

Normal and impaired visual development in children

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**Dedicated to my loving Family, my Parents and Grandpa
and to the memory of my beloved Grandma and Great Grandma**

„... Now do you not see that the eye embraces the beauty of the whole world?... It has measured the distances and sizes of the stars; it has found the elements and their locations; ... Oh excellent thing, superior to all others created by God!... What peoples, what tongues will fully describe your true function? The eye is the window of the human body through which it feels its way and enjoys the beauty of the world. Owing to the eye the soul is content to stay in its bodily prison, for without it such bodily prison is torture.”

- Leonardo da Vinci (1452-1519)

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PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS:**Full papers:**

- I. **Kozma P, Deák A.** The history of amblyopia. *Szemészet* 1998;135:63-69.
- II. **Kovács I, Kozma P, Fehér Á, Benedek Gy.** Late maturation of visual spatial integration in humans. *Proc Natl acad Sci USA* 1999;96:12204-12209.
- III. **Kozma P, Deák A, Janáky M, Benedek Gy.** Effect of late surgery for acquired esotropia on visual evoked potential - Is it an epiphenomenon? *J Pediatric Ophthalmol Strabismus* (in press).
- IV. **Kozma P, Deák A, Benedek Gy.** Recent data about visual development of children. *Szemészet* (accepted)

Abstracts published in international journals referenced by the Science Citation Index:

- I. **Kozma P, Kovács I, Benedek Gy.** Late maturation (age > 5) of long-range spatial interactions in humans. *Perception (Suppl)* 1997;26:116a.
- II. **Kozma P, Kovács I, Benedek Gy.** Late maturation of long-range interactions in humans [ARVO Abstract]. *Invest Ophthalmol Vis Sci* 1999;40:S410. Abstract nr 2161.

INTRODUCTION

„Every man takes the limits of his own field
of vision for the limits of the world.”

- Arthur Schopenhauer

The need for understanding visual development has received increasing attention in the last four decades (64). Until the early 1960s little was known about the anatomical and functional properties of the visual system of the newborn and of its subsequent development during infancy. A new impulse to the investigation of visual development was given by the classical, pioneering single cell studies of Hubel and Wiesel on cats (64). Hubel and Wiesel deprived one or both eyes of visual impulses from birth in cats. They found that closure of one eye caused more significant structural and morphological changes of the visual pathways than the closure of both eyes (213). When the occlusion by lid suture was performed only on one eye of the animals most cells in the visual cortex were innervated by the nondeprived eye and thus, the deprived eye nearly went blind (214,215). On the other hand, closure had no effect on the eyes and on the cells in the visual cortex of adult cats. Accordingly, Hubel and Wiesel were the first who described and termed the ‘critical period’ of vision. The critical period is a definite period of time, early in life during which the visual system is plastic and shows lability and is susceptible to environmental influence as well as to abnormal visual experience (16,50,98,216); if stimulus deprivation occurs during this period, visual development will be impaired. Hubel and Wiesel received the Nobel Prize in Medicine in appreciation of their work in 1981.

Since the work of Hubel and Wiesel there has been an explosion of morphological, electrophysiological and behavioral experiments that studied on animals and humans how postnatal visual development occurs and whether and how it could be affected by early visual deprivation or by manipulations of the visual environment (64). Ever since the visual system has become the model for the understanding of plasticity because it is a system where work at behavioral, anatomic, and physiological levels can be correlated to lead to study the basic mechanisms involved (50).

1.1. NORMAL VISUAL DEVELOPMENT

The study of vision in human infants has progressed considerably in parallel with the animal studies (64). It was shown, that critical periods also exist in the visual development of humans. The clearest demonstration of this came out in studies with strabismus. As developmental disorders occur and usually are reversible within the critical period it is important to study these intervals and to watch for and treat vision problems in infants and young children (196). It is generally held that the human visual system is immature at birth both anatomically and functionally and goes through substantial changes especially during the first few months of postnatal life (13,64,70). The development of the visual cortex occurs in a hierarchical order. The critical period seems to vary in onset and duration between different brain regions and even between layers of an individual cortical area. Lower levels of the visual system and deeper layers of the cortex mature earlier compared to the higher and more superficial ones (45,50,86). Different functions may emerge at different times and develop at different rates (133). It is widely held belief in Ophthalmology that the visual nervous system spans a relatively short period of maturation and becomes adult-like by the second year of age (223). Most of the developmental data below confirm this theory, although there are already suggestions for an extended maturational time frame of some of the visual functions. The diversity of the data is probably due to the various methods used by the different research groups. Only those visual functions and morphological structures will be detailed that are significantly related to the subject of this thesis without intending to be exhaustive.

