believed to have developed in response to exposure to environmental features that have a

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https://doi.org/10.1016/j.visres.2024.108439
Received 11 July 2023; Received in revised form 9 May 2024; Accepted 22 May 2024
Available online 18 June 2024

higher proportion of contours in those orientations, particularly for high spatial frequency stimuli. (Mitchell et al., 1973) For example, cityscapes tend to have greater prevalence of contours lying near the cardinal orientations rather than oblique orientations. (Coppola, Purves, McCoy, & Purves, 1998) This would manifest as stronger and more rapid electrophysiological responses and superior psychophysical threshold responses to cardinally oriented gratings compared to obliquely oriented gratings. For example, VEPs in adults in response to obliquely oriented gratings tend to elicit diminished amplitudes and longer peak latencies compared to the cardinal orientations; (Arakawa et al., 2000; Moskowitz & Sokol, 1985) exact reductions vary by protocol but has been estimated in one study of adults to result in amplitudes 1 to 2 μV smaller and peak latencies 2 to 3 ms longer (Moskowitz and Sokol, 1985). Similarly, these orientation-specific characteristics of the visual cortex have been demonstrated in functional magnetic resonance imaging (*fMRI*) of the human adult V1 (Freeman, Brouwer, Heeger, & Merriam, 2011).

Not all kinds of stimuli manifest the oblique effect in the human visual system. For example, studies that have employed dots or glass patterns demonstrate an "inverse oblique" effect, where the perception of oblique stimuli composed of dots is superior when oriented obliquely rather than horizontally and vertically. Such findings have been reported both electrophysiologically (Mikhailova, Gerasimenko, & Slavutskaya, 2018) and psychophysically (Gwiazda, Scheiman, & Held, 1984; Wilson, Loffler, Wilkinson, & Thistlethwaite, 2001). There are also situations where the types of meridional anisotropies are not easily classified and these variabilities may be related to the specific electrophysiological and psychophysical testing methodologies, such as the stimuli contrasts, spatial frequencies, color and types (e.g. texture, *Gabor* gratings or natural images), the neural site of the active electrodes, retinal eccentricities; and presentation modes (e.g. simultaneously or successively) (Yap & Boon, 2020; Yap, Luu, Suttle, Chia, & Boon, 2020). Hence, it is likely that the types and magnitudes of meridional anisotropies vary between different studies. Furthermore, age and uncorrected refractive errors are important factors in the normal development of meridional anisotropies (Yap & Boon, 2020).

While the oblique effect is frequently observed in the normal human adult visual system, the situation is unclear in children. Some psychophysical studies reported an oblique effect in children (Gwiazda et al., 1984; Held, Thorn, McLellan, Grice, & Gwiazda, 2003) whilst others did not. (Carkeet, Leo, Khoo, & Au Eong, 2003; Mayer, 1977; Teller, Morse, Borton, & Regal, 1974) Although some studies demonstrated that infants show the oblique effect electrophysiologically (Sokol, Moskowitz, & Hansen, 1987) and psychophysically, (Gwiazda et al., 1984; Held et al., 2003) a psychophysical study found 73 % of children aged 3 to 8 years demonstrated an oblique effect whilst 14 % did not show any anisotropy and 13 % demonstrated the opposite effect. (Gwiazda et al., 1984) In contrast, the oblique effect is often not observed electrophysiologically in children: A clinically and statistically significant electrophysiological horizontal effect has previously been reported in neurotypical children aged 3 to 9 years who have normal 20/20 visual acuity (VA) and was unaffected by their refractive error status. (Yap, Luu, Suttle, Chia, & Boon, 2019) The horizontal effect manifested as smaller amplitude electrophysiological responses (approximately 5 μV monocularly and 6 to 8 μV binocularly) to horizontal grating stimuli of 4 cycles per degree (cpd) as compared to vertical or oblique orientations. (Yap et al., 2019) One possible mechanism by which the horizontal effect occurs is as a form of residual meridional anisotropy from infantile astigmatism that lingers following the normal emmetropisation process where the magnitude of astigmatism is generally expected to diminish beyond 3 years of age. (Gwiazda, Bauer, Thorn, & Held, 1986) While uncorrected astigmatism during the critical period of visual development can modulate meridional anisotropies, such as in the case of meridional amblyopia (Gu et al., 2021; Yap et al., 2020), the development of the meridional anisotropies would depend on the magnitude and types of the refractive errors, customary viewing distances, state of accommodation and vergence, as there may be a tendency for one astigmatic focal line to be more frequently out-of-focus than the others (Yap & Boon, 2020).

Besides children aged 3 to 9 years, there is also evidence for the normal development of the horizontal effect in other age groups. For example, young adults aged 19 to 25 years were observed to have higher VEP amplitudes in response to obliquely oriented than cardinally oriented gratings, again at 4 cpd (Arakawa et al., 2000). A different study of newborn infants found poorer sensitivity towards horizontal than vertical gratings during psychophysical testing at low spatial frequencies (0.06 to 0.10 cpd) (Brown, Lindsey, Cammenga, Giannone, & Stenger, 2015). The spatial frequency at which meridional anisotropy is typically observed is different in infants compared to older children and adults, but each appears to be close to the peak of the contrast sensitivity functions for each age group, which suggests that meridional anisotropy is manifest more strongly for those stimuli which are most visible (Yap & Boon, 2020). The horizontal effect has also been demonstrated in adults viewing natural scenes which contain a broader range of spatial frequencies and orientation content (Essock et al., 2003). Essock et al. (2003) suggested that the horizontal effect observed for broadband scenes may be explained by standard models of contrast gain control, where the output of V1 cortical populations of cells is moderated by dividing their response by the sum of the activity of other populations of cells processing other orientations and spatial frequencies. As there are fewer neurons that processes oblique orientations than the cardinal orientation, the ability of the neurons that processes oblique orientations to decrease gain is less than for neurons that processes horizontal stimuli.

