SUNY COLLEGE OF OPTOMETRY
GRADUATE CENTER
FOR VISION RESEARCH

Differences between ON and OFF cortical function in patients with amblyopia

By

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Thesis

In partial satisfaction of the requirements for the degree of

Master of Science in Vision Science

State University of New York

College of Optometry

May 20, 2025

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ABSTRACT

Purpose: Evidence from psychophysical studies indicate that amblyopia affects ON more than OFF visual pathways. This prospective study aims to directly measure the effect of amblyopia on cortical responses driven by ON and OFF pathways with visual evoked potentials (VEPs).

Methods: Adults (18-65 years) with amblyopia (strabismic, anisometropic, mixed, or deprivational) and control subjects with binocularly normal-corrected vision were recruited. All subjects were screened with ATS-EDTRS best-corrected visual acuity (BCVA) and Randot Preschool stereoacuity. To be eligible, amblyopes must have an interocular difference of ≥2 logMAR (logarithmic minimum angle of resolution) lines, and controls must have BCVA within 1 logMAR line in both eyes and a stereoacuity of ≤100 arcsec. VEP was recorded with a portable lightweight headset (Wearable Sensing Inc.) that sampled the visual cortex with 9 dry electrodes. The visual stimuli presented were checkerboards with half checks equal to the background and half darker or lighter than the background (100% and 50% contrast, viewed through right eye, left eye, or both eyes, 900 trials). Eye fixation was monitored with an eye tracker (Eyelink 1000). The reliability of cortical responses was quantified with a correlation index that selected the 20 stimulus trials generating the strongest responses and measured the average of all possible correlations between trial pairs.

Results: We tested eight amblyopic subjects and two controls. The average amplitude of the cortical responses was marginally stronger for the AE than FE, but the difference was not statistically significant (23.00 ± 4.65 vs. 22.68 ± 5.62 microV, $p > 0.05$, Wilcoxon test). Differences in response amplitude between FE and AE were weaker for light than dark stimuli but also did not reach significance (-0.38 ± 4.81 vs. -0.26 ± 7.22 microV, $p > 0.05$, Wilcoxon test). The mean correlation index was larger in the FE than the AE, but this difference was not statistically significant (0.43 ± 0.20 vs. 0.40 ± 0.22, $p > 0.05$, Wilcoxon test). The FE-AE differences in mean correlation index were larger for light than dark stimuli, but again, the differences did not reach significance (0.09 ± 0.20 vs. -0.03 ± 0.22, $p > 0.05$, Wilcoxon Test). Within-subject comparisons in select individuals revealed variable VEP patterns. Control subjects showed no interocular or ON/OFF differences, while amblyopic participants displayed mixed results. Some were consistent with the hypothesis of reduced ON pathway strength in the AE, whereas others showed the opposite or no difference at all.

Conclusions: While some amblyopes may show ON/OFF pathway asymmetries, these effects are not consistently observable across all cases. Variability is inherent with VEP and may limit the ability to detect ON/OFF pathway differences at the group level, emphasizing the need for individualized analysis in amblyopia research.

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INTRODUCTION

Amblyopia is a developmental disorder at the level of the visual cortex characterized by reduced visual acuity and contrast sensitivity that cannot be attributed to any ocular or visual system abnormality (Levi, 2020). It typically arises from disruptions to visual input, such as anisometropia (unequal refractive error between both eyes), strabismus (eye turn), or deprivation (ptosis, or commonly, a cataract) during critical periods of visual development (Birch, 2013; Levi, 2020; Hubel & Wiesel, 1970). These disruptions result in persistent retinal blur in one eye, leading to imbalanced input to the visual cortex and subsequent deficits in visual processing.

Given its cortical origin, ON and OFF pathways have been considered. Traditional models of amblyopia assume equal cortical responses to lights and dark (Ding & Sperling, 2006; Ding & Levi, 2014); however, emerging evidence challenges this view. Similar to how monocular deprivation alters cortical responses in favor of the non-deprived eye (Hubel et al., 1977; Wiesel & Hubel, 1963), sustained optic blur reduces exposure to high spatial frequencies, shifting the ON/OFF balance toward OFF dominance (Kremkow et al., 2014; Pons et al., 2017; Jansen et al., 2019). This dark dominance correlates with human vision and natural scenes and is most pronounced at low spatial frequencies.

If low spatial frequencies preferentially drive OFF over ON cortical responses, then conditions like amblyopia, which impair processing of high spatial frequencies, should weaken the ON pathway during development. Supporting this via psychophysical models, Pons et al. (2019) showed that individuals with amblyopia exhibit poorer visual performance in light than dark stimuli, but this hypothesis has yet to be evaluated using objective physiological measures. The aim of this prospective study was to use visual evoked potentials (VEPs) to directly assess the effect of amblyopia on cortical responses driven by ON and OFF pathways.

SIGNIFICANCE

This study used VEP to assess ON and OFF visual pathway function in adults with amblyopia. Unlike psychophysical models predicting greater ON pathway deficits, we did not find significant differences in ON and OFF responses between amblyopic and control participants. These results highlight the difficulty of detecting subtle ON/OFF pathway abnormalities with electrophysiological measures.

