

ELECTROPHYSIOLOGICAL CHARACTERIZATION OF THE AMBLYOPIC NEURAL DEFICIT

Theses of the Ph.D dissertation

Judit Körtvélyes MD

Supervisor:
Prof. Zoltán Vidnyánszky
Ph.D, D.Sc.

Éva M. Bankó
Ph.D



Péter Pázmány Catholic University
Faculty of Information Technology and Bionics
Multidisciplinary Doctoral School of Sciences and Technology

Budapest, 2014

„The eyes are useless when the mind is blind.”

Introduction

Amblyopia, commonly known as lazy eye, is a developmental visual disorder, which starts at an early age. A key issue in its treatment is an early diagnosis. However, methods used to diagnose visual impairment in children are not efficient enough and cannot be applied successfully for wide range population screening at an early age. With 625 million children under the age of 5 years worldwide, more than 15 million may have amblyopia, and more than half of them will not be identified before they reach school age [15]. The consequences of not identifying and treating amblyopia early include permanent visual impairment, poor fine motor skills, adverse effects on school performance, social interactions and self-image. Permanent monocular visual impairment due to amblyopia is a risk factor for total blindness if the better seeing eye is injured or if the fellow eye is affected by disease later in life [16, 17].

In Hungary this is a prominent issue, since according to estimates the prevalence of amblyopia is larger here than in other developed countries (2-3% instead of 1%). In addition, among the goals of “Vision 2020”, a worldwide program launched by WHO to eliminate avoidable blindness, the fight against amblyopia receives high priority in Hungary, too. These facts add urgency to our efforts to learn more about this disorder.

The present dissertation focuses on whether and to what extent neural responses to the visual information coming from the amblyopic eye is suppressed during binocular viewing condition. It

also aims at uncovering the neural mechanisms of amblyopic disruption of early visual experience and understanding the nature of amblyopic deficits at different stages of visual information processing. Its final goal is to investigate cortical processing of the amblyopic eye outside the foveal area by scaling the stimulus size, thus, keeping the stimulated area of the visual cortex constant at different eccentricities.

Methods

Throughout the course of my work I have collected the patients, and performed the clinical examinations: refraction, visual acuity test (ETDRS chart), contrast sensitivity test (SWCT-1000), binocular vision tests (Bagolini striated glasses test, Worth 4 dot test, Lang stereo test, Titmus test), ocular alignment examination, anterior segment and fundus examination with slit lamp. I have used a wide array of experimental methods applicable in cognitive neuroscience research: psychophysics, electrophysiology with classical ERP. For writing experimental presentations and scripts for analyzing the results I used Matlab 7.1 (The MathWorks Inc., Natick, MA, USA) with various toolboxes for presentation (Psychtoolbox 2.54 - [18, 19]) and for data analysis (Psignifit - [20]) alongside other commercial software (Brain-Vision Analyzer 1.05 - EEG preprocessing, Brainproducts GmbH., Munich, Germany). I recorded EEG with a BrainAmp MR amplifier (Brainproducts GmbH., Munich, Germany) with 64 Ag/AgCl electrodes mounted in an EasyCap (EasyCap GmbH, Herrsching-Breitbrunn, Germany). I used

Statistica 9 for statistical analysis and iViewX Hi-Speed tracking column (SMI GmbH, Germany) for eye-tracking.

New scientific results

Thesis I: I have shown that the amblyopic effects present on the early ERP components in the case of monocular stimulation are not manifested in the ERP responses during binocular viewing, which suggests that input from the amblyopic eye is completely suppressed already at the earliest stages of visual cortical processing when stimuli are viewed by both eyes.

Published in [1]

I measured event-related potentials (ERP) to foveal face stimuli in amblyopic patients, both in monocular (amblyopic or fellow eye) and binocular viewing conditions. The results revealed no statistical difference in the amplitude and latency of early components of the ERP responses between the binocular and fellow eye stimulation. On the other hand, early ERP components were reduced and delayed in the case of monocular stimulation of the amblyopic eye as compared to the fellow eye stimulation or to binocular viewing, which is a well known signature of amblyopia. These results are in agreement with the most widely accepted view about the primary underlying mechanism of the amblyopic syndrome, which formulates that amblyopia is the result of the dominant eye's suppression of the visual input from the weaker eye.

