DOI:10.15774/PPKE.ITK.2015.009

ELECTROPHYSIOLOGICAL CHARACTERIZATION OF THE AMBLYOPIC NEURAL DEFICIT

Ph.D dissertation

Judit Körtvélyes MD

Scientific adviser:
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

DOI:10.15774/PPKE.ITK.2015.009

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

DOI:10.15774/PPKE.ITK.2015.009

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 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 Patrícia 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 Béci, András Bojárszky, 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 Lívia 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 my sister, my parents and grandparents for all their love and support, especially to my grandfather who always believed in me. I would like to thank my loving husband Kristóf for being beside me.

DOI:10.15774/PPKE.ITK.2015.009

SUMMARY OF ABBREVIATIONS

Abbreviation	Concept
AE	amblyopic eye
ANOVA	analysis of variance
ATS	Amblyopia Treatment Studies
BCVA	best corrected visual acuity
BO	binocular
BOLD	blood oxigenation-level dependent
Br	broad spatial spectrum
D	diopter
Dsph	spherical diopter
Dcyl	cylindrical diopter
EEG	electroencephalogram
ERP	event-related potential
ET	esotropia
Exp.	experiment
FE	fellow eye
FFA	fusiform face area
fMRI	functional magnetic resonance imaging
ITI	inter-trial interval
IQR	interquartile range
Lo	low-pass filtered
mfVEP	multifocal visual evoked potential
PEDIG	Pediatric Eye Disease Investigator Group
RT	reaction time
SCD	scalp current density
SNR	signal to noise ratio
SOA	stimulus onset asynchrony
RT	reaction time
rTMS	repetitive transcranial magnetic stimulation
VA	visual acuity
VEP	visual evoked potential
XT	exotropia

DOI:10.15774/PPKE.ITK.2015.009

TABLE OF CONTENTS

Chapter One
Introduction 7
1. Motivations 7
2. Amblyopia 7
2.1. What is amblyopia? 8
2.2. Causes of amblyopia 8
2.3. Strabismic and anisometropic amblyopia 9
2.4. Treatment 11
2.5. Electrophysiological deficits in amblyopia 13
2.6. Open questions 14
3. Goals of the dissertation 15
4. Methods 15

Chapter Two
The strength of interocular suppression 17
1. Motivations 17
2. Materials and methods 17
2.1. Subjects 17
2.2. Visual stimuli 19
2.3. Procedure 19
2.4. Data analysis 20
3. Results 21
3.1. Behavioral results 21
3.2. Amblyopic effects on amplitude and latency of the early ERP components 22
4. Discussion 24

Chapter Three
Amblyopic deficits in high-level object processing 26
1. Motivations 26
2. Materials and methods 27
2.1. Subjects 27
2.2. Visual stimuli and procedures 27
2.3. Electrophysiological acquisition and processing 29
2.4. Statistical analysis 30
2.5. Analysis of eye tracking data 31
3. Results 32
3.1. Behavioral results 32
3.2. Amblyopic effects on the averaged ERP responses 32
3.3. Amblyopic effects differ on trial-by-trial latency and amplitude 35
3.4. Results of the analysis of the ongoing oscillations 40
3.5. Results of the eye-tracking analysis 41
3.6. Average-referenced mean ERP responses show similar amblyopic effects 42
4. Discussion 43

Chapter Four
Amblyopic deficit beyond the fovea 46
1. Motivations 46
2. Materials and methods 47

DOI:10.15774/PPKE.ITK.2015.009

2.1. Subjects....47
2.2. Visual stimuli and procedures....48
2.3. Electrophysiological acquisition and processing....51
2.4. Statistical analysis....51
2.5. Analysis of eye-tracking data....52
3. Results....53
3.1. Behavioral results....53
3.2. Averaged ERPs show amblyopic deficit both at the fovea and perifovea....54
3.3. Amblyopic latency distributions display both foveal and perifoveal deficit....62
3.4. Fellow eye ERPs do not differ significantly from control ERPs....62
4. Discussion....64
4.1. Importance of cortical magnification....65
4.2. Deficient ERP response timing in amblyopia....65
4.3. Unaltered amblyopic ERP response strength at the periphery....66

Chapter Five
Conclusions and possible applications....67

Chapter Six
Summary....70
New scientific results....70
Bibliography....72

DOI:10.15774/PPKE.ITK.2015.009

Chapter One

INTRODUCTION

1. Motivations

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. For best results correction should happen no later then 3-5 years. 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. As a result, most of the children affected by visual impairments resulting in amblyopia are only diagnosed at school age when the impairment has fully developed and chances of effective therapy are significantly lower. 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.

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 1.6%). 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.

2. Amblyopia

The earliest clinical description of human amblyopia is generally credited to Le Cat in 1713. Pioneering work by David Hubel and Torsten Wiesel, based on animal models, led to the hypothesis that amblyopia is the result of competition between each eye’s afferents into the visual cortex during the formative stages of the visual system [15, 16]. Amblyopia literally means "dullness of vision" (from the Greek amblyos—dull; opia, from the stem ops—vision) [17]. It arises from abnormal visual experiences in early childhood. According to large population studies it occurs in 1.6-3.6% of the population [18–22] with evidence that the rate is even higher in medically underserved populations [23]. 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 [24]. Amblyopia accounts for more cases of unilateral reduced vision in children than all other causes combined [25].

DOI:10.15774/PPKE.ITK.2015.009

2.1. What is amblyopia?

Amblyopia has traditionally been defined by what it is not, rather than by what it is. Definitions often include aphorisms such as a disorder “in which the patient sees nothing and the doctor sees nothing” [26, 27]. It can be defined as a unilateral or, less commonly, bilateral reduction in best corrected visual acuity, not directly attributed to a structural abnormality of the eye or posterior visual pathways. Eyes appear normal on physical examination. Unilateral amblyopia is clinically defined as a two-line difference of best corrected visual acuity between the eyes. It is one of the most common causes of vision loss and primary causes are strabismus, anisometropia (significant difference in refractive error between the two eyes) and stimulus deprivation (in particular congenital cataract and ptosis). Early detection of amblyopia is crucial in obtaining the best response to treatment. If treated early in life, is completely or partially reversible [17].

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 [28, 29]. This fact adds urgency to our efforts to learn more about this disorder. The lifetime risk of blindness because of loss of the better eye is 1.2% [30]. If the better seeing eye is lost, the visual acuity of 10% of amblyopic eyes can improve [31]. These findings suggest there is some plasticity in the visual system of a few visually mature individuals with amblyopia.

Based on animal studies [32] and functional human neuroimaging [33], amblyopia can be defined as a disorder in which there is dysfunction in the processing of visual information. This dysfunction is usually detected and evident as reduced recognition visual acuity, although the abnormalities include many types of visual function [34] such as contrast-sensitivity function (CSF), vernier acuity as well as spatial distortion [35], abnormal spatial interactions [36, 37], impaired contour detection [38] and binocular abnormalities such as impaired stereoacuity and abnormal binocular summation. Although clinical ocular examination is most often entirely normal, microscopic anatomical and structural abnormalities have been found in the retina [39], lateral geniculate bodies [40], and visual cortex [41]. The visual deficiencies are thought to be irreversible after the first decade of life, by which time the developmental maturation window has been terminated.

2.2. Causes of amblyopia

The degradation of the image, and subsequent central suppression that leads to amblyopia, results from one of three causal processes (Table 1.1). About a third of amblyopia is caused by strabismus (ocular deviation), a third by anisometropia (unequal interocular refractive error), and a third by a combination of both disorder types [27, 42, 43]. Deprivation amblyopia

DOI:10.15774/PPKE.ITK.2015.009

results from occlusion of the pupil and lack of pattern stimulation. It seems to be rare, based on the incidence of the primary causative factors such as infantile cataract (2 to 4.5 of every 10000 births) [44, 45], corneal dystrophy, ptosis, media opacities, or excessive patching therapy for amblyopia treatment (reverse amblyopia) accounting for only up to 3% of cases [46], but it has the most potential to cause severe amblyopia.

	Features	**Unilateral or bilateral effect**
Strabismus (ocular misalignment)	The eyes do not receive corresponding images on the fovea	Unilateral
Anisometropia (difference in refractive error)	One foveal image is more blurred than the other	Unilateral
Deprivation (including ametropia—ie, large symmetric refractive errors)*	Physical obstruction of one image (eg. cataract, ptosis, or bilateral blur from uncorrected refractive error)	Either

Table 1.1. Causes of amblyopia [27]. *Amblyopia is the residual visual deficit after the physical obstruction is removed and appropriate optical correction is provided.

2.3. Strabismic and anisometropic amblyopia

Strabismic and anisometropic amblyopia differ in the spectrum of associated visual deficits despite their common effect on visual acuity. Levi and Klein found that in amblyopes with strabismus the deficits in optotype acuity and in Vernier acuity were disproportionately greater than the deficit in grating acuity, whereas anisometropic amblyopia is associated with proportional deficits in optotype, vernier, and grating acuity [47, 48]. There are two hypotheses regarding the source of differences in the pattern of visual deficits between these two types of amblyopia. First is the etiology hypothesis, the differences may reflect fundamentally different pathophysiological processes [49]. For example, sparse/irregular sampling may be associated with binocular competition between two discordant images in strabismus but not between the sharp versus defocused images in anisometropia. The second hypothesis is the effective age hypothesis, the different constellations of spatial deficits in anisometropic and strabismic amblyopia reflect the degree of visual maturation present at the onset of amblyopia [49]. That is anisometropic amblyopia may arise at an age where visual maturation is more complete [22]. Birch at al. found the same, that anisometropia may develop later, and become an etiologic factor for amblyopia primarily after 3 years of age or another

DOI:10.15774/PPKE.ITK.2015.009

alternative is that anisometropia may be present early but requires a longer duration than strabismus to cause amblyopia [22].

Both types of amblyopia show a selective decrease in foveal vision [35], however, tests of contrast sensitivity also indicate some peripheral field visual deficits [50]. The deficit is generally more limited to central vision in strabismic amblyopia [51], which is thought to be similar to peripheral vision, compared to anisometropic amblyopia, which is like blurred normal foveal vision [52, 53]. This distinction is in agreement with the differential effect of flankers in anisometropic and strabismic amblyopes in visual crowding experiments [36, 52, 54].

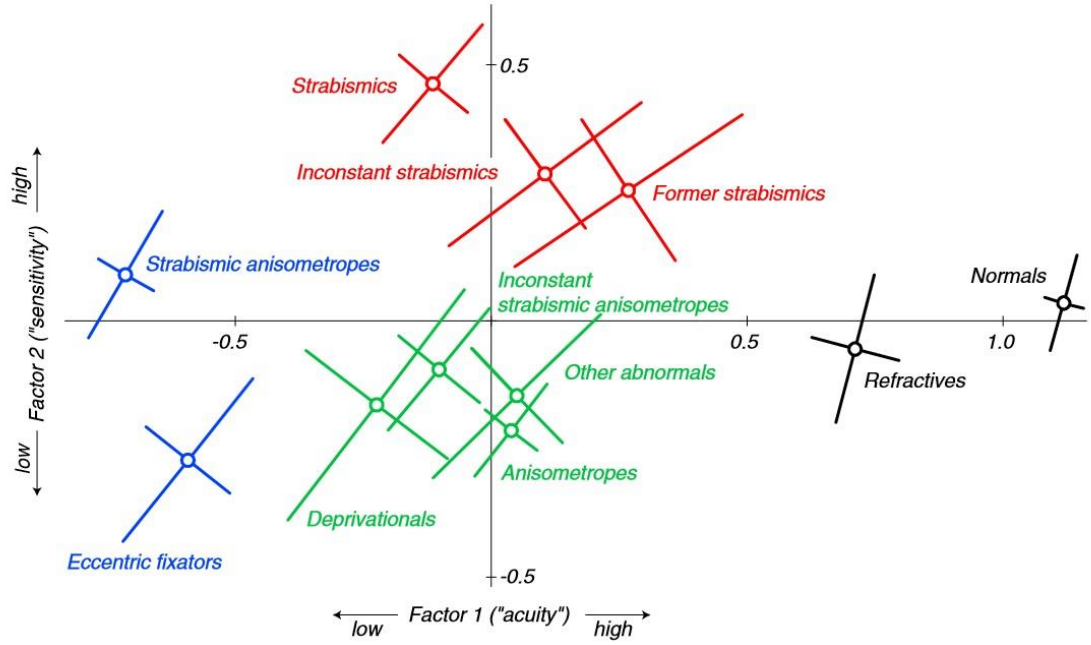

Figure 1.1. McKee's "amblyopia map": Factor 1 ("acuity"): acuity measures (optotype, Vernier, and grating). Factor 2 ("sensitivity"): contrast sensitivity measures (edge contrast and PelliRobson contrast thresholds). The coloring captures the four broad categories: normal or near-normal (black), moderate acuity loss with superior (red) or impaired (green) sensitivity, and severe acuity loss (blue). These four zones correspond roughly to a traditional classification scheme: normals (black), strabismics (red), anisometropes (green), and strabismic anisometropes (blue) [34].

In McKee's "amblyopia map" strabismics show supernormal sensitivity (edge contrast and PelliRobson contrast thresholds), well above that of the anisometropes. Anisometropes, despite their poor sensitivity, show an acuity (optotype, Vernier, and grating acuity) that is as good or perhaps slightly better than strabismics (Figure 1.1) [34]. Many eccentric fixators are probably strabismic anisometropes with severe visual acuity loss. In the same study two thirds of the anisometropes passed motion integration, randot circles tests, while only about 10% of constant strabismics passed both tests.

DOI:10.15774/PPKE.ITK.2015.009

There is evidence that using checkerboard patterns calcarine activity as measured with fMRI was most suppressed for low spatial frequency stimuli in strabismics, while in anisometropic patients it was most reduced for high frequency patterns [55, 56]. On the other hand, the fMRI study by Conner and colleagues [57] has failed to differentiate anisometropic and strabismic subtypes based on fMRI activation levels in retinotopic maps of V1 and V2, while animal studies of contour/motion integration and form detection also found similar deficiencies for the amblyopic eyes of both strabismic and amblyopic monkeys [58, 59]. Kiorpes and colleagues [60] in a macaque study also found that physiological changes associated with amblyopia were related to the severity, not the etiology, of the visual losses.

2.4. Treatment

In the past several years much has been published regarding the treatment of this disease, owing mostly to a series of Amblyopia Treatment Studies (ATS) undertaken by the Pediatric Eye Disease Investigator Group (PEDIG). These studies were designed to evaluate the traditional methods for treating amblyopia and provide evidence on which to base treatment decisions.

In general, treatment for amblyopia consists of depriving the healthy eye of visual input by patching or by optical or pharmaceutical penalisation to force the use of the amblyopic eye. In deprivation amblyopia, the cause of the visual deprivation needs to be addressed first and then the disorder should be treated similarly to other types of amblyopia. In anisometropic amblyopia, refractive errors need to be corrected with spectacles or contact lenses or refractive surgery. In strabismic amblyopia, conventional wisdom states that amblyopia should be treated first, and that correction of the strabismus will have little if any effect on amblyopia, although the timing of surgery is controversial [27].

Table 1.2 summarises the degrees of refractive error thought to induce amblyopia. With the optimum refractive correction in place, any residual visual deficit is, by definition, due to amblyopia. Convincing evidence indicates that continued spectacle wear is therapeutic in its own right, providing a clear image to the fovea of the amblyopic eye for perhaps the first time.

Patching, atropine

Patching and atropine have been used to treat amblyopia for hundreds of years. Only in the last 15 years have randomized clinical trials been conducted to evaluate the effectiveness of amblyopia treatment and to begin to define optimal treatment protocols. Occlusion therapy with patching of the dominant eye has been the cornerstone of amblyopia treatment. On average, 120 h of occlusion results in a one-line (0.1 logMAR) improvement in visual acuity at 6 years of age [61]. Beyond the critical period for plasticity, supervised patching (movie

DOI:10.15774/PPKE.ITK.2015.009

watching while dominant eye patched) has been shown to have positive impact for anisometropic, but not for strabismic amblyopia in adults [62].

Atropine is used as a 1% drop to the healthy eye, blocking parasympathetic innervation of the pupil and ciliary muscle and causing pupillary dilatation and loss of accommodation, thus blurring the vision at near and allowing the amblyopic eye to be used preferentially. Atropine penalization works less quickly than occlusion [63] and generally has been advocated for amblyopia with vision better than 20/100, because it may not be sufficient to switch fixation in severe amblyopia [24]. In some cases, occlusion and atropine penalization may be combined.

	Prescribing guidelines for children aged 2–3 years*	**Spectacle requirements before entry into recent randomised trials†**
Anisometropia **		
Hyperopic	≥+1·50D	≥+1·00D
Astigmatism	≥2·00D	≥1·50D
Myopic	≥–2·00D	≥–1·00D
Symmetric		
Hyperopia	≥+4·50D	>+3·00D
Myopia	≥–3·00D	>–3·00D

Table 1.2. Degrees of refractive error thought to induce amblyopia [27]. ** asymmetric refractive error, *Based on prescribing guidelines from the American Academy of Ophthalmology for refractive error recorded in a routine eye examination and the philosophy of preventing ambylopia. (American Academy of Ophthalmology. Pediatric eye evaluations, preferred practice pattern. San Francisco, CA, USA: American Academy of Ophthalmology, 2002.), †Based on the minimum amount of refractive error that should be first treated with spectacles, with respect to reduced visual acuity in recent randomised trials by the Pediatric Eye Disease Investigator Group (PEDIG) [64–66].

Levodopa and citocholine

Oral levodopa (which is used to treat Parkinson's disease) and citocholine have been reported in treatment of amblyopia and has shown effects seen on both visual acuity and functional MRI [67–72]. The neuropsychiatric side-effects of these drugs render their use unlikely in routine clinical practice for amblyopia treatment.

Repetitive transcranial magnetic stimulation (rTMS)

It has been reported that a single session of 1 Hz or 10 Hz repetitive transcranial magnetic stimulation (rTMS) and continuous theta burst stimulation (cTBS) of the visual cortex can improve contrast sensitivity in adults with amblyopia [73, 74].

Visual stimulation, perceptual learning

While it is widely believed that amblyopia cannot be treated successfully after the age of about 10, recent studies show that the adult human visual cortex retains a significant degree of plasticity. The stimuli used are very diverse, ranging from Gabor stimuli to different video games and dichoptic training (e.g. tetris) [75]. The perceptual learning therapy of the amblyopic eye leads to significant improvements in visual functions (e.g. visual acuity, stereopsis), especially when both eyes are stimulated simultaneously during the visual training as opposed to conventional procedures that severely penalize the good eye [75–86]. These findings raise the hope that perceptual learning could become a new therapeutic means for treating amblyopia beyond the sensitive period, which currently has no clinically validated treatment option.

2.5. Electrophysiological deficits in amblyopia

Several studies have been performed with electrophysiological methods used in humans and in animal models, to investigate the amblyopic dysfunction of the visual system. Visually evoked potentials provide direct means of measuring the electrical responses of the brain in humans with naturally occuring amblyopia. Using diffuse light flashes, several investigators have reported a decrease in the amplitude of the cortical response to stimulation of the amblyopic eye [87, 88], while others have found no difference between the two eyes [89–91]. When pattern stimuli are used, the results are more consistent, with most investigators reporting decreased amplitude and/or increased latency in the response obtained when stimuli are presented to the amblyopic eye [90–95]. However, most of these earlier studies have restricted the temporal presentation of the gratings or the repetition rate of the diffuse flash to only a small number of temporal frequencies [96].

The reduced function of the amblyopic eye evident in the VEP to spatial contrast is greater for high than for low spatial frequencies, and probably reflects abnormalities of the central portion of the visual field [97].

Most neurophysiologic studies conducted on human amblyopes has focused on the early, low-level visual cortical processing deficits - responsible for e.g. reduced visual acuity and contrast sensitivity [98, 99] -, which are reflected in the P1 component of the visual-evoked responses (VEPs) [41, 96, 100, 101]. However, higher order visual functions (e.g. global form and motion processing) are also affected [102–106], a recent study showing that global motion signal evokes reduced VEP in amblyopia [107].

Traditionally, amblyopia has been regarded as a disorder limited to the central retina [108], even though there exist studies that question this notion [50, 109]. Full-field pattern-reversal VEP studies [101, 110] support the dominantly central deficit in amblyopia based on the lack of interocular difference when using large check sizes (>60’), where response are

DOI:10.15774/PPKE.ITK.2015.009

thought to predominantly arise from neurons processing the periphery of the visual field [101, 111–113]. Stimulation of the amblyopic eye with small check sizes (<30'), on the other hand, which preferentially activates the foveal area [101, 111–113] as it only elicits measurable VEP responses up to 2-4 degrees eccentricity [111], yield drastically reduced and delayed VEP responses. Similar divergence is obtained in studies using small central and large annular stimuli for the stimulation of the fovea and perifovea, respectively [114, 115]. As opposed to full-field VEP, the multifocal VEP (mfVEP) technique is capable of directly investigating peripheral processing by stimulating the visual field at different eccentricities. These studies, on the other hand, tend to find amplitude and latency differences at the perifoveal region as well as the fovea, even though smaller in size [116–118].

2.6. Open questions

1. Previous research revealed that in monocular viewing condition, stimuli presented to the amblyopic eye lead to reduced and delayed visual evoked potentials (VEP) as compared to the stimulation of the fellow eye [41, 96, 100, 101, 107]. Similarly, fMRI responses are also decreased for stimuli presented in the amblyopic eye compared to the fellow eye both in monocular viewing condition as well as in the case when stimuli are presented separately to the amblyopic and fellow eye using red-green glasses [102, 114, 119–123]. However, it is not known whether and to what extent neural responses to the visual information coming from the amblyopic eye is suppressed during binocular viewing condition.

2. The extensive behavioral research in the past decades revealed that amblyopia involves both low level (e.g. reduced visual acuity and contrast sensitivity) [98, 99] and higher-order (e.g. global form and motion processing) visual deficits [102–106]. In agreement with this, human fMRI studies showed reduced fMRI responses throughout the visual processing hierarchy – including the lateral geniculate nucleus, the striate and extra-striate cortex [57, 102, 114, 121–123]. In spite of this, neurophysiologic research in human amblyopes has focused on the early, low-level visual cortical processing deficits, which are reflected on the P1 component of the visual-evoked responses (VEPs) [41, 96, 100, 101] with an exception of a recent study showing that global motion signal evokes reduced VEP in amblyopia [107]. As a result, it is not known how the temporal structure and strength of neural responses at the higher, object-specific stages of visual information processing are altered in human amblyopia.

DOI:10.15774/PPKE.ITK.2015.009

3. Traditionally, amblyopia has been regarded as a disorder limited to the central retina [108], even though there exist studies that question this notion [50, 109]. As the results collected over some four decades are equivocal, no consensus has been reached so far how the peripheral visual field is affected in amblyopia. Today only strabismic amblyopia is considered a deficit primarily of central vision as early psychophysical investigations found that contrast detection threshold [51], acuity [124–126] and binocular interactions [127] are similar between the two eyes from eccentricities of 20˚ on. This is in agreement with macaque single unit recording [60] and human fMRI studies [114] that also found no peripheral interocular differences in strabismic amblyopia. On the contrary, other studies investigating both strabismic and anisometropic amblyopes have shown decreased sensitivity of the amblyopic eye in the periphery for motion detection and discrimination [109] and contrast detection [50] in the eccentricity range of 10-30deg. The extent of the amblyopic loss in the periphery in both experiments was related to the degree of foveal loss rather than the type of amblyopia.

3. Goals of the dissertation

1. In accordance with the above, 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.

2. 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.

3. It's 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.

4. 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 aligmment 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

DOI:10.15774/PPKE.ITK.2015.009

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 - [128], [129]) and for data analysis (Psignifit - [130]) 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.

We chose faces for stimuli as opposed to the more conventional checkerboard or sine wave grating/Gabor patch stimuli in our experiments because they are natural, ecologically valid stimuli and it is possible to control their spatial frequency content just as well as using Gabor patches. In addition our research group is specialized for studying face processing with eletrophysiological and fMRI methods. Thus, we have prior knowledge about the validity of our single-trial peak detection approach on the event-related potentials evoked by faces. Even though it has been previously shown that there is a face specific processing deficit in amblyopia [102], the amblyopic deficit in early neural processing, as reflected in the P1 component, should not be significantly affected by the stimulus used.

Face processing is one of the most researched fields of cognitive neuroscience, since the majority of socially relevant information is conveyed by the face, rendering it as a stimulus of exquisite importance. Faces are considered a special class of stimuli with dedicated neural processing mechanisms that differ from that of other nonface objects. Opinions differ on the reason underlying their special status: one group of researchers claims that faces are processed by cortical areas entirely dedicated to face processing [131, 132], while others argue that the specific responses obtained for faces is a result of the type of judgment we are required to make whenever viewing a face: differentiating that individual face from the rest (i.e. subordinate level of categorization) and also the level of expertise with which we make these categorization judgments [133, 134]. Within the processing circuits there is evidence for a certain degree of separation between changeable (such as expression, lipspeech and eye gaze) and invariant facial attributes (such as identity and gender), the former being coded/processed predominantly in the superior temporal sulcus (STS), the later in the fusiform face area (FFA) [135]. This separation is not exclusive however, since there is significant overlap [136].

DOI:10.15774/PPKE.ITK.2015.009

Chapter Two

THE STRENGTH OF INTEROCULAR SUPPRESSION

1. Motivations

Amblyopia is a visual disorder affecting primarily foveal vision and is caused by an anomalous early visual experience. It has been suggested that suppression of the visual input from the weaker eye might be a primary underlying mechanism of the amblyopic syndrome (for review see [137]). In agreement with this, previous research revealed that in monocular viewing condition, stimuli presented to the amblyopic eye lead to reduced and delayed visual evoked potentials (VEP) as compared to the stimulation of the fellow eye [41, 96, 100, 101, 107]. Similarly, fMRI responses are also decreased for stimuli presented in the amblyopic eye compared to the fellow eye both in monocular viewing condition as well as in the case when stimuli are presented separately to the amblyopic and fellow eye using red-green glasses [102, 114, 119–123]. However, it is not known whether and to what extent neural responses to the visual information coming from the amblyopic eye is suppressed during binocular viewing condition.

To address this question we measured event-related potentials (ERP) to foveal face stimuli in amblyopic patients, both in monocular and binocular viewing conditions. We compared the ERP responses obtained in the binocular viewing condition to those in the monocular stimulation of the amblyopic and fellow eye. We reasoned that strong and efficient suppression of the visual input from the amblyopic eye in the binocular viewing condition would result in ERP responses very similar to those in the monocular stimulation of the fellow eye. On the other hand, if amblyopic input is not or only weakly suppressed during binocular stimulation, it might affect both the amplitude and delay of the early ERP components and thus result in altered ERP responses in the case of binocular compared to the fellow eye stimulation.

2. Materials and methods

2.1. Subjects

Twelve amblyopic subjects (5 females, 9 right-handed, mean age: 31 years) participated in the experiment. In six cases the amblyopic eye was their right eye. None of them had any history of neurological or psychiatric diseases and all had normal or corrected-to-normal visual acuity of the dominant fellow eye (see Table 2.1 for more details).

DOI:10.15774/PPKE.ITK.2015.009
THE STRENGTH OF INTEROCULAR SUPPRESSION

		Refraction		Visual Acuity (VA)			
Subject	Age/Gender	RE	LE	RE	LE	Interocular VA (logMAR)	Squint
A1	32/F	-0.5	+0.5 +1.75 129°	20/12.5	20/80	0.8	ø
A2	20/F	+1.75 +1.25 101°	-1.0 +0.75 82°	20/80	20/20	0.6	ø
A3	36/M	plan	+2.5	20/12.5	20/60	0.7	ø
A4	24/M	-0.25 -1.75 97°	-3.0 -0.75 73°	20/80	20/16	0.7	ø
S1	38/F	+1.5 +1.75 91°	+2.5 +1.0 84°	20/20	20/40	0.3	ø
S2	34/F	+1.25 -1.5 53°	+0.25 +0.25 62°	20/100	20/20	0.7	D=N10Δ ET
S3	24/M	+2.25 +1.0 177°	+3.75 +1.75 117°	20/16	20/30	0.3	D25Δ, N20Δ XT
S4	38/M	-0.25 -0.25 10°	-3.5	20/60	20/12.5	0.7	D=N16Δ ET
S5	22/M	+0.25	-0.25 -0.5 58°	20/80	20/10	0.9	D12Δ, N8Δ XT
S6	39/M	+1.25 -1.25 11°	+0.5 +1.5 95°	20/12.5	20/25	0.3	D=N8Δ ET
S7	23/M	+1.5 +1.25 100°	+2.75 +0.5 63°	20/40	20/12.5	0.5	D=N40Δ XT
S8	44/F	+0.75	+2.0	20/20	20/32	0.2	D=N6Δ ET

Table 2.1. Clinical details of amblyopic subjects (RE: right eye, LE: left eye, D: distant, N: near, ET: esotropia, XT: exotropia)

DOI:10.15774/PPKE.ITK.2015.009

2.2. Visual stimuli

Participants viewed images of human faces and performed a gender categorization task. Face-stimuli consisted of front view grayscale photographs of four female and four male neutral faces that were cropped and covered with a circular mask to eliminate the outer features. All images were equated for luminance and contrast. Stimuli were presented centrally on a uniform gray background and subtended 2 visual degrees, matching approximately the size of the fovea.