METHODS

Research protocol and informed consent forms were approved by the Institutional Review Board of The State University of New York College of Optometry (New York, NY). Health Insurance Portability and Accountability Act rules were followed, and informed consent was obtained from all participants.

Participants:

Participants were enrolled from SUNY College of Optometry and the University Eye Centre. Basic information, including demographics and refractive error, were obtained from their medical records.

<u>Eligibility inclusion criteria</u>*:* All participants were adults between the ages of 18 and 65 years.

Amblyopia Group: A) participants had a high-contrast best-corrected visual acuity (BCVA) of 20/32 (equivalent to 0.2 logMAR [logarithmic minimum angle of resolution]) or worse in the amblyopic eye, with an interocular difference of ≥2 logMAR lines. B) The causes of unilateral amblyopia were identified as anisometropic, strabismic, combined strabismic-anisometropic, or deprivational. Anisometropia was defined as an interocular difference of ≥1.00D sphere or a difference in astigmatic anisometropic cylinder of ≥1.50D on cycloplegic refraction. Strabismus included participants with ≤ 4PD microtropia or good alignment (Ortho – 6PD) status post-strabismus surgery only. The combined type included those with both anisometropia and strabismus. Deprivational was defined as a history of a congenital cataract.

Control Group: participants had high contrast BCVA of 20/25 or better in each eye, with an interocular difference of 1 logMAR line or less. Stereoacuity had to be ≤100 arcsec with the Randot Preschool Stereoacuity Test.

Exclusion Criteria: Because 20/400 is the lower limit of the acuity range of the electronic visual acuity system at a calibrated test distance of 3 meters, amblyopes with BCVA worse than 20/400 were not enrolled. Bilateral amblyopia and myopic amblyopes were also excluded.

Procedures:

All subjects were instructed to wear contact lenses (CLs) of best-corrected vision. If participants did not wear CLs, a trial lens from the University Eye Center containing the patient's most recent prescription was given.

Visual acuity was tested using Amblyopia Treatment Study (ATS) surrounded E-ETDRS visual acuity protocol with the electronic visual acuity (EVA) software program (i.e. a computerized visual acuity test that uses ETDRS charts originally designed for an Early Treatment Diabetic Retinopathy Study) developed by M&S Technologies, Inc. (Niles, IL). The system included a high resolution 13" desktop display monitor and a wireless control tablet for the examiner to discern correct and incorrect responses.

This study was performed in a dark room with ambient light illuminated. The computer screen was calibrated to the luminance level of 90-110 cd/m^2 with a digital lux meter for all testing. The EVA software utilized a stepwise process to determine threshold, alternating between larger and smaller letters. The single letter displayed was surrounded using crowding bars and set to a black optotype with a white background.

The testing started from 20/400 and reduced the letter size, depending on the subject's threshold acuity. The endpoint was determined by the software. Once a measurement was completed, VA results were displayed both in logMAR and in Score, but for the purpose of this study, only logMAR was used.

All participants were tested at 3 meters away from the monitor. Participants were always tested right eye first, then left. Thus, for amblyopic participants who had amblyopia in either the right or left eye, the order of testing for the amblyopic eye was randomized.

Stereoacuity was obtained at the standardized test distance of 40 cm using the Randot Preschool Stereotest, Fly, Wirt Circles, and Animals with the polarized glasses over best-corrected CLs.

To capture VEP recordings, subjects wore a portable lightweight headset (Wearable Sensing Inc.) that had nine dry electrodes transmitting signals wirelessly and sampling the visual cortex (**Figure 1**). O1, Oz, and O2 were electrodes placed on the scalp, representing the left, midline, and right occipital regions, respectively. The reference electrode was placed at Fz (mid-forehead). All visual stimuli were presented on a gamma corrected 24-inch LCD monitor (BenQ XL2420T, 120 Hz, mean luminance: 156 cd/m^2) and were generated with

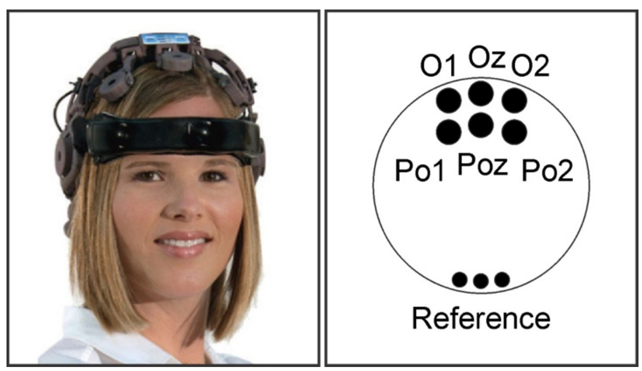


Figure 1. *Left*: demonstration of a participant wearing the lightweight headset used for VEP recordings. *Right*: electrode placement map illustrating scalp locations for VEP acquisition.

Psychtoolbox 3 and custom MATLAB software (MathWorks). The monitor was placed 70 cm away and observers used a chin rest to hold their heads steady.