### 1.2. The present study

It is important to understand meridional anisotropies in neurotypical children who have normal 20/20 VA, particularly as this finding may have clinical significance as a point of difference between amblyopic and non-amblyopic children, and also considering that high refractive errors may be amblyogenic. An understanding of the normal development of meridional anisotropies would help to support future electrophysiological studies in investigating amblyopia treatment outcomes, particularly refractive amblyopia.

Currently, it is not known if electrophysiological responses from VEPs in response to orientation-specific gratings in children would shift from a horizontal effect towards an oblique effect. As a period of four months is the typical time frame for amblyopic children to be reassessed during amblyopia treatment, this present study aims to monitor the changes in the pattern of the electrophysiological and psychophysical meridional anisotropies in neurotypical children aged approximately 4 to 9 years over a period of four months.

Whilst four months is a relatively short period of time, change within the visual processing of the visual system in neurotypical children over this time frame is possible since contrast sensitivity development is not yet adult-like at ages 10 to 19 years (Mäntyjärvi and Laitinen, 2001), and can still be variable in children below the age of 8–12 years. (Leat, Yadav, & Irving, 2009) Given that the horizontal effect is frequently observed at suprathreshold moderate contrast levels, it is important to understand if changes in meridional anisotropies would occur within four months because this is the same timeframe to evaluate children undergoing amblyopia treatment. Thus, we postulate that the horizontal effect may shift towards an oblique effect over a period of four months in neurotypical children with normal vision, defined as normal Snellen letter acuity of 20/20. The null hypothesis was that there would be no change in the pattern of meridional anisotropies as indicated by the amplitude of the C3 component of a transient orientation specific VEP (osVEP), latency and psychophysical grating acuity (GA) over four months. Therefore, it is expected that a horizontal effect, as indicated by a lower magnitude of C3 amplitude along the horizontal meridian compared to the other meridians, would still be present after four months.

## 2. Methods

### 2.1. Recruitment and ethical approvals

A longitudinal study of children was conducted over two visits (Visits 1 and 2). Participant inclusion criteria were having with normal vision (logMAR 0.00 high contrast letter acuity (or 20/20 Snellen equivalent) or better). Exclusion criteria were having an history of amblyopia and/or strabismus, systemic disease, ocular disease, and/or behavioural issues (e.g. developmental delay) and neurological conditions (e.g. epilepsy). Recruitment of participants was from a refraction clinic at KK Children's and Women's Hospital in Singapore and by advertisement.

Orientation-specific VEPs and psychophysical GAs were assessed at the visual electrophysiology laboratory at the Singapore National Eye Centre (SNEC) during both visits. 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, NSW, Australia (Approval number: 09364). Parents and guardians gave their informed consent and children six years of age and above provided assent.

This study examines the changes in osVEPs and psychophysical GA between two visits (Visit 1 data was reported previously (Yap et al., 2019). At Visit 1, a comprehensive eye examination comprising of VA (*HOTV logMAR distance chart, Good-lite Co, USA*), cover test, ocular motility, stereopsis (*Near 3-plates Frisby Stereotest, Stereotest Ltd, Fulwood, Sheffield, UK*), retinoscopy, autorefraction and manifest subjective refraction assessments (where possible) were obtained from the hospital records at the point of participant enrolment. To ensure that the participant met the inclusion criteria, cover test, Frisby stereotest and logMAR VA were re-assessed to ensure consistency. If the VA was subsequently found to be poorer than 0.05 logMAR, refraction was repeated to ensure that the children continued to meet the inclusion criteria of normal vision. Non-astigmats were defined as having $< 0.50$ DC and astigmats were defined as having $\geq 0.50$ DC, considering that low degrees of astigmatism can limit neural sensitivities (Charman and Voisin, 1993; Wolffsohn, Bhogal, & Shah, 2011).

### 2.2. The orientation-specific visual evoked potentials

Orientation-specific VEPs are originally developed to probe electrophysiological meridional anisotropies in children with refractive amblyopia, (Yap, Luu, Suttle, Chia, & Boon, 2021) and the current protocol has been reported in previous studies (Yap & Boon, 2020; Yap et al., 2019, 2020). In brief, these are single channel transient electrophysiological recordings under monocular and binocular stimulation using a 12° field-size achromatic sinewave grating of 4 cpd (Yap & Boon, 2020; Yap et al., 2019, 2020, 2021).

For monocular recordings, grating orientations were matched to the principal astigmatic axes of each eye, as follows: gratings in Meridian 1 were aligned with the most positive power meridian, and those in Meridian 2 were perpendicular to this. For example, for a refractive error of $+0.50 / -1.25 \times 180$, Meridian 1 consisted of horizontal gratings and Meridian 2 stimulus consisted of vertical gratings. In non-astigmats, the horizontal gratings were assigned as Meridian 1 and the vertical gratings were Meridian 2.

Binocular responses were recorded in response to grating stimuli orientated in four meridians (45°, 90°, 135° and 180°) regardless of the principal meridian of each eye. For each stimulus condition, two averages of 30 temporal cycles were successively recorded with onset duration 100ms, offset 400ms, therefore temporal frequency 2 Hz. The order of each stimulus condition was randomized at Michelson contrast 54 % and presented against a background of the same space-averaged luminance at a viewing distance of one meter.

Of the 29 subjects, 19 did not require refractive correction as their unaided VA was 0.00 logMAR. The remaining 10 participants wore full distance refractive correction during the recording, using their habitual prescription spectacles (6/29), a trial frame with the current subjective refraction findings (1/29), or newly prescribed spectacles for the children who did not have a history of wearing spectacles (3/29; one person with simple myopia −1.75 DS in each eye, and two persons with moderate astigmatism as follow: OD $-0.25–0.75 \times 180$ VA 0.02 logMAR, OS plano $-1.75 \times 180$ VA 0.02 logMAR, and OD $+ 0.50–1.25 \times 180$ VA 0.00 logMAR, OS $+ 1.00–1.50 \times 180$ VA 0.00 logMAR). The new spectacles were made according to the subjective refraction findings, and trial frames were used on one subject because the habitual spectacle prescription were subsequently found to be outdated. Subjects who received new spectacles were given 10 to 20 min to adapt to their refractive correction before electrophysiological testing.