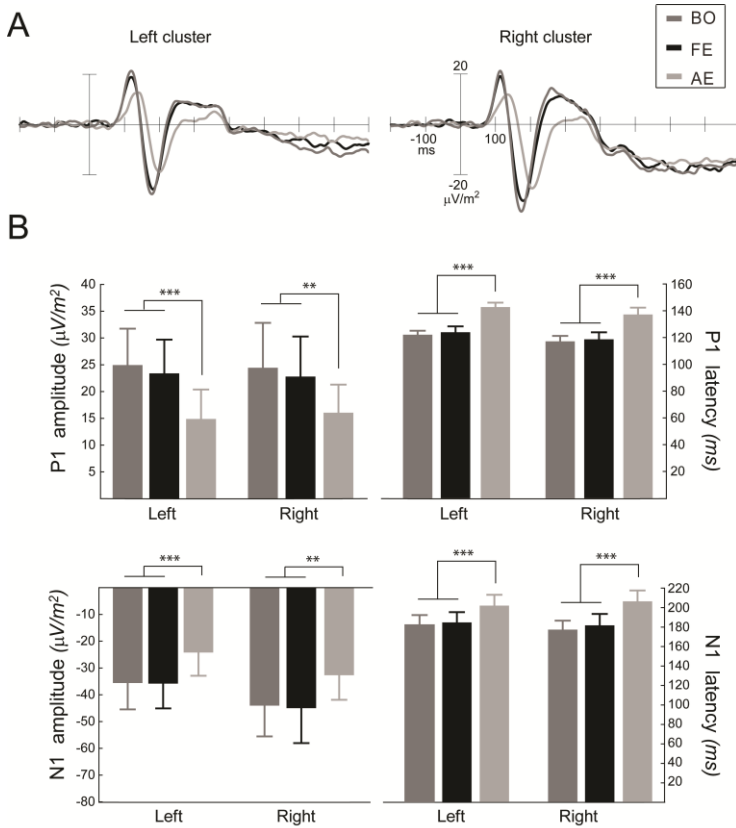


Figure 1. Electrophysiological results. (A) Amblyopic effects on the grand average ERPs of the left and right electrode cluster (P7, P9, PO7, and PO9 and P8, P10, PO8, and PO10). (B) Amblyopic effects on the P1 and N170 component amplitude and latency. Stimulation of the amblyopic eye resulted in reduced amplitudes and increased latencies of both early visual ERP components compared with either the fellow eye or the binocular viewing condition, while the latter two differed neither in amplitude nor in latency (N=12, ** $p < 0.01$; *** $p < 0.001$).

Thesis II: I have shown that during foveal stimulation the amblyopic disruption of early visual experience leads to deficits both in the strength and timing of higher-level, face specific visual cortical responses, reflected in the N170 component, and that these effects differ between strabismic and anisometropic patients.

Published in [2]

By measuring event related potentials (ERP) to foveal face stimuli I have characterized the amblyopic effects on the N170 component, reflecting higher-level structural face processing. Single trial analysis revealed that latencies of the ERP components increased and were more variable in the amblyopic eye compared to the fellow eye both in strabismic and anisometropic patient groups. Moreover, there was an additional delay of N170 relative to the early P1 component over the right hemisphere, which was absent in the fellow eye, suggesting a slower evolution of face specific cortical responses in amblyopia. On the other hand, distribution of single trial N170 peak amplitudes differed between the amblyopic and fellow eye only in the strabismic but not in the anisometropic patients. Furthermore, the amblyopic N170 latency increment but not the amplitude reduction correlated with the interocular differences in visual acuity and fixation stability.