Experiments were conducted in a dark room and performed monocularly; the eye not being tested was covered with a patch. Subjects were presented with checkerboard stimuli, in which each check size was 0.45° (**Figure 2**). Half of the checks were equal to the background and the other half darker (OFF stimuli) or lighter (ON stimuli) than the background. 150 of the stimulus trials were presented at 100% contrast and 150 trials at 50% contrast through the right eye, left eye, and both eyes (900 trials total). Eye fixation was controlled and monitored with an eye tracker (Eyelink 1000); if a participant blinked during a stimulus or fixation was lost, the same block was restarted after a short break.

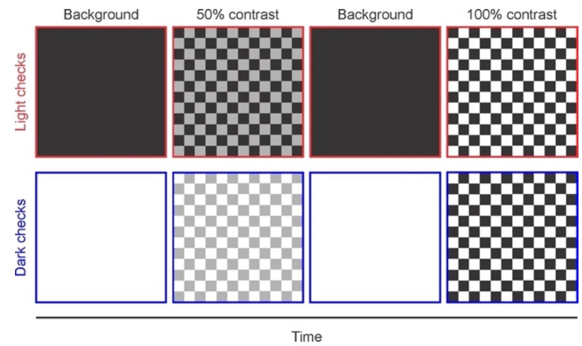


Figure 2. Example of visual stimuli used in the experiment. *Top:* light check patterns *Bottom*: dark check patterns

Statistical Analysis:

To quantify the strength and reliability of visual responses, we calculated a correlation index that selected the 20 stimulus trials generating the strongest responses and then measured all possible correlations between pairs of responses to single trials. Wilcoxon test, a non-parametric test, was used to analyze significance.

RESULTS

A total of 16 adults were recruited for the study, comprising 11 individuals in the amblyopia group and 5 in the control group. Three participants from the amblyopia group were excluded for not meeting the inclusion criteria, and three from the control group were excluded due to excessive data noise. Consequently, data from 10 participants were included in the final analysis. Demographic details are presented in **Table 1**. The control group consisted of an equal number of male and female participants, whereas the amblyopia group had a higher proportion of females. The mean ages of the two groups were comparable (amblyopia: 26.18 ± 7.91 years; control: 24 ± 0.94 years). All participants identified as non-Hispanic, with both groups containing an equal distribution of Asian and White individuals. The control group had the same BCVA between right and left eyes (-0.16 ± 0.09 logMAR, Snellen equivalent 20/20) and stereopsis was 40 seconds of arc. The amblyopic group had poor or no stereopsis and an average BCVA of 0.301 ± 0.079 logMAR in the amblyopic eye (AE) (Snellen VA 20/40) and -0.707 ± 0.125 logMAR in the fellow eye (FE) (Snellen VA 20/20).

Table 1. Baseline Demographic Information (Total N = 10)

Characteristics	Amblyopic Group (N = 8)	Control Group (N = 2)
Sex (F/M)	6/2	1/1
Age, Years (mean ± SD) [min,max]	26.18 ± 7.91 [21,45]	24 ± 0.947 [23,24]
Cause of Amblyopia		
Anisometropia	3	N/A
Strabismus	2	N/A
Mixed	2	N/A
Deprivational	1	N/A
Ethnicity		
Hispanic	0	0
Non-Hispanic	8	2
Race		
White	4	1
African American	0	0
Asian	4	1
Declined	0	0
Mean LogMAR VA (mean ± SD) (Snellen VA)		
	AE: 0.301 ± 0.079 (20/40) FE: -0.707 ± 0.125 (20/20)	OD: -0.16 ± 0.09 (20/20) OS: -0.16 ± 0.09 (20/20)
Stereopsis, arc sec [min,max]		
Preschool	[Nil, 200]	[40, 40]
Fly	[Nil, 3552]	[3552, 3552]
Animal	[Nil, 100]	[100, 100]
Wirt Circles	[50, 800]	[40, 40]

The average amplitude of the cortical responses was marginally stronger for the AE than FE, but the difference was not statistically significant (23.00 ± 4.65 vs. 22.68 ± 5.62 microV, $p > 0.05$, Wilcoxon test). Differences in response amplitude between FE and AE were weaker for light than dark stimuli but also did not reach significance (-0.38 ± 4.81 vs. -0.26 ± 7.22 microV, $p > 0.05$, Wilcoxon test). The mean correlation index was larger in the FE than the AE, but this difference was not statistically significant (0.43 ± 0.20 vs. 0.40 ± 0.22, $p > 0.05$, Wilcoxon test). The FE-AE differences in mean correlation index were larger for light than dark stimuli, but again, the differences did not reach significance (0.09 ± 0.20 vs. -0.03 ± 0.22, $p > 0.05$, Wilcoxon Test).

No significant differences were found between the amblyopic and control groups in ON and OFF pathway responses. To explore potential within-subject differences, we selected participants from each group with reliable VEP signals and compared ON and OFF responses between their eyes.