Subjects fixated on a central target on the monitor (black dot with a 2 mm diameter) at 1-meter and recording was only conducted when they fixated correctly. The subject's fixation was monitored through visual observation, and the viewing distance was maintained by checking that the subjects were leaning back against an appropriately positioned seat backrest during testing.

### 2.3. Equipment

The osVEPs were recorded using the Espion System (Diagnosys LLC, Massachusetts, USA) at a sampling rate of 5 kHz and a band-pass filter of 0.312 – 100 Hz and a recording window of 1 s per sweep. Active, reference and ground electrodes were 9 mm gold-cup surface electrodes applied at $O_z$ (occipital midline), $C_z$ (central midline) and $F_z$ (frontal midline) respectively using electroencephalogram (EEG) conductance paste and micropore tape. The electrode montage was a variation on the International 10 – 20 configuration (Odom et al., 2004), to match previous studies (Yap et al., 2019, 2020, 2021) and the impedance was regularly sampled to ensure that it is below 8 kΩ. The stimuli were generated using the ViSaGe Mk II (Cambridge Research Systems, UK) and presented on a calibrated 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 ViSaGe stimulus generator is a 14-bit system which was able to generate the stimulus specified at the viewing distances used. For psychophysical GA testing (see below), the system made it possible to present 35.2 cpd gratings without aliasing at a viewing distance of 2.2 m.

### 2.4. Psychophysical grating acuity

The psychophysical GA was assessed using a *two-alternative location non-forced-choice (2-ANFC)* preferential-*looking (PL)* computerized test (School of Optometry and Vision Science (SOVS) – Centre for Eye Health (CFEH) Psychophysical Testing Suite, Sydney, Australia) which was programmed using Matlab (Version R2017a, MathWorks Inc, Massachusetts, USA). The decision to use a non-forced-choice task was made in the interest of time because multiple measurements from the different orientations had to be taken within the children's limited attention span. This sacrifices the convergence precision to 63 % (Yap et al., 2019, 2020, 2021).

The psychophysical GA was assessed at a viewing distance of 2.2 m with the room lights turned off. This viewing distance differs from osVEP because the monitors had to be able to present spatial frequencies up to ceiling value in the GA staircase without aliasing (35.2 cpd). In contrast, osVEP is not a threshold task and the viewing distance can be maintained at the regular 1-meter viewing distance in the laboratory.

Stimuli were designed to be the same as the VEP stimuli, with the only differences being that their total field size was 3°, that they were located either 2° left or 2° right of fixation and that the spatial frequencies varied according to the subject's responses. Subjects were assessed monocularly and binocularly and they were asked to identify the location (verbally or by pointing) to the stimulus. They were encouraged to guess if they were unsure; however, if the child was still unable to decide, an incorrect answer was entered. Threshold GA was calculated as the average of the last four reversals of an adaptative psychophysical *1 down 1 up staircase,* (Klein, 2001). The starting spatial frequency was 2 cpd with a 3-dB step size, which was then halved to 1.5 dB, then halved again to 0.75 dB and then halved to 0.375 dB (maximum presented at 35 cpd).

### 2.5. Statistical analysis

The main outcome measures in this present study were the electrophysiological (osVEP C3 amplitudes and latencies) and the psychophysical GA. While each of the osVEP components (C1, C2 and C3) (Odom et al., 2016) were analyzed under masked conditions, only the C3 component was chosen for the analysis as the measurement has been found to be highly repeatable and to produce the highest amplitude responses of the three components. (Yap et al., 2021) The C3 amplitude was computed from the peak of the preceding wave and the latency of each component was calculated as the time taken from stimulus onset. The statistical software package SPSS (Version 23, IBM Corp, New York, USA) was used for the following analyses: Linear mixed model analysis (LMM) was conducted to investigate the effect of stimulus meridian (Meridians 1 and 2), astigmatism subgroups (astigmats, non-astigmats) and visit (Visits 1 and 2) on osVEP C3 amplitude, C3 latency and psychophysical GA, as this method of analysis allowed the monocular data of each eye to be analyzed. However, the LMM was not required to analyze the binocular data. Repeated measures ANCOVA was conducted to investigate the within-subject differences in four meridians (45°, 90°, 135° and 180°) on the dependent variables of osVEP C3 amplitude, C3 latency and psychophysical GA, with age as a covariate; pairwise comparison was conducted across the four meridians with Bonferroni correction. Natural logarithmic transformation was applied to GA to satisfy normality assumptions of LMM and explained in terms of octaves and equivalent logMAR acuities for the ease of comparison. The criterion for statistical significance was a p-value of 5 %.

## 3. Results

### 3.1. Subjects

Twenty-seven children, of median age 5.8 years (range: 3.9 to 9.2) years, with normal letter VA (OD 0.00 ± 0.01 and OS 0.00 ± 0.01 logMAR) completed Visit 2. Of the 29 subjects from Visit 1, (Yap et al., 2019) two did not attend Visit 2 due to inconvenient timing (one subject had oblique astigmatism and the other was emmetropic). Nineteen subjects were non-astigmats (18/19 did not require refractive correction at the stimulus viewing distances, one of whom had bilateral myopia −1.75 D.S., aged 7.0 years) and eight had astigmatism. Their refractive profiles are summarized in Table 1. The mean time frame between visits 1 and 2 was 4.46 ± 1.03 months (range 3.3 to 7.5 months), which took slightly longer than the proposed four-month timeframe because five subjects came back only after five to eight months.