2.3. Procedure

Gender categorization was measured by a two-alternative forced choice procedure. Subjects were required to judge the gender of the face images (female/male) as accurately and fast as possible, indicating their choice with one of the mouse buttons. Button assignment was left for female and right for male for half of the subjects and was reversed for the other half. Each stimulus was presented for 250 ms followed by a response window which lasted until the subjects responded but was maximized in 2 s (Figure 2.1). The fixation point was present throughout the entire trial. In the experiment, the inter-trial interval (ITI) was randomized in the range of 1600–1800 ms. Viewing was monocular with the amblyopic eye (AE) in one block and with the dominant fellow eye (FE) in another while the unused eye was patched, while in yet another block viewing was binocular (BO). Each participant completed one run per eye yielding 128 trials each. Stimulus presentation was controlled by MATLAB 7.1. (The Math-Works) using the Cogent 2000 toolbox (http://www.vislab.ucl.ac.uk/cogent.php).

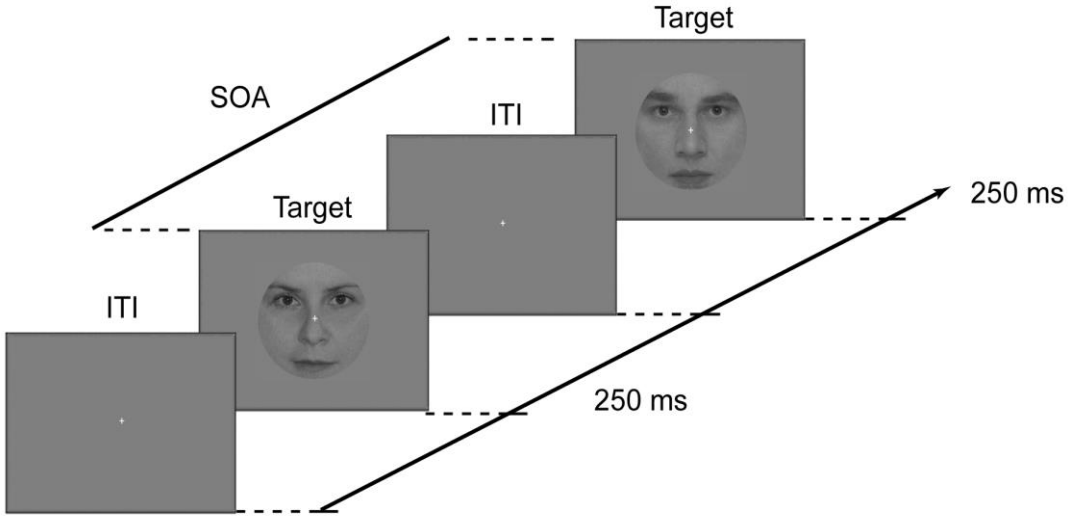

Figure 2.1. Experimental design. In experiment 1 the inter-trial interval (ITI) was randomized in the range of 1600–1800 ms after the response had been made.

In the EEG experiment, visual stimuli were presented on a 26” LG LCD monitor at a refresh rate of 60 Hz and were viewed from 56 cm.

2.4. Data analysis

Behavioral Data Analysis

Responses and reaction times were collected during both experiments. Data was rank transformed where needed to correct for inhomogeneity of variances and entered into one-way repeated-measures ANOVAs with eye (BO vs. FE vs. AE) as within subject factor with Greenhouse-Geisser correction for non-sphericity; post-hoc t-tests were computed using Tukey HSD tests.

Electrophysiological Recording and Analysis

EEG data were acquired using a BrainAmp MR (Brainproducts GmbH., Munich, Germany) amplifier from 60 Ag/AgCl scalp electrodes placed according to the extended 10-20 international electrode system and mounted on an EasyCap (Easycap GmbH, Herrsching-Breitbrunn, Germany) with four additional periocular electrodes placed at the outer canthi of the eyes and above and below the right eye for the purpose of recording the electrooculogram. All channels were referenced to joint earlobes online; the ground was placed on the nasion. All input impedance was kept below 5 kΩ. Data were sampled at 1000 Hz with an analog bandpass of 0.016–250 Hz and re-referenced offline using a Laplacian transform on spherical spline interpolated data (4th order splines, maximum degree of Legendre polynomials:10, lambda: 10^{-5}) to generate scalp current density (SCD) waveforms. The SCD data is reference independent and displays reduced volume conduction eliminating raw EEG contamination from saccadic potentials [138]. Subsequently, a digital 0.1 Hz 12 dB/octave Butterworth Zero Phase high-pass filter was used to remove DC drifts, and a 50 Hz notch filter was applied to minimize line-noise artifacts. Finally, a 24 dB/octave low-pass filter with a cutoff frequency of 30 Hz was applied. Data was segmented (see below) and trials that contained voltage fluctuations exceeding ±100 μV, or electro-oculogram activity exceeding ±50 μV were rejected. Data processing was done using BrainVision Analyzer (Brainproducts GmbH., Munich, Germany).

The trial-averaged EEG waveform – i.e. the event-related potential (ERP) – was computed as follows. Data was segmented into 1000 ms epochs starting from 200 ms preceding the stimuli. Segments were baseline corrected over a 200 ms pre-stimulus window, artifact rejected and averaged to obtain the ERP waveforms for each subject for each condition. Subject ERPs were averaged to compute the grand average ERP for visualization

DOI:10.15774/PPKE.ITK.2015.009

purposes. Statistical analysis was performed on early component peaks (P1, N170) of the averaged ERP waveform. Early peak amplitudes were computed as follows: peak latency was determined individually on pooled electrodes from left and right clusters (P7, P9, PO7, and PO9 and P8, P10, PO8, and PO10) separately, while mean peak amplitudes were measured over the individual electrodes in the above clusters in a 10 ms window centered on the peak latencies. The clusters included electrodes where P1 and N170 showed their maxima, which happened to coincide due to the SCD transform. Amplitude and latency values were rank transformed where needed to correct for inhomogeneity of variances and analyzed by three-way repeated-measure ANOVAs with eye (BO vs. FE vs. AE), side (2) and electrode (4) as within-subject factors separately for each component. Greenhouse-Geisser correction was applied to correct for possible violations of sphericity. Post-hoc t-tests were computed using Tukey HSD tests.

We assessed the relationship using Pearson correlation between the relative changes (AE-FE) in ERP component amplitude and latency and the difference in interocular visual acuity (VA) (AE-FE) expressed in logMAR values obtained at a distance of 4 m with the best refractive correction, the difference in performance (FE-AE) and in reaction time (RT) (AE-FE). Latency and amplitude measures can be treated as independent, while measured values over the different hemispheres and different behavioral measurements are strongly dependent on each other. Therefore, the significance threshold was set to p=0.025 (pBonf =0.05) to correct for the multiple comparisons problem.

3. Results

3.1. Behavioral results

Performance in the gender categorization task was decreased when stimuli were presented in the amblyopic eye (rank ANOVA: main effect of eye: $F_{(2,22)}$=5.57, $p_{G\text{-}Gcorr}$=0.021, post hoc: p=0.036, p=0.014 compared with binocular viewing and the fellow eye conditions, respectively, Figure 2.2A). Similar amblyopic effects were found on the reaction times: responses with amblyopic viewing were significantly slower than in the other two conditions (main effect of eye: $F_{(2,22)}$=14.58, $p_{G\text{-}Gcorr}$=0.0003, post hoc: p=0.0008 and p=0.0003 compared with the binocular viewing and the fellow eye condition, respectively, Figure 2.2B) Importantly, however, performance and reaction times did not differ between the presentation to the fellow eye and the binocular viewing condition (post hoc: BO vs. FE p=0,911 and p=0,84 for performance and RTs, respectively).

DOI:10.15774/PPKE.ITK.2015.009

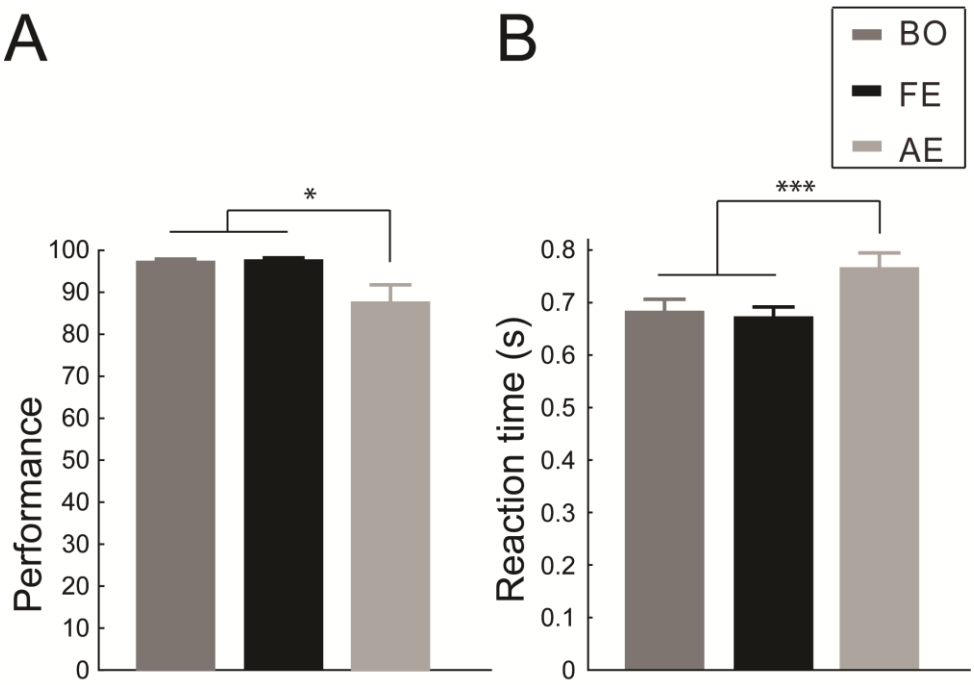

Figure 2.2. Behavioral results. (A) Accuracy and (B) reaction times in the binocular, fellow eye and amblyopic viewing conditions. In all cases the amblyopic eye performed worse/slower, while there was no difference between the fellow eye and binocular viewing (N=12, * p<0.05; *** p<0.001).

3.2. Amblyopic effects on amplitude and latency of the early ERP components

Electrophysiological results revealed that amblyopia has a profound effect on the amplitude and latency of the early event-related potential (ERP) components. Viewing with the amblyopic eye resulted in reduced amplitudes (rank ANOVA: main effect of eye: $F_{(2,22)}$=11.00, $p_{G\text{-}Gcorr}$=0.0036 and $F_{(2,22)}$=8.28, $p_{G\text{-}Gcorr}$=0.007 for the components P1 and N170, respectively; post hoc: AE vs. BO p=0.0008, AE vs. FE p=0.0035 for the component P1, post hoc: AE vs. BO p=0.0065, AE vs. FE p=0.0043 for the component N170) and increased latencies (main effect of eye: $F_{(2,22)}$=18.18, $p_{G\text{-}Gcorr}$=0.0004 and $F_{(2,22)}$=25.47, $p_{G\text{-}Gcorr}$<0.0001 for the components P1 and N170, respectively, post hoc AE vs. BO p=0.0002, AE vs. FE p=0.0002, for the component P1, post hoc: AE vs. BO p=0.0001, AE vs. FE p=0.0002, for the component N170) compared with the fellow eye and the binocular viewing condition for both early ERP components (Figure 2.3A). However, in accordance with the behavioral results, there was no difference in the early ERP responses between the fellow eye presentation and the binocular viewing condition (post hoc: BO vs. FE p=0.79 and p=0.98 for the P1 and N170 amplitude, respectively; p=0.89 and p=0.63 for the P1 and N170 latency, respectively).

DOI:10.15774/PPKE.ITK.2015.009

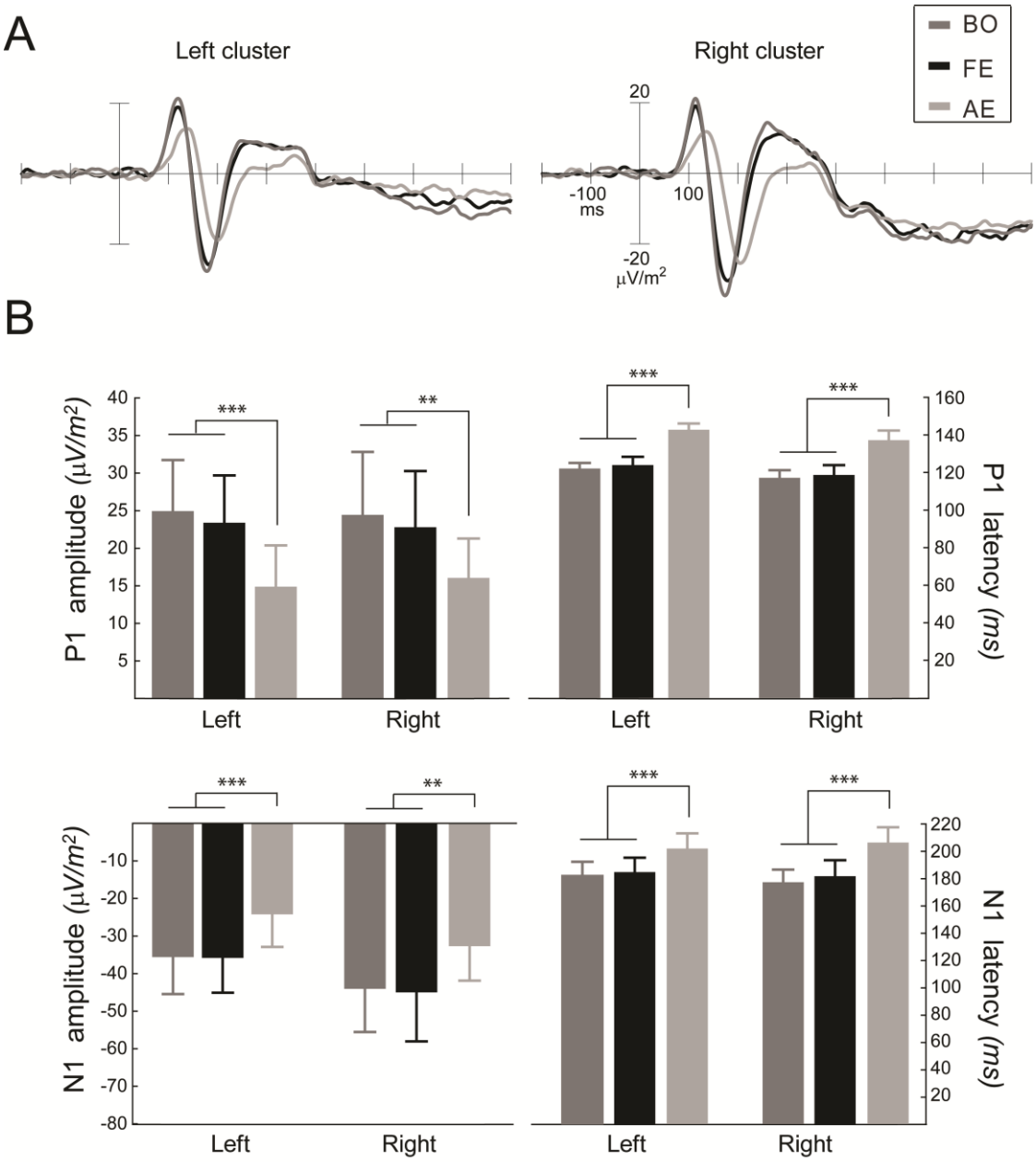

Figure 2.3. Electrophysiological results. (A) Amblyopic effects on the grand average ERPs of the left and right electrode cluster (P7, P9, PO7, and PO9 and P8, P10, PO8, and PO10). (B) Amblyopic effects on the P1 and N170 component amplitude and latency. Stimulation of the amblyopic eye resulted in reduced 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).

Next, we tested the relationship between the amblyopic effects measured on the ERP components (i.e. interocular difference in the amplitude and latency of the early components) and the amblyopic impairment in visual acuity (VA, logMAR), face gender categorization performance and reaction times. We found significant correlation between the amblyopic effects on the behavioral measures and on the latency of the N170 component over the right hemisphere (N170 latency vs. VA r=0.66, *p*=0.019; N170 latency vs. performance r=0.67,

DOI:10.15774/PPKE.ITK.2015.009

p=0.017; N170 latency vs. RT r=0.63, *p*=0.027). Amblyopic effects on the N170 over the left hemisphere and on the P1 component showed no correlation with the amblyopic impairments found on the behavioral measures. Behavioral impairments also did not correlate with the amblyopic effects on the amplitudes of either component (see Table 2.2).

		P1			N170		
	Hemisphere	VA	Perf	RT	VA	Perf	RT
Amplitude	Right	r=-0.0057 *p*=0.986	r=-0.2569 *p*=0.420	r=0.2862 *p*=0.367	r=0.1101 *p*=0.733	r=0.3062 *p*=0.333	r=0.4302 *p*=0.163
	Left	r=0.5536 *p*=0.062	r=0.4975 *p*=0.100	r=.2820 *p*=0.375	r=0.2328 *p*=0.467	r=0.1216 *p*=0.707	r=0.3967 *p*=0.202
Latency	Right	r=0.5201 *p*=0.083	r=0.3429 *p*=0.275	r=0.4405 *p*=0.152	**r=0.6608 *p*=0.019**	**r=0.6709 *p*=0.017**	**r=0.6326 *p*=0.027**
	Left	r=0.1585 *p*=0.623	r=0.2876 *p*=0.365	r=0.1824 *p*=0.570	r=0.4341 *p*=0.159	r=0.3994 *p*=0.198	r=0.5375 *p*=0.071

Table 2.2. Pearson r and p values of the correlation analysis between the amblyopic effect on peak amplitudes/latencies and the amblyopic effect on behavioral measures. N= 12, VA: visual acuity, Perf: performance, RT: reaction time. Significant correlations are indicated by bold face.

4. Discussion

The results revealed no difference in the amplitude and latency of early P1 and N170 components of the ERP responses between the binocular and fellow eye stimulation. This is in accordance with the behavioral results showing that face gender categorization performance and reaction times are identical when stimuli are presented binocularly or to the fellow eye. On the other hand, in agreement with previous results we found strong amblyopic effects on the behavioral measures as well as on the P1 and N170 ERP components in the case of monocular stimulation of the amblyopic eye.

Previous research investigating interocular suppression in healthy visual systems revealed that suppression processes might start very early in visual processing [138–141]. Furthermore, previous psychophysical [142, 143] and fMRI [105, 106, 119] studies provided converging evidence that information conveyed by the non-dominant stimuli during binocular rivalry might almost entirely be suppressed in ventral areas of the visual cortex. In addition, an fMRI study investigating the processing of faces in amblyopia using anaglyph stimuli found almost no activation in FFA during amblyopic stimulation as the magnitude of the amblyopic effects on the fMRI responses to faces increased as one moves to more downstream visual cortical areas, such as FFA [102]. These results are at odds with ours showing reduced, but still clearly identifiable amblyopic responses in the N170 component. The most parsimonious

DOI:10.15774/PPKE.ITK.2015.009

explanation for this discrepancy might lie in the difference in stimulus presentation, as it is reasonable to assume that the stronger signal reduction for the stimuli presented to the amblyopic eye in the Lerner et al [102] compared with the current study might be due to the fact that interocular suppression of the amblyopic eye might be stronger when the fellow eye is open and fixating as compared to when it is closed as was the case in our study. FMRI studies also revealed the dominant eye response differs less from the binocular response than does the amblyopic eye response both in cortical area and mean level of activation [145]. Moreover, both a delay and an amplitude reduction was found in the early visual cortical hemodynamic response function (HRF) of amblyopic eye stimulation under the suppressed binocular condition [146]. However the BOLD signal is only an indirect measure of the underlying neural response integrated in time, having a much worse temporal resolution compared with the ERP response. Therefore, our findings of suppression early in time strengthen the above results obtained with fMRI.

In conclusion, our findings are in agreement with these previous results, by showing that input from the amblyopic eye is completely suppressed already at the earliest stages of visual cortical processing during binocular viewing.

Chapter Three

AMBLYOPIC DEFICITS IN HIGH-LEVEL OBJECT PROCESSING

1. Motivations

The extensive behavioral research in the past decades revealed that amblyopia involves both low level (e.g. reduced visual acuity and contrast sensitivity) [98, 99] and higher-order (e.g. global form and motion processing) visual deficits [102–106]. In agreement with this, human functional magnetic resonance imaging (fMRI) studies showed reduced fMRI responses throughout the visual processing hierarchy – including the lateral geniculate nucleus, the striate and extra-striate cortex [57, 102, 114, 119, 121–123]. In spite of this, neurophysiologic research in human amblyopes has focused on the early, low-level visual cortical processing deficits, which are reflected on the P1 component of the visual-evoked responses (VEPs) [41, 96, 100, 101] with an exception of a recent study showing that global motion signal evokes reduced VEP in amblyopia [107]. As a result, it is not known how the temporal structure and strength of neural responses at the higher, object-specific stages of visual information processing are altered in human amblyopia.

To address this question we measured event-related potential (ERP) responses to foveal face stimuli in amblyopic patients. More specifically, our goal was to characterize the amblyopic deficits in the face-selective N170 ERP component, reflecting higher level structural processing of facial information (for a review see [147]) and originating from a network of occipito-temporal cortical areas [148–150] and compare it to the amblyopic effects present already at the P1 ERP component, which marks primarily the low-level cortical processing of visual features. Importantly, we used single trial analysis, which enabled us to investigate the amblyopia-related deficits selectively in the amplitude and latency of the ERP components. This was critical because neurophysiological research on strabismic cats suggests [151–153] that neuronal response latencies could be more variable in visual cortical neurons driven by the amblyopic eye, which would manifest itself in reduced amplitudes of the averaged ERP responses [154] and thus might account at least partly for the strong reduction of the averaged P1 amplitudes in previous studies [41, 96, 100, 101]. Furthermore, the current study was designed to be able to test whether ongoing oscillations at the time of stimulus onset differ between the stimulation of the amblyopic eye and fellow eye, since ongoing oscillations are known to affect evoked neural responses [155–157] and thus, could contribute to the amblyopic deficits measured in the ERPs. We recorded eye movements during the ERP

DOI:10.15774/PPKE.ITK.2015.009

experiment to investigate the relationship between the stability of fixation and the ERP component amplitudes and latencies. This was important, because previous research suggested that decreased fixation stability exhibited by the amblyopic eye [158, 159] might modulate multi-focal VEP responses [116].

2. Materials and methods

2.1. Subjects

Nineteen amblyopic patients (five anisometropic, six had their right eye as the amblyopic eye, four left-handed, ten females, mean±sd age: 30±8 years) gave their informed and written consent to participate in the study, which was approved by the ethics committee of Semmelweis University. However, one of them had to be excluded due to his poor performance on the task with both eyes. All subjects were examined by an ophthalmologist and fitted with optimal correction Table 3.1 details their medical parameters.

2.2. Visual stimuli and procedures

Participants performed a two-alternative forced choice gender categorization task with morphed female/male face images. Detailed description of image processing can be found in [14]. The level of task difficulty was adjusted individually to achieve 80-90% accuracy in both eyes by choosing face pairs with different female/male content for the eyes (typically 25/75% and 5/95% gender content for the fellow and amblyopic eye, respectively; Figure 3.1A). On half of the trials, subjects were presented with noisy, decreased phase coherence face images [14], while on the other half of the trials subjects viewed 100% phase coherence images. In the current study, however, we will present and discuss only the results obtained with the 100% phase coherence face stimuli, while results obtained with the noisy faces will be presented elsewhere. Stimuli subtended 2 visual degrees, matching approximately the size of the fovea and were presented centrally on a uniform gray background.

Each trial started with a cue, a brief change (100 msec) in color of the fixation dot followed by the face stimulus for 250 msec with a fixed SOA of 1350 msec on 80% of the total trials and 2350 msec on 20% of the trials. Subjects were instructed to pay attention following the cue and were explicitly told about the 1350 msec SOA. However, they were not informed about the extra 1 sec delay in 20% of the trials, which meant they always expected the faces 1250 msec following the cue. A response window of 2 sec was given, which terminated when the subjects responded. Trials were separated by a random ITI of 800–1200 msec (Figure 3.1B) and a fixation point was present throughout the entire block. Viewing was monocular, alternated between blocks, while the other eye was patched.

		Refraction		Visual Acuity (VA)			
Subject	Age/Gender	RE	LE	RE	LE	Interocular VA (logMAR)	Squint
A1	32/F	-0.5	+0.5 / +1.75 129°	20/12.5	20/80	0,8	ø
A2	25/F	-0.25 / -0.5 135°	+3.75 / +2.25 155°	20/16	20/80	0,7	ø
A3	20/F	+1.75 / +1.25 101°	-1.0 / +0.75 82°	20/80	20/20	0,6	ø
A4	36/M	plano	+2.5	20/12.5	20/63	0,7	ø
A5	24/M	-0.25 / -1.75 97°	-3.0 / -0.75 73°	20/80	20/16	0,7	ø
S1	38/F	+1.5 / +1.75 91°	+2.5 / +1.0 84°	20/20	20/40	0,3	ø
S2	34/F	+0.25 / -0.25 12°	plano / -0.75 178°	20/63	20/12.5	0,7	D14Δ, N10Δ ET
S3	34/F	+1.25 / -1.5 53°	+0.25 / +0.25 62°	20/100	20/20	0,7	N=D10Δ ET
S4	40/F	+1.75	+3.5	20/12.5	20/50	0,6	ø
S5	29/F	-0.5	plano / -0.5 132°	20/16	20/40	0,4	ø
S6	22/M	-3.75 / +3.5 159°	-2.25 / +2.0 130°	20/20	20/32	0,2	ø
S7	46/F	-1.5 / -1.0 140°	+0.25 / -1,75 19°	20/20	20/125	0,8	D18Δ, N25Δ ET
S8	22/M	+0.25	-0.25 / -0.5 58°	20/80	20/10	0,9	D12Δ, N8Δ XT
S9	22/M	+1.5	+3.0 / +0.5 75°	20/10	20/63	0,8	D4Δ, N6Δ ET
S10	39/M	+1.25 / -1.25 11°	+0.5 / +1.5 95°	20/12.5	20/25	0,3	D8Δ, N8Δ ET
S11	23/M	+1.5 / +1.25 100°	+2.75 / +0.5 63°	20/40	20/12.5	0,5	D=N40Δ XT
S12	24/M	+2.25 / +1.0 177°	+3.75 / +1.75 117°	20/16	20/32	0,3	D25Δ, N20Δ XT
S13	25/F	-4.25 / -0.5 16°	-4.5 / -0.75 176°	20/20	20/32	0,2	D=N25Δ XT
S14	38/M	+1.5 / -0.5 141°	+1.75 / -0.75 175°	20/40	20/20	0,3	D=N16Δ ET
S15	44/F	+0.75	+2.0	20/20	20/32	0,2	D=N6Δ ET

Table 3.1. Clinical details of amblyopic subjects (RE: right eye, LE: left eye, D: distant, N: near, ET: esotropia, XT: exotropia)

DOI:10.15774/PPKE.ITK.2015.009

Each participant completed four runs for each eye yielding 192 trials altogether for each stimulus type per eye and altogether 80 trials per eye where the face images where delayed.

Stimulus presentation was controlled by MATLAB 7.1. (The MathWorks Inc., Natick, MA) using the Cogent 2000 toolbox (www.vislab.ucl.ac.uk/Cogent/) and were presented on a 26" LG LCD monitor at a refresh rate of 60 Hz and were viewed from 56 cm.