Substantial changes and rapid visual development occurs during the first 6 months of postnatal life. Infants probably can discriminate between *colors* (26,38,210), have preference for moving stimuli (151) and can process complex motion information (109) by 3-4 months of age. *Optokinetic nystagmus* (OKN) (12,13,60,134,150), *saccadic eye movements* (13,18,143) and *fixation* are present from birth (53,60,103) but become mature only by 6 months of age. *Depth perception, discrimination* (9,13,28,203), *smooth pursuit* (13,52,103,104) and *eye alignment* (60) develop to full maturity also around the age of 6 months. Although *visual acuity, stereopsis* and *contrast sensitivity* emerge and improve dramatically within the first 6 months after birth (11,13), they reach adult levels sometime between 1 and 5 years of age (20,57,82,143), 3 and 9 years of age (21,28,66,67,88,169) and by 2 to 5 years (11,32) of age individually. *Binocular vision* and *fusion* also emerge around 1.5-4 months (29,31,130,158) and mature between 1 to 7 years of age (15,95). Based on the findings of visual evoked potential studies there are some suggestions that

adult-like acuities can already be observed in 4 to 7 months old infants (60,138). The *visual field* is supposed to reach adult values between 6 months (135,142) and 5 years (125,140) depending on the technique and stimulus applied (135,189). Wilson et al. however report a much slower maturation, that lasts up to 10 years of age (220). A slower development of contrast sensitivity was found by Beazley et al. also up to early adolescence (19).

The *ocular media* are clear from birth (13). The intraocular and orbital structures seem to be well developed at birth, however dramatic morphological, anatomical and physiological changes occur in them during infancy that continue in the first few years of life (156). The most significant changes happen in the course of the first 6 to 12 months, but the development e.g., in the volume of the *orbit* can last up to age 6-8 years while in the case of the *eyeball* it continues to mature until around 13 years of age (23,78,199).

At birth the human visual system is immature at the level of retina, lateral geniculate nucleus (LGN), and visual cortex, too (70). The *retina* develops intensively during the first 6 months of life and comes to its full maturity around age 1-4 years (1,90,225). The *LGN* reaches adult volume by the end of the first 6 months (54,69,100), but the morphological maturation and the development of different visual functions occur between 8 months to 2 years (69,70,94,100).

The primary visual pathway becomes functional around the age of 2-3 months (33,34). Recent data by Sloper et al. however, demonstrated that the central visual pathways continue to mature after the age of 5 (191). The *myelinisation* of the optic nerve lasts until 2 years of age (66,104,138). Some of the extrastriatal visual areas and intracortical interneurons probably have a much longer myelinisation period (13,224).

After birth within 6 months to first year of life the morphology and the volume of the *visual cortex* changes rapidly. Recent studies however suggested that there is a continuous increase in the neuronal number until 6 years after birth (176). This can imply a prolonged structural maturation of the human visual cortex. At about 4 months of age V1 reaches adult volume, much earlier than the brain as a whole (69,70,101,131). Adult values of synaptic density are reached at the age of 4 years in the primary, while at the age of 11 years (99,102) in higher cortical areas. More recent Functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET) data suggest that the human cortex as well as the visual cortex has a prolonged development, that involves structural changes and maturation even in adulthood (41,71,195). An extended maturational period of visual functions has also been suggested by some groups who reported that children may have difficulties in recognition of incomplete objects (74) as well as in visual

integration and form identification when it is based on contrasts in texture (10,188), motion (96) or color (97).

1.2. ABNORMAL VISUAL DEVELOPMENT: AMBLYOPIA

Amblyopia is generally defined as reduced visual acuity, - for diagnostic purposes at least 2 Snellen lines difference between the eyes (122) -, of usually one eye that occurs in the absence of ocular structural abnormalities and is due to abnormal visual experience early in life. *Strabismus* or *squint* is the misalignment of the visual axes.

Visual experience during development is necessary for normal vision. If visual experience early in life is abnormal a disorder called amblyopia develops. Amblyopia together with strabismus is the most common functional visual disorders in early childhood (133). Children are most susceptible to the effects of abnormal visual experience between 9 months and 2 years of age, and sensitivity declines between 2 and 8 years of age (51,171,208). Advance in the understanding of amblyopia are based on the pioneering work of Wiesel and Hubel in experimental animals in the early 1960s (214,215). An enormous amount of data has been collected from experiments in kittens, young monkeys and also in humans since then (58).