Of the eight astigmats in this present study, two had simple myopic astigmatism (aged 5.3 years: OD −0.25–0.75 × 180, OS plano −1.75 × 180; aged 7.0 years: OD plano −2.25 × 5, OS plano −1.75 × 160), five had compound myopic astigmatism (aged 4.6 years: OD −0.25–2.25 × 15, OS −0.75–1.00 × 160; aged 6.6 years: OD −3.50 D.S., OS −3.75–0.50 x 160; aged 6.9 years: OD −1.25–1.25 × 180, OS −0.75–2.25 x 175; aged 7.6 years OD −1.00–0.50 × 15, OS −2.25 D.S.; aged 9.2 years: OD −2.25–3.00 × 5, OS −1.75–3.50 × 175), and one had compound hyperopic astigmatism (aged 7.4 years: OD + 0.50–1.25 x 180, OS + 1.00–1.50 x 180).

Whilst the focus of this present study is on neurotypical children, it is important to note that early-onset myopia and high astigmatism may be considered atypical refractive development. Those with moderate to high degree of early-onset myopia may not entirely satisfy the definition of “typically developing” due to the absence of the horizontal effect as was observed in one subject who was aged 6.6 years (OD −3.50 D.S., OS −3.75–0.50 x 160). In addition, high astigmatism during childhood may produce unusually high magnitudes of the horizontal effect, as observed in another subject who was aged 9.2 years OD −2.25–3.00 x 5, OS −1.75–3.50 x 175), even though the VA was corrected to 20/20. In this particular subject, the binocular horizontal effect was found to be two times greater than usual (17.7 μV instead of 6 to 8 μV which was the average finding for the other participants). Besides these two subjects, the electrophysiological findings of the rest of the myopic subjects did not behave differently compared to the rest of the children. Given that the inclusion and exclusion of these two subjects in the statistical analysis did not affect the outcome, they were included in this present study.

**Table 1**
Summary of the refractive profile of astigmats and non-astigmats in this study.

| | Astigmats | Non-astigmats |
|---|---|---|
| N | 8<br>(8/8 with-the-rule)<br>(5/8 Compound Myopic Astigmatism; 2/8 Simple Myopic Astigmatism;<br>1/9 Compound Hyperopic Astigmatism) | 19 |
| Mean Refractive Error (D.S. / D.C.) | OD + 0.83 D.S. / −1.57 D.C.<br>OS −0.92 D.S. / −1.75 D.C. | OD −0.19 DS / 0.00 DC<br>OS −0.19 DS / 0.00 DC |
| Power Range (D.S. / D.C.) | OD + 2.50 to −3.50 D.S. / −0.50 to −3.00 D.C.<br>OS + 3.00 to −3.75 D.S. / −0.50 to −3.50 D.C. | OD + 0.25 to −1.75 D.S.<br>OS + 0.75 to −1.75 D.S. |
| Refractive History | 7/8 Current spectacle wearers<br>1/8 Just started wearing spectacles | 18/19 No refractive error1/19 Myopic (−1.75 DS) and just started wearing spectacles |

### 3.2. Longitudinal analysis

The data from this present study (Visit 2) are presented in Figs. 1 and 2 alongside previous study’s data (Visit 1) for the ease of comparison.

Over an averaged period of four months, there was significant improvement in monocular osVEP C3 amplitude ($p = 0.034$; $F_{1,\,176.81} = 5.05$) and monocular psychophysical GA ($p < 0.001$; $F_{1,\,141.58} = 15.23$) when the results from all the meridians tested in the astigmats and non-astigmats are pooled together and corrected to a reference age of 6.1–6.3 years respectively. There was no change in C3 latency. The improvement in monocular GA was 0.28 octaves (approximately 1-line on the logMAR chart), it being 3.77 ± 1.09 cpd (0.25 ± 0.06 ln units) higher in Visit 2 (21.31 ± 0.77 cpd), compared to Visit 1 (17.55 ± 0.78 cpd) (Fig. 1a). Monocular osVEP C3 amplitude was 4.50 ± 2.11 μV higher in Visit 2 (30.08 ± 1.7 μV) compared to Visit 1 (25.58 ± 1.14 μV) (Fig. 1b). However, binocular measures were not statistically significantly different after 4 months for binocular GA, osVEP C3 amplitude or latency (Fig. 2).

### 3.3. Meridional anisotropies

These are the observations in terms of meridional anisotropies in the Visit 2 data, unless otherwise stated:

***(1) Horizontal effect observed from osVEP C3 amplitude***

Meridional anisotropy was evident in osVEP C3 amplitude measures ($p = 0.03$; $F_{1,176.81} = 5.05$) in which Meridian 2 (30.20 ± 1.53 μV) responses were 4.73 ± 2.11 μV higher than Meridian 1 (25.47 ± 1.45 μV) (Fig. 1b). The measurements were pooled from both astigmats and non-astigmats in order to determine if there is a trend for the meridional