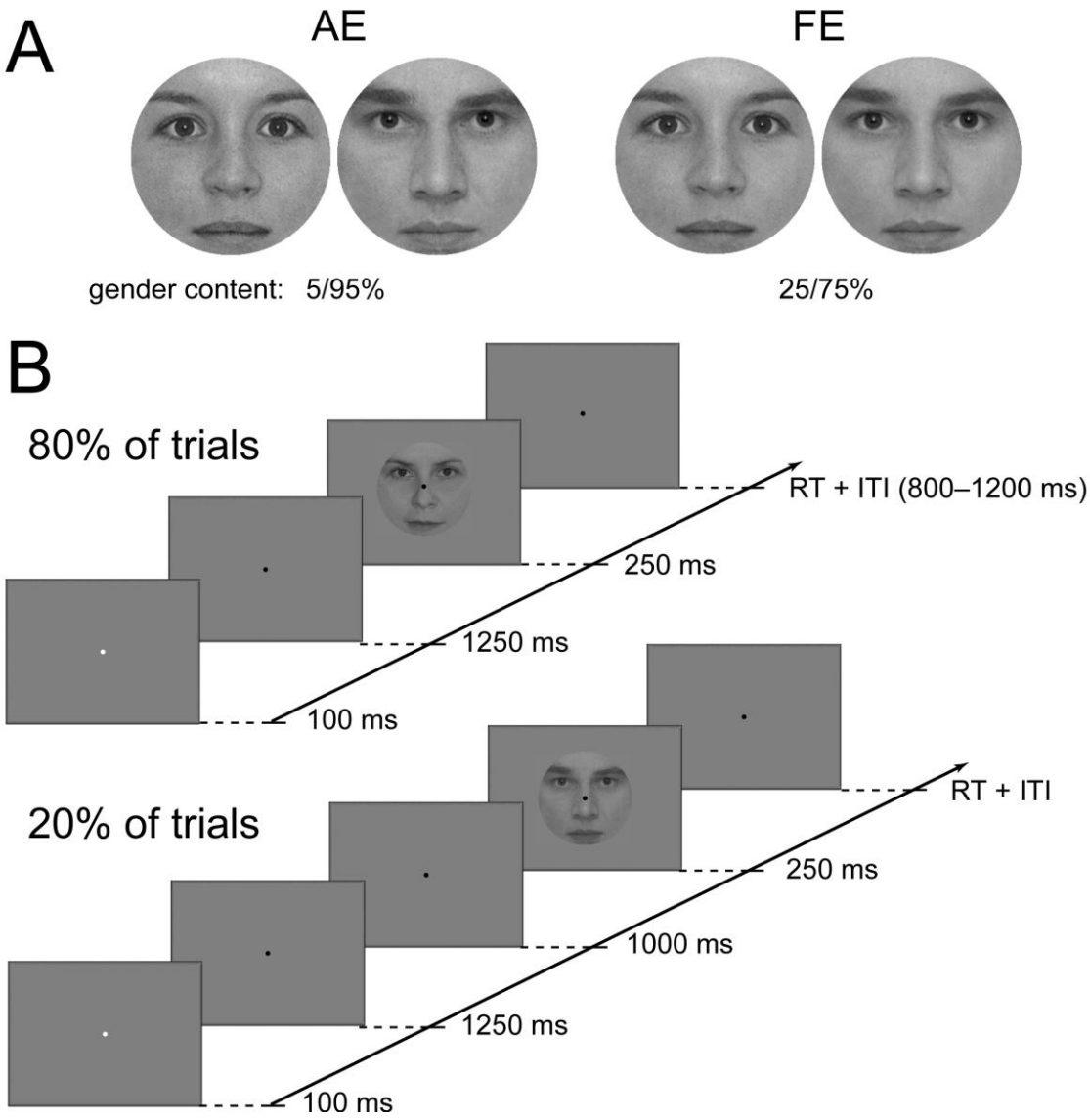

Figure 3.1. Stimuli and experimental protocol. (A) Typical gender composition of stimuli presented into the amblyopic (left panel) and fellow eye (right panel). (B) Experimental protocol, which shows the general stimulus sequence (upper panel) and those 20% of all trials where the face was presented later than expected (bottom panel).

2.3. Electrophysiological acquisition and processing

EEG data was acquired using a BrainAmp MR (Brainproducts GmbH., Munich, Germany) amplifier from 60 Ag/AgCl scalp electrodes placed according to the extended 10-20

international electrode system, mounted on an EasyCap (Easycap GmbH, Herrsching-Breitbrunn, Germany) with four additional periocular electrodes placed at the outer canthi of the eyes and above and below the right eye for the purpose of recording the electrooculogram. All channels were referenced to joint earlobes online; the ground was placed on the nasion. All input impedance was kept below 5 kΩ. Data were sampled at 1000 Hz with an analog bandpass of .016–250 Hz and was re-referenced offline using a Laplacian transform on spherical spline interpolated data to generate scalp current density (SCD) waveforms. The SCD data is reference independent and displays reduced volume conduction eliminating raw EEG contamination from saccadic potentials [160], [138]. Moreover its peaks and troughs are sharper and larger than those of the original scalp potential [161], which makes it better suited for single-trial peak detection compared to raw surface potentials. Data was band-pass filtered from .1-30 Hz (using digital .1 Hz 12 dB/octave Butterworth Zero Phase high-pass filter, 30 Hz 24 dB/octave low-pass filter, and 50 Hz notch filter), segmented, artifact rejected and baseline corrected in a 200 msec pre-stimulus window directly preceding the presentation of the stimulus in the case of ERP analysis and preceding the expected presentation of the face in the case of the wavelet analysis. 1000 msec long epochs (-200 – 800 msec relative to stimulus) were used for creating the trial-averaged event-related potentials and for single trial peak analysis. On the other hand, to detect a possible baseline oscillation difference between amblyopic and fellow eyes a single-trial wavelet analysis was performed on 3000 msec long data segments starting from the presentation of the cue (i.e. -1350 to 1650 msec relative to the expected stimulus onset) on the 2350 msec cue-face SOA trials. Thus, no evoked potentials were present that could affect the wavelet transform of the baseline period due to the large window length of lower frequencies. Data processing was done using BrainVision Analyzer (Brainproducts GmbH., Munich, Germany), while time-frequency spectrum was calculated using Matlab's *cmor* function over the frequency range of 1-30 Hz with a bandwidth of 1 Hz, and central frequency of also 1 Hz.

2.4. Statistical analysis

Accuracy, RTs for correct trials, and visual acuity (VA) as expressed in logMAR values obtained at a distance of 6 m with the best refractive correction were analyzed as behavioral measures. On both the averaged and single-trial ERPs, P1 and N170 component peaks were detected and analyzed on electrode-clusters (PO7, PO9, P7, and P9, and PO8, PO10, P8, and P10 for left and right clusters, respectively). In the case of average ERPs peak latency was determined individually on pooled electrodes from left and right clusters separately, while mean peak amplitudes were measured over the individual electrodes of the clusters in a 10 msec window centered on the peak latencies. In the case of the single-trial peak detection, minima and maxima for P1 and N170, respectively, were detected on each trial for each

DOI:10.15774/PPKE.ITK.2015.009

electrode in a 100 msec time window centered on the individual peak latency of the respective component measured on the averaged ERPs. The amplitude and corresponding time of the extrema were taken as the amplitude and latency of the component on the given trial. The trial was rejected if the detected extrema was located at the beginning or end of the time window. The single trial amplitude and latency values were pooled from the four electrodes on each side and the distribution of the values was characterized by calculating the median and the interquartile range (IQR), which is a measure of spread and is computed as the difference of the upper and lower quartile of the data, and thus describes the middle 50% of the data values. For the P1-N170 peak-to-peak analysis N170 – P1 latency difference was calculated on a trial-by-trial basis and the distributions were characterized as above. To characterize ongoing oscillations log power and phase concentration (kappa) was computed – the latter using the circStat Matlab toolbox [162] – in the delta, theta and alpha frequency bins by pooling data from 2-3, 4-7 and 8-12 Hz, respectively.

The above measures were compared using mixed-effects ANOVAs with eye (fellow: FE vs. amblyopic: AE), side (L vs. R), electrode – only in the case of averaged ERP amplitudes –, and frequency (delta vs. theta vs. alpha) – only in the case of wavelet results – as within-subject factors and etiology (anisometropia vs. strabismus) as a between-subject factor using Tukey HSD tests for post-hoc comparison. Greenhouse-Geisser correction was applied to correct for possible violations of sphericity where the levels of a within-subject factor exceeded two. In the case where the assumption for homogeneity of variances was not met due to the higher variance of measurements from the AE, values were first rank transformed before being entered into the statistical test, which is noted by rANOVA (rank ANOVA) when detailing statistical results.

We also assessed the relationship between the interocular changes in median/IQR of the distributions, ERP peak amplitudes/latencies and the interocular visual acuity using Pearson correlation. For use in the correlation analysis we calculated the difference of the measures derived from the amblyopic and the fellow eye in a way that positive values meant amblyopic deficit, the larger the difference, the bigger the deficit. Latency and amplitude measures can be treated as independent, while measured values over the different hemispheres and different measurements derived from latency/amplitude are strongly dependent on each other. Therefore, the significance threshold was set to p=.025 (p_{Bonf} =.05) to correct for the multiple comparisons problem.

2.5. Analysis of eye tracking data

We tracked the gaze direction of all subjects while they performed the EEG experiment. However, we were able to record useable eye movement data only for ten patients due to the strong reflection of glasses that many were wearing. Eye-gaze direction was assessed using a

summary statistic approach. Trials were binned based on the viewing eye and mean eye position (x and y values) was calculated for periods when the face stimulus was present on each trial. From each of the two eye-gaze direction dataset, spatial maps of eye-gaze density were constructed. The root mean squares (RMS) of the density values for these maps were computed [163], as a measure of fixation stability, higher RMS values meaning less stable fixation. Unfortunately, out of the ten patients only two were anisometropic. Therefore, we could not analyze the data with etiology as a factor and entered them into a paired Student's t-test instead.

3. Results

3.1. Behavioral results

Based on pilot sensitivity measures the gender difference between female and male stimuli was adjusted separately for the amblyopic and fellow eye in each observer to achieve similar gender categorization performance in the two eyes. As a result of this, accuracy (median±SD: 89±4 % and 87±11 % for FE and AE, respectively) did not differ between eyes (rANOVA, main effect of eye: $F_{(1,16)}$=2.66, p=.12). Reaction times to correct trials (median±SD: 776±53 msec and 796±82 msec for FE and AE, respectively) were also not significantly different between the two eyes (main effect of eye: $F_{(1,16)}$=1.92, p=.19). Furthermore, there was no significant difference between the strabismic and anisometropic amblyopes for either measure (eye × etiology interaction: $F_{(1,16)}$=2.15, p=.16 and $F_{(1,16)}$=.02, p=.90 for accuracy and RT, respectively) and their average optotype visual acuity (VA) also did not differ significantly (Mann-Whitney U-test: $Z_{(N1=13,N2=5)}$=-1.28, p=.20). These behavioral results imply that the amblyopic effects found on the ERP responses cannot be explained based on differences in overall task difficulty between the amblyopic and the fellow eye.

3.2. Amblyopic effects on the averaged ERP responses

The results revealed strong amblyopic effects on the amplitude and latency of the P1 and N170 components of the event-related potentials. Viewing with the amblyopic eye resulted in reduced amplitudes (rANOVA, main effect of eye: $F_{(1,16)}$=17.43, p=.0007 and $F_{(1,16)}$=22.85, p=.0002 for the components P1 and N170, respectively) compared with the fellow eye for both ERP components (Figure 3.2). The interocular difference in the amplitudes of both P1 and N170 components was similar over the two hemispheres (no eye × side interaction: all $F \leq .74$, $p \geq .40$), even though amplitudes were larger over the right compared to the left hemisphere, which was significant in the case of N170 but remained only a non-significant trend for P1 (rANOVA, main effect of side: $F_{(1,16)}$=3.90, p=.066 and $F_{(1,16)}$=7.21, p=.016 for P1 and N170, respectively), irrespective of the eye of stimulation.

DOI:10.15774/PPKE.ITK.2015.009

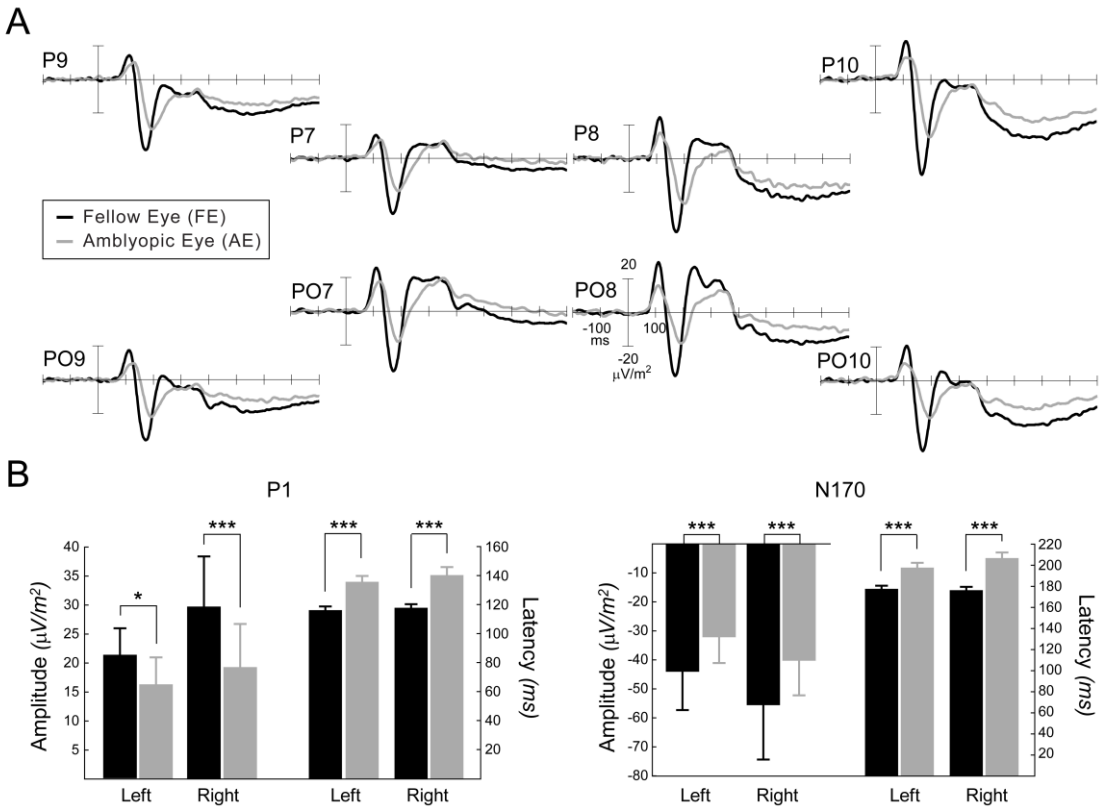

Figure 3.2. Results of the averaged event-related potentials. (A) Averaged waveforms of the ERPs to faces. (B) Statistical analysis of the amplitude and latency of components P1 (left panel) and N170 (right panel). The fellow and amblyopic eye is displayed in black and grey, respectively. Results of the statistical analysis may seem to differ from the effect displayed on the averaged waveforms, which is due to subjects showing smaller amblyopic effects (i.e. larger amplitudes from AE) being overrepresented in the mean waveform. Error bars indicate ±SEM (N=18, *p<.05, ***p<.001).

Amblyopic viewing also resulted in increased latencies relative to stimulation of the fellow eye in both components (rANOVA, main effect of eye: $F_{(1,16)}$=35.93, p<.0001 and $F_{(1,16)}$=41.58, p<.0001 for the components P1 and N170, respectively). Importantly, the amblyopic effects on the response latencies differed in the case of the two ERP components. Interocular difference in N170 latency was significantly larger over the right hemisphere (31 msec) than over the left hemisphere (20 msec) (rANOVA, eye × side interaction: $F_{(1,16)}$=8.46, p=.01), whereas no hemispheric asymmetry was found in case of the latency of the P1 component (22 and 20 msec for right and left hemispheres, respectively; rANOVA, eye × side interaction: $F_{(1,16)}$=.02, p=.88) (Figure 3.2B). These results suggest that – in addition to the delayed onset of the neural responses in the amblyopic eye, reflected in the increased latency of the P1 component – there might be a right hemisphere specific deficit in the temporal development of the higher level face-specific neural processes reflected in the N170 component. To directly test this possibility, we compared the temporal intervals between the P1 and N170 peaks in the amblyopic and fellow eyes by subtracting P1 latencies from N170 latencies. A significant eye × side interaction (rANOVA $F_{(1,16)}$=5.38, p=.034) revealed

DOI:10.15774/PPKE.ITK.2015.009

significantly longer peak-to-peak latencies in the amblyopic eye compared to the fellow eye over the right hemisphere only (p=.018, 57 vs. 65 msec for fellow and amblyopic eye, respectively), while there was no significant difference between peak-to-peak latency over the left hemisphere (p=.99, 60 vs. 61 msec for fellow and amblyopic eye, respectively). The amblyopic effects on the P1 and N170 amplitudes and latencies were similar in the case of strabismic and anisometropic patients (no significant eye × etiology interaction: all $F \leq 1.62$, $p \geq .22$).

It is important to note, that even though we conducted all analyses on SCD transformed data instead of the average-referenced potential that is more conventional in clinical and research studies, all of the main findings of the averaged event-related potential analysis hold true for the average-referenced data as well (Figure 3.3).

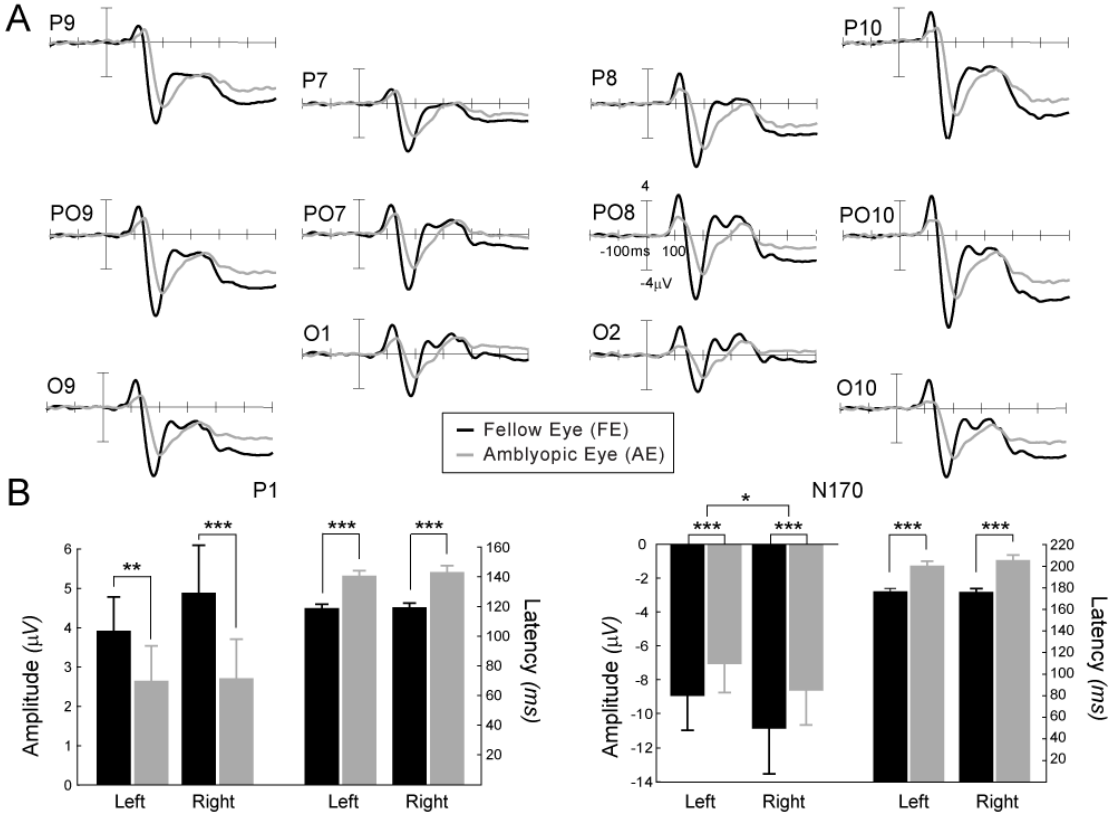

Figure 3.3. Results of the average-referenced mean event-related potentials. (A) Averaged waveforms of the ERPs to faces. (B) Statistical analysis of the amplitude and latency of components P1 (left panel) and N170 (right panel). The fellow and amblyopic eye is displayed in black and grey, respectively. Error bars indicate ±SEM (N=18, *p<.05, **p<.01, ***p<.001).

We also tested whether there was any correlation between the interocular difference in optotype acuity (VA) of our participants and the strength of the amblyopic effects on the P1 and N170 components. Significant correlation was found between the interocular VA and the interocular latency difference in the case of both P1 and N170 components over the right

DOI:10.15774/PPKE.ITK.2015.009

hemisphere: subjects with bigger VA difference between eyes had more delayed ERP responses from the amblyopic compared with the fellow eye in the right hemisphere (r=.56, *p*=.015 and r=.61, *p*=.008 for P1 and N170, respectively). However, no correlation was found between the VA and the left hemisphere latency of the P1 and N170 or the VA and the amplitude of the ERP components (all r≤.40 *p*≥.097). Furthermore, VA difference also did not correlate with the peak-to-peak latency differences of P1-N170 in either hemisphere (r=.23, *p*=.35 and r=-.08, *p*=.75 for left and right hemisphere, respectively).

3.3. Amblyopic effects differ on trial-by-trial latency and amplitude

Single trial analysis of the P1 and N170 peak distributions revealed a much more refined pattern of amblyopic deficits compared to those of the averaged ERP analysis (Figure 3.4). We found significant interocular difference in amplitude distributions only in the case of the N170 component: amplitude median and spread was reduced in the case of the amblyopic eye compared to the fellow eye (rANOVA, main effect of eye: $F_{(1,16)}$=7.06, *p*=.017 and ANOVA, main effect of eye: $F_{(1,16)}$=.54, *p*=.47 for amplitude median and IQR, respectively). In the case of the P1 amplitudes a similar amblyopic effect was present only as a non-significant trend (rANOVA, main effect of eye: $F_{(1,16)}$=3.86, *p*=.067 and $F_{(1,16)}$=3.52, *p*=.078 for amplitude median and IQR, respectively). Furthermore, the amblyopic effects on the ERP amplitudes differed between the strabismic and the anisometropic group (Figure 3.5). The N170 amplitude distributions in the amblyopic eye differed from those in the fellow eye only in the strabismic but not in the anisometropic patients. Moreover, this interocular amplitude median difference in the strabismic group was more pronounced over the right hemisphere, though also present in the left hemisphere (rANOVA, eye × side × etiology interaction: $F_{(1,16)}$=9.5, *p*=.007; post hoc FE vs. AE *p*=.029 and *p*=.0002 for strabismic and *p*=.19 and *p*=.99 for anisometropic patients over the left and right HS, respectively). In contrast to the N170 component, amplitude distributions of the P1 component were shifted towards smaller amplitudes and had smaller spread when faces were presented in the amblyopic eye of the anisometropic but not of the strabismic patients (rANOVA, eye × etiology interaction: $F_{(1,16)}$=5.28, *p*=.035; post hoc FE vs. AE: *p*=.05 and *p*=.98 for the anisometropic and strabismic group, respectively for amplitude median; rANOVA, eye × etiology interaction: $F_{(1,16)}$=11.35, *p*=.004; post hoc FE vs. AE: *p*=.032 and *p*=.51 for the anisometropic and strabismic group, respectively for amplitude IQR).

Thus, the results of the single trial analysis revealed much more moderate amblyopic effects on the amplitude distributions than expected based on the results of the analysis of the averaged ERP amplitudes as well as showed that they differ between strabismic and anisometropic amblyopes. These inter-group differences could not have been detected by analyzing the averaged ERP responses, even though they were present as slight trends which

were far from being significant (eye × etiology interaction: $F_{(1,16)}$=1.62, p=.22 and $F_{(1,16)}$=1.20, p=.29 for P1 and N170 averaged ERP amplitudes). It is important to note, however, that the size of the two patient groups differed in the present experiment (N=5 and N=13 for anisometropic and strabismic patients, respectively). This implies that the lack of amblyopic effects on the N170 amplitude medians in the case of the smaller anisometropic patient group could stem from insufficient statistical power. The difference in group size is less of a concern in the case of the inter-group difference in amblyopic effects found in the P1 amplitude distributions as null results were obtained in the larger strabismic patient group. To test whether the group difference in the amblyopic effects on the N170 amplitude medians could be accounted for by the reduced statistical power in the case of the smaller anisometropic patient group, we conducted a non-parametric bootstrapping procedure. We created a distribution of effect size by conducting ANOVAs on all possible combinations of five strabismic patients and compared the F-values (main effect of eye) we obtained by analyzing the anisometropic patients alone against this distribution. Decreasing the size of the strabismic group to five did indeed result in a drop of statistical power. Only about ¼th of the patient combinations resulted in significant interocular N170 amplitude median differences (Figure 3.6). Importantly, however, there was no overlap between the F-value found in the five anisometropic patients and the values of the strabismic distribution, i.e. all of the F-values were larger than that of the anisometropic patients. Thus, the probability – obtained from this non-parametric test – that the anisometropic F-value comes from the strabismic distribution is p=0, supporting the possibility that N170 amplitude medians are differently affected in the two groups.

Analysis of the peak latency distributions revealed a significant shift towards longer latencies and an increased spread in the amblyopic compared to the fellow eye in the case of both P1 (rANOVA, main effect of eye: $F_{(1,16)}$=43.01, p<.0001 and ANOVA main effect of eye: $F_{(1,16)}$=23.12, p<.0001 for latency median and IQR, respectively) and N170 components (rANOVA, main effect of eye: $F_{(1,16)}$=44.78, p<.0001 and ANOVA, main effect of eye: $F_{(1,16)}$=22.05, p=.0002 for latency median and IQR, respectively). There was no difference in the amblyopic effects on latency distributions between the strabismic and anisometropic groups for either component (no eye × etiology interaction: all $F \leq .85$, $p \geq .37$). Importantly, the results of our single trial analysis, showing that neuronal response latencies are much more variable in the amblyopic eye compared to the fellow eye imply that a major part of amblyopic effects found on the P1 and N170 amplitudes in the averaged ERP analysis in the current study – and most probably the strong decrease of P1 amplitudes of averaged VEP responses found in previous studies [41, 96, 100, 101] – are due to the increased latency jitter of the neural responses in amblyopia.