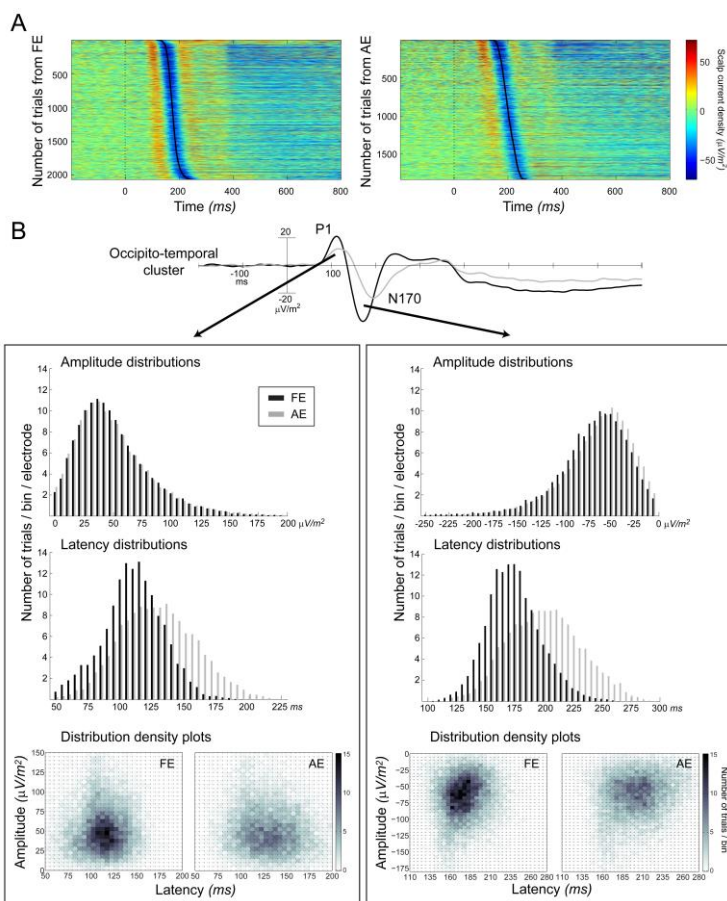


Figure 2. ERP images, amplitude and latency distributions of single trial responses. (A) ERP images of single trial responses from the fellow (left panel) and amblyopic eyes (right panel) of all 18 subjects pooled and averaged from P7, P8, P9, P10, PO7, PO8, PO9, PO10 and sorted according to the detected N170 latency (black line). x-axis: time in ms, y-axis: individual EEG traces, colors represent amplitude values. Evoked responses in the amblyopic eye are less time-locked, which is indicated by the smaller slope of the sorted latencies. (B) Histograms of the amplitude and latency distributions

of both eyes along with their 2D density plots of components P1 (left panel) and N170 (right panel) showing a higher inter-trial variability of component latencies arising from stimulation of the amblyopic eye compared with the fellow eye. Black and grey bars correspond to fellow and amblyopic eyes, respectively and histograms and density plots are averaged over subjects (N=18).

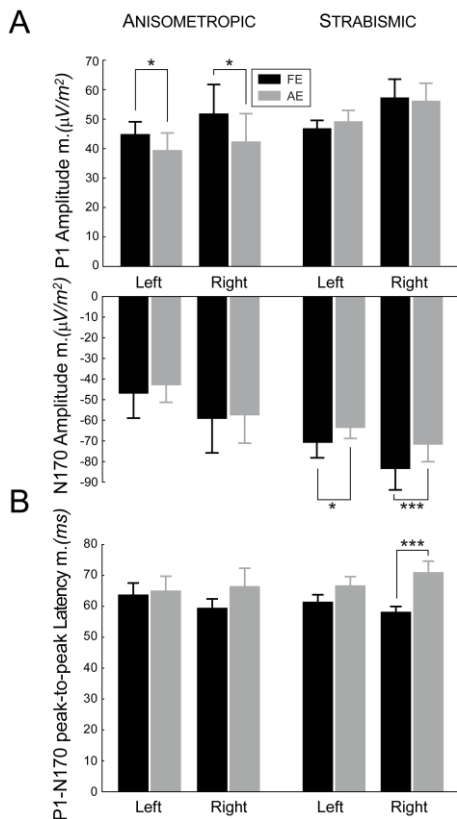


Figure 3. Face specific amblyopic deficits. (A) Amplitude medians of P1 and N170 components split into anisometric (displayed on the left, N=5) and strabismic (displayed on the right, N=13) groups. There was significant interocular difference in P1 amplitude medians

only in the anisometric, while in N170 amplitude medians only in the strabismic group. (B) P1-N170 peak-to-peak latencies split into groups, showing significantly bigger interocular difference over the right hemisphere in both groups (as indicated by the lack of eye \times etiology interaction $F_{(1,16)}=1.68$, $p=.21$), even though the difference did not reach the significance level in the case of the anisometric group due to a lack of statistical power ($p=.18$). Error bars indicate \pm SEM (* $p<.05$, *** $p<.001$).

There was no difference in the anticipatory neural oscillations between stimulation of the amblyopic and the fellow eye implying that impairment of the neural processes underlying generation of stimulus-driven visual cortical responses might be the primary reason behind the observed amblyopic effects.