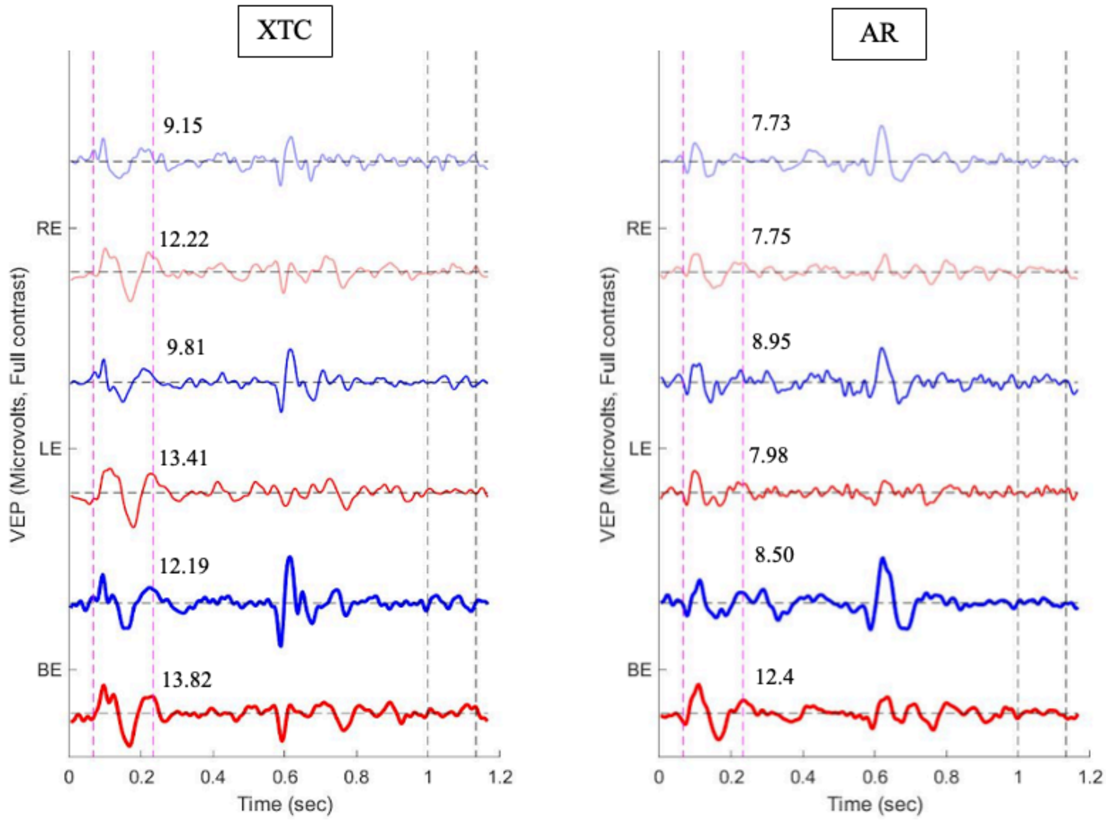


Figure 3. Raw VEP traces from two control subjects in response to ON (light) and OFF (dark) stimuli, recorded with the right eye (RE), left eye (LE), and both eyes (BE) open. Blue traces represent responses to dark stimuli; red traces represent responses to light stimuli. Each condition (RE, LE, BE) was tested with light and dark stimulus types. Numbers above each VEP trace indicate the corresponding amplitude. No observable differences in waveform shape, amplitude, or latency were found between RE and LE recordings, or between ON/OFF stimulus conditions.

Raw VEP traces from control subjects were recorded under ON (light) and OFF (dark) stimulus conditions, tested individually for each eye and then with both eyes open (**Figure 3**). The sequence of recordings followed a consistent order: right eye (RE) under dark, then light conditions; left eye (LE) under dark, then light; and finally, both eyes open under dark, then light. Across both control subjects, no observable interocular differences were noted in waveform shape, amplitude, or latency in ON/OFF stimulus conditions.

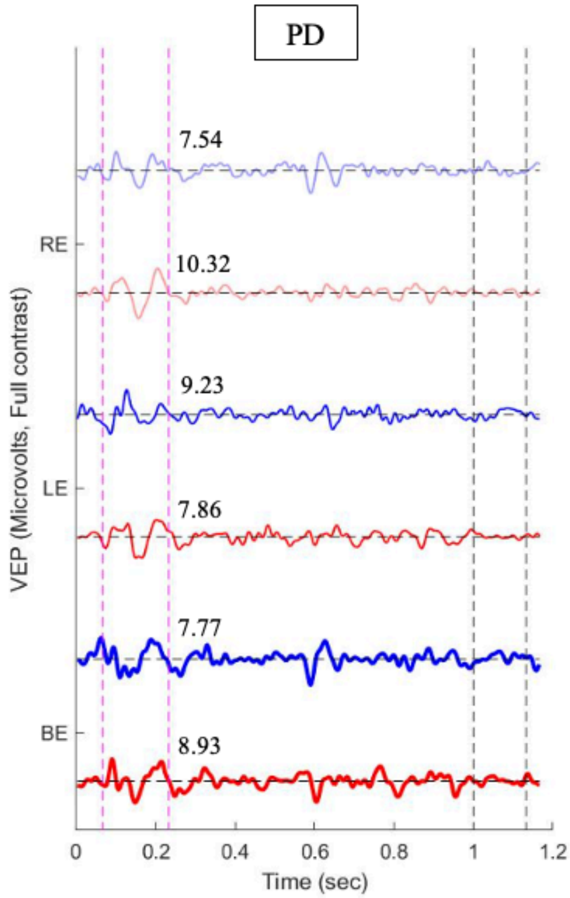


Figure 4. Raw VEP traces from an amblyopic subject in response to ON (light) and OFF (dark) stimuli, recorded with the right eye (RE), left eye (LE), and both eyes (BE) open. Blue traces represent responses to dark stimuli; red traces represent responses to light stimuli. Each condition (RE, LE, BE) was tested with light and dark stimulus types. Numbers above each VEP trace indicate the corresponding amplitude.