DOI:10.15774/PPKE.ITK.2015.009

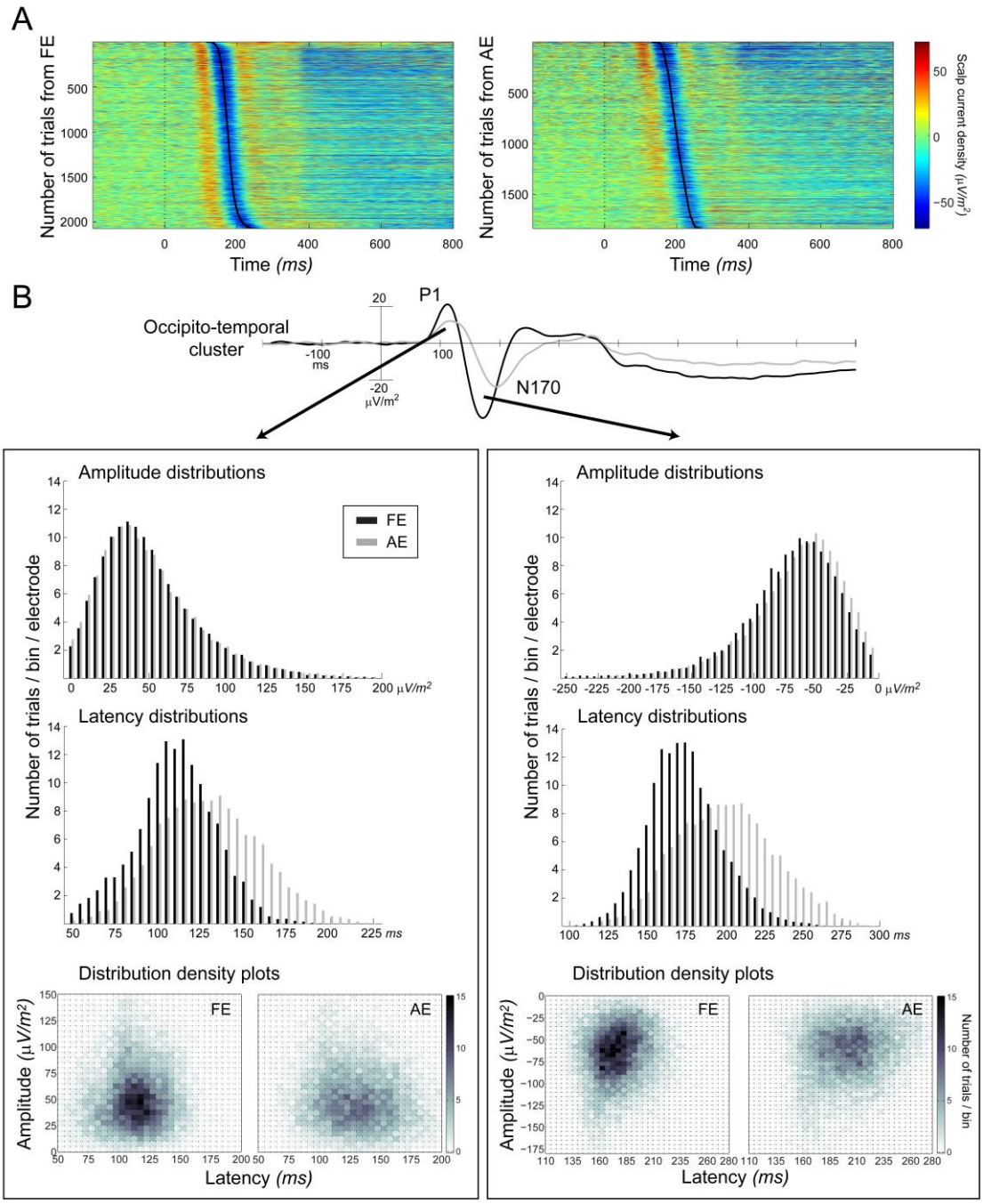

Figure 3.4. ERP images, amplitude and latency distributions of single trial responses. (A) ERP images of single trial responses from the fellow (left panel) and amblyopic eyes (right panel) of all 18 subjects pooled and averaged from P7, P8, P9, P10, PO7, PO8, PO9, PO10 and sorted according to the detected 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).

DOI:10.15774/PPKE.ITK.2015.009

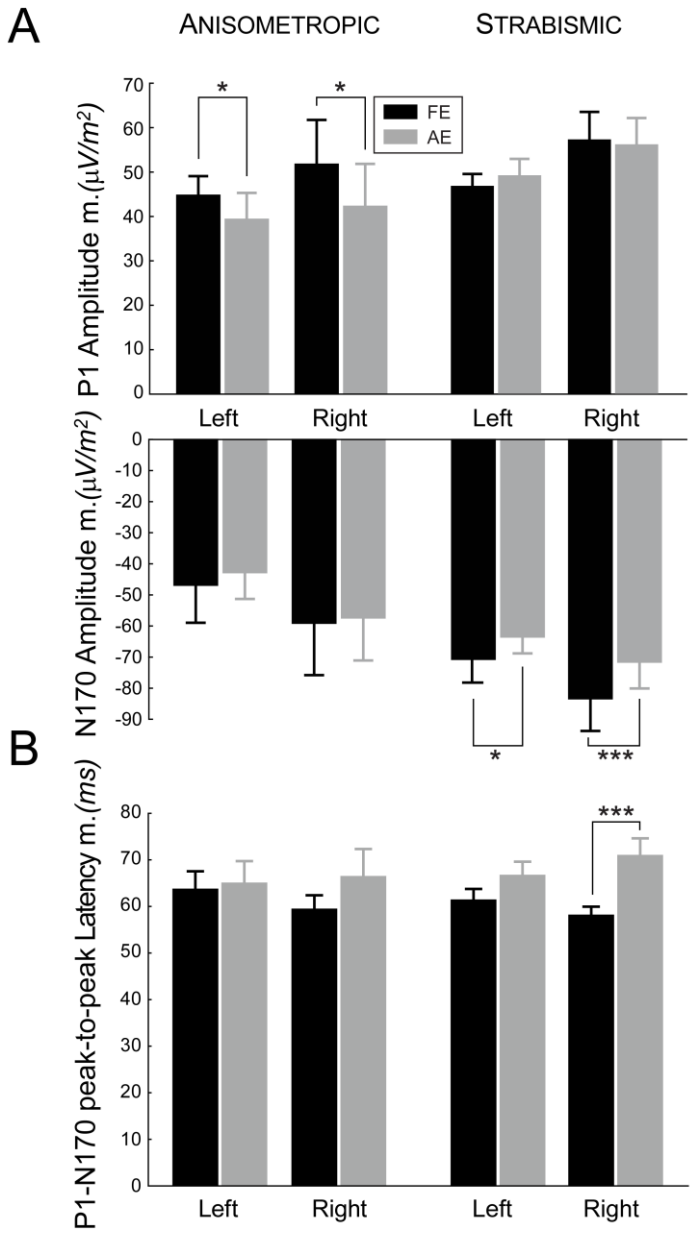

Figure 3.5. Face specific amblyopic deficits. (A) Amplitude medians of P1 and N170 components split into anisometropic (displayed on the left, N=5) and strabismic (displayed on the right, N=13) groups. There was significant interocular difference in P1 amplitude medians only in the anisometropic, while 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 × etiology interaction $F_{(1,16)}=1.68$, p=.21), even though the difference did not reach the significance level in the case of the anisometropic group due to a lack of statistical power (p=.18). Error bars indicate ±SEM (*p<.05, ***p<.001).

DOI:10.15774/PPKE.ITK.2015.009

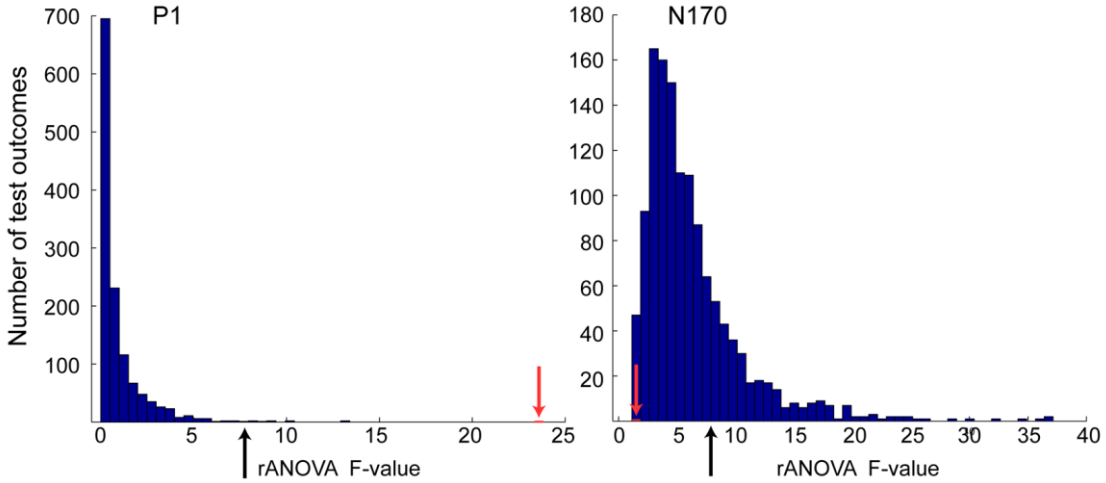

Figure 3.6. Distribution of effect size for main effect of eye obtained from analyzing all possible combinations of five strabismic patents The F-values for main effect of eye in the anisometropic patient group are shown in red with red arrows, while the F-value corresponding to the α=0.05 parametric significance threshold ($F_{(1,4)}$=7.71, p=.05) is shown with black arrows.

The results of the analysis on averaged ERPs revealed hemispheric asymmetry in the amblyopic effect on N170 peak latencies, suggesting slower or additional face-related processing over the right hemisphere in amblyopia. Directly comparing processing times between peaks P1 and N170 on a single-trial level (Figure 3.5B), the amblyopic eye displayed significantly longer peak-to-peak latencies compared with the fellow eye (rANOVA, main effect of eye: $F_{(1,16)}$=6.48, *p*=.017 for peak-to-peak latency median). However, a significant eye × side interaction ($F_{(1,16)}$=8.33, p=.010) revealed this in fact was only true over the right hemisphere (*p*=.0002; mean±SE: 58.3±1.6 vs. 69.6±3.1 msec for fellow and amblyopic eye, respectively), while the difference between peak-to-peak latency medians over the left hemisphere did not reach the significance level (*p*=.12; 61.9±2.0 vs. 66.1±2.4 msec for fellow and amblyopic eye, respectively). This pattern of larger difference over the right hemisphere was true for both amblyopic groups (no eye × side × etiology interaction: $F_{(1,16)}$=.31, *p*=.58). Importantly, in agreement with the results of the averaged ERP component analysis, it was found that both P1 and N170 latency medians in the right hemisphere were positively correlated with the VA (Figure 3.7A): the more delayed the ERP components were in the amblyopic eye compared to that of the fellow eye, the larger the interocular differences in VA were (r=.57, *p*=.013 and r=.61, *p*=.008 for P1 and N170, respectively). Interocular VA, however, did not correlate with the interocular difference in peak-to-peak amplitude of P1-N170 (Figure 3.7B) (r=.26, *p*=.30 and r=.22, *p*=.38 for left and right HS, respectively). Furthermore, no correlation was found between VA and the latency medians of the P1 and N170 components over the left hemisphere and between VA and the amplitude medians of the P1 and N170 component (Figure 3.7C) over either of the two hemispheres (all r≤.37 *p*≥.12).

DOI:10.15774/PPKE.ITK.2015.009

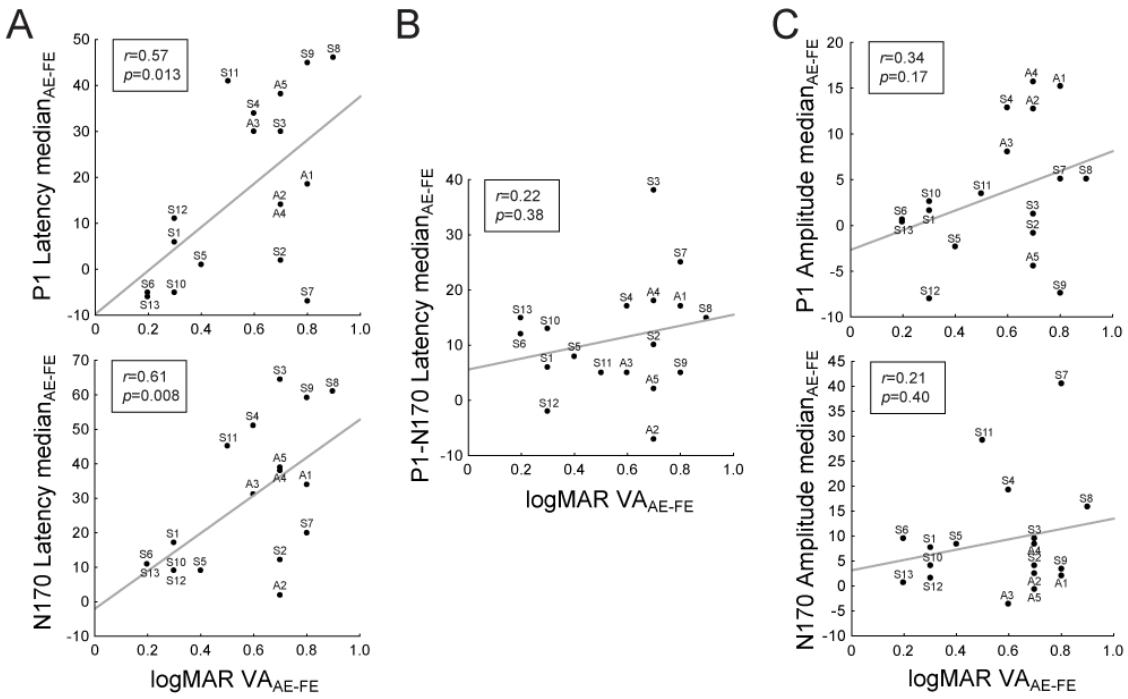

Figure 3.7. Pearson correlations of interocular visual acuity with (A) P1, N170 latency medians, (B) P1-N170 peak-to-peak latency medians and (C) P1, N170 amplitude medians over the right hemisphere only, derived from the single-trial analysis.

3.4. Results of the analysis of the ongoing oscillations

To test the possibility that difference in the amplitude or phase of ongoing oscillations at the time of stimulus onset between the stimulation of the amblyopic eye and fellow eye might contribute to the amblyopic deficits measured in the ERP responses we analyzed the wavelet transform of the electrophysiological signal from those 20% of trials, where presentation of the face stimulus was delayed by 1 sec. We calculated kappa as the phase concentration measure of all trials at the time of the expected stimulus onset for three frequency bands that are known to affect the evoked response: delta (2-3 Hz), theta (4-7 Hz) and alpha (8-12 Hz). Strength of the oscillations was characterized as the log mean power at the time of the expected stimulus. ANOVA on ranked kappa data revealed no concentration differences between eyes (Figure 3.8A) ($F_{(1,16)}$=.68, p=.41), which was the case for both amblyopic groups (eye × etiology interaction: $F_{(1,16)}$=1.89, p=.19). There was also no difference between frequencies or hemispheres and no interaction between these variables (all $F \geq 1.35$ $p \leq .26$). Analysis on ranked power data also showed no significant difference between eyes (Figure 3.8B) ($F_{(1,16)}$=1.34, p=.26) irrespective of etiology (eye × etiology interaction: $F_{(1,16)}$=.44, p=.52). The lack of differences in ongoing oscillations at the time of stimulus onset between the stimulation of the amblyopic eye and fellow eye implies that the amblyopic deficits found

in the current study are caused primarily by the impairment of the neural processes underlying generation of evoked visual cortical responses.

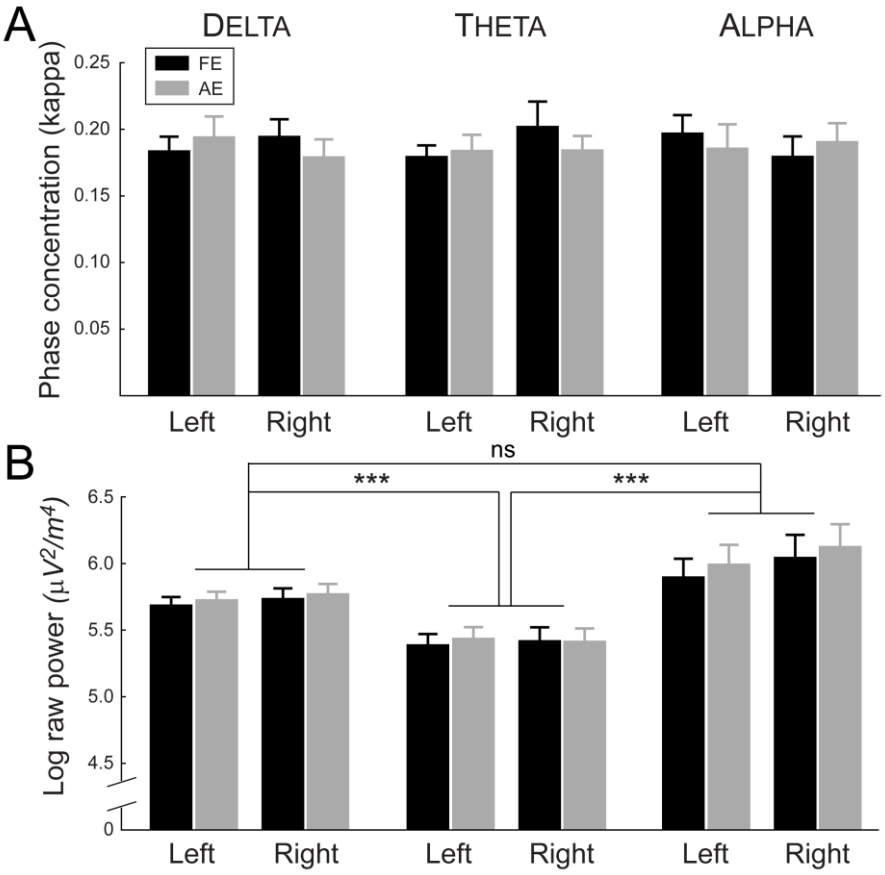

Figure 3.8. Characterization of baseline oscillations. (A) Phase concentration values as indexed by kappa in three frequency bins (delta: 2-3 Hz, theta: 4-7 Hz, alpha: 8-12 Hz) that are known to affect evoked responses. (B) Mean log power of the three frequency bins. There was significant difference only between frequencies ($F_{(2,32)}$=16.78, $p_{G\text{-}Gadj}$=.0002) (post-hoc t-tests: p=.0008, p=.0001 and p=.074 for T vs. D, T vs. A and D vs. A, respectively), as expected based on the general characteristics of the EEG signal [154]. Both kappa and power values were calculated at the time of expected face onset, while faces were presented only a second later. Error bars indicate ±SEM (N=18, ***p<.001).

3.5. Results of the eye-tracking analysis

The results revealed that in agreement with previous findings [116, 158, 159] fixations were more stable in the case of the fellow eye as compared to the amblyopic eye (Figure 3.9A) ($t_{(9)}$=-2.65, *p*=.028). We also tested whether there is a relationship between fixation stability and VA, amplitude and latency of the ERP components. Although, the results revealed that subjects with larger interocular fixation stability difference tended to have higher interocular VA difference, this trend failed to reach the significance level (r=.54, *p*=.10). On the other hand, there was a significant correlation between the magnitude of the interocular difference in fixation stability and in latency median of the P1 and N170 components over the right

DOI:10.15774/PPKE.ITK.2015.009

hemisphere (Figure 3.9B) (r=.70, *p*=.024 and r=.71, *p*=.021 for P1 and N170, respectively). However, we found no correlation between the fixation stability and interocular amplitude median difference in the case of either component (all |r|≤.35 *p*≥.31). These results suggest that there might be a functional relationship between the amblyopic deficits in fixation stability and the delayed onset of neural responses in amblyopia.

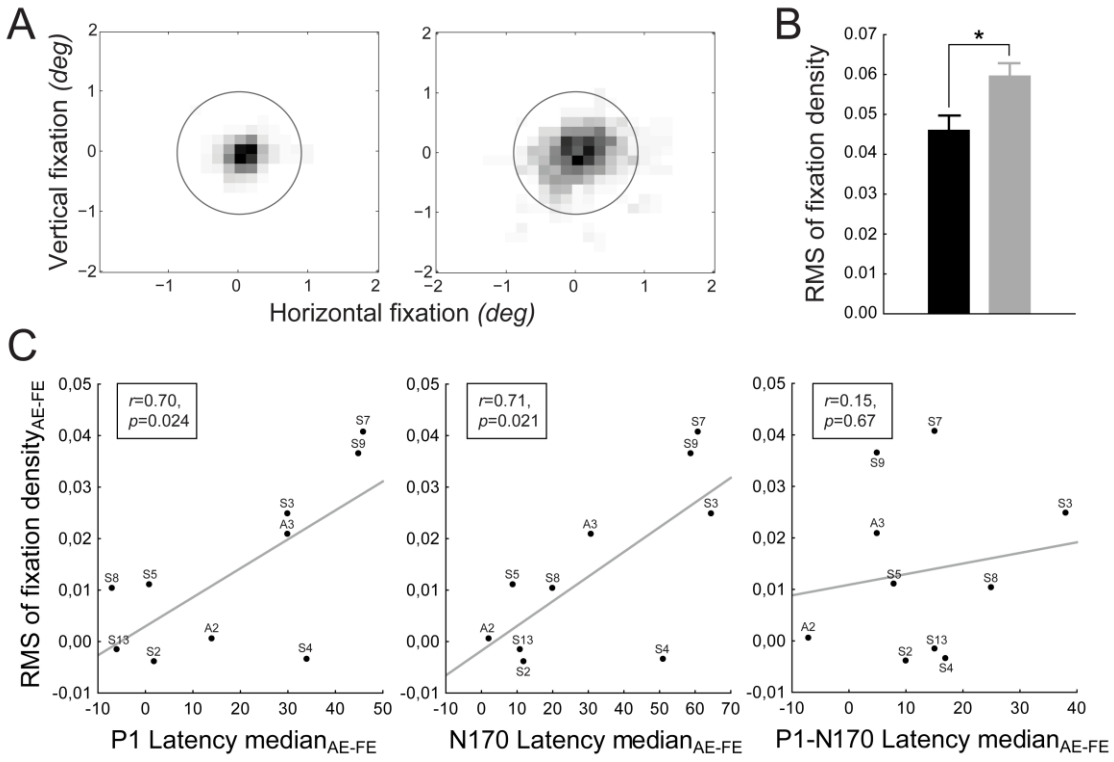

Figure 3.9. Fixation stability of the fellow and amblyopic eyes. (A) Gaze-density plots of a typical subject (S3). The circle indicates the spread of the stimulus. (B) Group differences in fixation stability; black: FE, gray: AE. (C) Correlation of the root-mean-square (RMS) of fixation positions with interocular visual acuity (VA) difference. Error bars indicate ±SEM (N=10, *p<.05).

3.6. Average-referenced mean ERP responses show similar amblyopic effects

To facilitate comparison between this and most clinical studies, we conducted the peak analysis on average referenced mean ERPs as well. However, to do this we chose slightly different electrode clusters compared to analyses of the Laplace transformed data, since this later transform can change the whole spatial distribution to emphasize local difference in peak topography. The cluster alteration only concerned electrodes for P1, for which we chose the more conventional cluster of electrodes PO7, PO9, O1, and O9 and PO8, PO10, O2, and O10, while we kept electrodes P7, P9, PO7, and PO9 and P8, P10, PO8, and PO10 for analyzing the N170 component.

DOI:10.15774/PPKE.ITK.2015.009

The results revealed equally strong amblyopic effects on the amplitude and latency of the P1 and N170 components as obtained when analyzing the SCD data (Figure 3.3). Viewing with the amblyopic eye resulted in reduced amplitudes (main effect of eye: $F_{(1,16)}$=10.44, p=.0052 and $F_{(1,16)}$=8.95, p=.0086 for the components P1 and N170, respectively) and increased latencies (main effect of eye: $F_{(1,16)}$=26.8, p<.0001 and $F_{(1,16)}$=49.77, p<.0001 for the components P1 and N170, respectively) compared with the fellow eye for both ERP components. The amblyopic effects on the P1 and N170 amplitudes and latencies were similar in the case of strabismic and anisometropic patients (no significant eye × etiology interaction: all F≤1.90, p≥.19). The interocular difference in N170 latency remained larger over the right hemisphere (29.6 ms) than over the left hemisphere (24 ms), however it just failed to reach significance (eye × side interaction: $F_{(1,16)}$=4.42, p=.052), whereas no hemispheric asymmetry was found in the case of the latency of the P1 component (23.7 and 22 ms for right and left hemispheres, respectively; eye × side interaction: $F_{(1,16)}$=.31, p=.58). The direct P1-N170 peak-to-peak latency measure also only showed a strong trend for this asymmetry (eye × side interaction: $F_{(1,16)}$=3.81, p=.069; 56.5 vs. 62.5 ms, for FE and AE, respectively over the right and 57.6 vs. 59.5 ms, for FE and AE, respectively over the left hemisphere).

4. Discussion

The results revealed that both the strength and the temporal structure of higher-level, object specific visual cortical responses, reflected in the N170 component of the ERP responses evoked by face stimuli (for review see [147], are altered in amblyopia and that the amblyopic effects on the amplitude of the N170 component differ between strabismic and anisometropic patients. We also showed that these object specific visual cortical processing deficits cannot be explained by differences in ongoing oscillations between the stimulation of the amblyopic eye and fellow eye or by the amblyopic effects present already on the earlier P1 component of the evoked ERP responses.

It has been suggested that neural processing of the visual information coming from the amblyopic eye is delayed as compared to that originating from the fellow eye [110, 151, 153]. In fact, delayed onset of the visual cortical responses, reflected in the increased latency of the P1 component was a consistent finding of previous human neurophysiological research in [41, 96, 100, 101]. In agreement with this, in the current study we found that the latencies of both P1 and N170 components are strongly increased in the amblyopic compared to the fellow eye. More importantly, however, we also showed that in the case of the amblyopic eye P1-N170 peak-to-peak latency in the right hemisphere is significantly larger than that in the left hemisphere, whereas there was no hemispheric difference in P1-N170 peak-to-peak latency in

the case of the fellow eye. Furthermore, the magnitude of P1-N170 peak-to-peak latency in the left hemisphere during stimulation of the amblyopic eye was similar to that in the fellow eye. Thus, the amblyopic increase of the P1-N170 peak-to-peak latency in the right hemisphere provides evidence that higher-level face specific neural processes generating the right hemisphere N170 component evolve more slowly in the amblyopic eye than in the fellow eye. The right hemispheric lateralization of the amblyopic deficit in the temporal development of the N170 component is in agreement with the results of previous research showing strong right hemisphere dominance in face processing [132, 164–166].

The results also revealed that in strabismic patients the strength of the higher-level, object specific visual cortical responses reflected in the N170 amplitudes are reduced in the amblyopic eye compared to the fellow eye. Importantly, the observed amblyopic effect on the N170 amplitudes cannot be explained by an overall reduction in the strength of neural responses throughout the visual processing hierarchy in the case of stimulating the affected eye. This is supported by the facts that we found no interocular differences in P1 amplitudes in strabismic amblyopes and that the amblyopic N170 amplitude reduction – in accordance with the well known right hemisphere dominance of face processing [132, 164–166] – was stronger over the right than over the left hemisphere. Previous research showed that the face-related N170 ERP component dominantly originates from a network of face-specific visual cortical areas of the occipito-temporal cortex, including the fusiform face area (FFA) [148–150]. Thus, the reduction of N170 amplitudes in strabismic patients found in the current study is in agreement with the previous neuroimaging results, showing decreased fMRI responses in face responsive visual cortical areas in amblyopia [102, 114]. However, it is important to note that in case of the previous fMRI studies it is not known whether the observed amblyopic effects originate from the deficits associated with the anticipatory, early evoked or late sustained neural processes, which are integrated in the fMRI responses. Therefore, the amblyopic effects found on the N170 component in the current study represent the first evidence for neural deficits in the higher-level face related evoked visual cortical responses in amblyopia. Furthermore, it is reasonable to assume that similar amblyopic deficits might also be present in the higher-level visual cortical responses to other object categories and would be reflected in the N1 components of the ERP responses. This is supported by previous results showing decreased fMRI responses to foveally presented line drawings of common objects in higher-level visual cortical areas in amblyopia [102, 114].

Intriguingly, the results of the current study suggest that differential neural dysfunctions might underlie the amblyopic effects on the strength and on the onset of the visual cortical responses. First, amblyopic deficits differ between the strabismic and anisometropic patients only in amplitudes but not in the latencies of ERP components, suggesting that the strength but not the timing of neural responses might be differentially

DOI:10.15774/PPKE.ITK.2015.009

affected depending on the cause of amblyopia. Second, the magnitude of the amblyopic effect on the latencies but not on the amplitudes of ERP components correlates with the interocular difference in optotype acuity as well as with the fixation stability of the patients independently of the etiology. Interestingly, the existence of two different components of amblyopic effects has also been suggested by the results of a recent fMRI study [167] showing that behavioral acuity deficits correlate only with the amblyopic effects measured on the strength of functional connectivity between visual cortical and subcortical regions but not with the amblyopic decrease of the BOLD responses in these regions. Based on these results it is tempting to speculate that fMRI response strengths and ERP amplitudes on the one side and functional connectivity measured with fMRI and ERP response latency on the other side might reflect two dissociable components of neural dysfunctions in amblyopia.