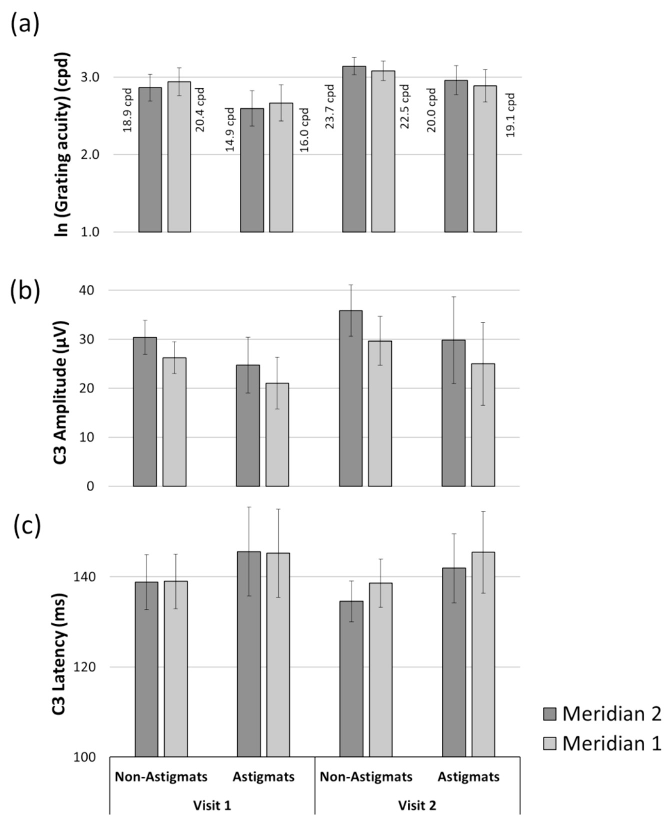


**Fig. 1.** Monocular evaluation of (a) psychophysical grating acuity, (b) orientation-specific visual evoked potentials (osVEP) C3 amplitudes and (c) C3 latency in neurotypical children with and without astigmatism. All children in this study have normal visual acuity (logMAR 0.00 or Snellen 20/20). For ease of comparison, the natural logarithmic values of psychophysical grating acuity are labelled on the graph in terms of cycles per degree (cpd), and the data from this present study (Visit 2) are presented alongside the data from the previous study (Visit 1). Error bars indicate the 95% confidence intervals for each parameter.

anisotropy in this cohort to resemble a horizontal effect. Given that Meridian 1 was defined as horizontal in all the non-astigmats (180°) and was approximately horizontal in all the astigmats (15° – 160°), it is reasonable to generalize this observation as a monocular horizontal effect. Similarly, the binocular osVEP C3 amplitude in the horizontal meridian was 5.88 ± 1.43 µV to 7.01 ± 1.57 µV lower than the oblique (135°: p = 0.009) and vertical (90°: p = 0.001) meridians respectively (Fig. 2b), indicating a binocular horizontal effect. As the horizontal meridian had the poorest C3 amplitude, these statistically significant findings confirm the horizontal effect, but where no significant effects were found at the 45° meridian, this may be due to insufficient statistical power since there are fewer subjects in Visit 2 compared to Visit 1.

***(2) Possible oblique effect observed from psychophysical grating acuity***

While there were no statistically significant differences indicating a horizontal or oblique effect from the monocular data, one oblique meridian (135° oriented gratings) from the binocular results had significantly lower thresholds (0.39 octaves, which is equivalent to approximately 1½ lines on the logMAR chart; p = 0.02) than one cardinal meridian (vertically oriented gratings), suggesting a potential oblique effect (Fig. 2a).

***(3) Vertical meridian had the shortest binocular C3 latency***

Orientation-specific VEP C3 latency did not show any significant meridional anisotropy when assessed monocularly (Fig. 1c), although binocular measurements showed that the horizontal (p = 0.03) and oblique meridians (45°: p = 0.001 and 135°: p < 0.0001) were 3.52 ±

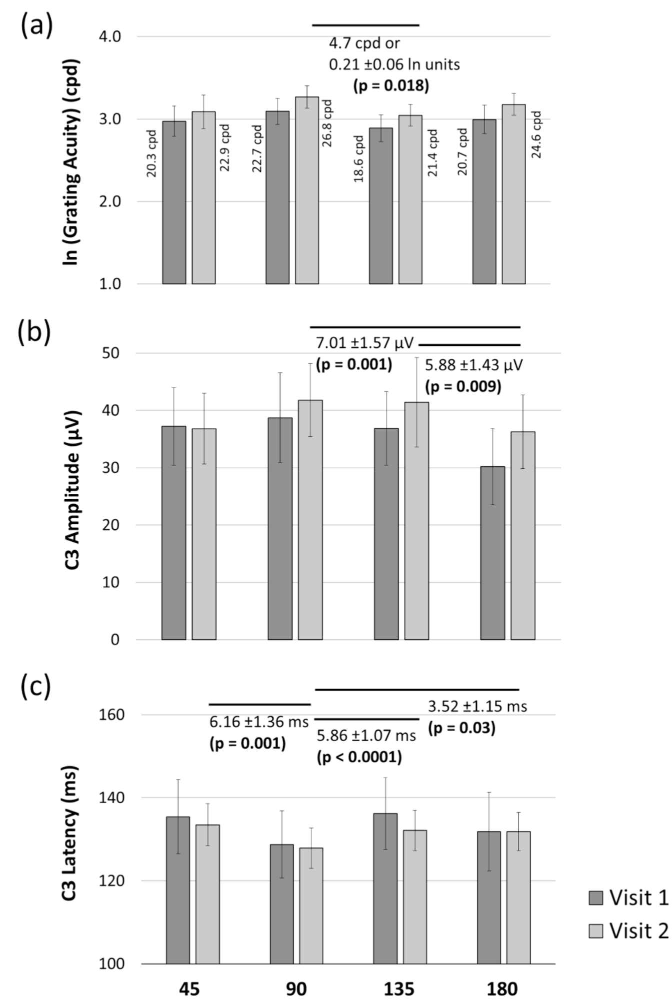


**Fig. 2.** Binocular evaluation of (a) psychophysical grating acuity, (b) orientation-specific visual evoked potentials C3 amplitudes and (c) C3 latency in neurotypical children with normal visual acuity (logMAR 0.00 or Snellen 20/20). For ease of comparison, the natural logarithmic values of psychophysical grating acuity are labelled on the graph in terms of cycles per degree (cpd), and, the data from this present study (Visit 2) are presented alongside the data from the previous study (Visit 1). Error bars indicate the 95% confidence intervals for each parameter.

1.15 ms, 6.16 ± 1.36 ms and 5.86 ± 1.07 ms longer than the vertical meridian respectively (Fig. 2c). This indicates both a horizontal and oblique effect relative to the vertically oriented gratings.