Thesis III: I have shown that amblyopic deficits exist in the event-related potential responses recorded outside the central visual field, which, however, differ in nature from the observed foveal deficits: they are dominantly characterized by a deficiency in timing of neural responses, while the contribution of response magnitude reduction to the observed effects is negligible.

Published in [3]

I have investigated the amblyopic effect on event-related potentials (ERPs) with foveal and perifoveal stimuli, either matched in size

based on cortical magnification or presented as large annular stimuli in two separate experiments.

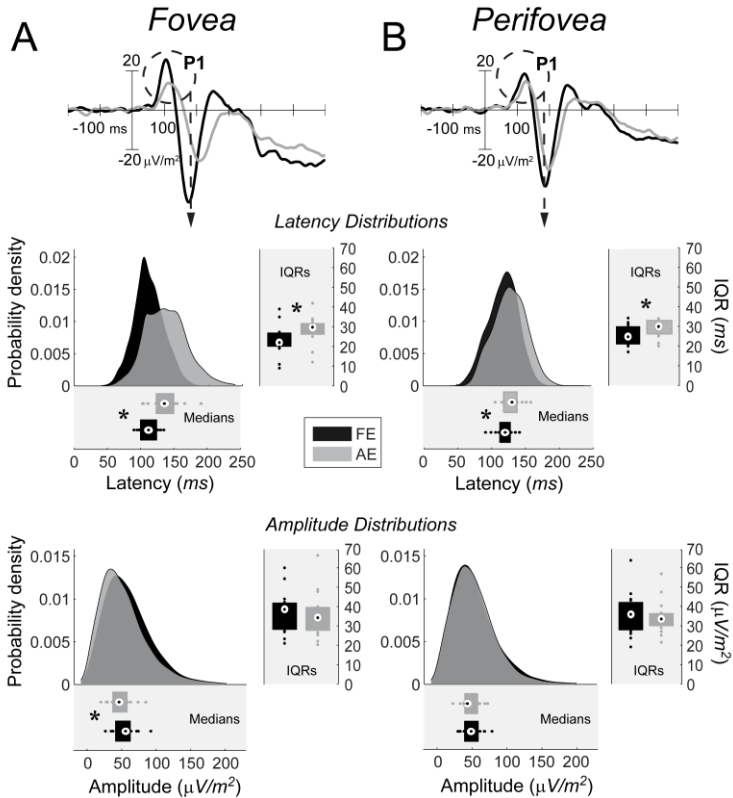


Figure 4. P1 amplitude and latency distributions obtained over the right hemisphere in the case of foveal (A) and perifoveal (B) stimuli, which were matched in size according to the cortical magnification factor. The top panel shows averaged ERPs from the right electrode cluster (P8, P10, PO8, and PO10), while probability density functions (pdf) of latency and amplitude distributions of the two eyes are depicted in the middle and bottom panel, respectively. Pdfs were estimated individually using a normal kernel function, averaged

across subjects and serve visualization purposes only. Individual parameters of the distributions (colored dots) are plotted below (medians) and to the right (interquartile ranges, IQRs) of each distribution panel, where the black dot and the box indicate the median and the 25%-75% range (IQR) of the data sets, respectively (FE: fellow eye, AE: amblyopic eye, N=15, asterisks denote significant interocular differences: $p < 0.013$, negative is down for the ERP traces).

Latency and amplitude of averaged ERPs and their single-trial distributions were analyzed. When stimulating the fovea, latency and amplitude of the early averaged ERP components increased and were reduced, respectively in the amblyopic compared with the fellow eye. Importantly, perifoveal stimulation also elicited similar amblyopic deficits, which were clearly significant in the case of using cortical magnification scaled stimuli. However, single-trial peak analysis revealed that foveal and perifoveal effects differed in nature: peak amplitudes were reduced only in foveal stimulation, while latencies were delayed and jittered both at the fovea and perifovea. The findings revealed the existence of amblyopic deficits at the perifovea when the stimulated cortical area was matched in size to that of foveal stimulation. In addition, the results emphasize the importance of controlling for cortical magnification when evaluating amblyopic vision in the periphery.

Conclusions and possible applications

To conclude, the results of the present study have revealed that despite the common perception of amblyopia as a foveal disorder, deficits exist outside the fovea as well. The results suggest that the amblyopic deficit observed in evoked responses outside the fovea can mainly be regarded as a timing deficit, while at the fovea it is a combination of decreased response strength and faulty timing. This overall uncertainty in response timing might form the neural basis for increased internal noise. In addition, these results emphasize the importance of controlling for cortical magnification when evaluating amblyopic vision in the periphery.