Our results also show that the neural deficits might differ based on the etiology of the amblyopia, although this study was not specifically designed to investigate inter-group differences and further experiments with equal group sizes are needed to corroborate these findings. The two most prevalent amblyogenic factors are unequal interocular refractive error (resulting in anisometropic amblyopia) and ocular deviation (leading to strabismic amblyopia). Both types of amblyopia show a selective decrease in foveal vision [35], however, tests of contrast sensitivity also indicate some peripheral field visual deficits [50]. The deficit is generally more limited to central vision in strabismic amblyopia [51], which is thought to be similar to peripheral vision, compared to anisometropic amblyopia, which is like blurred normal foveal vision [52, 53]. This distinction is in agreement with the differential effect of flankers in anisometropic and strabismic amblyopes in visual crowding experiments [36, 52, 54]. Nevertheless, there is no clear understanding or consistent difference found between these two types of amblyopia in the neuroimaging and neurophysiology literature. There is evidence that using checkerboard patterns calcarine activity was most suppressed for high spatial frequency stimuli in anisometropic patients, while in strabismics it was most reduced for low frequency patterns [55, 56]. On the other hand, the fMRI study by Conner and colleagues [57] has failed to differentiate anisometropic and strabismic subtypes based on fMRI activation levels in retinotopic maps of V1 and V2, while animal studies of contour/motion integration and form detection also found similar deficiencies for the amblyopic eyes of both strabismic and anisometropic monkeys [58, 59] Kiorpes and colleagues [60] in a macaque study also found that physiological changes associated with amblyopia were related to the severity, not the etiology, of the visual losses. Our results showing different patterns of amplitude median decrease in the two groups imply that single-trial analysis of event-related potentials can be a sensitive and powerful research tool for further studies to directly investigate the differences in neural deficits between anisometropic and strabismic amblyopes.

DOI:10.15774/PPKE.ITK.2015.009

Chapter Four

AMBLYOPIC DEFICIT BEYOND THE FOVEA

1. Motivations

Traditionally, amblyopia has been regarded as a disorder limited to the central retina [108], even though there exist studies that question this notion [50, 109]. As the results collected over some four decades are equivocal, no consensus has been reached so far how the peripheral visual field is affected in amblyopia. Today only strabismic amblyopia is considered a deficit primarily of central vision as early psychophysical investigations found that contrast detection threshold [51], acuity [124–126] and binocular interactions [127] are similar between the two eyes from eccentricities of 20˚ on. This is in agreement with macaque single unit recording [60] and human fMRI studies [114] that also found no peripheral interocular differences in strabismic amblyopia. On the contrary, other studies investigating both strabismic and anisometropic amblyopes have shown decreased sensitivity of the amblyopic eye in the periphery for motion detection and discrimination [109] and contrast detection [50] in the eccentricity range of 10-30deg. The extent of the amblyopic loss in the periphery in both experiments was related to the degree of foveal loss rather than the type of amblyopia.

Electrophysiological studies have also lead to different results concerning the periphery in amblyopia. Full-field pattern-reversal visual evoked potential (VEP) studies [101, 110] support the dominantly central deficit in amblyopia based on the lack of interocular difference when using large check sizes (>60’), where response are thought to predominantly arise from neurons processing the periphery of the visual field [101, 111–113]. Stimulation of the amblyopic eye with small check sizes (<30’), on the other hand, which preferentially activates the foveal area [101, 111–113] as it only elicits measurable VEP responses up to 2-4 degrees eccentricity [111], yield drastically reduced and delayed VEP responses. Similar divergence is obtained in studies using small central and large annular stimuli for the stimulation of the fovea and perifovea, respectively [114, 115]. As opposed to full-field VEP, the multifocal VEP (mfVEP) technique is capable of directly investigating peripheral processing by stimulating the visual field at different eccentricities. These studies, on the other hand, tend to find amplitude and latency differences at the perifoveal region as well as the fovea, even though smaller in size [116–118].

Therefore, our primary goal in this study was 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. In a separate

DOI:10.15774/PPKE.ITK.2015.009

experiment we also investigated this issue using large annular stimuli, which ignore cortical magnification. We hypothesized that if amblyopic deficits exist outside the fovea, controlling for cortical magnification could reveal interocular differences, which might otherwise be masked by large full-field stimulation [50, 114]. We utilized single-trial peak detection to uncover the nature of the deficits found. To rule out the possibility that the amblyopic effects are simply due to the loss of higher spatial frequencies as a result of decreased acuity – a phenomenon inevitably occurring during amblyopic viewing and known to affect ERP components [113, 168] – we measured ERPs to low-pass filtered stimuli as well.

2. Materials and methods

2.1. Subjects

Fifteen (Exp.1; mean±sd age: 28±7 years) and fourteen amblyopic patients (Exp.2; mean±SD age: 37±10 years) gave their informed and written consent to participate in the study, which was approved by the ethics committee of Semmelweis University and was in accordance with the Declaration of Helsinki. All subjects were examined by an ophthalmologist and fitted with optimal correction. Inclusion criteria for amblyopic patients were the following: best corrected visual acuity of the fellow eye of 20/20 or better, best corrected visual acuity of the amblyopic eye in the range of 20/25 – 20/200 with no ocular organic abnormalities present (except for refraction error or squint). Table 4.1 details their medical parameters. Experiment 2 was also conducted on fourteen healthy control subjects (seven females, mean±SD age: 26±4 years), medication free with no history of neurological or ophthalmologic diseases. All of them had normal or corrected-to-normal visual acuity and gave their informed and written consent to participate in the study, which was approved by the ethical committee of Semmelweis University and followed the tenets of the Declaration of Helsinki.

Eye dominance of normal subjects was determined using a variation of the Dolman method also known as the "hole-in-the-card test". The subject was given a CD with a small hole in the middle, instructed to hold it with both hands and then instructed to view a distant object (the experimenter nose) through the hole with both eyes open. The eye that the experimenter saw through the hole corresponded to the dominant eye of the subject. The procedure was repeated ten times to confirm dominance. The dominant eye of amblyopic patients corresponds to their non amblyopic eye.

DOI:10.15774/PPKE.ITK.2015.009

		Refraction		Visual Acuity (*logMAR VA*)		
Subject	**Age/Gender**	**RE**	**LE**	**RE**	**LE**	**Exp.**
Anisometropic						
GB	40/F	+3.5 +1.25 120°	-0.25 -0.25 132°	20/60 (*0.5*)	20/12.5 (*-0.2*)	Exp.1
HB	19/F	+1.0 +2.5 30°	plan	20/40 (*0.3*)	20/20 (*0*)	Exp.2
HK	31/F	-0.5	+0.5 +1.75 129°	20/12.5 (*-0.2*)	20/80 (*0.6*)	Exp.1
KG	32/M	-8.5 -3.5 178°	-3.0 -0.75 11°	20/200 (*1*)	20/12.5 (*-0.2*)	Exp.1+2
KF	24/F	-0.25 -0.5 135°	+3.75 +2.25 155°	20/16 (*-0.1*)	20/80 (*0.6*)	Exp.1+2
SE	52/F	+4.0 -6.0 15° add +2.0	+1.0 add +2.0	20/50 (*0.4*)	20/16 (*-0.1*)	Exp.2
SzB	24/M	+0.5	+3.5 +2.0 35°	20/20 (*0*)	20/80 (*0.6*)	Exp.2
VA	35/M	plan	+2.5	20/12.5 (*-0.2*)	20/60 (*0.5*)	Exp.1+2
Strabismic						
HA	28/F	-0.5	-0.5 132°	20/16 (*-0.1*)	20/40 (*0.3*)	Exp.1
KJ	21/M	+0.25	-0.25 -0.5 58°	20/80 (*0.6*)	20/10 (*-0.3*)	Exp.1
MCs	34/M	+1.5	+1.5	20/20 (*0*)	20/80 (*0.6*)	Exp.2
NB	18/M	+4.75 +1.25 86°	+5.5 +1.0 106°	20/12.5 (*-0.2*)	20/32 (*0.2*)	Exp.2
SzV	19/F	+0.5 -0.5 72°	+0.5	20/80 (*0.6*)	20/16 (*-0.1*)	Exp.1
VO	24/F	-4.25 -0.5 16°	-4.5 -0.75 176°	20/20 (*0*)	20/32 (*0.2*)	Exp.1
Strabismic-Anisometropic						
AA	37/F	+1.5 +1.75 91°	+2.5 +1.0 84°	20/20 (*0*)	20/40 (*0.3*)	Exp.2
BA	42/M	+3.0 +3.0 180° add +1.0	+4.0 +2.25 175° add +1.0	20/20 (*0*)	20/125 (*0.8*)	Exp.2
CsJ	33/F	+1.25 -1.5 53°	+0.25 +0.25 62°	20/100 (*0.7*)	20/20 (*0*)	Exp.1
DCs	39/F	+1.75	+3.5	20/12.5 (*-0.2*)	20/50 (*0.4*)	Exp.2
KCs	45/F	-1.5 -1.0 140°	+0.25 -1.75 19°	20/20 (*0*)	20/125 (*0.8*)	Exp.2
KV	34/F	+0.75 +0.25 22°	+3.0 +1.0 107°	20/20 (*0*)	20/125 (*0.8*)	Exp.1+2
KHZs	21/M	+1.5	+3.0 +0.5 75°	20/10 (*-0.3*)	20/60 (*0.5*)	Exp.1
SchA	38/M	+1.25 -1.25 11°	+0.5 +1.5 95°	20/12.5 (*-0.2*)	20/25 (*0.1*)	Exp.1
SI	22/M	+1.5 +1.25 100°	+2.75 +0.5 63°	20/40 (*0.3*)	20/12.5 (*-0.2*)	Exp.1
TK	23/M	+2.25 +1.0 177°	+3.75 +1.75 117°	20/16 (*-0.1*)	20/32 (*0.2*)	Exp.1+2

Table 4.1. Clinical details of amblyopic patients in Experiment 1 and 2. The rightmost column indicates the experiment the given subject took part in. Visual acuity is given both in Snellen fraction and in LogMAR units in parentheses (RE: right eye, LE: left eye).

2.2. Visual stimuli and procedures

In Experiment 1 participants viewed face images tilted 5˚ to the right or left from the vertical meridian. Six black and white face photographs (three male and three female) were taken from our face database and cropped to 254×254 pixels, covered with a circular mask to eliminate external facial features and equated for luminance and contrast. The faces were either displayed without further manipulation, containing a broad spatial spectrum (*Br*), or low-pass filtered at 3 cycles/image (*Lo*) using the Image-J tool [169] (Figure 4.1A). The high frequency cut-off for the low-pass filter was chosen to exclude spatial frequencies higher than 1.5 cpd in the case of foveal stimuli (2˚), as contrast sensitivity of the amblyopic eye at 1.5 cpd assessed by the Sine Wave Contrast Test was found to be in the normal range for all of our subjects (Figure 4.1C). We chose faces for stimuli as opposed to the more conventional checkerboard or sine wave grating/Gabor patch stimuli for the following reasons: i) they are natural, ecologically valid stimuli better suited to investigate processing deficits that limit amblyopic

DOI:10.15774/PPKE.ITK.2015.009

patients in real life. ii) We could control their spatial frequency content just as well as using Gabor patches, by filtering out unwanted frequencies. iii) We have prior knowledge about the validity of our single-trial peak detection approach on the event-related potentials evoked by faces: they tend to be big, thus having a good SNR, compared with ERPs evoked by simple stimuli. Even though it has been previously shown that there is a face specific processing deficit in amblyopia [102], the amblyopic deficit in early neural processing, as reflected in the P1 component, should not be significantly affected by the stimulus used.

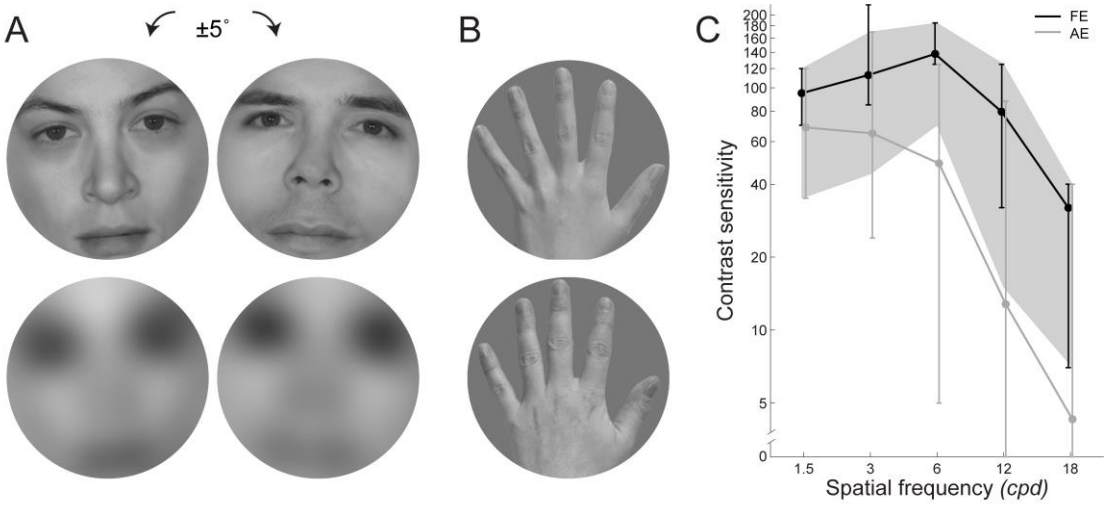

Figure 4.1. Exemplar stimuli from Experiment 1 (A) showing unfiltered stimuli with broad spatial frequency content and 1.5 cpd low-pass filtered stimuli rotated ±5˚ for the orientation categorization task. (B) Exemplar hand stimuli from Experiment 2, which were used in the face-hand categorization task along with unfiltered stimuli from Experiment 1. (C) Contrast sensitivity function of amblyopic patients participating in Experiment 1. Dots indicate the group average, while error bars show the lowest and highest sensitivity measure in the group. The highest spatial frequency that was within the normal range (grey shaded region) for all participants was 1.5 cpd. (FE: fellow eye, AE: amblyopic eye; N=15).

On half of the trials, faces were presented centrally subtending 2˚ (corresponding to the size of the fovea), while on the other half, they were presented at 5˚ eccentricity along either the upper or the lower vertical meridian. The vertical meridian was used to avoid the known naso-temporal asymmetries of strabismic amblyopes [118, 126], which would have increased the within-subject variance had the perifoveal stimuli been presented along the horizontal meridian. To control for the decrease in the retinal and cortical representation of the visual field towards the periphery, the 2˚ images were scaled with the cortical magnification factor and presented at the size of 4.7˚ in the perifoveal condition (covering 2.65˚-7.35˚ eccentricity). Image size was determined with the formula $M_{linear} = \frac{A}{E + E_2}$ provided by Horton and Hoyt [170] using $A = 29.2mm$ $E_2 = 3.67^\circ$ as calculated for human V1 [171].

Each trial started with a cue, a brief change (100 ms) in the color of the fixation dot followed by the face stimulus for 250 ms with a fixed SOA of 1350 ms. A response window of 2 s was given, which terminated when the subjects responded. Patients' task was to judge the orientation of the face images and indicate a leftward or rightward tilt with the left or right mouse button, respectively. Trials were separated by a random ITI of 800–1200 ms. A fixation dot was present throughout the entire block and subjects were instructed to maintain fixation throughout the experiment. Stimuli were presented on a uniform gray background. *Br* and *Lo* face stimuli were presented with equal probability within a block in random order as were foveal and perifoveal presentation of these stimuli. Viewing was monocular, alternating between blocks, while the other eye was patched. Each participant completed four runs for each eye yielding 108 trials altogether for each stimulus type per eye (for a total of 864 trials). Stimulus presentation was controlled by MATLAB 7.1 (The MathWorks Inc., USA) using the Cogent 2000 toolbox (http://www.vislab.ucl.ac.uk/cogent_2000.php) and were presented on a 26" LG IPS panel LCD monitor with large viewing angles at a refresh rate of 60 Hz and were viewed from 56 cm.

In Experiment 2 stimuli consisted of four faces, chosen from the set of faces used in Experiment 1, and four hand photographs which were also covered with a circular mask. Stimuli were presented in two sizes following a study by Lerner et al [114]: 2 degrees in diameter for stimulation of the foveal region, while to stimulate the perifovea a 15-degree diameter stimuli were used with a 1.5-degree black disc placed on the fixation spot for better isolation from the foveal activation. Stimuli were presented centrally (viewing distance of 50cm) on a uniform black background.

Stimuli were displayed for 250 ms, and appeared in random order. Inter-trial interval was randomized between 500 and 900 ms, which was measured after button press. The fixation point was present trough out the trial. Subjects were tested in a dimly lit room where they were instructed to fixate the blue spot in the center of the monitor and to perform a two-alternative forced choice face-hand categorization task by pressing either the left or right mouse button. Testing was monocular, while the other eye was patched. Foveal and perifoveal stimuli were presented in different blocks making four types of blocks in total (Foveal – dominant / fellow eye, Foveal – nondominant / amblyopic eye, Perifoveal – dominant / fellow eye, Perifoveal – nondominant / amblyopic eye). Block order was randomized with fellow and amblyopic eye alternating. There were a total of 96 trials for each block (i.e. stimulation) type, out of which 48 trials were face trials. In the current paper, we only consider these trials. Other experimental procedures were identical to Experiment 1.

DOI:10.15774/PPKE.ITK.2015.009

2.3. Electrophysiological acquisition and processing

Detailed technical description of acquisition and preprocessing can be found at Bankó et al., 2013 [2]. Briefly, EEG data was acquired using a BrainAmp MR (Brainproducts GmbH., Germany) amplifier from 60 Ag/AgCl scalp electrodes mounted on an EasyCap (Easycap GmbH., Germany) with four additional periocular electrodes for recording the electrooculogram. All input impedance was kept below 5 kΩ. Channels were referenced to joint earlobes online with the nasion as ground and were re-referenced offline using a Laplacian transform on spherical spline interpolated data to generate scalp current density (SCD) waveforms. This was done to eliminate contamination of saccadic potentials and to make the data better suited for single trial peak detection (for more information see [2]). Data were band-pass filtered from 0.1-30 Hz including a 50 Hz notch filter, segmented (-200 – 600 ms relative to stimulus), artifact rejected and baseline corrected. Data processing was done using BrainVision Analyzer (Brainproducts GmbH., Germany).

In Experiment 2 all acquisition and processing steps were identical to Experiment 1, except the high-pass filter was set to 0.5 Hz to eliminate slow baseline shifts as a result of sweating.

2.4. Statistical analysis

Accuracy, calculated as percent correct responses, and reaction time were evaluated as behavioral measures. P1 and N170 component peaks were detected and analyzed on electrodes showing maximum deviation relative to baseline in the group average in the expected time period corresponding to the ERP peaks (PO7, PO9, P7, and P9, and PO8, PO10, P8, and P10 for left and right clusters, respectively for both components). In the case of averaged ERPs, peak latency was determined on the left and right clusters separately, while mean peak amplitudes were measured over the individual electrodes of the clusters in a 10-ms window. For single-trial peak analysis, peaks were detected on each trial for each electrode as maximum and minimum activity for P1 and N170, respectively in an 80-ms time window centered on the individual peak latency of the respective component measured on the averaged ERPs. The amplitude and corresponding time of the local extremes were taken as the amplitude and latency of the component on a given trial. Single trial amplitude and latency values were pooled from electrodes on each side and the distribution of the values was characterized by calculating the median and the interquartile range (IQR), which is a measure of spread and is computed as the difference of the upper and lower quartile of the data, and thus describes the middle 50% of the data values [2].

Foveal and perifoveal data were analyzed separately by repeated-measures ANOVAs with within-subject factors of eye (FE vs. AE) and filtering (*Br* vs. *Lo*) for behavioral

measures; eye, filtering, side (L vs. R) and electrode (4) for averaged ERP amplitude; and eye, filtering and side for averaged ERP latency and single-trial electrophysiological measures, as the latter were pooled across electrodes for obtaining more reliable estimates of the central tendency and dispersion of the distributions. Tukey HSD tests were used for post-hoc comparisons. Homogeneity of variances was tested using Bartlett's test for equal variances and in case this assumption was not met due to the higher variance of measurements from the AE, values were first rank transformed before being entered into the statistical test, which is noted by the superscript 'r' for rank ANOVA next to F-values when detailing statistical results. As many separate ANOVAs were conducted for analyzing the behavioral and electrophysiological data, significance level was set to p=0.013 (~0.05/4 – four main comparisons of: two positions × two independent measures) to control for the inflated type I error rate as a result of multiple comparisons. The significance level for fixation measurements was kept at p=0.05. We also conducted correlation analyses between the amblyopic effect on behavioral and electrophysiological measures using Spearman rank correlation. The interocular difference of all variables was taken as the index of the amblyopic effect.

In Experiment 2 statistical analysis was performed on the latency and amplitude of averaged event-related responses (ERPs) by repeated-measures ANOVAs. There were two types of analysis: one contrasting the fellow and amblyopic eye of amblyopic observers (with *eye*, *side* and *electrode* (for amplitude only) as within-subject factors; the other comparing the dominant eyes for amblyopic and control observers (with group as between-subject factor, side and electrode (for amplitude only) as within-subject factors) separately for foveal and perifoveal stimulation. Post-hoc analyses and correction for unequal variances were done similarly as in Experiment 1. As many separate ANOVAs were conducted for analyzing the electrophysiological data, significance level was set to p=0.013 (~0.05/4 – four separate comparisons of: two positions × two independent measures) to control for the inflated type I error rate as a result of multiple comparisons.

2.5. Analysis of eye-tracking data

We tracked the gaze direction of all subjects using the iViewX Hi-Speed tracking column (SMI GmbH., Germany) while they performed the EEG experiment. However, we were able to record useable eye movement data for only nine patients due to the strong reflection of glasses that many were wearing. Trials were binned based on the viewing eye, stimulus type, and stimulus position, then for each eye position measurement (i.e. a pair of (x,y) coordinates) geometrical distance from the fixation point was calculated. The median distance of each of the eight stimulation conditions was used as a measure of fixation stability in each subject, higher distance values meaning less stable fixation. Analysis was carried out using three-way

repeated-measures ANOVA with eye (FE vs. AE), filtering (*Br* vs. *Lo*) and position (fovea vs. perifovea) as within-subject factors.

3. Results

3.1. Behavioral results

In the case of foveal presentation, accuracy was impaired, while reaction times (RT) increased in amblyopic vision compared to viewing with the fellow eye (Figure 4.2; eye: $F^r_{(1,14)}=47.45$, $p<0.0001$ and $F_{(1,14)}=22.05$, $p=0.0003$ for accuracy and RT, respectively), which was true for both *Br* and *Lo* stimuli (all eye × filtering: $F_{(1,14)}<1.85$, $p>0.20$). Nevertheless, filtering the faces had an additional effect in foveal vision further degrading accuracy in both eyes, which was due to the removal of higher frequencies including the characteristic frequencies for judging faces (filtering: $F^r_{(1,14)}=10.10$, $p=0.0067$). It tended to increase reaction times as well, however it failed to reach significance (filtering: $F_{(1,14)}=6.70$, $p=0.021$).

In the case of perifoveal presentation, however, accuracy did not differ between the two eyes (eye: $F_{(1,14)}=3.02$, $p=0.10$). Nevertheless, subjects were still significantly slower in responding when viewing with their amblyopic eye (eye: $F_{(1,14)}=21.57$, $p=0.0004$). Low-pass filtering resulted in a drop in accuracy (filtering: $F_{(1,14)}=24.53$, $p=0.0002$) and a slowing of RTs, similarly to that observed for foveal stimuli (filtering: $F_{(1,14)}=34.12$, $p<0.0001$). These effects were consistent across eyes and types of stimuli (all eye × filtering: $F_{(1,14)}<0.65$, $p>0.44$).

The results of the eye-tracking analysis revealed that in agreement with previous findings [2, 116, 158, 159, 172] the ability of the amblyopic eye to fixate the central fixation mark was poor compared with the fellow eye (Figure 4.2C; eye: $F_{(1,8)}=9.39$, $p=0.015$). Importantly, however this difference was constant across the visual field. Overall fixation stability was not affected by either stimulus position (position: $F_{(1,8)}=0.04$, $p=0.85$, eye × position: $F_{(1,8)}=0.85$, $p=0.38$) or low-pass filtering (filtering: $F_{(1,8)}=1.79$, $p=0.22$).

There were no systematic relationships between the amblyopic effect in any of the behavioral measures and the interocular difference in electrophysiological measures. A possible explanation for the lack of correlations is that the task was too easy to expect a substantial modulation in the behavioral results.

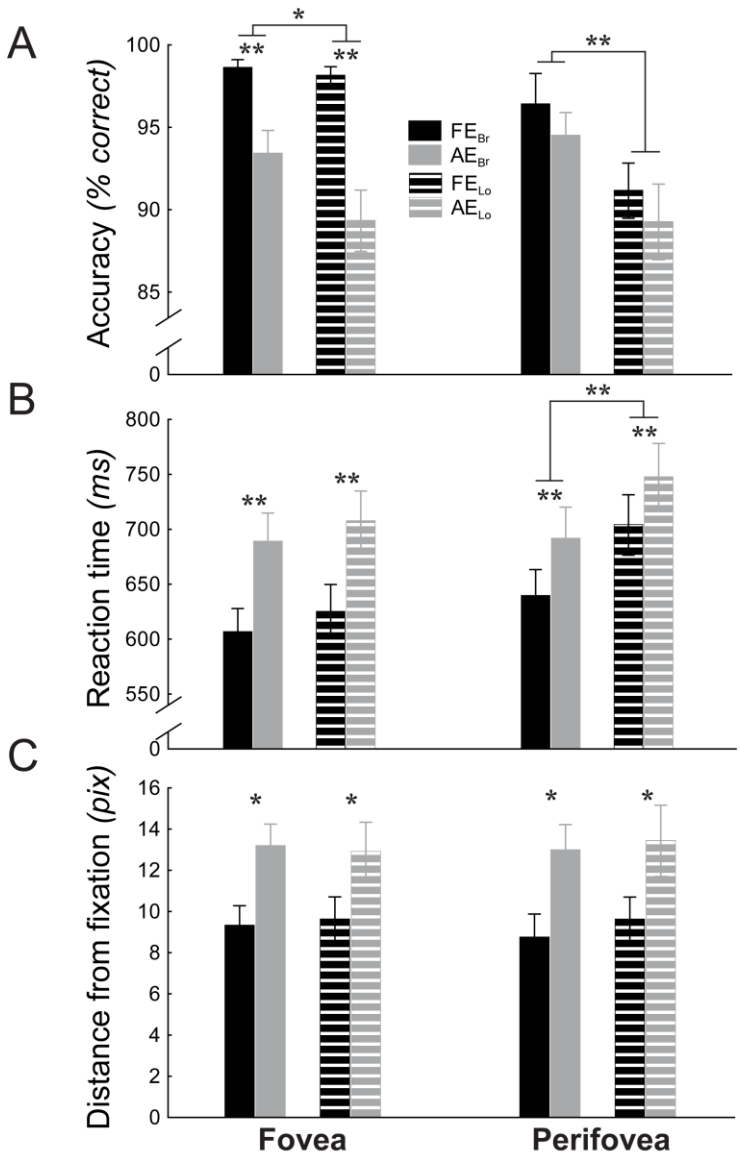

Figure 4.2. Behavioral results: accuracy (A), reaction times (B) and fixation stability (C). Results obtained from the amblyopic eye (AE) are shown in grey, while results from the fellow eye (FE) are black (Br: faces with broad spatial frequency content, solid columns, Lo: low-pass filtered face stimuli, striped columns; asterisks denote significant differences: *p<0.013, **p<0.001; N=15).

3.2. Averaged ERPs show amblyopic deficit both at the fovea and perifovea

Foveal stimulation

The results revealed strong amblyopic effects on the amplitude and latency of the P1 and N170 components of the averaged event-related potentials in the case of foveal stimuli (Figure 4.3A and Figure 4.4A), which were in accordance with previous findings [2, 41, 97, 100, 101]. Viewing with the amblyopic eye led to reduced amplitudes (Figure 4.7A; eye: $F^{r}_{(1,13)}=9.08$, $p=0.0099$ and $F_{(1,13)}=25.95$, $p=0.0002$ for components P1 and N170, respectively) and delayed latencies (eye: $F_{(1,13)}=19.69$, $p=0.0007$ and $F^{r}_{(1,13)}=10.72$, $p=0.0060$ for P1 and N170,

respectively) compared with the fellow eye for both ERP components (for statistics see Table 4.2). These effects were similar for both *Br* and *Lo* stimuli as no significant eye × filtering interactions were found. Interestingly, the only effect low-pass filtering had on the averaged ERPs was a decrease in the averaged ERP amplitudes of the P1 component in both eyes. In the case of the P1 component, this effect was modulated by the hemisphere the ERPs were measured over: the amplitude drop was significant over the left, while only a trend over the right hemisphere (eye × side: $F^{r}_{(1,13)}$=6.84, p=0.021, post-hoc: FE vs. AE p_{Left}=0.0002 and p_{Right}=0.039).