***(4) No significant differences in meridional anisotropies between astigmats and non-astigmats and similar patterns in both Visits 1 and 2***

There were no significant differences in meridional anisotropies between astigmats and non-astigmats in this present study (Visit 2) and the pattern of meridional anisotropies are the same as that observed from the previous study (Visit 1) (Yap et al., 2019) with the addition of a horizontal effect for C3 latency relative to the vertical meridian in the present study. Comparing astigmats with the non-astigmats, however, the overall psychophysical GA was approximately 1-line poorer on the logMAR VA chart (3.89 ± 1.09 cpd; p < 0.001; $F_{1,141.58} = 12.72$), osVEP C3 amplitudes were 5.40 ± 2.11 µV lower (p = 0.01; $F_{1,176.81} = 6.58$) and the C3 latencies were 6.79 ± 2.66 ms longer (p = 0.01; $F_{1,206.14} = 6.52$).

## 4. Discussion

Children with normal 20/20 VA aged 3.8 to 9.2 years continued to manifest a horizontal effect, as a diminished osVEPs C3 amplitude under horizontal grating stimulation, after being followed for approximately four months in this present study. This indicates the limited propensity for the orientation-tuning properties of the visual cortex at V1 to change during this time frame in children with normal vision. The duration of monitoring was even longer in 5/27 subjects by five to eight months due to delayed follow-up visits. In the neural time domain, there is evidence of both the horizontal and oblique effects, where horizontally and obliquely oriented stimuli produced significantly longer C3 latencies than the vertically oriented stimuli. This indicates that the neural processing was faster and more efficient under vertical meridian stimulation than the other meridians.

In this present study and in the earlier studies, the horizontal effect is a consistent finding in neurotypical children regardless of their astigmatism status, (Yap et al., 2019) but not in amblyopic children. (Yap et al., 2020) However, early-onset myopia and astigmatism deserves special attention due to their potential impact on visual development. As observed in one subject with early-onset myopia, the horizontal effect may be absent. Even if the horizontal effect is observed, there is a possibility that the use of spectacles during early childhood may have aided the visual development in some cases. For example, older children with high astigmatism tend to have unusually high magnitudes of the horizontal effect, as observed in both previous and this present study (Gu et al., 2021).

Although the present cohort had normal high contrast letter VA, under moderate contrast levels the astigmatic children over two visits were overall found to have significantly poorer osVEP C3 amplitudes, latencies and psychophysical GAs than the non-astigmatic children. This mismatch between letter VA, electrophysiological measures at V1 and psychophysical GA suggests that higher visual pathway processing may compensate for low level processing deficits. Alternatively, as high contrast letter acuity is typically assessed under static high contrast conditions, and the stimuli in the present study were moderate contrast and temporally modulated at 2 Hz, the visual perception task of electrophysiological and psychophysical GA were more demanding than for a static high contrast stimulus. Therefore, these findings could have reflected immaturities in spatial vision, such as contrast sensitivity which is known to be still maturing within this age group.

In terms of monocular psychophysical GA, the horizontal effect was not observed at either of the two visits. There is, however, evidence of an oblique effect that is produced binocularly as the vertical meridians allowed significantly better grating resolution acuity than the oblique meridians. This agrees with a few previous psychophysical studies that reported the oblique effect in infants (Gwiazda et al., 1978; Leehey, Moskowitz-Cook, Brill, & Held, 1975) and children, (Gwiazda et al., 1984; Birch, Gwiazda, Bauer, Naegele, & Held, 1983) but disagrees with other studies that did not find any oblique effect. (Mayer, 1977; Teller et al., 1974) Of the studies that have not found any orientation differences, it has been hypothesized that this might be due to preferences in forced preferential looking tasks or may indicate insufficient exposure to biases in oriented objects in the visual environment (Birch et al., 1983).

Through a period of four months, monocular psychophysical GAs was found to improve significantly by 0.28 octaves (approximately 1-line on the logMAR chart or 3.8 cpd) although letter acuity was still normal. Given that letter recognition VA and psychophysical GAs have differing developmental time courses, (Stiers, Vanderkelen, & Vandenbussche, 2003) the results from this present study indicate that a select channel for the moderate contrast spatial vision was still developing in this age group. The rapid development phase for high spatial vision tends to be within the first three years of life, as found electrophysiologically (Salomão, Ejzenbaum, Berezovsky, Sacai, & Pereira, 2008) and psychophysically. (Elgohary, Abuelela, & Eldin, 2017). Additionally, attention and cooperation can be quite different in a 3-years-old child compared to a 7-years-old during psychophysical and osVEP measurements and moderate contrast grating acuity was found to vary with age. For this reason, the LMM included age as a factor. Interestingly, binocular psychophysical GA in this present study was not found to improve at Visit 2 (approximately 21.4 to 26.8 cpd) nor reach expected acuities for high contrast gratings in children aged 5 years 9 months (i.e. 36.1 cpd). (Stiers et al., 2003) The use of moderate contrast stimuli could play a role in this, as in the case of monocular GAs in this present study. It is also possible that the maturation of the binocular system requires more time than the monocular pathways to develop as that depends on the combined neural inputs from each eye.

In a similar trend to the monocular results from psychophysical GAs, a clinically and statistically significant electrophysiological improvement was observed as osVEP C3 amplitude increased by 4.5 μV over a period of four months under monocular stimulation. The increased osVEP C3 amplitudes reflects the increased signal strength which may either be related to the developing *GABA* inhibitory neurons or changes in the activity profile of V1, as previous studies suggest that the V1 dominates the osVEP in younger children whereas extra-striate activity tends to dominate later in life. (Thompson, Fritsch, & Hardy, 2017) In contrast, electrophysiological signals that were generated binocularly did not increase significantly. This indicates that a period of four months may be insufficient for binocular summation to develop significantly and may require more time for the combined neural inputs from each eye to increase. As this signal feeds forward to higher areas of visual processing that account for perception, this may also explain the binocular psychophysical GA findings of no change over 4 months. Likewise, osVEP C3 latency did not change significantly over a period of four months, suggesting that it was not only repeatable within-visits but also between each visit. The data from osVEP C3 latency (mean 144.6 ms) reflects the normal neuronal integration, which was comparable to previously published adult studies of approximately 150 to 200 ms. (Kriss et al., 1984).