The participant is a mixed amblyope (refractive and strabismic). The **AE is the LE** (BCVA 0.301 logMAR [20/40 Snellen]) and the FE is the RE (BCVA logMAR 0 [20/20 Snellen]).

As expected, the amplitude of the ON response is lower in the AE compared to the FE; however, the OFF response is unexpectedly stronger in the AE.

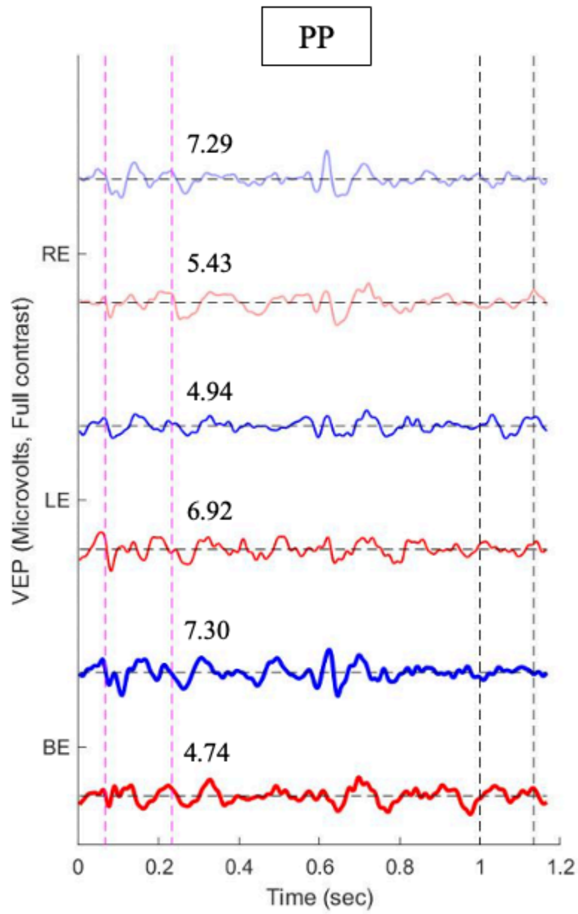
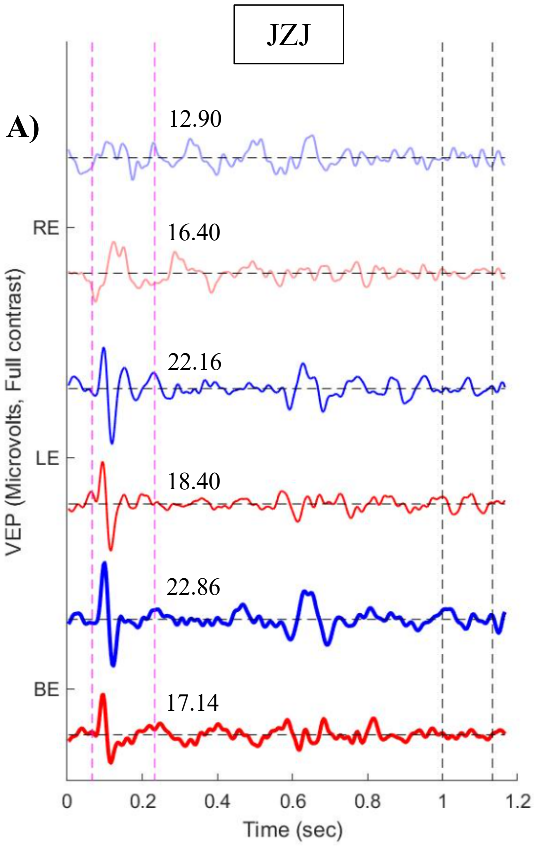
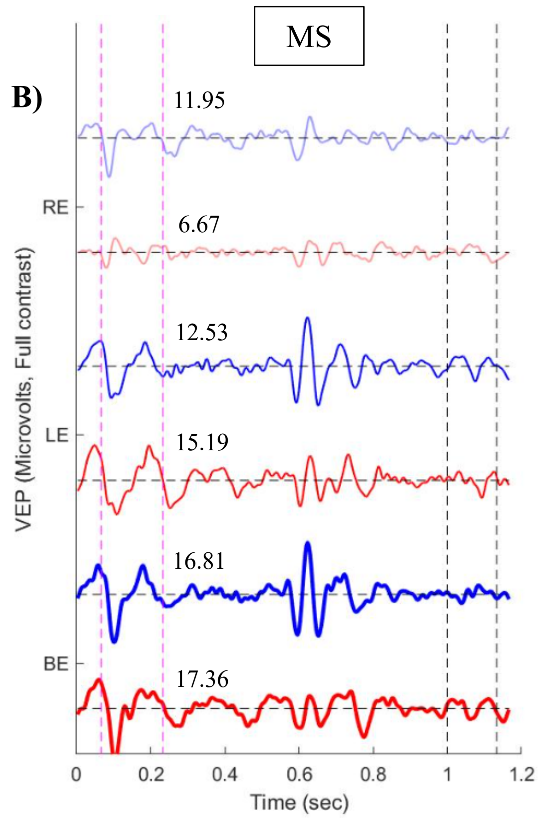


Figure 5. Raw VEP traces from an amblyopic subject in response to ON (light) and OFF (dark) stimuli, recorded with the right eye (RE), left eye (LE), and both eyes (BE) open. Blue traces represent responses to dark stimuli; red traces represent responses to light stimuli. Each condition (RE, LE, BE) was tested with light and dark stimulus types. Numbers above each VEP trace indicate the corresponding amplitude.