Perifoveal stimulation

Stimulation of the perifoveal region when controlling for cortical magnification, yielded clear amblyopic deficits on the amplitude and latency of both ERP components similar to those found in foveal stimulation (Figure 4.3B, Figure 4.4B and Table 4.2): averaged component amplitudes were reduced, while latencies increased in the amblyopic eye compared with the fellow eye for both ERP components. Here too, these effects were present for both *Br* and *Lo* stimuli with the exception of P1 latency, where only *Br* stimuli differed between eyes, while the trend for *Lo* stimuli did not reach significance. Low-pass filtering the perifoveal images affected neither the amplitude nor the latency of ERP components.

Large-field perifoveal stimulation

Averaged component amplitude and latency of P1 were not significantly affected by amblyopic viewing (Fig. S3B; eye: $F_{(1,13)}$=2.37, p=0.15 and $F_{(1,13)}$=1.03, p=0.33 for component amplitude and latency, respectively) but showed a non-significant reduction and increase, respectively over the left hemisphere as indicated by a trend in the eye × side interaction (eye × side: $F_{(1,13)}$=3.03, p=0.11 and $F_{(1,13)}$=4.50, p=0.054 for component amplitude and latency, respectively). Component N170 exhibited a slight but significant amblyopic effect similar to foveal stimulation in the case of latency (eye: $F_{(1,13)}$=39.37, p<0.0001), while the decrease in amplitude remained a non-significant trend (eye: $F^{r}_{(1,13)}$=7.33, p=0.018). (Figure 4.3C).

Taken together, amblyopia affects the component amplitude and latency of averaged ERPs under both foveal and perifoveal stimulation, but for the latter to be statistically evident it is advisable to keep the area of the activated cortex equal as stimulation is moved towards the periphery of the visual field. Importantly, however, amblyopic effects at the perifovea were small in contrast to foveal stimulation, which was statistically significant for most measures (Table 4.2).

Fovea		Perifovea	
Amplitude	**Latency**	**Amplitude**	**Latency**
P1		**P1**	
eye:	**eye:**	**eye:**	**eye:**
$F_{(1,14)}$=14.18, p=0.0021	**$F^r_{(1,14)}$=60.21, p<0.0001**	**$F_{(1,14)}$=11.11, p=0.0049**	**$F_{(1,14)}$=15.67, p=0.0014**
filtering:	filtering:	filtering:	filtering:
$F_{(1,14)}$=23.42, p=0.0003	$F^r_{(1,14)}$<0.001, p=0.98	$F_{(1,14)}$=1.50, p=0.24	$F_{(1,14)}$=1.08, p=0.32
eye × filtering:	eye × filtering:	eye × filtering:	**eye × filtering:**
$F_{(1,14)}$=0.93, p=0.35	$F^r_{(1,14)}$=0.05, p=0.83	$F_{(1,14)}$=2.97, p=0.11	**$F_{(1,14)}$=9.08, p=0.0093**
			FE_{Br} vs. AE_{Br} p=0.0002,
			FE_{Lo} vs. AE_{Lo} p=0.021
eye × position: $F_{(1,14)}$=5.58, p=0.033 and **$F^r_{(1,14)}$=16.45, p=0.0011** for amplitude and **latency**, respectively			
N170		**N170**	
eye:	**eye: $F^r_{(1,14)}$=49.71,**	**eye:**	**eye:**
$F_{(1,14)}$=23.28, p=0.0003	**p<0.0001**	**$F_{(1,14)}$=16.49, p=0.0012**	**$F_{(1,14)}$=19.73, p=0.0005**
filtering:	filtering:	filtering:	filtering:
$F_{(1,14)}$=2.05, p=0.17	$F^r_{(1,14)}$=1.17, p=0.29	$F_{(1,14)}$=2.45, p=0.14	$F_{(1,14)}$=0.59, p=0.46
eye × filtering:	eye × filtering:	eye × filtering:	eye × filtering:
$F_{(1,14)}$=3.77, p=0.073	$F^r_{(1,14)}$=0.01, p=0.93	$F_{(1,14)}$=0.03, p=0.86	$F_{(1,14)}$=0.38, p=0.54
eye × position: $F_{(1,14)}$=14.18, p=0.0021 and $F^r_{(1,14)}$=10.03, p=0.0069 for amplitude and latency, respectively			

Table 4.2. Amplitude and latency statistics for the averaged ERP responses. Significant effects are highlighted by bold face. ANOVA conducted on ranked data is denoted by the superscript 'r'.

Single-trial amplitude amblyopic deficit is restricted to the fovea

We were interested whether this magnitude difference between fovea and perifovea simply reflected a quantitative decrease in the deficits towards the periphery as has been suggested [51, 126, 127] or qualitative changes may underlie amblyopic processing deficits at the periphery compared with the fovea. However, the results from the averaged ERP peak analysis are insufficient to pin down the nature of the amblyopic effects, due to the contamination of the observed amplitude by the elevated trial-to-trial ERP latency jitter in the amblyopic compared with the fellow eye [2], which is a result of impaired temporal structure of neural responses elicited by stimulating the amblyopic eye [151–153]. Therefore, we have performed a single-trial peak analysis on the responses obtained from faces with broad spatial frequency content by detecting peaks on each trial and evaluating component amplitude and latency

DOI:10.15774/PPKE.ITK.2015.009

distributions. This enabled us to tease apart the contribution of changes in single-trial amplitude and latency to the amblyopic effects observed at the fovea and perifovea.

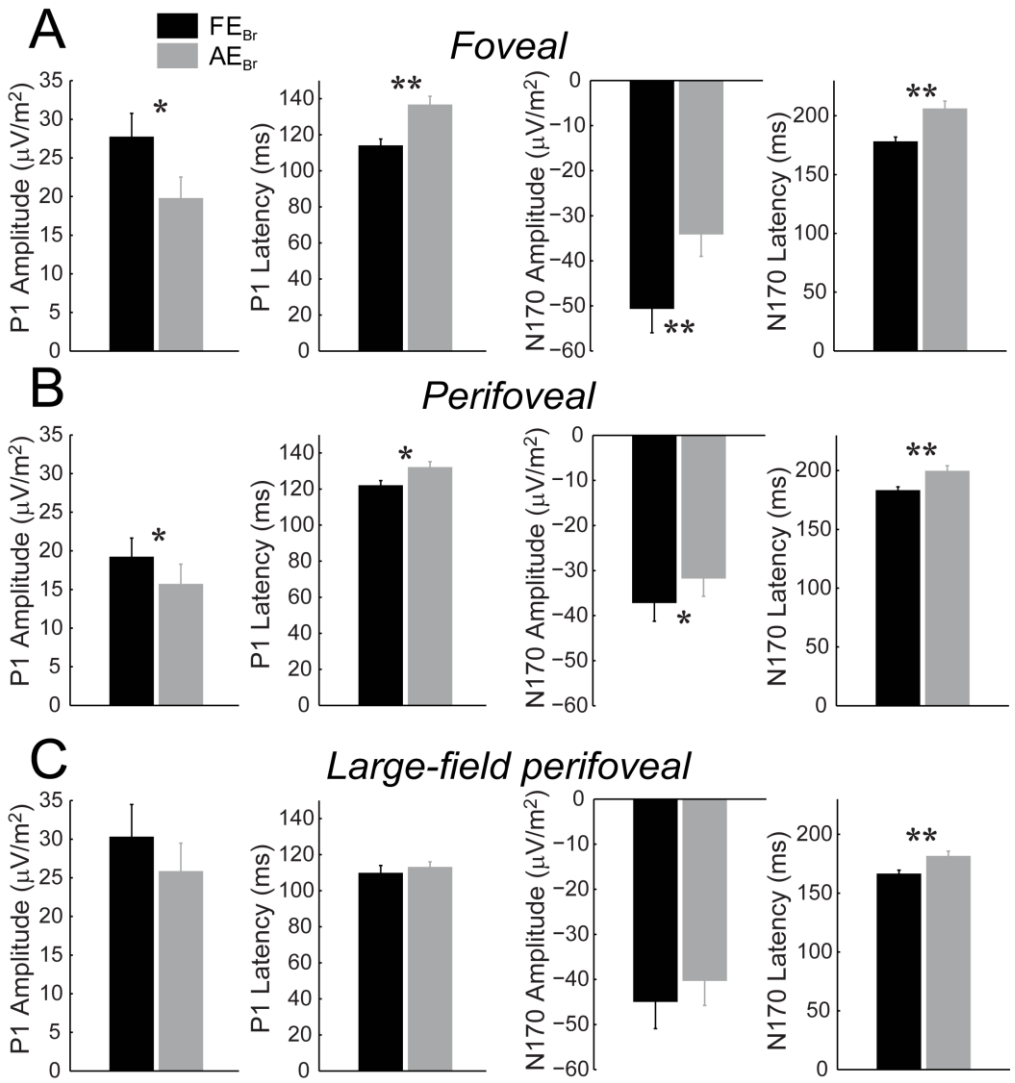

Figure 4.3. Amplitude and latency of averaged event-related potentials of amblyopic subjects for foveal (A) and perifoveal (B) presentation. Stimuli were matched in size according to the cortical magnification factor. (N=15); (C) Statistics for large-field perifoveal stimuli from Exp. 2 are shown for comparison. Similar trends can be found as in panel A and B, but large-field stimulation masks the amblyopic deficits, decreasing the sensitivity to detect them (N=14). (AE: amblyopic eye, yellow, FE: fellow eye, blue; asterisks denote significant differences: *p<0.013, **p<0.001).

Foveal stimulation

In the case of foveal stimulation, single-trial response amplitudes were reduced significantly in the amblyopic compared with the fellow eye for both ERP components, which was evident in a shift of the amplitude distributions towards smaller values as indicated by a decrease in their medians (Figure 4.5A and Figure 4.6A, see Table 4.3 for statistics). This drop, however, was only significant on the right side in the case of P1, while present over both hemispheres but

DOI:10.15774/PPKE.ITK.2015.009

more pronounced on the right side for N170. Dispersion of the amplitude values coming from the amblyopic eye was similar to that of the fellow eye, thus, the spread of component amplitude distributions was not altered by amblyopic viewing.

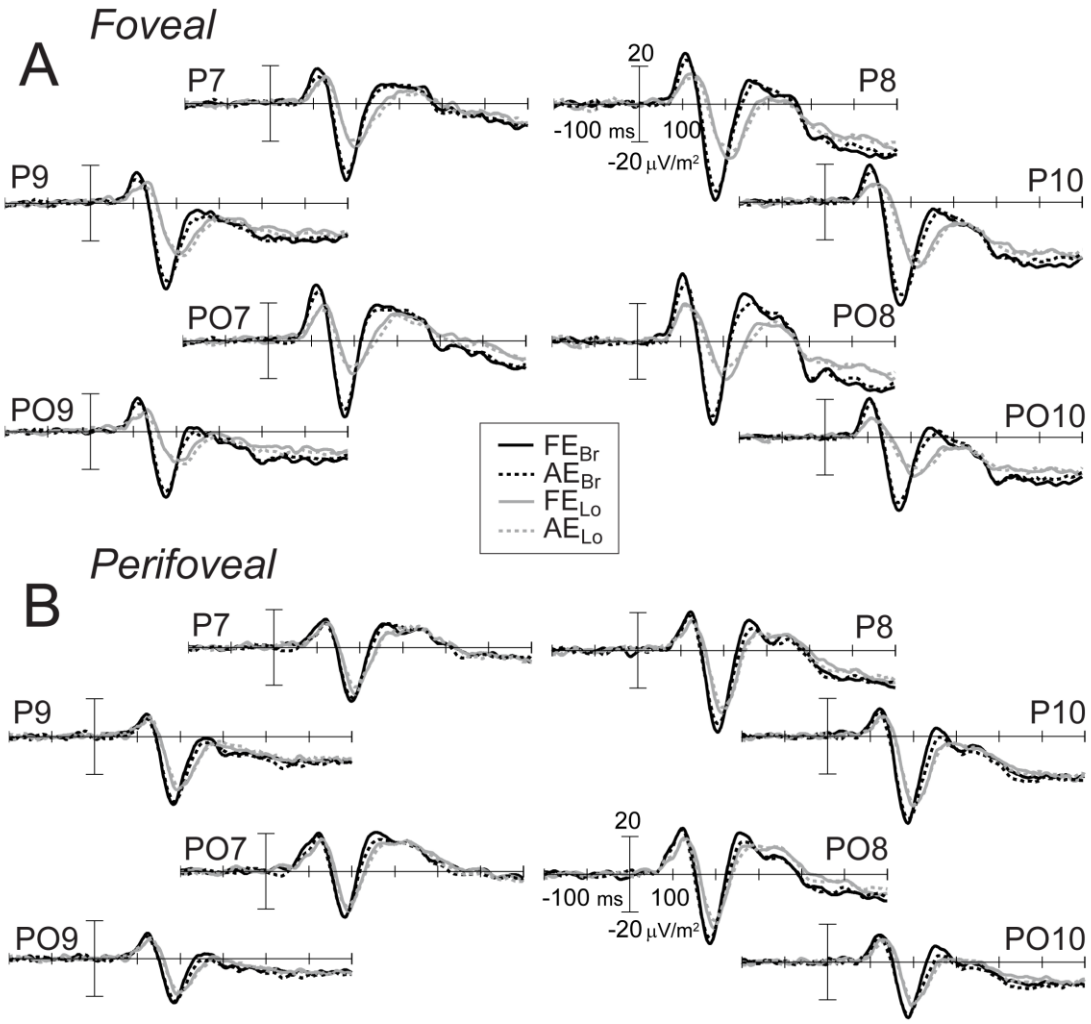

Figure 4.4. Averaged event-related potentials of amblyopic subjects from Experiment 1 for foveal (A) and perifoveal (B) presentation. Stimuli were matched in size according to the cortical magnification factor. Time courses from the amblyopic (AE) and fellow eye (FE) are shown in grey and black, respectively (Br: faces with broad spatial frequency content, solid lines; Lo: low-pass filtered face stimuli, dashed lines; N=15; negative is down).

Perifoveal stimulation.

Importantly, however, amplitude distributions corresponding to peripheral stimulation, unlike in foveal stimulation, were not affected by amblyopia. Distributions, as characterized by their median and spread, were similar across all stimulation condition for both components (Figure 4.5B and Figure 4.6B, Table 4.3).

DOI:10.15774/PPKE.ITK.2015.009

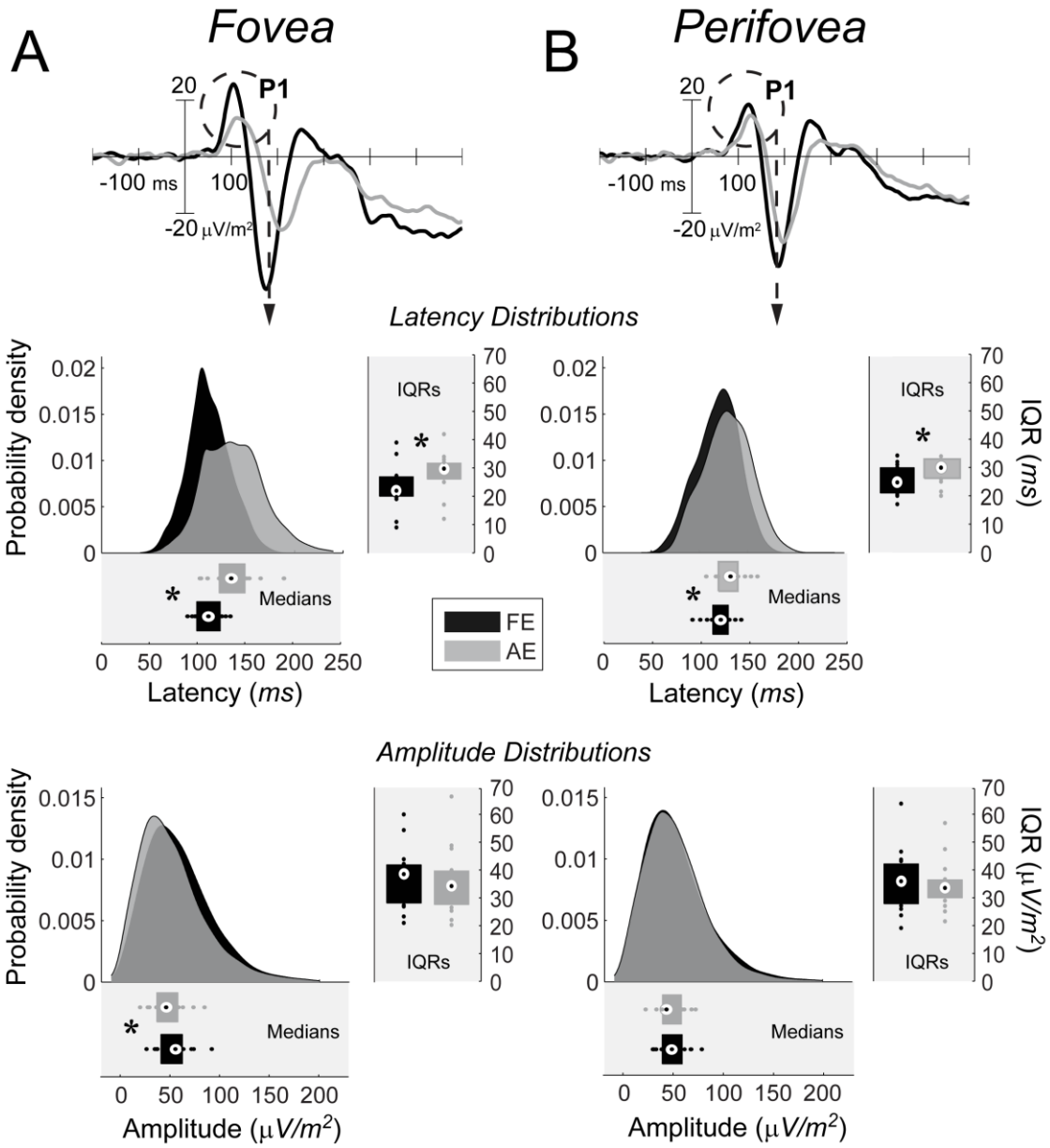

Figure 4.5. P1 amplitude and latency distributions obtained over the right hemisphere in the case of foveal (A) and perifoveal (B) stimuli, which were matched in size according to the cortical magnification factor. The top panel shows averaged ERPs from the right electrode cluster (P8, P10, PO8, and 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 (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).

DOI:10.15774/PPKE.ITK.2015.009

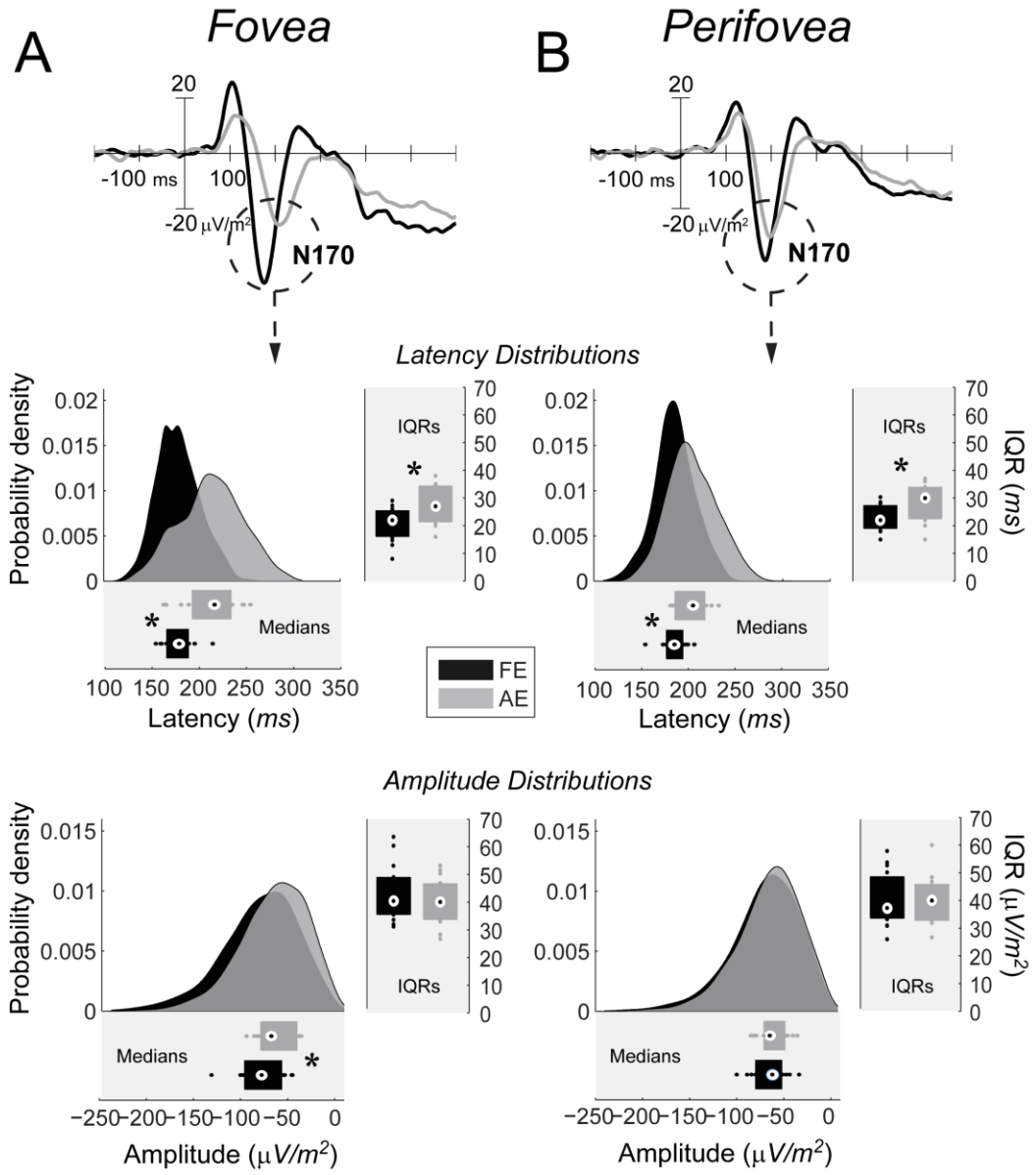

Figure 4.6. N170 amplitude and latency distributions obtained over the right hemisphere in the case of foveal (A) and perifoveal (B) stimuli, which were matched in size according to the cortical magnification factor. The top panel shows averaged ERPs from the right electrode cluster (P8, P10, PO8, and 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 (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).

DOI:10.15774/PPKE.ITK.2015.009

Fovea		Perifovea	
Amplitude median	**Amplitude jitter**	**Amplitude median**	**Amplitude jitter**
P1		**P1**	
eye: **$F_{(1,14)}$=7.99, p=0.013**	eye: $F_{(1,14)}$=0.025, p=0.88	eye: $F_{(1,14)}$=0.36, p=0.56	eye: $F_{(1,14)}$=0.22, p=0.64
eye × side: $F_{(1,14)}$=3.74, p=0.073 **FE_{Br} vs. AE_{Br}** p_{Left}=0.29, **p_{Right}=0.0022**	eye × side: $F_{(1,14)}$=3.25, p=0.093	eye × side: $F_{(1,14)}$=0.099, p=0.76	eye × side: $F_{(1,14)}$=2.51, p=0.14
N170		**N170**	
eye: **$F_{(1,14)}$=18.87, p=0.0007**	eye: $F_{(1,14)}$=0.76, p=0.40	eye: $F_{(1,14)}$=2.78, p=0.12	eye: $F_{(1,14)}$=0.24, p=0.63
eye × side: $F_{(1,14)}$=5.86, p=0.029 **FE_{Br} vs. AE_{Br}** **p_{Left}=0.0018,** **p_{Right}=0.0002**	eye × side: $F_{(1,14)}$=1.76, p=0.21	eye × side: $F_{(1,14)}$=2.68, p=0.12	eye × side: $F_{(1,14)}$=0.01, p=0.93
Latency median	**Latency jitter**	**Latency median**	**Latency jitter**
P1		**P1**	
eye: **$F^r_{(1,14)}$=83.70, p<0.0001**	**eye:** **$F^r_{(1,14)}$=6.1, p=0.013**	**eye:** **$F_{(1,14)}$=54.05, p<0.0001**	eye: $F_{(1,14)}$=6.44, p=0.024
eye × side: $F^r_{(1,14)}$=0.09, p=0.77	eye × side: $F^r_{(1,14)}$=1.69, p=0.21	eye × side: $F_{(1,14)}$< 0.001, p=0.98	eye × side: $F_{(1,14)}$=6.29, p=0.025 **FE_{Br} vs. AE_{Br}** p_{Left}=0.81, **p_{Right}=0.0029**
N1		**N1**	
eye: **$F^r_{(1,14)}$=47.32, p<0.0001**	**eye: $F_{(1,14)}$=26.81, p=0.0001**	**eye:** **$F_{(1,14)}$=30.62, p<0.0001**	**eye: $F_{(1,14)}$=12.19, p=0.0036**
eye × side: $F^r_{(1,14)}$=4.72, p=0.047	eye × side: $F_{(1,14)}$=0.50, p=0.49	eye × side: $F_{(1,14)}$=1.56, p=0.23	**eye × side:** **$F_{(1,14)}$=9.54, p=0.008** **FE_{Br} vs. AE_{Br}** p_{Left}=0.060, **p_{Right}=0.0002**

Table 4.3. Median and interquartile range statistics for the amplitude and latency distributions. Significant effects are highlighted by bold face. ANOVA conducted on ranked data is denoted by the superscript ‘r’.

DOI:10.15774/PPKE.ITK.2015.009

3.3. Amblyopic latency distributions display both foveal and perifoveal deficit

Foveal stimulation

P1 and N170 latency distributions were affected by amblyopic viewing, which led to a shift towards longer latencies (i.e. elevated medians) and to an increase in trial-to-trial latency jitter (i.e. larger spreads) (Figure 4.5A and Figure 4.6A, Table 4.3). These effects were similar across hemispheres, except in the case of the N170 latency medians, where the right hemisphere displayed a bigger amblyopic delay compared to the left hemisphere (median difference: 38ms vs. 21ms), which remained a non-significant trend. This replicates our previous results showing a selective processing deficit for faces in amblyopia [2].

Perifoveal stimulation

When faces were presented at the perifovea, P1 and N170 latency distributions coming from the amblyopic eye displayed a pattern similar to foveal stimulation: increased medians and spreads compared with the fellow eye (Figure 4.5B and Figure 4.6B, Table 4.3). Latency medians were larger over both hemispheres, while the spread of latency distributions displayed a significant difference between amblyopic and normal viewing only over the right hemisphere.

Taken together, averaged component amplitude reduction at the fovea stems from a mixture of single-trial amplitude decrease and the elevation of trial-to-trial latency jitter. In contrast, at the perifovea it is predominantly the result of increased trial-to-trial component jitter. Thus, the apparent averaged amplitude reduction in the latter case arises from averaging and is not due to a decrease in response magnitude. Conversely, the amblyopic delay in component latencies is present for both foveal and perifoveal stimulation, indicating a true neural deficit outside the fovea.

3.4. Fellow eye ERPs do not differ significantly from control ERPs

We were interested how closely the responses obtained from the fellow eye of amblyopic subjects approximate the ERPs of healthy subjects. In light of the null result concerning the comparison of component P1 of the fellow and amblyopic eyes of amblyopes under large-field perifoveal presentation, it would be important to know whether the fellow eye can be considered normal in respect to the amplitude and latency of its evoked responses. Therefore, we conducted Experiment 2 on fourteen healthy control subjects and compared the ERPs obtained from their dominant eye to that of the fellow eye of the amblyopic subjects in a

DOI:10.15774/PPKE.ITK.2015.009

between-subject design. In addition, we compared their amblyopic eye to the control non-dominant eye for perifoveal stimulation.