PREVALENCE, SIGNIFICANCE AND SOCIOECONOMIC ASPECTS

Amblyopia together with strabismus has always been an interesting issue during the last centuries. Its continuous timelessness is due to its high prevalence in the general population (1.0 to 4.0%) (210) as well as to its detrimental, long-term effect on personality (8) and on occupation of the amblyopes (164). Amblyopia accounts for more cases of vision impairment than all other causes (ocular diseases and trauma) combined (209,210). In those with strabismus or anisometropia 40-60% of them develops amblyopia. Strabismus, among others has two horizontal types: eso- and exotropia. Children with esotropia (inward deviation) shows an approximately four times greater incidence of amblyopia than those with exotropia (outward deviation) (46).

ORIGIN, HISTORY, DEFINITION AND CLASSIFICATION

Amblyopia is originated from the Greek words: amblys (blunt, dull) and opsia (eye, cheek, face, seeing). The term amblyopia was already known in ancient times, but it had another meaning: decreased vision. Le Cat was the first in the 17th century who provided the first clinical description of human amblyopia. Its real history began at that time. According to von Graefe's definition in 1888, it is the condition when "The doctor sees nothing and the patient very little." (209). Many different definitions has evolved since the end of the 19th century but none of them seems to be perfect. Reduced visual acuity has only classically been regarded as the defining feature of amblyopia, since acuity represents solely one limit of the spatial visual capacity. Actually, functional amblyopia is a developmental disorder of spatial vision that is potentially reversible by occlusion therapy during a developmental critical period and associated with the presence of strabismus, anisometropia, or form deprivation early in life (43,122,209). When strabismus and amblyopia develop together a condition called strabismic amblyopia occurs. The notion that amblyopia is a developmental disorder was first articulated by Worth in 1903. Functional amblyopia should be distinguished from organic amblyopia, which is poor vision caused by structural abnormalities of the eye or brain and irreversible to treatment. In the view of the present thesis strabismic amblyopia is going to be described in detail.

ANATOMICAL BASIS OF AMBLYOPIA

The neural basis of amblyopia has been less thoroughly explored. What vision scientists claim has not been changed since the times of Javal who recognized in 1896 that the seat of anomaly in amblyopia lies centrally and its effect is not equally distributed across the retina. Recently, Movshon and Kiorpes (110) have found that the neural basis of amblyopia begins but does not end in V1. The primary effects may involve extrastriate visual areas, too (111).

TREATMENT OF AMBLYOPIA

Amblyopia is difficult to detect, because it develops early in life. Treatment for amblyopia and strabismus nevertheless should be instituted as soon as the diagnosis is made to achieve the best possible outcome since it is only reversible within the so-called critical period. A recent paper by Simmers & Gray (185) however suggests a very unique and interesting finding that patching of the good eye can improve several visual functions even after the critical period, and thus age is not a limiting factor in the initiation of the treatment. It was also shown that strabismic amblyopia may be reversible in adults who have lost the use of their good eye (183). This finding also confirms

the notion that critical period for cure of amblyopia lasts longer than the critical period for its creation (51). The general rule of thumb is that every child under 9 years of age should undergo a trial of amblyopia therapy (80,146,223).

The first step in treatment is the correction of any significant refractive error that may be present in the amblyopic eye (122,164) by accurately prescribed spectacles that compensates for the full cycloplegic findings. The second and more important aspect of amblyopia therapy is occlusion or patching of the better eye that increases the number of cortical cells responding to the amblyopic eye. Occlusion therapy is continued until the vision of both eyes becomes equal or until no improvement has been noticed after a 3-months period of treatment (183). Penalization, Cambridge vision stimulator (CAM) and pleoptics are alternatives to occlusion but do not work better than patching (80). Other nonsurgical treatments of amblyopia include orthoptics and neurotransmitter, e.g., levodopa replacement (79,127,160,209). Surgery should probably wait until amblyopia has been treated. Although, it was reported that no significant difference was found in the outcome of surgery when amblyopia was fully or only partially treated (126). The aim of strabismus surgery is not only cosmetic but also has functional benefits, such as development of binocularity, reestablishment of the fusional reflex and prevention of sensorial and motor complications. Weakening procedure is called recession, strengthening procedure is called resection. It has been shown that overall results are favorably influenced by early alignment of the eyes. Good eye alignment can be achieved in later years, but normal sensory adaptation (achievement of binocular fusion and stereoscopic depth perception) becomes more difficult as the child grows older (164). By age 8, the sensory status is generally so fixed that it cannot be effectively influenced by treatment (8).