The participant is a deprivational amblyope. The **AE is the LE** (BCVA 0.301 logMAR [20/40 Snellen]) and the FE is the RE (BCVA logMAR -0.0969 [20/16 Snellen]).

This participant showed a stronger ON response and a weaker OFF response in the AE compared to the FE.


JZJ
A)
12.90
16.40
22.16
18.40
22.86
17.14
RE
LE
BE
VEP (Microvolts, Full contrast)
0
0.2
0.4
0.6
0.8
1
1.2
Time (sec)


MS
B)
11.95
6.67
12.53
15.19
16.81
17.36
RE
LE
BE
VEP (Microvolts, Full contrast)
0
0.2
0.4
0.6
0.8
1
1.2
Time (sec)

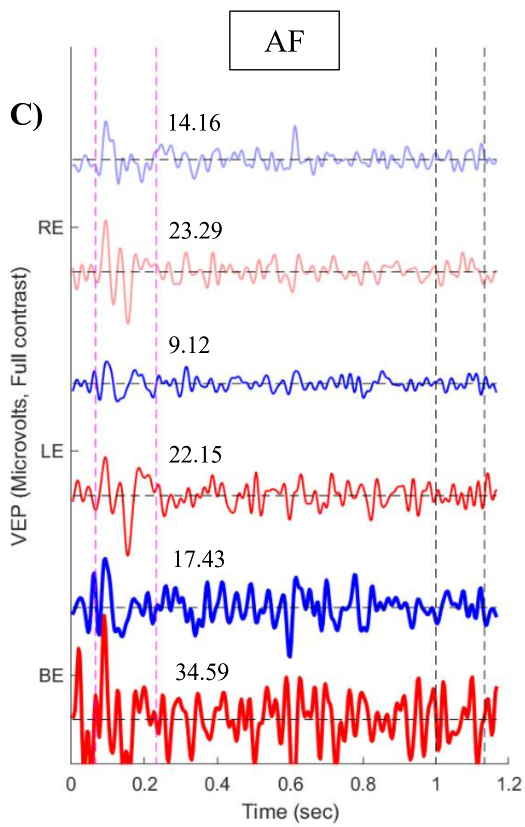

AF
C)
14.16
23.29
9.12
22.15
17.43
34.59
RE
LE
BE
VEP (Microvolts, Full contrast)
0
0.2
0.4
0.6
0.8
1
1.2
Time (sec)

Figure 6. Raw VEP traces from amblyopic subjects in response to ON (light) and OFF (dark) stimuli, recorded with the right eye (RE), left eye (LE), and both eyes (BE) open. Blue traces represent responses to dark stimuli; red traces represent responses to light stimuli. Each condition (RE, LE, BE) was tested with light and dark stimulus types. Numbers above each VEP trace indicate the corresponding amplitude.

A. The participant is a strabismic amblyope. The **AE is the RE** (BCVA 0.204 logMAR [20/32 Snellen]) and the FE is the LE (BCVA logMAR 0 [20/20 Snellen]).

B. The participant is a refractive amblyopia. The **AE is the RE** (BCVA 0.398 logMAR [20/50 Snellen]) and the FE is the LE (BCVA logMAR -0.097 [20/16 Snellen]).

C. The participant is a microtropic amblyope. The **AE is the LE** (BCVA 0.204 logMAR [20/32 Snellen]) and the FE is the LE (BCVA logMAR -0.301 [20/10 Snellen]).

In these participants, their AE had overall weaker VEP amplitudes compared to the FE, especially in the ON condition.

In contrast to the control group, raw VEP traces from individual participants with amblyopia showed variable patterns of visual pathway function. While reduced amplitude in the AE relative to the FE was anticipated across both ON and OFF stimulus conditions (with a more pronounced reduction in the ON response), this pattern was not consistent. One participant exhibited stronger OFF but weaker ON responses in the AE (**Figure 4)**, whereas another participant showed the opposite (stronger ON and weaker OFF responses in the AE) (**Figure 5)**. However, some participants followed the expected pattern, in which the AE had overall weaker VEP amplitudes compared to the FE, especially in the ON condition (**Figure 6**). Notably, participant JZJ repeated the study on four separate occasions and consistently demonstrated this pattern (**Figure 7**).