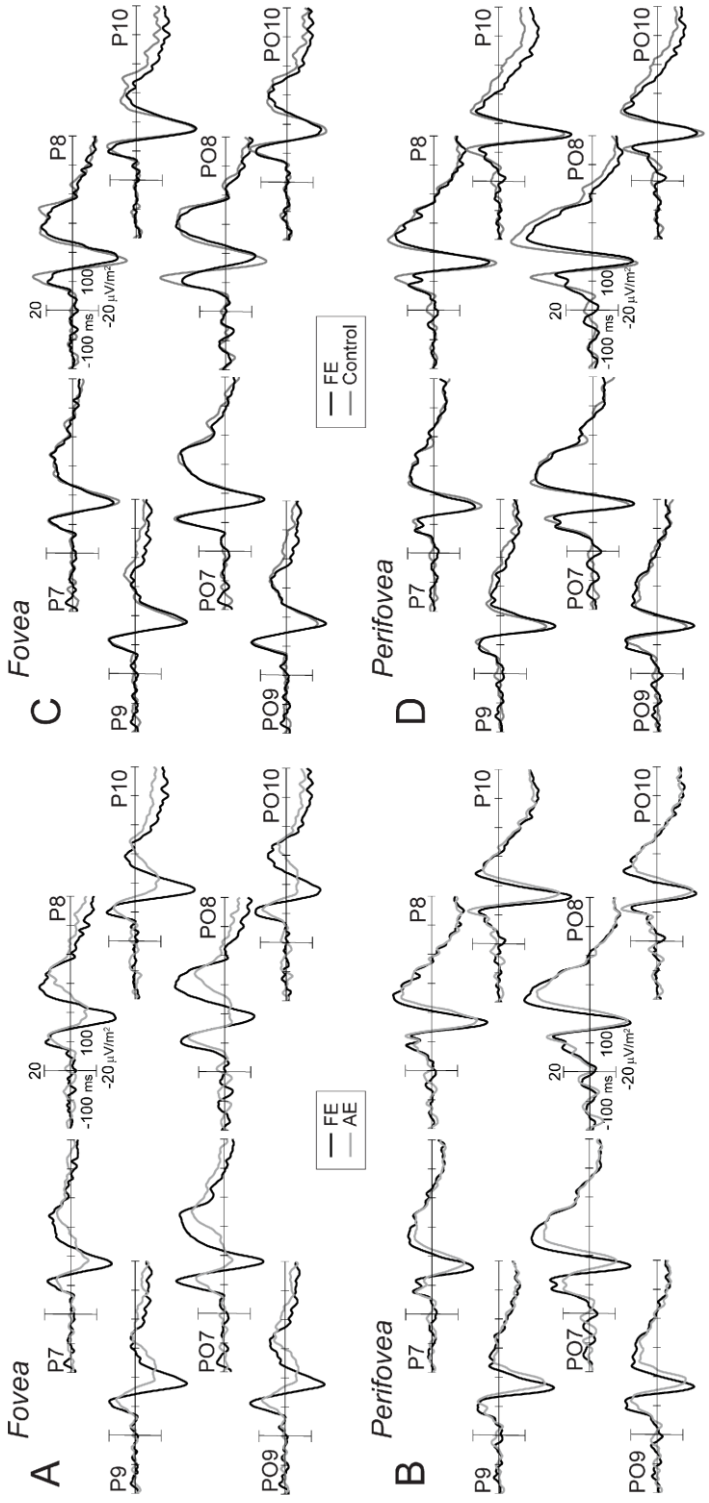

Figure 4.7. Averaged event-related potentials from Experiment 2. ERPs of amblyopic subjects for foveal (A) and large-field perifoveal (B) stimuli. Signal from the amblyopic eye (AE) is shown in light grey while ERPs from the fellow eye (FE) are blue. Comparison between the averaged ERPs from the dominant eyes of amblyopic patients (black) and control subjects (dark gray) for foveal (C) and large-field perifoveal (D) stimulation ($N_{amblyope}$=14, $N_{control}$=14, negative is down).

Foveal stimulation

The results did not reveal any significant differences between the dominant eye of the two groups of subjects on the amplitude and latency of either ERP component in the case of foveal stimuli (Figure 4.7C). There were no significant main effects of group or group × side interactions either for P1 (all $F_{(1,26)}<1.72$, $p>0.20$) or for N170 (all $F_{(1,26)}<1.66$, $p>0.21$).

Large-field perifoveal stimulation

Similarly to the results obtained in the foveal stimulation, we failed to find significant differences in the case of perifoveal stimulation as well (Figure 4.7D). There were also no significant main effects of group or group × side interactions either for P1 (all $F_{(1,26)}<1.91$, $p>0.18$) or for N170 (all $F_{(1,26)}<1.40$, $p>0.24$).

In agreement with the within-subject analysis of amblyopic patients, ERPs obtained from the amblyopic eye did not differ from those of control subjects in the case of P1 latency and N170 amplitude (group: $F_{(1,26)}=0.06$, $p=0.81$ and $F_{(1,26)}=0.31$, $p=0.58$, respectively), where we also found no significant interocular differences between fellow and amblyopic eye. Similarly, N170 latency of the amblyopic eye was significantly longer than that of the non-dominant eyes of controls (group: $F_{(1,26)}=8.56$, $p=0.0071$) corresponding to the significant interocular difference found within amblyopic patients. However, amblyopic P1 amplitude also differed from controls (group: $F_{(1,26)}=4.71$, $p=0.039$), despite the fact that no significant interocular difference was found between the amblyopic and fellow eye in this respect. In agreement with the results of Experiment 1, this also suggests that the amblyopic deficit in P1 amplitude extends beyond the fovea.

Thus, it can be concluded that the measure of averaged ERPs is insensitive to any difference in electrophysiological activity that might exist between the dominant eyes of amblyopes and normal subjects. This finding is also backed by VEP studies where no difference was found either in the latency and peak-to-peak amplitude of the P100 VEP [117] and the P50 PERG component or in retinocortical time (RCT) between the fellow eye of amblyopes and normal control subjects [101].

4. Discussion

We have shown that amblyopic deficits exist in the event-related potential responses recorded outside the central visual field. This can be reliably detected when the size of the peripheral stimulus corresponds to the size of the fovea scaled by cortical magnification. Stimulating a much larger cortical area, on the other hand, may render the deficit statistically unnoticeable. Our results have revealed for the first time that foveal and peripheral deficits differ in nature.

DOI:10.15774/PPKE.ITK.2015.009

Deficit at the fovea arises as a mixture of decreased single-trial amplitude and delayed, uncertain timing of the ERP responses. Conversely, the amblyopic deficit outside the fovea is dominantly characterized by a deficiency in timing of neural responses, while the contribution of response magnitude reduction to the observed effects is negligible.

4.1. Importance of cortical magnification

Our results, demonstrating that the sensitivity of the ERPs for detecting amblyopic effects at the perifovea might depend on adequate stimulus scaling, may help to reconcile the divergent electrophysiological results concerning the presence or absence of the amblyopic deficit outside the fovea [101, 111–113, 116–118]. Full-field VEP an mfVEP also differ in stimulation field size: in an mfVEP stimulus it is scaled with eccentricity [173] using the cortical magnification formula computed by Horton and Hoyt [170], while typical clinical pattern-reversal VEP applications use a homogeneous large stimulation field minimally 15 degree in diameter [112], which does not scale with check size, hence ignoring cortical magnification. Same holds true for large annular stimuli that are also frequently used to stimulate the perifovea [114, 115, 85, 151]. Thus, by using full-field VEPs or annular central stimuli [114] to investigate perifoveal or peripheral processing, many more neurons are activated in perifoveal compared to foveal stimulation. Due to the extensive summation of activity evoked by a large number of neurons throughout the whole periphery [50], small extrafoveal deficits could in principle fail to reach significance, hence they will go undetected. Thus, our results stress the notion that magnification scaling is a highly important variable that influences the elicited pattern evoked potential [111]. Our findings also closely parallels the psychophysical results of Katz and colleagues [50], who showed that peak contrast sensitivity of the amblyopic eyes at the periphery benefitted more from an increase in stimulus size, reaching the sensitivity of the fellow eyes for large central stimuli. They concluded that spatial summation across the extent of the stimulus field increased peak contrast sensitivity at least for the amblyopic eye [50].

4.2. Deficient ERP response timing in amblyopia

The amblyopic deficit in timing of the neural responses are similar in nature across the visual field apart from the fact that the interocular difference at the perifovea appears to be attenuated compared with the difference at the fovea for both latency delay and jitter. Neurophysiological research on strabismic cats has revealed that neuronal response latencies in primary visual cortical neurons driven by the amblyopic eye are also delayed [151, 153] and highly variable as reflected by decreased neural synchrony [152] compared with visual neurons driven by the fellow eye. The increased variance in the timing of neural activity represents an increase in internal neural noise, which comprises random internal noise – a crucial factor in many

DOI:10.15774/PPKE.ITK.2015.009

models used to explain the psychophysical performance of the amblyopic eye [174–177]. This ties in with our results of greater trial-to-trial variability of ERP component latency coming from the amblyopic eye, implying that an overall uncertainty in the timing of neural responses might underlie the increase in internal noise observed in amblyopia. Similar timing deficiencies have been found in autism spectrum disorder (ASD) by Milne [178], where the trial-to-trial variability (i.e. jitter) of P1 latency was found to be significantly higher than that of the matched control group, suggesting that individuals with ASD are less able to synchronize the activity of stimulus-related cell assemblies and display increased neural noise compared with healthy controls.

4.3. Unaltered amblyopic ERP response strength at the periphery

In the ERPs obtained with perifoveal stimulation we have found very weak, non-significant interocular changes in the single-trial amplitude as compared with the strong reduction at the fovea. There are at least two phenomena, which could possibly account for this. First, it has been shown, that induced refractive error causes amplitude reduction of VEP components, which is most pronounced for stimuli with higher spatial frequency (e.g. checks of 5-40’ of arc) [168, 179]. Since our sensitivity for high spatial frequencies decreases towards the periphery of the visual field, stimulation further away from the fovea becomes less susceptible to the effects of degraded visual acuity. In accordance, the acuity deficit of the amblyopic eye, also lessens towards the periphery [124–126]. Our finding, that the removal of higher spatial frequency content from the stimuli reduced the amplitude of the P1 component only at the fovea but not at the periphery is also in agreement with the above. Thus, the degraded visual acuity of the amblyopic eye could have contributed to the amblyopic amplitude reduction under foveal viewing in the case of P1, while did not effect single-trial amplitudes at the perifovea. Nevertheless, it is important to note, that the amblyopic effect on the averaged ERPs was present for low-pass filtered stimuli, indicating it is not simply the result of the inability of the amblyopic eye to perceive high spatial frequencies. Second, unsteady fixation, a known problem for amblyopic patients [2, 116, 158, 159, 172], can also lead to reductions in the observed amplitude. Artificially induced fixation errors greatly affect VEP waveforms especially at the fovea, but the effects have been found to be minimal outside the central 5-6˚ of the visual field in the case of approximately 1˚ fixation error [116, 180]. Thus, unsteady fixation is likely to contribute to amblyopic averaged amplitude reduction at the fovea. Nevertheless, it is unclear whether fixation instability affects true evoked potential magnitude or increases the trial-to-trial latency variability of the responses. To elucidate this, further studies using induced fixation instability are needed.

DOI:10.15774/PPKE.ITK.2015.009

Chapter Five

CONCLUSIONS AND POSSIBLE APPLICATIONS

From our studies on the neural mechanisms of amblyopia the following conclusions can be drawn.

1. 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.
2. The amblyopic disruption of early visual experience also alters the development of higher-order, object specific visual information processing in humans and thus our results suggest that amblyopia might provide a unique opportunity for the investigation of the neural mechanisms of compensatory plasticity in visual object processing.
3. Despite the common perception of amblyopia as a foveal disorder, deficits exist outside the fovea as well. Our 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.

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.

Visual training as a potential treatment of amblyopia

Several studies have provided evidence for improved vision in amblyopic adults following training. The studies have mostly employed three different kinds of intervention: monocular perceptual learning (PL), monocular videogame play (VGP) and dichoptic PL/VGP.

The argument that perceptual learning succeeds where everyday experience fails in amblyopic adults is that the less plastic brain of the adult requires “attention and action using the amblyopic eye, supervised with feedback” in order to provide effective treatment [181].

In initial PL studies the participants were required to perform fine discrimination tasks in monocular condition. Even with 40–50 hours of perceptual learning, most adults achieve only 0.1–0.2 logMAR improvements in visual acuity (1–2 lines). Serious limitation of this method is that the task is typically repetitious, boring and the improvements are specific to the trained task and do not transfer readily to other tasks.

Action video games are able to capture attention thus, sustain interest for a prolonged time because of the varied visual tasks, story lines and rewards provided by the games for making correct discriminations. A recent evaluation of an of-the-shelf action game (Medal of Honor: Pacific Assault) found that just 20 hours of play with the fellow eye patched resulted in a mean improvement of 0.15 logMAR. Hussain et al. (2014) have developed a contrast-based videogame for treating both adults and children with amblyopia [182].

While these monocular training methods are directed toward improving the visual performance of the amblyopic eye, an alternative approach is to treat amblyopia by reducing the suppression by training dichoptically.

Eastgate and colleagues have developed a virtual reality display system on which interactive games are played via stereo display, with different elements of the ‘scene’ visible to the two eyes (at the same contrast) [183]. Hess and colleagues have developed a version of the video game Tetris that can be played on an iPod and is viewed dichoptically, with blocks visible to the good eye displayed at a lower contrast than those visible to the amblyopic eye such that they appeared the same to the two eyes [48]. After playing the game for 1 hour each day for 2 weeks subjects exhibited significantly greater improvement in visual acuity (1.6 lines) and stereopsis when training had been dichoptic rather than using just the amblyopic eye [49].

Vedamurthy and colleagues have developed a game which was designed to incorporate the benefits of perceptual learning, action videogame play, and dichoptic training. They could have expected to see an additive effect, leading to larger improvements in VA than each of the methods on its own. However, the magnitude of improvement was 1.4 lines on a logMAR chart after 40 hours of training. They also found significant improvement in contrast sensitivity, quality of life (the fear of losing the good eye) and reading speed. Faster reading speed can be a direct result of the fast-paced nature of first-person-shooter action video games, which require fast actions and eye movements to identify game bots [62].

When directly looking at improvement in stereopsis -, which would be the ultimate goal in amblyopia therapy - as a result of various training methods, the following can be said. Stereopsis can be improved in anisometropic amblyopia through either monocular or dichoptic

DOI:10.15774/PPKE.ITK.2015.009

training; however, individuals with strabismic amblyopia fare better with dichoptic training than with monocular training and better yet with direct training of stereopsis [184].

Thus, drawing from amblyopia training results obtained so far in the literature and from our expertise in attention research, we are currently taking part in the development of a video game based 3D virtual reality training software, directly targeting stereopsis improvement that suitably addresses sensory and attention deficits that occur in amblyopia. The envisaged tool could meet an important clinical need for restoring stereovision in amblyopes through manual interactivity in 3D space and even preserving visual functions through healthy aging [12].

DOI:10.15774/PPKE.ITK.2015.009

Chapter Six

SUMMARY

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.

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

DOI:10.15774/PPKE.ITK.2015.009

patent 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. 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. 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.

DOI:10.15774/PPKE.ITK.2015.009

BIBLIOGRAPHY

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, "Impared foveal and peripheral face processig 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.

DOI:10.15774/PPKE.ITK.2015.009

Publications cited in the dissertation

[15] T. N. Wiesel and D. H. Hubel, “Single-cell responses in striate cortex of kittens deprived of vision in one eye,” *J. Neurophysiol.*, vol. 26, pp. 1003–1017, Nov. 1963.
[16] T. N. Wiesel, “Postnatal development of the visual cortex and the influence of environment,” *Nature*, vol. 299, no. 5884, pp. 583–591, Oct. 1982.
[17] G. K. von Noorden, “Amblyopia: a multidisciplinary approach. Proctor lecture.,” *IOVS*, vol. 26, no. 12, pp. 1704–1716, Dec. 1985.
[18] G. Kvarnström, P. Jakobsson, and G. Lennerstrand, “Screening for visual and ocular disorders in children, evaluation of the system in Sweden,” *Acta Paediatr.*, vol. 87, no. 11, pp. 1173–1179, Nov. 1998.
[19] G. Kvarnström, P. Jakobsson, and G. Lennerstrand, “Visual screening of Swedish children: An ophthalmological evaluation,” *Acta Ophthalmologica Scandinavica*, vol. 79, no. 3, pp. 240–244, 2001.
[20] M. Eibschitz-Tsimhoni, T. Friedman, J. Naor, N. Eibschitz, and Z. Friedman, “Early screening for amblyogenic risk factors lowers the prevalence and severity of amblyopia,” *J AAPOS*, vol. 4, no. 4, pp. 194–199, Aug. 2000.
[21] C. Williams, R. A. Harrad, I. Harvey, J. M. Sparrow, and ALSPAC Study Team, “Screening for amblyopia in preschool children: results of a population-based, randomised controlled trial. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood,” *Ophthalmic Epidemiol*, vol. 8, no. 5, pp. 279–295, Dec. 2001.
[22] E. E. Birch, “Amblyopia and binocular vision,” *Progress in Retinal and Eye Research*, vol. 33, pp. 67–84, Mar. 2013.
[23] K. Simons, “Amblyopia characterization, treatment, and prophylaxis,” *Surv Ophthalmol*, vol. 50, no. 2, pp. 123–166, Apr. 2005.
[24] C. Wu and D. G. Hunter, “Amblyopia: diagnostic and therapeutic options,” *Am. J. Ophthalmol.*, vol. 141, no. 1, pp. 175–184, Jan. 2006.
[25] D. DeSantis, “Amblyopia,” *Pediatr. Clin. North Am.*, vol. 61, no. 3, pp. 505–518, Jun. 2014.
[26] Gunter K. vonNoorden, M.D.; Emilio C. Campos, M.D., *Binocular Vision and Ocular Motility Theory and Management of Strabismus*, Sixth Edition. Mosby Inc., 2002.
[27] J. M. Holmes and M. P. Clarke, “Amblyopia,” *Lancet*, vol. 367, no. 9519, pp. 1343–1351, Apr. 2006.
[28] 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.
[29] 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.
[30] J. Rahi, S. Logan, C. Timms, I. Russell-Eggitt, and D. Taylor, “Risk, causes, and outcomes of visual impairment after loss of vision in the non-amblyopic eye: a population-based study,” *Lancet*, vol. 360, no. 9333, pp. 597–602, Aug. 2002.
[31] J. S. Rahi, S. Logan, M. C. Borja, C. Timms, I. Russell-Eggitt, and D. Taylor, “Prediction of improved vision in the amblyopic eye after visual loss in the non-amblyopic eye,” *Lancet*, vol. 360, no. 9333, pp. 621–622, Aug. 2002.
[32] D. H. Hubel and T. N. Wiesel, “The period of susceptibility to the physiological effects of unilateral eye closure in kittens,” *J. Physiol. (Lond.)*, vol. 206, no. 2, pp. 419–436, Feb. 1970.
[33] B. G. Goodyear, D. A. Nicolle, G. K. Humphrey, and R. S. Menon, “BOLD fMRI response of early visual areas to perceived contrast in human amblyopia,” *J. Neurophysiol.*, vol. 84, no. 4, pp. 1907–1913, Oct. 2000.
[34] S. P. McKee, D. M. Levi, and J. A. Movshon, “The pattern of visual deficits in amblyopia,” *J Vis*, vol. 3, no. 5, pp. 380–405, 2003.
[35] R. Sireteanu and M. Fronius, “Human amblyopia: structure of the visual field,” *Exp Brain Res*, vol. 79, no. 3, pp. 603–614, 1990.

DOI:10.15774/PPKE.ITK.2015.009

[36] U. Polat, Y. Bonneh, T. Ma-Naim, M. Belkin, and D. Sagi, “Spatial interactions in amblyopia: effects of stimulus parameters and amblyopia type,” *Vision Res.*, vol. 45, no. 11, pp. 1471–1479, May 2005.
[37] D. M. Levi, S. Hariharan, and S. A. Klein, “Suppressive and facilitatory spatial interactions in amblyopic vision,” *Vision Res*, vol. 42, no. 11, pp. 1379–1394, May 2002.
[38] I. Kovács, U. Polat, P. M. Pennefather, A. Chandna, and A. M. Norcia, “A new test of contour integration deficits in patients with a history of disrupted binocular experience during visual development,” *Vision Res.*, vol. 40, no. 13, pp. 1775–1783, 2000.
[39] C. Williams and D. Papakostopoulos, “Electro-oculographic abnormalities in amblyopia,” *Br J Ophthalmol*, vol. 79, no. 3, pp. 218–224, Mar. 1995.
[40] G. K. von Noorden and M. L. Crawford, “The lateral geniculate nucleus in human strabismic amblyopia,” *Invest. Ophthalmol. Vis. Sci.*, vol. 33, no. 9, pp. 2729–2732, Aug. 1992.
[41] A. R. Davis, J. J. Sloper, M. M. Neveu, C. R. Hogg, M. J. Morgan, and G. E. Holder, “Electrophysiological and psychophysical differences between early- and late-onset strabismic amblyopia,” *Invest. Ophthalmol. Vis. Sci*, vol. 44, no. 2, pp. 610–617, Feb. 2003.
[42] C. Williams, “Amblyopia,” *Clin Evid (Online)*, vol. 2009, 2009.
[43] Pediatric Eye Disease Investigator Group, “The clinical profile of moderate amblyopia in children younger than 7 years,” *Arch. Ophthalmol.*, vol. 120, no. 3, pp. 281–287, Mar. 2002.
[44] J. M. Holmes, D. A. Leske, J. P. Burke, and D. O. Hodge, “Birth prevalence of visually significant infantile cataract in a defined U.S. population,” *Ophthalmic Epidemiol*, vol. 10, no. 2, pp. 67–74, Apr. 2003.
[45] J. S. Rahi and C. Dezateux, “National cross sectional study of detection of congenital and infantile cataract in the United Kingdom: role of childhood screening and surveillance. The British Congenital Cataract Interest Group,” *BMJ*, vol. 318, no. 7180, pp. 362–365, Feb. 1999.
[46] S. Hatt, A. Antonio-Santos, C. Powell, and S. S. Vedula, “Interventions for stimulus deprivation amblyopia,” *Cochrane Database Syst Rev*, no. 3, p. CD005136, 2006.
[47] D. M. Levi and S. Klein, “Differences in vernier discrimination for grating between strabismic and anisometropic amblyopes,” *Invest. Ophthalmol. Vis. Sci.*, vol. 23, no. 3, pp. 398–407, Sep. 1982.
[48] D. M. Levi and S. Klein, “Hyperacuity and amblyopia,” *Nature*, vol. 298, no. 5871, pp. 268–270, Jul. 1982.
[49] D. M. Levi and S. A. Klein, “Equivalent intrinsic blur in amblyopia,” *Vision Res.*, vol. 30, no. 12, pp. 1995–2022, 1990.
[50] L. M. Katz, D. M. Levi, and H. E. Bedell, “Central and peripheral contrast sensitivity in amblyopia with varying field size,” *Doc Ophthalmol*, vol. 58, no. 4, pp. 351–373, Dec. 1984.
[51] R. F. Hess and J. S. Pointer, “Differences in the neural basis of human amblyopia: the distribution of the anomaly across the visual field,” *Vision Res.*, vol. 25, no. 11, pp. 1577–1594, 1985.
[52] D. M. Levi and T. Carney, “The effect of flankers on three tasks in central, peripheral, and amblyopic vision,” *J Vis*, vol. 11, no. 1, p. 10, 2011.
[53] D. M. Levi and S. A. Klein, “Vernier acuity, crowding and amblyopia,” *Vision Research*, vol. 25, no. 7, pp. 979–991, 1985.
[54] Y. S. Bonneh, D. Sagi, and U. Polat, “Spatial and temporal crowding in amblyopia,” *Vision Res.*, vol. 47, no. 14, pp. 1950–1962, Jun. 2007.
[55] M. Y. Choi, K. M. Lee, J. M. Hwang, D. G. Choi, D. S. Lee, K. H. Park, and Y. S. Yu, “Comparison between anisometropic and strabismic amblyopia using functional magnetic resonance imaging,” *Br J Ophthalmol*, vol. 85, no. 9, pp. 1052–1056, Sep. 2001.
[56] K. M. Lee, S. H. Lee, N. Y. Kim, C. Y. Kim, J. W. Sohn, M. Y. Choi, D. Gyu Choi, J. M. Hwang, K. Ho Park, D. S. Lee, Y. Suk Yu, and K. Hyun Chang, “Binocularity and spatial frequency dependence of calcarine activation in two types of amblyopia,” *Neurosci. Res.*, vol. 40, no. 2, pp. 147–153, Jun. 2001.
[57] I. P. Conner, J. V. Odom, T. L. Schwartz, and J. D. Mendola, “Retinotopic maps and foveal suppression in the visual cortex of amblyopic adults,” *J. Physiol. (Lond.)*, vol. 583, no. Pt 1, pp. 159–173, Aug. 2007.

DOI:10.15774/PPKE.ITK.2015.009

[58] L. Kiorpes, “Visual processing in amblyopia: animal studies,” *Strabismus*, vol. 14, no. 1, pp. 3–10, Mar. 2006.
[59] P. Kozma and L. Kiorpes, “Contour integration in amblyopic monkeys,” *Vis. Neurosci*, vol. 20, no. 5, pp. 577–588, Oct. 2003.
[60] L. Kiorpes, D. C. Kiper, L. P. O’Keefe, J. R. Cavanaugh, and J. A. Movshon, “Neuronal correlates of amblyopia in the visual cortex of macaque monkeys with experimental strabismus and anisometropia,” *J. Neurosci*, vol. 18, no. 16, pp. 6411–6424, Aug. 1998.
[61] C. E. Stewart, D. A. Stephens, A. R. Fielder, M. J. Moseley, and MOTAS Cooperative, “Modeling dose-response in amblyopia: toward a child-specific treatment plan,” *Invest. Ophthalmol. Vis. Sci.*, vol. 48, no. 6, pp. 2589–2594, Jun. 2007.
[62] I. Vedamurthy, M. Nahum, S. J. Huang, F. Zheng, J. Bayliss, D. Bavelier, and D. M. Levi, “A dichoptic custom-made action video game as a treatment for adult amblyopia,” *Vision Res.*, Apr. 2015.
[63] Pediatric Eye Disease Investigator Group, “A comparison of atropine and patching treatments for moderate amblyopia by patient age, cause of amblyopia, depth of amblyopia, and other factors,” *Ophthalmology*, vol. 110, no. 8, pp. 1632–1637; discussion 1637–1638, Aug. 2003.
[64] Pediatric Eye Disease Investigator Group., “A randomized trial of atropine vs. patching for treatment of moderate amblyopia in children,” *Arch. Ophthalmol.*, vol. 120, no. 3, pp. 268–278, Mar. 2002.
[65] J. M. Holmes, R. T. Kraker, R. W. Beck, E. E. Birch, S. A. Cotter, D. F. Everett, R. W. Hertle, G. E. Quinn, M. X. Repka, M. M. Scheiman, D. K. Wallace, and Pediatric Eye Disease Investigator Group, “A randomized trial of prescribed patching regimens for treatment of severe amblyopia in children,” *Ophthalmology*, vol. 110, no. 11, pp. 2075–2087, Nov. 2003.
[66] M. X. Repka, R. W. Beck, J. M. Holmes, E. E. Birch, D. L. Chandler, S. A. Cotter, R. W. Hertle, R. T. Kraker, P. S. Moke, G. E. Quinn, M. M. Scheiman, and Pediatric Eye Disease Investigator Group, “A randomized trial of patching regimens for treatment of moderate amblyopia in children,” *Arch. Ophthalmol.*, vol. 121, no. 5, pp. 603–611, May 2003.
[67] I. Gottlob and E. Stangler-Zuschrott, “Effect of levodopa on contrast sensitivity and scotomas in human amblyopia,” *Invest. Ophthalmol. Vis. Sci.*, vol. 31, no. 4, pp. 776–780, Apr. 1990.
[68] I. Gottlob, J. Charlier, and R. D. Reinecke, “Visual acuities and scotomas after one week levodopa administration in human amblyopia,” *Invest. Ophthalmol. Vis. Sci.*, vol. 33, no. 9, pp. 2722–2728, Aug. 1992.
[69] I. Gottlob, S. S. Wizov, and R. D. Reinecke, “Visual acuities and scotomas after 3 weeks’ levodopa administration in adult amblyopia,” *Graefes Arch. Clin. Exp. Ophthalmol.*, vol. 233, no. 7, pp. 407–413, Jul. 1995.
[70] L. E. Leguire, K. L. Komaromy, T. M. Nairus, and G. L. Rogers, “Long-term follow-up of L-dopa treatment in children with amblyopia,” *J Pediatr Ophthalmol Strabismus*, vol. 39, no. 6, pp. 326–330; quiz 345–346, Dec. 2002.
[71] E. C. Campos, C. Schiavi, P. Benedetti, R. Bolzani, and V. Porciatti, “Effect of citicoline on visual acuity in amblyopia: preliminary results,” *Graefes Arch. Clin. Exp. Ophthalmol.*, vol. 233, no. 5, pp. 307–312, May 1995.
[72] E. C. Campos, R. Bolzani, C. Schiavi, A. Baldi, and V. Porciatti, “Cytidin-5’-diphosphocholine enhances the effect of part-time occlusion in amblyopia,” *Doc Ophthalmol*, vol. 93, no. 3, pp. 247–263, 1997 1996.
[73] S. Clavagnier, B. Thompson, and R. F. Hess, “Long lasting effects of daily theta burst rTMS sessions in the human amblyopic cortex,” *Brain Stimul*, vol. 6, no. 6, pp. 860–867, Nov. 2013.
[74] B. Thompson, B. Mansouri, L. Koski, and R. F. Hess, “Brain plasticity in the adult: modulation of function in amblyopia with rTMS,” *Curr. Biol.*, vol. 18, no. 14, pp. 1067–1071, Jul. 2008.
[75] F. Sengpiel, “Plasticity of the Visual Cortex and Treatment of Amblyopia,” *Curr. Biol.*, vol. 24, no. 18, pp. R936–R940, Sep. 2014.