VISUAL FUNCTIONS IN AMBLYOPIA

Visual functions that develop slowly seem most susceptible to the effects of abnormal visual input. In amblyopia the most prominent deficit is in spatial vision. Spatial resolution, measured by either Snellen (optotype) or grating acuity, of the strabismic amblyopes is reduced in the central field but normal in the periphery (184). When tested through the amblyopic eye, amblyopes also have decreased contrast sensitivity at high spatial and low temporal frequencies in the central visual field (212) and decreased visual discrimination ability (Vernier acuity or positional acuity) (58,133,209). The grating acuity deficit is relatively small compared to Vernier acuity (51,91,110). Strabismic amblyopes also appear to have an additional loss of positional uncertainty often accompanied by aberrations of space perception (mislocalize targets), spatial distortion. Binocular

interactions are also abnormal in amblyopia. Dark adaptation in all (91) and color vision (133,209) in most of the amblyopic eyes is normal. The spatial visual performance of the amblyopic eye, thus resembles the performance of both immature and peripheral visual systems (110-112,133).

1.2.1. VISUAL EVOKED POTENTIALS AND AMBLYOPIA

VISUAL EVOKED POTENTIAL (VEP) IN GENERAL

Most of our knowledge of amblyopia has been gained through subjective psychophysiological techniques and objective electrophysiological methods carried out on human amblyopes (42). Electrophysiological methods such as visually evoked potentials (VEPs) can differentiate more easily between abnormalities in retinal and cortical functions than do psychophysical methods. VEP is a gross electrical signal generated at the occipital cortex in response to visual stimulation (40,161). The electrical activity is recorded by scalp electrodes, which are usually placed midoccipitally (Oz, 10-20 system) about 1 (foveal)-3 cm above the inion (40). VEPs are typically recorded in response to flash of light or pattern stimuli. VEP pattern stimuli usually generated on an oscilloscope or on a video monitor are either phase-reversed (also called pattern reversal, contrast reversal, or counterphase modulation) or flashed on and off. Pattern reversal checkerboards are the most commonly used stimuli in clinical settings (25). These consist of light and dark checks, that reverses periodically from black to white and back at a selected alternation rate while maintaining a constant mean luminance on the retina (40,65). The field size, retinal location and specific stimulus parameters, such as pattern size, contrast, and rate of presentation of pattern stimuli can be varied (65). Within the central region, the fovea and the parafovea can be stimulated differentially by varying check size. Bodis-Wollner et al. (25) pointed out that checks of 10-15 minutes stimulate the fovea optimally, while larger checks, such as 50 minutes, stimulate parafoveal regions. (65). VEP recordings require proper, constant fixation and concentration from the subjects since in their absence the observed VEP changes can easily be misinterpreted as clinically significant.

MATURATION

Waveforms of the pattern reversal VEPs were found to change rapidly during the first several months after birth from a broad, single slow positive component with a latency of 190 to 250 ms in infants to a simple triphasic negative-positive-negative complex: N80-P100-N145 (N1-P1-N2).

The most rapid changes occur during the first few months of life but gradual changes can be seen throughout the formative years. The first positive component (P100) at 100 ms emerges at different time for different check sizes (140'-17.5') from 2 weeks to 10 weeks after birth (226). During maturation the N1-P1 amplitude becomes higher and P1 latency becomes shorter for all check-sizes (207). It is generally assumed that the shortening of VEP *latency* with age is due in part to the maturation of the myelination of the optic fibers (63). It is generally agreed that *latencies* of pattern reversal VEPs to small checks (< 20) (by 9 years) reach mature levels at a slower rate than to larger checks (by 3-4months) (85,149,226). The N1P1 and P1N2 *amplitudes* however were not affected between 2 months to 9 years of age and were significantly higher than those of adults by 2 to 3 factors (226). The maturation rate of VEPs probably differs according to the technique and stimulation applied. By approximately 3 months most normal infants give evidence of a binocular VEP (13), which is due to the fact that binocular input to cortical neurons is not found until about 13 weeks on average (29,30).

PATTERN REVERSAL VEP IN AMBLYOPIA

The P100 component is the most frequently studied component of the VEP. It is of macular origin (47,84,226) and its amplitude and latency are frequently measured parameters in clinical studies at various spatial frequencies (check sizes) (24,65,193). The latency improves while the amplitude decreases with increasing check size (170). Thus, the P100 component can be best elicited by small size checks (25) and seems to be the best indicator of binocular interaction. Shawkat and Kriss showed that the P100 component especially of the reversal VEP is also the most useful tool to differentiate normals from amblyopes (89). Difference between amplitude rates of amblyopes and normals decrease with increasing check-size and similar effect can be seen between the amblyop and fellow eyes of the amblyopes. Contrary to the flash VEP, the pattern VEP has been shown to be a sensitive detector of amblyopia, particularly when small (< 20-minute) checks are used (5,65,193,194). The VEP amplitude of the first major positive wave (P1) in the amblyopic eye is reduced compared to the normal eye (5,25,89), but the latency values are normal or only slightly increased (6,65,192-194). Accordingly, latency is not as sensitive a marker of amblyopia as amplitude (65).