The key strength of this study is the utilization of the osVEP protocol, which is a sensitive and repeatable technique in assessing the meridional anisotropies in children. (Yap et al., 2021) To ensure repeatable results, we have taken minimally two successive recordings for each meridian, and utilized the two osVEP waveforms that had similar morphologies. The two osVEP recordings were also within the 95 % limits of agreement based on the coefficient of repeatability from Bland-Altman analysis (Yap et al., 2021).

Given that this is a longitudinal assessment of the meridional anisotropies in neurotypical children with normal 20/20 Snellen VA (logMAR 0.00), this present study is an important normative reference for future studies that investigate treatment effects of refractive amblyopia. This is especially so, because the follow-up evaluation in this present study is approximately four months, which is also the typical follow-up duration in most clinical settings.

Limitations of this study are the small sample size and the absence of any near addition (plus) lenses to compensate for the 1-metre test distance. The latter, however, is unnecessary because the children in this cohort are likely to exert normal accommodation. While the current sample size small, it is sufficiently powered to indicate an effect if there is a significant finding of meridional anisotropy. Even if there is a possibility of insufficient statistical power in the situation where no significant effect is found, it would most likely be a very small effect size if a larger sample size is used to clarify these findings. Therefore, the horizontal effect that is reported in this present study is relevant when evaluating amblyopia treatments or interventions in young children, and it confirms the necessity to take into account of the effect of normal visual maturation and learning effects when re-evaluating children who are undergoing amblyopia treatment.

## 5. Conclusion

This present study demonstrated that the electrophysiological horizontal effect to temporally modulated moderate contrast grating stimuli persists in neurotypical children after a period of four months. There were no meridional anisotropies observed for psychophysical GA at both visits 1 and 2, but the oblique effect was emerging for binocular psychophysical GA at visit 2. These children tend to experience relative deficits in visual function for moderate contrast gratings compared to high contrast letters, especially in children with astigmatism, but these visual functions tended to improve over the four months. This finding confirms the current knowledge that the electrophysiological horizontal effect is present in the visual system of children aged 3 to 9 years in response to suprathreshold moderate contrast 4 cpd oriented grating stimuli, but not in the psychophysical threshold perception of such stimuli.

## CRediT authorship contribution statement

**Tiong Peng Yap:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Chi D. Luu:** Writing – review & editing, Supervision, Methodology. **Catherine M. Suttle:** Writing – review & editing, Supervision, Methodology. **Audrey Chia:** Conceptualization, Resources, Methodology. **Mei Ying Boon:** Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

We wish to acknowledge the Visual Electrophysiology Laboratory at the Singapore National Eye Centre (SNEC) and Singapore Eye Research Institute (SERI) for supporting this research project. We also thank our ophthalmology, optometry and nursing colleagues from the Paediatric Ophthalmology and Strabismus Department at KK Women's and Children's Hospital (KKH) for assisting in the recruitment of our subjects in this study. We acknowledge the Guide Dogs NSW/ACT for funding the development of the SOVS-CFEH Psychophysical Test Suite, which was adapted by the authors for psychophysical assessments.