DOI:10.15774/PPKE.ITK.2015.009

[76] U. Polat, T. Ma-Naim, M. Belkin, and D. Sagi, “Improving vision in adult amblyopia by perceptual learning,” *Proc. Natl. Acad. Sci. U.S.A.*, vol. 101, no. 17, pp. 6692–6697, Apr. 2004.
[77] Y. Zhou, C. Huang, P. Xu, L. Tao, Z. Qiu, X. Li, and Z.-L. Lu, “Perceptual learning improves contrast sensitivity and visual acuity in adults with anisometropic amblyopia,” *Vision Res.*, vol. 46, no. 5, pp. 739–750, Mar. 2006.
[78] R. W. Li, K. G. Young, P. Hoenig, and D. M. Levi, “Perceptual learning improves visual performance in juvenile amblyopia,” *Invest. Ophthalmol. Vis. Sci.*, vol. 46, no. 9, pp. 3161–3168, Sep. 2005.
[79] R. W. Li, S. A. Klein, and D. M. Levi, “Prolonged perceptual learning of positional acuity in adult amblyopia: perceptual template retuning dynamics,” *J. Neurosci.*, vol. 28, no. 52, pp. 14223–14229, Dec. 2008.
[80] J. Ding and D. M. Levi, “Recovery of Stereopsis Through Perceptual Learning in Human Adults with Abnormal Binocular Vision,” *PNAS*, vol. 108, no. 37, pp. 15035–15036, Sep. 2011.
[81] X.-Y. Liu, T. Zhang, Y.-L. Jia, N.-L. Wang, and C. Yu, “The therapeutic impact of perceptual learning on juvenile amblyopia with or without previous patching treatment,” *Invest. Ophthalmol. Vis. Sci.*, vol. 52, no. 3, pp. 1531–1538, Mar. 2011.
[82] Z. Hussain, B. S. Webb, A. T. Astle, and P. V. McGraw, “Perceptual learning reduces crowding in amblyopia and in the normal periphery,” *J. Neurosci.*, vol. 32, no. 2, pp. 474–480, Jan. 2012.
[83] R. W. Li, C. Ngo, J. Nguyen, and D. M. Levi, “Video-game play induces plasticity in the visual system of adults with amblyopia,” *PLoS Biol.*, vol. 9, no. 8, p. e1001135, Aug. 2011.
[84] R. F. Hess, B. Mansouri, and B. Thompson, “A new binocular approach to the treatment of amblyopia in adults well beyond the critical period of visual development,” *Restor. Neurol. Neurosci.*, vol. 28, no. 6, pp. 793–802, 2010.
[85] P. J. Knox, A. J. Simmers, L. S. Gray, and M. Cleary, “An exploratory study: prolonged periods of binocular stimulation can provide an effective treatment for childhood amblyopia,” *Invest. Ophthalmol. Vis. Sci.*, vol. 53, no. 2, pp. 817–824, Feb. 2012.
[86] J. Li, B. Thompson, D. Deng, L. Y. L. Chan, M. Yu, and R. F. Hess, “Dichoptic training enables the adult amblyopic brain to learn,” *Curr. Biol.*, vol. 23, no. 8, pp. R308–309, Apr. 2013.
[87] I. Nawratzki, E. Auerbach, and H. Rowe, “The electrical response in retina and occipital cortex following photic stimulation of normal and amblyopic eyes,” *Am. J. Ophthalmol.*, vol. 61, no. 3, pp. 430–435, Mar. 1966.
[88] A. M. Potts and T. Nagaya, “Studies on the visual evoked response: 3. Strabismus amblyopia and hysterical amblyopia,” *Doc Ophthalmol*, vol. 26, pp. 394–402, 1969.
[89] R. S. Fishman and R. M. Copenhaver, “Macular disease and amblyopia. The visual-evoked response,” *Arch. Ophthalmol.*, vol. 77, no. 6, pp. 718–725, Jun. 1967.
[90] H. Spekreijse, L. H. Khoe, and L. H. van der Tweel, “A case of amblyopia; electrophysiology and psychophysics of luminance and contrast,” *Adv. Exp. Med. Biol.*, vol. 24, no. 0, pp. 141–156, 1972.
[91] D. M. Levi, “Patterned and unpatterned visual evoked responses in strabismic and anisometropic amblyopia,” *Am J Optom Physiol Opt*, vol. 52, no. 7, pp. 455–464, Jul. 1975.
[92] S. Sokol and B. Bloom, “Visually evoked cortical responses of amblyopes to a spatially alternating stimulus,” *Invest Ophthalmol*, vol. 12, no. 12, pp. 936–939, Dec. 1973.
[93] G. B. Arden, W. M. Barnard, and A. S. Mushin, “Visually evoked responses in amblyopia,” *Br J Ophthalmol*, vol. 58, no. 3, pp. 183–192, Mar. 1974.
[94] S. Sokol and D. Nadler, “Simultaneous electroretinograms and visually evoked potentials from adult amblyopes in response to a pattern stimulus,” *Invest. Ophthalmol. Vis. Sci.*, vol. 18, no. 8, pp. 848–855, Aug. 1979.
[95] U. Yinon, L. Jakobovitz, and E. Auerbach, “The visual evoked response to stationary checkerboard patterns in children with strabismic amblyopia,” *Invest Ophthalmol*, vol. 13, no. 4, pp. 293–296, Apr. 1974.

DOI:10.15774/PPKE.ITK.2015.009

[96] R. E. Manny and D. M. Levi, “The visually evoked potential in humans with amblyopia: pseudorandom modulation of uniform field and sine-wave gratings,” *Exp Brain Res*, vol. 47, no. 1, pp. 15–27, 1982.
[97] D. M. Levi and R. E. Manny, “The Pathophysiology of Amblyopia: Electrophysiological Studies,” *Ann N Y Acad Sci*, vol. 338, no. 1, pp. 243–260, 1980.
[98] R. F. Hess, “Contrast sensitivity assessment of functional amblyopia in humans,” *Trans Ophthalmol Soc U K*, vol. 99, no. 3, pp. 391–397, 1979.
[99] D. M. Levi and R. S. Harwerth, “Contrast sensitivity in amblyopia due to stimulus deprivation,” *Br J Ophthalmol*, vol. 64, no. 1, pp. 15–20, Jan. 1980.
[100] S. J. Anderson, I. E. Holliday, and G. F. Harding, “Assessment of cortical dysfunction in human strabismic amblyopia using magnetoencephalography (MEG),” *Vision Res*, vol. 39, no. 9, pp. 1723–1738, May 1999.
[101] V. Parisi, M. E. Scarale, N. Balducci, M. Fresina, and E. C. Campos, “Electrophysiological detection of delayed postretinal neural conduction in human amblyopia,” *Invest. Ophthalmol. Vis. Sci*, vol. 51, no. 10, pp. 5041–5048, Oct. 2010.
[102] Y. Lerner, P. Pianka, B. Azmon, H. Leiba, C. Stolovitch, A. Loewenstein, M. Harel, T. Hendler, and R. Malach, “Area-specific amblyopic effects in human occipitotemporal object representations,” *Neuron*, vol. 40, no. 5, pp. 1023–1029, Dec. 2003.
[103] D. M. Levi, C. Yu, S.-G. Kuai, and E. Rislove, “Global contour processing in amblyopia,” *Vision Res*, vol. 47, no. 4, pp. 512–524, Feb. 2007.
[104] E. M. Rislove, E. C. Hall, K. A. Stavros, and L. Kiorpes, “Scale-dependent loss of global form perception in strabismic amblyopia,” *J Vis*, vol. 10, no. 12, p. 25, 2010.
[105] A. J. Simmers, T. Ledgeway, R. F. Hess, and P. V. McGraw, “Deficits to global motion processing in human amblyopia,” *Vision Res*, vol. 43, no. 6, pp. 729–738, Mar. 2003.
[106] A. J. Simmers, T. Ledgeway, and R. F. Hess, “The influences of visibility and anomalous integration processes on the perception of global spatial form versus motion in human amblyopia,” *Vision Res*, vol. 45, no. 4, pp. 449–460, Feb. 2005.
[107] C. Hou, M. W. Pettet, and A. M. Norcia, “Abnormalities of coherent motion processing in strabismic amblyopia: Visual-evoked potential measurements,” *J Vis*, vol. 8, no. 4, pp. 2.1–12, 2008.
[108] H. M. Burian, “The behavior of the amblyopic eye under reduced illumination and the theory of functional amblyopia,” *Doc Ophthalmol*, vol. 23, no. 1, pp. 189–202, Dec. 1967.
[109] D. M. Levi, S. A. Klein, and P. Aitsebaomo, “Detection and discrimination of the direction of motion in central and peripheral vision of normal and amblyopic observers,” *Vision Res.*, vol. 24, no. 8, pp. 789–800, 1984.
[110] S. Sokol, “Abnormal evoked potential latencies in amblyopia.,” *Br J Ophthalmol*, vol. 67, no. 5, pp. 310–314, May 1983.
[111] J. T. Meredith and G. G. Celesia, “Pattern-reversal visual evoked potentials and retinal eccentricity,” *Electroencephalogr Clin Neurophysiol*, vol. 53, no. 3, pp. 243–253, Mar. 1982.
[112] J. V. Odom, M. Bach, M. Brigell, G. E. Holder, D. L. McCulloch, A. P. Tormene, and Vaegan, “ISCEV standard for clinical visual evoked potentials (2009 update),” *Doc Ophthalmol*, vol. 120, no. 1, pp. 111–119, Feb. 2010.
[113] M. Russell Harter, “Evoked cortical responses to checkerboard patterns: Effect of check-size as a function of retinal eccentricity,” *Vision Research*, vol. 10, no. 12, pp. 1365–1376, Dec. 1970.
[114] Y. Lerner, T. Hendler, R. Malach, M. Harel, H. Leiba, C. Stolovitch, and P. Pianka, “Selective fovea-related deprived activation in retinotopic and high-order visual cortex of human amblyopes,” *Neuroimage*, vol. 33, no. 1, pp. 169–179, Oct. 2006.
[115] D. M. Levi and J. W. Walters, “Visual evoked responses in strabismic and anisometropic amblyopia: effects of check size and retinal locus.,” *Am J Optom Physiol Opt*, vol. 54, no. 10, pp. 691–698, Oct. 1977.
[116] B. Zhang, S. S. Stevenson, H. Cheng, M. Laron, G. Kumar, J. Tong, and Y. M. Chino, “Effects of fixation instability on multifocal VEP (mfVEP) responses in amblyopes,” *J Vis*, vol. 8, no. 3, pp. 16.1–14, 2008.

DOI:10.15774/PPKE.ITK.2015.009

[117] M. Moschos, I. Margetis, S. Tsapakis, G. Panagakis, I. Chatzistephanou, and E. Iliakis, "Multifocal visual evoked potentials in amblyopia due to anisometropia," *Clin Ophthalmol*, vol. 4, pp. 849–853, 2010.

[118] M. Yu, B. Brown, and M. H. Edwards, "Investigation of multifocal visual evoked potential in anisometropic and esotropic amblyopes," *Invest. Ophthalmol. Vis. Sci.*, vol. 39, no. 11, pp. 2033–2040, Oct. 1998.

[119] G. R. Barnes, R. F. Hess, S. O. Dumoulin, R. L. Achtman, and G. B. Pike, "The cortical deficit in humans with strabismic amblyopia," *J. Physiol. (Lond.)*, vol. 533, no. Pt 1, pp. 281–297, May 2001.

[120] I. P. Conner, J. V. Odom, T. L. Schwartz, and J. D. Mendola, "Monocular activation of V1 and V2 in amblyopic adults measured with functional magnetic resonance imaging," *J AAPOS*, vol. 11, no. 4, pp. 341–350, Aug. 2007.

[121] R. F. Hess, B. Thompson, G. Gole, and K. T. Mullen, "Deficient responses from the lateral geniculate nucleus in humans with amblyopia," *Eur. J. Neurosci*, vol. 29, no. 5, pp. 1064–1070, Mar. 2009.

[122] X. Li, S. O. Dumoulin, B. Mansouri, and R. F. Hess, "Cortical deficits in human amblyopia: their regional distribution and their relationship to the contrast detection deficit," *Invest. Ophthalmol. Vis. Sci*, vol. 48, no. 4, pp. 1575–1591, Apr. 2007.

[123] L. Muckli, S. Kiess, N. Tonhausen, W. Singer, R. Goebel, and R. Sireteanu, "Cerebral correlates of impaired grating perception in individual, psychophysically assessed human amblyopes," *Vision Res.*, vol. 46, no. 4, pp. 506–526, Feb. 2006.

[124] D. G. Kirschen and M. C. Flom, "Visual acuity at different retinal loci of eccentrically fixating functional amblyopes," *Am J Optom Physiol Opt*, vol. 55, no. 3, pp. 144–150, Mar. 1978.

[125] R. F. Hess and R. J. Jacobs, "A preliminary report of acuity and contour interactions across the amblyope's visual field," *Vision Research*, vol. 19, no. 12, pp. 1403–1408, 1979.

[126] R. Sireteanu and M. Fronius, "Naso-temporal asymmetries in human amblyopia: Consequence of long-term interocular suppression," *Vision Research*, vol. 21, no. 7, pp. 1055–1063, 1981.

[127] R. Sireteanu, M. Fronius, and W. Singer, "Binocular interaction in the peripheral visual field of humans with strabismic and anisometropic amblyopia," *Vision Research*, vol. 21, no. 7, pp. 1065–1074, 1981.

[128] D. H. Brainard, "The Psychophysics Toolbox," *Spat Vis*, vol. 10, no. 4, pp. 433–6, 1997.

[129] D. G. Pelli, "The VideoToolbox software for visual psychophysics: transforming numbers into movies," *Spatial Vision*, vol. 10, pp. 437–442, 1997.

[130] 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.

[131] N. Kanwisher, "Domain specificity in face perception," *Nat. Neurosci*, vol. 3, no. 8, pp. 759–763, Aug. 2000.

[132] N. Kanwisher, J. McDermott, and M. M. Chun, "The fusiform face area: a module in human extrastriate cortex specialized for face perception," *J. Neurosci.*, vol. 17, no. 11, pp. 4302–11, Jun. 1997.

[133] M. J. Tarr and I. Gauthier, "FFA: a flexible fusiform area for subordinate-level visual processing automatized by expertise," *Nat. Neurosci*, vol. 3, no. 8, pp. 764–769, Aug. 2000.

[134] C. M. Bukach, I. Gauthier, and M. J. Tarr, "Beyond faces and modularity: the power of an expertise framework," *Trends Cogn. Sci. (Regul. Ed.)*, vol. 10, no. 4, pp. 159–166, Apr. 2006.

[135] J. V. Haxby, E. A. Hoffman, and M. I. Gobbini, "The distributed human neural system for face perception," *Trends. Cogn. Sci.*, vol. 4, no. 6, pp. 223–233, Jun. 2000.

[136] A. J. Calder and A. W. Young, "Understanding the recognition of facial identity and facial expression," *Nat. Rev. Neurosci.*, vol. 6, no. 8, pp. 641–51, Aug. 2005.

[137] J. Li, B. Thompson, C. S. Y. Lam, D. Deng, L. Y. L. Chan, G. Maehara, G. C. Woo, M. Yu, and R. F. Hess, "The role of suppression in amblyopia," *Invest. Ophthalmol. Vis. Sci*, vol. 52, no. 7, pp. 4169–4176, Jun. 2011.

DOI:10.15774/PPKE.ITK.2015.009

[138] L. Melloni, C. M. Schwiedrzik, E. Rodriguez, and W. Singer, "(Micro)Saccades, corollary activity and cortical oscillations," *Trends Cogn. Sci. (Regul. Ed.)*, vol. 13, no. 6, pp. 239–245, Jun. 2009.
[139] F. Tong and S. A. Engel, "Interocular rivalry revealed in the human cortical blind-spot representation," *Nature*, vol. 411, no. 6834, pp. 195–199, May 2001.
[140] J.-D. Haynes, R. Deichmann, and G. Rees, "Eye-specific effects of binocular rivalry in the human lateral geniculate nucleus," *Nature*, vol. 438, no. 7067, pp. 496–499, Nov. 2005.
[141] K. Wunderlich, K. A. Schneider, and S. Kastner, "Neural correlates of binocular rivalry in the human lateral geniculate nucleus," *Nat. Neurosci.*, vol. 8, no. 11, pp. 1595–1602, Nov. 2005.
[142] F. Moradi, C. Koch, and S. Shimojo, "Face adaptation depends on seeing the face," *Neuron*, vol. 45, no. 1, pp. 169–175, Jan. 2005.
[143] D. Alais and D. Melcher, "Strength and coherence of binocular rivalry depends on shared stimulus complexity," *Vision Res*, vol. 47, no. 2, pp. 269–279, Jan. 2007.
[144] B. N. Pasley, L. C. Mayes, and R. T. Schultz, "Subcortical discrimination of unperceived objects during binocular rivalry," *Neuron*, vol. 42, no. 1, pp. 163–172, Apr. 2004.
[145] A. Algaze, C. Roberts, L. Leguire, P. Schmalbrock, and G. Rogers, "Functional magnetic resonance imaging as a tool for investigating amblyopia in the human visual cortex: a pilot study," *J AAPOS*, vol. 6, no. 5, pp. 300–308, Oct. 2002.
[146] R. Farivar, B. Thompson, B. Mansouri, and R. F. Hess, "Interocular suppression in strabismic amblyopia results in an attenuated and delayed hemodynamic response function in early visual cortex," *J Vis*, vol. 11, no. 14, 2011.
[147] B. Rossion and C. Jacques, "Does physical interstimulus variance account for early electrophysiological face sensitive responses in the human brain? Ten lessons on the N170," *Neuroimage*, vol. 39, no. 4, pp. 1959–1979, Feb. 2008.
[148] I. Deffke, T. Sander, J. Heidenreich, W. Sommer, G. Curio, L. Trahms, and A. Lueschow, "MEG/EEG sources of the 170-ms response to faces are co-localized in the fusiform gyrus," *NeuroImage*, vol. 35, no. 4, pp. 1495–1501, May 2007.
[149] K. Linkenkaer-Hansen, J. M. Palva, M. Sams, J. K. Hietanen, H. J. Aronen, and R. J. Ilmoniemi, "Face-selective processing in human extrastriate cortex around 120 ms after stimulus onset revealed by magneto- and electroencephalography," *Neurosci Lett*, vol. 253, no. 3, pp. 147–50, Sep. 1998.
[150] B. Sadeh, I. Podlipsky, A. Zhdanov, and G. Yovel, "Event-related potential and functional MRI measures of face-selectivity are highly correlated: a simultaneous ERP-fMRI investigation," *Hum Brain Mapp*, vol. 31, no. 10, pp. 1490–1501, Oct. 2010.
[151] G. W. Eschweiler and J. P. Rauschecker, "Temporal integration in visual cortex of cats with surgically induced strabismus," *Eur. J. Neurosci.*, vol. 5, no. 11, pp. 1501–1509, Nov. 1993.
[152] P. R. Roelfsema, P. König, A. K. Engel, R. Sireteanu, and W. Singer, "Reduced synchronization in the visual cortex of cats with strabismic amblyopia," *Eur. J. Neurosci.*, vol. 6, no. 11, pp. 1645–1655, Nov. 1994.
[153] W. Singer, M. von Grünau, and J. Rauschecker, "Functional amblyopia in kittens with unilateral exotropia. I. Electrophysiological assessment," *Exp Brain Res*, vol. 40, no. 3, pp. 294–304, 1980.
[154] D. Regan, *Human brain electrophysiology: evoked potentials and evoked magnetic fields in science and medicine*. Elsevier, 1989.
[155] W. Klimesch, P. Sauseng, S. Hanslmayr, W. Gruber, and R. Freunberger, "Event-related phase reorganization may explain evoked neural dynamics," *Neurosci Biobehav Rev*, vol. 31, no. 7, pp. 1003–1016, 2007.
[156] A. Mazaheri and O. Jensen, "Rhythmic pulsing: linking ongoing brain activity with evoked responses," *Front Hum Neurosci*, vol. 4, p. 177, 2010.
[157] C. E. Schroeder and P. Lakatos, "Low-frequency neuronal oscillations as instruments of sensory selection," *Trends Neurosci*, vol. 32, no. 1, pp. 9–18, Jan. 2009.

DOI:10.15774/PPKE.ITK.2015.009

[158] H. E. Bedell, Y. L. Yap, and M. C. Flom, “Fixational drift and nasal-temporal pursuit asymmetries in strabismic amblyopes,” *Invest. Ophthalmol. Vis. Sci*, vol. 31, no. 5, pp. 968–976, May 1990.
[159] C. M. Schor and C. Westall, “Visual and vestibular sources of fixation instability in amblyopia,” *Invest. Ophthalmol. Vis. Sci*, vol. 25, no. 6, pp. 729–738, Jun. 1984.
[160] F. Babiloni, C. Babiloni, F. Carducci, L. Fattorini, P. Onorati, and A. Urbano, “Spline Laplacian estimate of EEG potentials over a realistic magnetic resonance-constructed scalp surface model,” *Electroencephalogr Clin Neurophysiol*, vol. 98, no. 4, pp. 363–373, Apr. 1996.
[161] F. Perrin, O. Bertrand, and J. Pernier, “Scalp current density mapping: value and estimation from potential data,” *IEEE Trans Biomed Eng*, vol. 34, no. 4, pp. 283–288, Apr. 1987.
[162] P. Berens, “CircStat: A MATLAB Toolbox for Circular Statistics,” *J Stat Softw*, vol. 31, no. 10, pp. 1–21, Sep. 2009.
[163] J. S. Winston, R. N. Henson, M. R. Fine-Goulden, and R. J. Dolan, “fMRI-adaptation reveals dissociable neural representations of identity and expression in face perception,” *J Neurophysiol*, no. 92, pp. 1830–1839, Apr. 2004.
[164] U. Hasson, I. Levy, M. Behrmann, T. Hendler, and R. Malach, “Eccentricity bias as an organizing principle for human high-order object areas,” *Neuron*, vol. 34, no. 3, pp. 479–490, Apr. 2002.
[165] A. Puce, T. Allison, J. C. Gore, and G. McCarthy, “Face-sensitive regions in human extrastriate cortex studied by functional MRI,” *J Neurophysiol*, vol. 74, no. 3, pp. 1192–9, Sep. 1995.
[166] Z. V. J. Woodhead, R. J. S. Wise, M. Sereno, and R. Leech, “Dissociation of sensitivity to spatial frequency in word and face preferential areas of the fusiform gyrus,” *Cereb. Cortex*, vol. 21, no. 10, pp. 2307–2312, Oct. 2011.
[167] X. Li, K. T. Mullen, B. Thompson, and R. F. Hess, “Effective connectivity anomalies in human amblyopia,” *Neuroimage*, vol. 54, no. 1, pp. 505–516, Jan. 2011.
[168] M. R. Harter and C. T. White, “Effects of contour sharpness and check-size on visually evoked cortical potentials,” *Vision Research*, vol. 8, no. 6, pp. 701–711, Jun. 1968.
[169] M. D. Abramoff, P. J. Magalhães, and S. J. Ram, “Image processing with ImageJ,” *Biophotonics Intern*, vol. 11, no. 7, pp. 36–42, 2004.
[170] J. C. Horton and W. F. Hoyt, “The representation of the visual field in human striate cortex. A revision of the classic Holmes map,” *Arch. Ophthalmol.*, vol. 109, no. 6, pp. 816–824, Jun. 1991.
[171] R. F. Dougherty, V. M. Koch, A. A. Brewer, B. Fischer, J. Modersitzki, and B. A. Wandell, “Visual field representations and locations of visual areas V1/2/3 in human visual cortex,” *J Vis*, vol. 3, no. 10, p. 1, Oct. 2003.
[172] E. G. González, A. M. F. Wong, E. Niechwiej-Szwedo, L. Tarita-Nistor, and M. J. Steinbach, “Eye Position Stability in Amblyopia and in Normal Binocular Vision,” *IOVS*, vol. 53, no. 9, pp. 5386–5394, Aug. 2012.
[173] H. A. Baseler, E. E. Sutter, S. A. Klein, and T. Carney, “The topography of visual evoked response properties across the visual field,” *Electroencephalography and Clinical Neurophysiology*, vol. 90, no. 1, pp. 65–81, Jan. 1994.
[174] D. M. Levi, S. A. Klein, and I. Chen, “The response of the amblyopic visual system to noise,” *Vision Res.*, vol. 47, no. 19, pp. 2531–2542, Sep. 2007.
[175] D. M. Levi and S. A. Klein, “Noise provides some new signals about the spatial vision of amblyopes,” *J. Neurosci.*, vol. 23, no. 7, pp. 2522–2526, Apr. 2003.
[176] C. Huang, L. Tao, Y. Zhou, and Z.-L. Lu, “Treated amblyopes remain deficient in spatial vision: a contrast sensitivity and external noise study,” *Vision Res.*, vol. 47, no. 1, pp. 22–34, Jan. 2007.
[177] D. H. Baker, T. S. Meese, and R. F. Hess, “Contrast masking in strabismic amblyopia: attenuation, noise, interocular suppression and binocular summation,” *Vision Res.*, vol. 48, no. 15, pp. 1625–1640, Jul. 2008.

DOI:10.15774/PPKE.ITK.2015.009

[178] E. Milne, “Increased Intra-Participant Variability in Children with Autistic Spectrum Disorders: Evidence from Single-Trial Analysis of Evoked EEG,” *Front Psychol*, vol. 2, Mar. 2011.

[179] M. R. Harter and C. T. White, “Evoked cortical responses to checkerboard patterns: Effect of check-size as a function of visual acuity,” *Electroencephalography and Clinical Neurophysiology*, vol. 28, no. 1, pp. 48–54, Jan. 1970.

[180] M. Menz, C. Poloschek, M. Menz, M. Wang, P. Penrose, and E. Sutter, “The Effect Of Fixation Error On The Multifocal VEP,” *Invest. Ophthalmol. Vis. Sci.*, vol. 43, no. 12, p. 4740, Dec. 2002.

[181] D. M. Levi, “Prentice award lecture 2011: removing the brakes on plasticity in the amblyopic brain,” *Optom Vis Sci*, vol. 89, no. 6, pp. 827–838, Jun. 2012.

[182] Z. Hussain, A. T. Astle, B. S. Webb, and P. V. McGraw, “The challenges of developing a contrast-based video game for treatment of amblyopia,” *Front Psychol*, vol. 5, p. 1210, 2014.

[183] R. M. Eastgate, G. D. Griffiths, P. E. Waddingham, A. D. Moody, T. K. H. Butler, S. V. Cobb, I. F. Comaish, S. M. Haworth, R. M. Gregson, I. M. Ash, and S. M. Brown, “Modified virtual reality technology for treatment of amblyopia,” *Eye (Lond)*, vol. 20, no. 3, pp. 370–374, Mar. 2006.

[184] D. M. Levi, D. C. Knill, and D. Bavelier, “Stereopsis and amblyopia: A mini-review,” *Vision Research*, 2015.