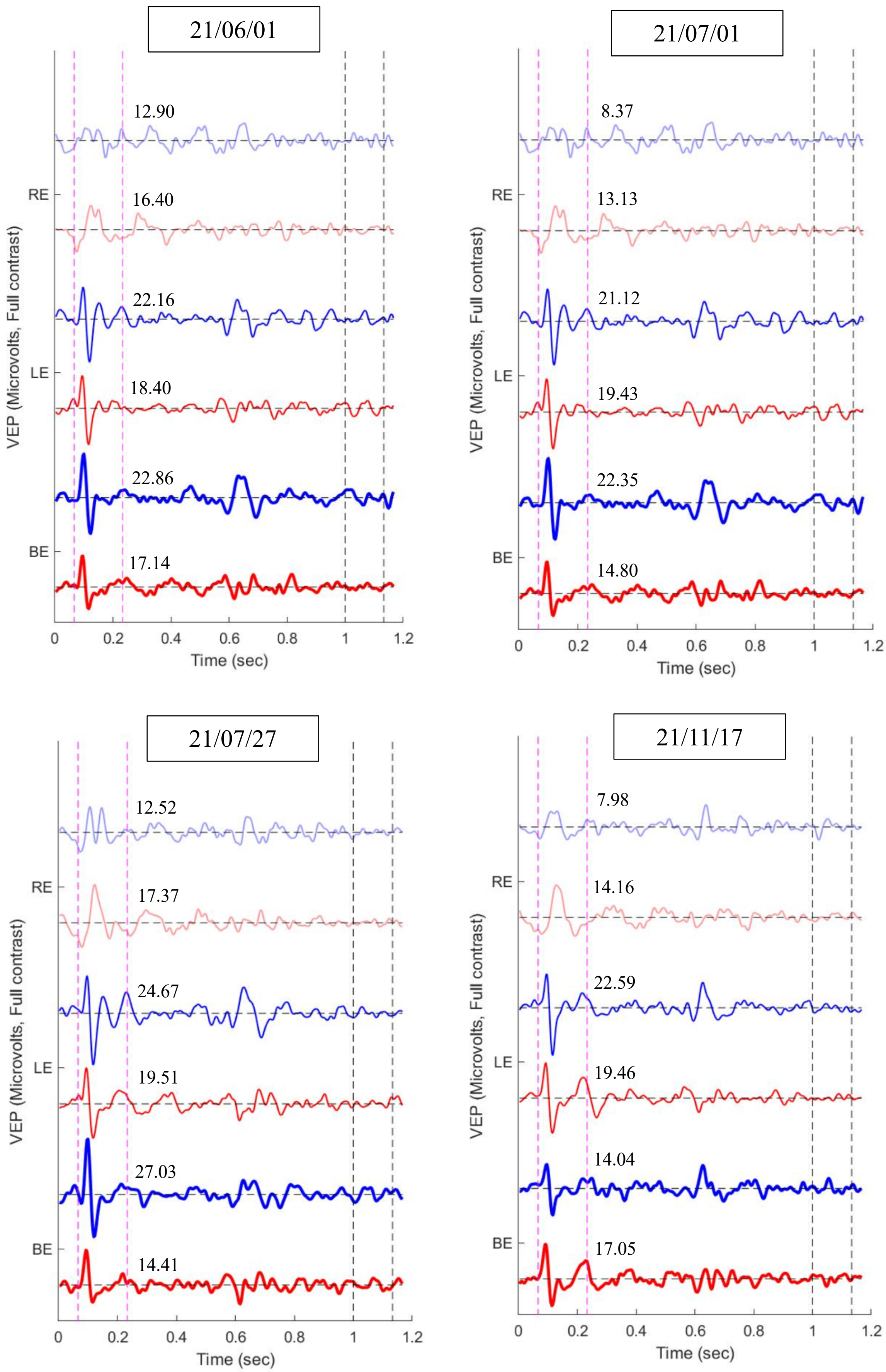

21/06/01
12.90
16.40
22.16
18.40
22.86
17.14
RE
LE
BE
VEP (Microvolts, Full contrast)
Time (sec)
0
0.2
0.4
0.6
0.8
1
1.2
21/07/01
8.37
13.13
21.12
19.43
22.35
14.80
21/07/27
12.52
17.37
24.67
19.51
27.03
14.41
21/11/17
7.98
14.16
22.59
19.46
14.04
17.05

Figure 7. Raw VEP traces from an amblyopic subject in response to ON (light) and OFF (dark) stimuli, recorded with the right eye (RE), left eye (LE), and both eyes (BE) open. Blue traces represent responses to dark stimuli; red traces represent responses to light stimuli. Each condition (RE, LE, BE) was tested with light and dark stimulus types. Numbers above each VEP trace indicate the corresponding amplitude.

The participant is a strabismic amblyope. The **AE is the RE** (BCVA 0.204 logMAR [20/32 Snellen]) and the FE is the LE (BCVA logMAR 0 [20/20 Snellen]). The VEP traces are from the same participant recorded across four separate occasions. Across all sessions, the AE exhibited lower amplitudes compared to the FE, with a consistently reduced ON response.

DISCUSSION

Given the growing psychophysical evidence suggestive a selective vulnerability of the ON pathway in amblyopia, our study aimed to explore whether this physiological distinction could be captured through objective electrophysiological methods. Results showed no statistically significant difference in ON vs. OFF responses between amblyopic and control groups.