Summing up, VEP is a valuable, noninvasive clinical tool for assessing visual function, e.g., binocularity as well as for diagnosing amblyopia and predicting its treatment success in infants and preverbal children (89,201).

1.2.2. AMBLYOPIA, STRABISMUS AND BINOCULARITY

As discussed earlier esotropia is an inward deviation of the visual axes not controlled by fusional mechanisms and can lead to amblyopia if not treated properly (87). Esotropias belong to two main groups: congenital or infantile and acquired esotropias. When an esotropia occurs within 6 months after birth it is referred to as infantile and when it occurs beyond 6 months of age it is referred to as acquired esotropia (210). From the aspect of this thesis acquired esotropia developed together with amblyopia will be in focus.

Both strabismus and amblyopia have great impact on binocularity. When amblyopia occurs early in life it can result in lack of binocularity. In the absence of binocularity fusion and stereopsis cannot evolve. In infantile and acquired esotropia, the sensorial component (fusion and stereopsis) of binocularity is impaired, while the motor part is not affected (146). Fusion is an acquired reflex (9,197). The potential advantages of fusion include improved stereoacuity, improvement in the development of fine motor skills (168) and stability of ocular alignment (7,148). It is widely believed that the development of fusion is rare if ocular alignment does not occur or not stable enough during the critical period of development for binocular vision (129).

In humans, according to clinical experience, binocularity is not fully established at birth and it is not functional until the second to fourth months of life (28,95,158). If strabismus occurs during maturation it can lead to poor binocular vision (146), but it has very little effect on binocularity after 6 to 8 years of age (15). However, there are some suggestions that fusional mechanisms may be modified even after the age of normal visual maturation (7 to 9 years of age) (167). Though there is no agreement about the exact timing of maturation it seems that binocular vision has the longest critical period (114,182), and the critical period of development is prolonged when amblyopia is present (44).

If surgical treatment is performed before the age of five most congenital and acquired esotropic patients experience some level of binocularity and development of fusion postoperatively (126). The later a squint is acquired the more likely it is that binocular vision will be restored after a successful operation (59,121,123,222). This is due to a greater initial opportunity for fusion development. The amount of fusion development depends on the time of the onset of strabismus. Thus, the debate about the timing of corrective surgery in acquired esotropia is less vivid; there is only a few data available on it in the literature. Early surgery, however may be beneficial and also improves the chance of surgical success in acquired esotropia (126). In acquired strabismus early surgery refers mostly to the duration of squint before surgery. Under the age of 2 years surgery

should be carried out within 3 months and after the age of 2 within 6 months from the onset to be considered early. Delay of surgical intervention tends to produce and strengthen unfavourable sensory and motor complications. In cases of congenital esotropia, early corrective surgery appears to be indicated for the development of cortical binocularity, that is presumably a prerequisite for fusion and stereopsis. In acquired strabismus however, the entire argument for early realignment of eyes is to prevent those unfavourable complications and to return the eyes as quickly as possible to a position where fusion and fusion reflex can be re-established.

We report our results on the effect of late strabismic surgery on binocularity and on pattern reversal VEP in children suffering from acquired esotropia in *Study 2*. We were motivated by the fact that no similar study has been done, yet in humans or animals near the end of the critical period.

1.3. CONTOUR-DETECTION

The world around us at a certain moment is very complex; consists of many objects and surfaces at various distances that differ in their quality, color, contrast and have different meanings and importance for the observer. It is a basic issue in the history of psychology how object perception and recognition occur. Perception is a process of drawing meaning from the stimulation that reaches our sensory receptors. Perception of a stimulus may be affected by relations that exist between the stimulus and its apparent context and background. Grouping and segregation are crucial in the early stages of perception. Segregation occurs according to Gestalt (1910) principles: objects are grouped together, because they are close (proximity), have similar features (similarity), they follow in the same direction (good continuation), they move in the same direction (common fate), have symmetry or form continuous, enclosed contours (closure). Our perception is dominated by contours, which are fundamental to perceiving an object's shape (173,184).