Moreover, we have shown that the amblyopic disruption of early visual experience also alters the development of higher-order, object specific visual information processing in humans and thus the results suggest that amblyopia might provide a unique opportunity for the investigation of the neural mechanisms of compensatory plasticity in visual object processing. Understanding the nature of amblyopic deficits at different stages of visual information processing might also aid the development of more efficient approaches for the treatment of amblyopia.

Finally, we have provided electrophysiological support for the hypothesis that suppression of the visual input from the weaker eye is the primary underlying mechanism of the amblyopic syndrome by demonstrating that the input from the amblyopic eye is completely suppressed already at the earliest stages of visual cortical

processing during binocular viewing. These findings underline the importance of considering suppression when treating amblyopia.

Taken together, the findings of the above series of studies can help us understand the neural mechanisms of amblyopia in more depth. Thus, they might aid in the development of a more efficient screening method as well as training protocols for visual impairments resulting in amblyopia in childhood. Importantly, the close monitoring of the changes in the uncovered neural correlates during training could bring about more effective personalized protocols, which is our future goal.

Acknowledgments

Foremost, I would like to thank my supervisor, *Prof. Zoltán Vidnyánszky* for his support and helpful guidance throughout my study and research. I owe special thanks to my other supervisor, *Éva Bankó*, for her enthusiasm, motivation, continuous practical and theoretical support. I am very grateful to the Doctoral School, especially to *Prof. Tamás Roska* and *Prof. Péter Szolgay* for providing the opportunity to spend my Ph.D years in a multi-disciplinary environment. I am also very thankful to *Prof. János Németh*, head of Department of Ophthalmology, Semmelweis University to support my work.

I would like to thank to *Zsuzsanna Vágó* and *Prof. Árpád Csurgay* for giving me a deeper understanding of mathematics and physics. I would like to express my sincere gratitude to *Prof. József Hámori* and *Prof. György Karmos* for sharing their knowledge with me and for their encouragement.

Very special thanks to *Patricia Domsa* who introduced me to the world of pediatric ophthalmology, for her invaluable support and teaching.

I am also grateful to all my close colleagues, *Viktor Gál*, *István Kóbor*, *Petra Hermann*, *Balázs Knakker*, *Gergely Pápay* and *Vanda Nemes* for all their help, fruitful discussions and the time we spent together.

I say thanks to all my fellow Ph.D students especially to *Norbert Bérci*, *András Bojársky*, *Balázs Karlócai*, *Ferenc Lombai*,

Dániel Szolgay, Barnabás Hegyi, Balázs Gergely Soós, Béla Weiss, Kálmán Tornai and Zoltán Kárász for their help.

I owe a lot to *Lívía Adorján* and *Katinka Tivadarné Vida* for their practical and official aid. I am also very thankful to *Viktória Sifter* from the Library.

I am indebted to all of the *patients* and healthy *controls* who participated in our experiments.

In addition thanks are also due to all my *friends* for being so patient during my busy days.

Last but certainly not least I am tremendously grateful to *family* for all their love and support, especially to my loving husband *Kristóf* for being beside me.

Publications

The author's journal publications

- [1] J. Körtvélyes, E. M. Bankó, A. Andics, G. Rudas, J. Németh, P. Hermann, and Z. Vidnyánszky, "Visual cortical responses to the input from the amblyopic eye are suppressed during binocular viewing," *Acta. Biol. Hung.*, vol. 63 Suppl 1, pp. 65–79, 2012.
- [2] É. M. Bankó, J. Körtvélyes, J. Németh, B. Weiss, and Z. Vidnyánszky, "Amblyopic deficits in the timing and strength of visual cortical responses to faces," *Cortex*, vol. 49, no. 4, pp. 1013–1024, 2013.
- [3] É. M. Bankó, J. Körtvélyes, J. Németh, and Z. Vidnyánszky, "Amblyopic deficit beyond the fovea: delayed and variable single-trial ERP response latencies, but unaltered amplitudes," *Invest. Ophthalmol. Vis. Sci.*, vol. 55, no. 2, pp. 1109–1117, Feb. 2014.