ON and OFF pathways remain cortically segregated and exhibit differences in spatial frequencies and response latency in the visual cortex (Jin et al., 2008; Komban et al., 2014; Kremkow et al., 2014, 2016). Prolonged exposure to low spatial frequencies in the cortex corresponding to the amblyopic eye have disrupted the ON/OFF response balance, leading to a cortex that is more OFF-dominated (Kremkow et al., 2014; Pons et al., 2017). Our findings do not support the conclusions of Pons et al. (2019) whose work serves as the basis for the current investigation.

A plausible explanation could be that ON pathway dysfunction in amblyopia may be too subtle for current VEP techniques to reliably detect. While psychophysical models can isolate specific perceptual deficits, VEPs measure broad cortical activity averaged across large neuronal populations and multiple trials. This averaging, along with natural variability between individuals, may reduce the sensitivity of VEP in detecting mild pathway-specific disruptions. The heterogeneity of amblyopia in our sample likely played a role as well. Participants with mild amblyopia may have relatively preserved ON/OFF function due to partial visual experience and compensatory mechanisms. Conversely, those with more severe amblyopia, characterized by reduced visual acuity and unstable fixation, often produced noisy or unreliable VEP signals that led to their exclusion from the final analysis. The combination of individual variability and the limitations of VEP may obscure subtle pathway differences that are more readily captured through psychophysical assessment.

Our findings highlight the potential (and challenges) of using VEP to investigate ON pathway dysfunction in amblyopia. Although we were unable to confirm this impairment, our exploratory analysis suggests that ON/OFF imbalances may be present in some amblyopes but masked when responses are averaged.

Limitation:

This study has several limitations that should be considered when interpreting the findings. First, the eye-tracking system was incompatible with glasses, as the presence of lenses frequently interfered with the pupil tracker's ability to detect and reliably track the eye. As a result, all participants were required to wear CLs for best-corrected vision, but some participants had never worn CLs before. They may have experienced discomfort and dryness, unfamiliarity, or adaptation issues, which could have affected their visual performance. Additionally, the eye tracker was inconsistent, often requiring repeated calibration due to tracking interruptions. This technical instability may have compromised data quality and disrupted participants' attention.

VEP signals are also known to vary substantially between individuals due to differences in cortical anatomy, attention, and signal-to-noise ratio. In our study, some participants exhibited particularly noisy VEP recordings, making it difficult to extract reliable responses. Thus, several data had to be excluded from analysis. Even among data that was included, the quality of the VEP signal varied, which may have influenced the robustness of the group-level comparisons.

These limitations underscore the difficulty of integrating eye tracking and electrophysiological measures in vision research, emphasizing the need for improved equipment reliability and signal quality in future studies.

Clinical Significance:

This study did not provide conclusive evidence of ON pathway deficits in individuals with amblyopia using VEP; however, selective ON pathway weakness may still contribute. Future amblyopia therapies could benefit from specifically targeting and enhancing ON pathway function through bright, flickering, or contrast-increasing stimuli that preferentially engage ON cells and may support pathway-specific rehabilitation.

An additional clinical application lies in monitoring neuroplastic changes during treatment. VEPs can be recorded before, during, and after intervention to objectively assess functional changes in the visual cortex. This approach is particularly valuable for non-verbal children or patients who are unable to communicate their visual experiences, offering clinicians an objective way to track therapeutic progress.

The development of neurofeedback-based interventions using real-time VEP monitoring also presents an innovative and promising therapeutic avenue. By training patients to produce more normative VEP responses, such techniques could promote adaptive changes in visual processing. These strategies emphasize the importance of neuroplasticity in amblyopia and suggest that monitoring and modulating specific visual pathways may become an integral part of future treatments.

CONCLUSION

No significant differences in ON and OFF pathway responses were observed between amblyopic and control participants using VEP. These findings suggest that electrophysiological measures may have limited sensitivity in detecting subtle ON/OFF pathway abnormalities at the group level, emphasizing the need for individualized analysis in amblyopia research.

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ACKNOWLEDGMENT

I would like to express my deepest gratitude to my supervisor, Dr. Jingyun Wang, for her invaluable guidance, encouragement, and support throughout this project. Her mentorship has been instrumental in shaping both this work and my growth as a researcher. Thank you for taking a chance on me and looking after my well-being (as well as Jerry's and Xiao's) with such care and generosity. Your belief in me made all the difference.

I also wish to thank my committee members, Dr. Qasim Zaidi and Dr. Jose Manuel-Alonso, for their expertise throughout this project, without which this work would not have been possible. A special thank you goes to Dr. Jian Zhong Jin for generously providing the figures, conducting the statistical analyses that strengthened this work, and offering valuable assistance with running the experiment.

To my fellow MS classmates, your camaraderie, support, and shared dedication have made this journey not only meaningful but truly memorable. You have made the toughest days feel lighter and the best ones truly special. I also extend sincere appreciation to the Graduate Center for Vision Research and faculty members who taught the courses and seminars. Their passion and insights shaped this MS experience and the way I see and approach research.

Lastly, heartfelt thanks to my family for their love, patience, and encouragement, and to Mira, my cat, who deserved co-authorship on my ARVO abstract for her constant companionship and impeccable editorial oversight. Everyone's support has been the foundation of this accomplishment, and I am forever grateful.