In order to segment the visual image and to form object boundaries in the course of perceptual organization, local orientation information has to be integrated across the visual field. The efficiency of the integrating mechanism can be estimated psychophysically in a contour-detection task that employs orientational noise (48,61,115,119). Contour-integration is part of the segregation process. The Gestalt laws that are mostly influence contour-integration are good-continuation ((61) - isilinear paths of Gabor patches are easier to detect) and closure (115). It is



easier to detect a contour when it follows these laws. Pettet, McKee and Gryzwacz (159) reported that in addition to closure and good continuation, the geometric properties, e.g., alignment, are also substantial in contour detection.

Contour detection makes it possible for us to detect contours quickly and easily and to discern figure from ground. The neuronal connections that give rise to this perceptual effect are referred to as long-range interactions. Thus, how we see the world depends very much on the organization of the neuronal circuits in the visual cortex and the synapses between cells within the cortex. The pattern of connectivity is determined as much by past experience as by actual stimulation. Their functional architecture seems to be dynamic and context dependent. The neuronal connections can either be facilitatory or inhibitory. Facilitation is a local process that can produce global activity through long-range interactions along a path when local constraints are met. The strength of the interaction is directly proportional to retinal distance. Facilitatory long-range horizontal intrinsic connections run over long distances in the visual cortex and interconnect cells with similar stimulus preferences. The cells in the primary visual cortex are sensitive to bars and edges of specific orientation and respond to stimuli from a certain location of the retina. These orientation selective cells facilitate one another when simultaneously stimulated and cause an enhanced response. Gabor functions, named after a Hungarian scientist Gábor Dénes, are the product of a sine wave multiplied by a smooth bell-shaped (Gaussian) envelope (35). They roughly model the receptive field structure of simple cells in V1 (105). Therefore, they are appropriate stimuli for the examination of these small spatial filters and their interactions in V1. Gabor patches are widely used stimuli in contour detection tasks because they also lack edge cues, their contrast, size, spatial frequency, orientation, phase and location in space can be manipulated. Performance on contour detection task is dependent on orientation (61) as well as on the parameters of Gabor patches. The contour and its surrounding also appear to influence contour detection (35).

Contour detection ability develops postnatally and the maturation may be dependent on the maturation of V1. The development of the long-range interactions depends on the maturational state of the layers within the primary visual cortex and follows a hierarchical pattern of development. In the primary visual cortex vertical or intracolumnar connections that process local features of the visual field develop before horizontal or intercolumnar connections that are necessary for the integration of these local features into an image (36). Until recently, very little was known about their maturation. Long-range interactions are thought to refine postnatally in an experience-dependent fashion (39). Burkhalter et al. (36) reported that long-range interactions develop at various time in the different layers of the primary visual cortex - within layer 2/3

develop after connections within layers 4B, 5 and 6. In layers 2/3 they are still immature even at 2 years of age in humans (36,39,163). There is also some psychophysical indication that the development of these connections in humans lasts longer than the development of other primary functions in infancy (10) and they are assumed to mature around school-age (188), but the exact age has not been determined, yet.

Thus, it is essential to study contour detection developmentally. The more so since the integration process has been assumed to be constant throughout life after the primary visual functions are established in infancy. Work with infants may provide insight into mechanisms of cortical development. To study human developmental pattern of spatial integration between orientation selective cells of the primary visual cortex we used a card-test version (118,157) of a contour detection task in children (5-14 years) with normal vision. These developmental results will be reported in *Study 1*.

AIMS OF THE STUDY

Our knowledge about the development of the different visual functions in normal humans and in those suffering from any visual disorder e.g., amblyopia, still not complete, although has been studied extensively. The exact timing of the maturation of human visual functions and thus, the length of plasticity and the so-called critical period is remained to be a question. The lack of evidence in this field can be due to poor compliance of young children and the absence of standard and reliable evaluating as well as research methods for children. The general belief that the critical period terminates by the end of the second year of life has been kept for long. The results achieved so far are somewhat controversial. The accurate settling of the critical period would give the opportunity to more children for functional recovery, since impaired visual functions can be restored with a good chance before its critical period is over (51). A large number of articles has been studied the effect of early and late treatment methods e.g., in strabismic amblyopia. Unfortunately, there is no agreement in either the timing of surgery or the timing for the best results to be obtained, yet.

In the view of the above mentioned notions the aim of this study was twofold:

- 1.) To determine the length of the critical period in normal visual development by examining a less known visual function, the spatial integration ability of children in different age groups up to adolescence. Thus, to support or defeat the current belief that 'the maturation of the

perceptual functions completes by the age of two and cognitive development can be expected afterwards’.