The authors' conference publications

- [4] J. Körtvélyes, É. M. Bankó, J. Németh, and Z. Vidnyánszky, "Impaired foveal and peripheral face processing in amblyopia," *36th Annual Meeting of the European Paediatric Ophthalmological Society*, Bad Neuheim, Germany, 2010.
- [5] J. Körtvélyes, É. M. Bankó, V. Gál, G. Pápay, P. Domsa, J. Németh, and Z. Vidnyánszky, "Neural correlates of fovea-related impairment of visual object processing in amblyopia," *Investigative Ophthalmology & Visual Science 50: Paper E-3820*, *ARVO Annual Meeting*, Fort Lauderdale, USA, 2009.
- [6] J. Körtvélyes, É. M. Bankó, V. Gál, G. Pápay, P. Domsa, J. Németh, and Z. Vidnyánszky, "Neural correlates of fovea-related impairment of visual object processing in amblyopia," *Frontiers in Systems Neuroscience online: Paper online*, 2009.

- [7] J. Körtvélyes, “Neural Dynamics of Shape-specific Visual Information Processing in Amblyopia,” *Péter Pázmány Catholic University PhD Proceedings*, 2008, pp. 65–68.
- [8] É. M. Bankó, J. Körtvélyes, A. Andics, J. Németh, V. Gál, and Z. Vidnyánszky, “Impairment in object-specific visual processing in amblyopia: a neurophysiological study.,” *Frontiers in Neuroscience, 13th Meeting of the Hungarian Neuroscience Society (MITT)*, Budapest, 2011.
- [9] É. M. Bankó, J. Körtvélyes, J. Németh, P. Hermann, and Z. Vidnyánszky, “Increased latency and timing uncertainty of visual cortical responses in amblyopia,” *Neuroscience Meeting Planner, Society for Neuroscience, Program No. 798.20*, Washington, DC, 2011.
- [10] É. M. Bankó, J. Körtvélyes, J. Németh, and Z. Vidnyánszky, “Electrophysiological correlates of impaired foveal and peripheral face processing in amblyopia.,” *Proc. FENS Forum*, Amsterdam, 2010, vol. 5, 137.1.
- [11] P. Domsa, J. Körtvélyes, V. Gál, and Z. Vidnyánszky, “Multiple object tracking in amblyopia,” *Perception* 36, 2007, p. 88.
- [12] K. Markó, J. Körtvélyes, G. Drótos, Á. Bankó, J. Németh, Z. Vidnyánszky, and É. M. Bankó, “Video game training in amblyopia,” *Annual Congress of the Hungarian Ophthalmological Society 2015*, Pécs, 2015.

The author's other journal publications

- [13] É. M. Bankó, J. Körtvélyes, B. Weiss, and Z. Vidnyánszky, “How the visual cortex handles stimulus noise: insights from amblyopia,” *PLoS ONE*, vol. 8, no. 6, p. e66583, 2013.
- [14] E. M. Bankó, V. Gál, J. Körtvélyes, G. Kovács, and Z. Vidnyánszky, “Dissociating the effect of noise on sensory processing and overall decision difficulty,” *J. Neurosci*, vol. 31, no. 7, pp. 2663–2674, Feb. 2011.

Cummulative Impact Factor of international journal papers: 20.9

Number of independent citations: 30

Selected Publications Cited in the Dissertation

- [15] C. Wu and D. G. Hunter, “Amblyopia: diagnostic and therapeutic options,” *Am. J. Ophthalmol.*, vol. 141, no. 1, pp. 175–184, Jan. 2006.
- [16] R. Harrad and C. Williams, “Risk, causes and outcomes of visual impairment after loss of vision in the non-amblyopic eye, a population-based study, by J. S. Rahi, S. Logan, C. Timms, I. Russel-Eggitt, and D. Taylor. *Lancet* 360:597-602, 2002,” *Surv Ophthalmol*, vol. 48, no. 2, p. 235, Apr. 2003.
- [17] V. Tommila and A. Tarkkanen, “Incidence of loss of vision in the healthy eye in amblyopia,” *Br J Ophthalmol*, vol. 65, no. 8, pp. 575–577, Aug. 1981.
- [18] D. H. Brainard, “The Psychophysics Toolbox,” *Spat Vis*, vol. 10, no. 4, pp. 433–6, 1997.
- [19] D. G. Pelli, “The VideoToolbox software for visual psychophysics: transforming numbers into movies,” *Spatial Vision*, vol. 10, pp. 437–442, 1997.
- [20] F. A. Wichmann and N. J. Hill, “The psychometric function: I. Fitting, sampling, and goodness of fit,” *Percept Psychophys*, vol. 63, no. 8, pp. 1293–313, Nov. 2001.