## References

Arakawa, K., Tobimatsu, S., Kurita-Tashima, S., Nakayama, M., Kira, J. I., & Kato, M. (2000). Effects of stimulus orientation on spatial frequency function of the visual evoked potential. *Experimental Brain Research, 131*(1), 121–125.
Birch, E. E., Gwiazda, J., Bauer, J. A., Jr, Naegele, J., & Held, R. (1983). Visual acuity and its meridional variations in children aged 7–60 months. *Vision Research, 23*(10), 1019–1024.
Brown, A. M., Lindsey, D. T., Cammenga, J. G., Giannone, P. J., & Stenger, M. R. (2015). The contrast sensitivity of the newborn human infant. *Investigative Ophthalmology Vision Science, 56*(1), 625–632.
Carkeet, A., Leo, S. W., Khoo, B. K., & Au Eong, K. G. (2003). Modulation transfer functions in children: pupil size dependence and meridional anisotropy. *Investigative Ophthalmology & Visual Science, 44*(7), 3248–3256.
Charman, W. N., & Voisin, L. (1993). Optical aspects of tolerances to uncorrected ocular astigmatism. *Optometry and Vision Science, 70*(2), 111–117.
Coppola, D. M., Purves, H. R., McCoy, A. N., & Purves, D. (1998). The distribution of oriented contours in the real world. *Proceedings of the National Academy of Sciences of the United States of America, 95*(7), 4002–4006.
Elgohary, A. A., Abuelela, M. H., & Eldin, A. A. (2017). Age norms for grating acuity and contrast sensitivity measured by Lea tests in the first three years of life. *International Journal of Ophthalmology, 10*(7), 1150–1153.
Essock, E. A., DeFord, J. K., Hansen, B. C., & Sinai, M. J. (2003). Oblique stimuli are seen best (not worst!) in naturalistic broad-band stimuli: a horizontal effect. *Vision Research, 43*(12), 1329–1335.
Freeman, J., Brouwer, G. J., Heeger, D. J., & Merriam, E. P. (2011). Orientation decoding depends on maps, not columns. *The Journal of Neuroscience, 31*(13), 4792–4804.
Gu, L., Wang, Y., Feng, L., Li, S., Zhang, M., Ye, Q., Zhuang, Y., Lu, Z., Li, J., & Yuan, J. (2021). Meridian-Specific and Post-Optical Deficits of Spatial Vision in Human Astigmatism: Evidences From Psycho-Physical and EEG Scalings. *Frontiers in Psychology, 12*, Article 595536.
Gwiazda, J., Brill, S., Mohindra, I., & Held, R. (1978). Infant visual acuity and its meridional variation. *Vision Research, 18*(11), 1557–1564.
Gwiazda, J., Scheiman, M., & Held, R. (1984). Anisotropic resolution in children's vision. *Vision Research, 24*(6), 527–531.
Gwiazda, J., Bauer, J., Thorn, F., & Held, R. (1986). Meridional amblyopia does result from astigmatism in early childhood. *Clinical Vision Sciences, 1*, 145–152.
Held, R., Thorn, F., McLellan, J., Grice, K., & Gwiazda, J. (2003). *Early astigmatism contributes to the oblique effect and creates its Chinese-Caucasian difference*, In Andre, J., Owens, D.A., & Harvey, L.O. Jr. (Eds.). *Visual perception: The influence of* H. W. Leibowitz. 2003, American Psychological Association: Washington, DC, US. p. 81–94.
Klein, S. A. (2001). Measuring, estimating, and understanding the psychometric function: A commentary. *Perception & Psychophysics, 63*(8), 1421–1455.
Kriss, A., Spekreijse, H., Verduyn Lunel, H.F.E., Braamhaar, I., de Waal, B.J., Barrett, G., A comparison of pattern onset, offset and reversal responses: effects of age, gender and check size, in Evoked potentials ll, R. Nodar, Barber, C., Editor. 1984, Butterworths: New York. p. 553–561.
Leat, S. J., Yadav, N. K., & Irving, E. L. (2009). Development of visual acuity and contrast sensitivity in children. *J. Optom., 2*, 19–26.
Leehey, S. C., Moskowitz-Cook, A., Brill, S., & Held, R. (1975). Orientational anisotropy in infant vision. *Science (New York, N.Y.), 190*(4217), 900–902.
Mäntyjärvi, M., & Laitinen, T. (2001). Normal values for the Pelli-Robson contrast sensitivity test. *Journal of Cataract and Refractive Surgery, 27*(2), 261–266.
Mayer, M. J. (1977). Development of anisotropy in late childhood. *Vision Research, 17*(6), 703–710.
Mikhailova, E. S., Gerasimenko, N. Y., & Slavutskaya, A. V. (2018). Effects of line orientation in visual evoked potentials. Spatial dynamics, and gender differences of neural oblique effect. *bioRxiv*, Article 323782.
Mitchell, D. E., Freeman, R. D., Millodot, M., & Haegerstrom, G. (1973). Meridional amblyopia: evidence for modification of the human visual system by early visual experience. *Vision Research, 13*(3), 535–558.
Moskowitz, A., & Sokol, S. (1985). Effect of stimulus orientation on the latency and amplitude of the VEP. *Investigative Ophthalmology & Visual Science, 26*(2), 246–248.
Odom, J. V., Bach, M., Barber, C., Brigell, M., Marmor, M. F., Tormene, A. P., Holder, G. E., & Vaegan. (2004). Visual evoked potentials standard (2004). *Documenta Ophthalmologica, 108*(2), 115–123.
Odom, J. V., Bach, M., Brigell, M., Holder, G. E., McCulloch, D. L., Mizota, A., Tormene, A. P., & International Society for Clinical Electrophysiology of Vision. (2016). ISCEV standard for clinical visual evoked potentials: (2016 update). *Documenta Ophthalmologica, 133*(1), 1–9.
Salomão, S. R., Ejzenbaum, F., Berezovsky, A., Sacai, P. Y., & Pereira, J. M. (2008). Age norms for monocular grating acuity measured by sweep-VEP in the first three years of age. *Arquivos Brasileiros de Oftalmologia, 71*(4), 475–479.
Sokol, S., Moskowitz, A., & Hansen, V. (1987). Electrophysiological evidence for the oblique effect in human infants. *Investigative Ophthalmology & Visual Science, 28*(4), 731–735.
Stiers, P., Vanderkelen, R., & Vandenbussche, E. (2003). Optotype and Grating Visual Acuity in Preschool Children. *Investigative Ophthalmology & Visual Science, 44*(9), 4123–4130.
Teller, D. Y., Morse, R., Borton, R., & Regal, D. (1974). Visual acuity for vertical and diagonal gratings in human infants. *Vision Research, 14*(12), 1433–1439.
Thompson, D. A., Fritsch, D. M., Hardy, S. E., & POW Study Group. (2017). The changing shape of the ISCEV standard pattern onset VEP. *Documenta Ophthalmologica, 135*(1), 69–76.
Wilson, H. R., Loffler, G., Wilkinson, F., & Thistlethwaite, W. A. (2001). An inverse oblique effect in human vision. *Vision Research, 41*(14), 1749–1753.
Wolffsohn, J. S., Bhogal, G., & Shah, S. (2011). Effect of uncorrected astigmatism on vision. *Journal of Cataract and Refractive Surgery, 37*(3), 454–460.
Yap, T. P., Luu, C. D., Suttle, C. M., Chia, A., & Boon, M. Y. (2019). Electrophysiological and Psychophysical Studies of Meridional Anisotropies in Children With and Without Astigmatism. *Investigative Ophthalmology & Visual Science, 60*(6), 1906–1913.
Yap, T. P., & Boon, M. Y. (2020). Electrodiagnosis and treatment monitoring of children with refractive amblyopia. *Advances in Ophthalmology and Optometry, 5*, 1–24.
Yap, T. P., Luu, C. D., Suttle, C. M., Chia, A., & Boon, M. Y. (2020). Effect of stimulus orientation on visual function in children with refractive amblyopia. *Investigative Ophthalmology & Visual Science, 61*(5), 5.
Yap, T. P., Luu, C. D., Suttle, C. M., Chia, A., & Boon, M. Y. (2021). Characterising the orientation-specific pattern-onset visual evoked potentials in children with bilateral refractive amblyopia and non-amblyopic controls. *Documenta Ophthalmologica, 142*(2), 197–211.