- 2.) To study what type of changes can occur in children during the assumed critical period of a visual disorder called ‘amblyopia’ when the treatment is considered to be late. To determine whether it is worth performing late surgery at all and if we can expect functional changes besides cosmetical benefits.

STUDY I.

MATURATION OF VISUAL SPATIAL INTEGRATION

Three different experiments were conducted within Study I. The development of spatial integration was tested in the ‘*main study*’. The basis of the findings of the ‘*main study*’ was tested in the ‘*learning study*’ and the ‘*spatial range study*’.

SUBJECTS AND METHODS

STIMULI

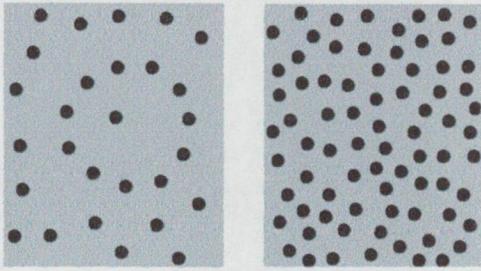
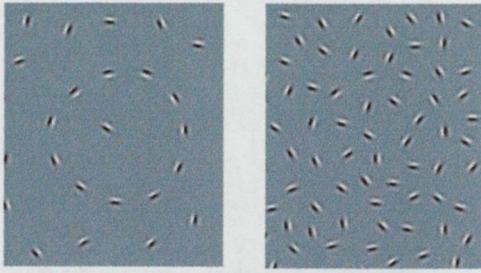
Two different sets of cards were used: orientation- and color-defined (Figure 1). The cards were generated on a Silicon Graphics Indy R4000 computer. The orientation-defined cards were printed on a 24000dpi printer, and the color-defined cards on an Epson Stylus Color 800 printer. *Gabor patches* were used as the stimuli on the orientation-defined cards. Carrier frequency of the Gabor patches was 5 c/deg at a 57 cm viewing distance, and their contrast was about 95%. Each card consisted of a closed chain of colinearly aligned Gabor patches (contour) and a background of randomly oriented and positioned Gabor patches (noise). Spacing between elements along the contour and spacing in the background were controlled independently. The algorithm allowed us to keep the smallest permitted separation between background elements while avoiding spurious spacings. At small signal-to-noise ratios, background elements were allowed to get into the spaces between contour elements, but orientation alignment was avoided. A new random shape and background was computed for each card. The length of the contours was constant, and the contours had a continuously positive curvature with no inflection points. Contour spacing was kept constant (7λ , where λ = wavelength of Gabor patches) with increasing background density across the cards. The value of D (relative noise density), where $D = \text{noise spacing}/\text{contour}$

spacing, defined the difficulty level of each card. D was varied across cards in 0.05 stepsize. Variations of D allowed for the isolation of long-range integration (first and second-order) mechanisms. When $D > 1$, the contour could be detected by using element density information (Figure 1) because the contour elements were closer to each other than the noise elements. However, when $D \leq 1$, this cue was not available and it was impossible to detect the contour without orientation specific long-range interactions. As the value of D decreased the strength of lateral connections increased. The actual strength of the long-range interactions in each subject could be defined by the value of D of the last correctly recognized card (D_{\min}) (threshold). On the color-defined cards the contour and the background were made up of *colored patches* instead of Gabor stimuli. The luminance contrast and the size of the colored patches were randomized to ensure that the contour was purely defined by chromatic contrast and not by luminance contrast. 13% of all dots were red and 87% were green across the cards. The contour locations were equivalent to that of the orientation-defined cards. The difficulty level of the color set was matched exactly with the corresponding orientation-defined set on 156 adult subjects. Thus, this procedure provided us with essentially the same task demands for both the orientation and the color-defined cards.

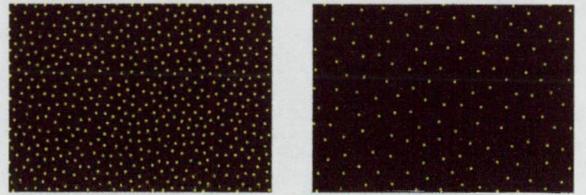
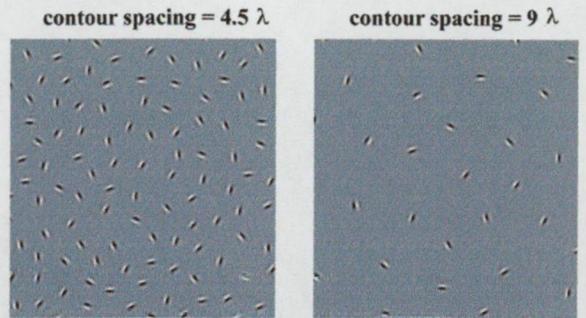
The contours on the cards could not be detected purely by local filters or by neurons with large receptive field sizes corresponding to the size of the contour. The path of the contour could only be found by the integration of local orientation measurements. The noise forced the subject to do these local measurements at the scale of the individual Gabor signals, and to rely solely on long-range interactions between local filters while connecting the signals perceptually. Luminance information did not play a role in either the color-, or the orientation-defined contour-detection cards. All visual cues were removed except for the long-range correlation among oriented elements (Figure 1). Therefore, the cards were supposed to isolate the long-range spatial interactions of low-level vision.

We used a battery of 10 orientation-defined contour integration cards, developed earlier by Kovács, Polat and Norcia (118), in the '*main study*'. The D of the cards ranged between 1.1-0.65. In the '*learning*' and '*spatial range*' studies new sets of 15 cards with increased range of D were generated, where the value of D varied between 1.2-0.5 in each set. The value of D also ranged between 1.2-0.5 in the color-defined set.

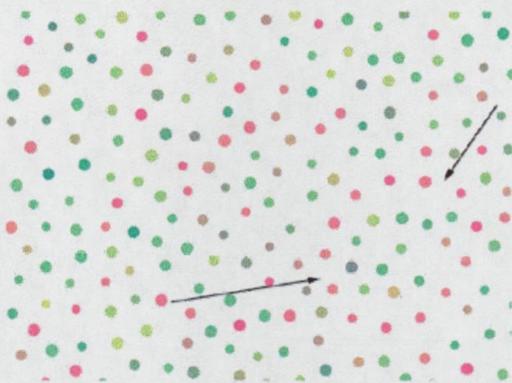
a)

 $D=1.05$ $D=0.8$

b)

 $D=0.85$

c)

 $D=0.9$

d)

all elements

red elements

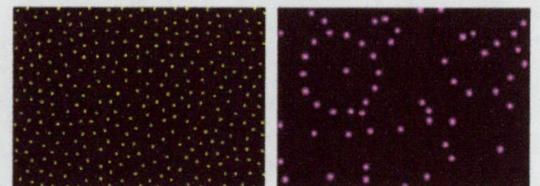
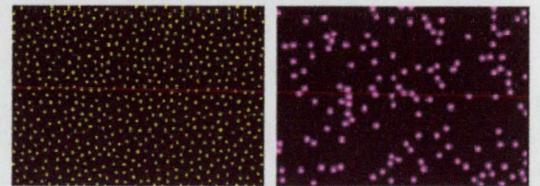
 $D=0.8$  $D=0.6$

Figure 1. a) Two samples of the orientation-defined cards with a small and a higher D value. b) Samples of the sets with small and large contour spacings. c) One sample of the color-defined cards. d) The ratio of red elements compared to all elements on the color-defined cards with two different D values. Without orientation- and color information there is no density cue on the cards.

PROCEDURE

The subjects were tested by using contour detection paradigm (61,115). The card version of the task was chosen, because it was found to be more suitable to test a large number of young children. Prior to the contour detection task the visual acuity of the children had been tested with E cards or Snellen cards depending on their age, and their stereovision with Randot test. Those with visual disorder, e.g., strabismus and amblyopia (2-5 subjects in each age group; 18 subjects in the entire sample), and those with momentary inability to cooperate with the experimenter (5 in the entire sample) were excluded from the study. All included subjects had normal or corrected-to-normal visual acuity. The two eyes of the subjects were tested separately, by testing the right eye first which further excluded subjects with a possibility of amblyopia (contour detection performance might be impaired, and imbalanced in the two eyes of amblyopes (92,118,157)) in the '*main study*'. In the course of the 'learning' and 'spatial range' studies binocular presentation of the cards was applied. In the contour detection task the subjects' task was to identify the location of the contour and to trace the contour within each card by following the path of the contour with their finger. Subjects were not forced to guess if they could not find the contour. The subjects were tested from a distance of about 0.50 m. The cards were presented in an increasing order of difficulty using a staircase method. One suprathreshold card was applied as an explanatory example of the task before the test. We determined D_{\min} in one session for each subject.

In our '*main study*' 510 subjects (413 children and 97 adults - 219 males, 291 females) were examined. The children ranged in age from 5 to 14 years in 5 different age groups (5-6 (n=88), 6-7 (n=98), 9-10 (n=75), 10-11 (n=64), 13-14 (n=88)). The group of 97 adults aged 19-30 years served as control. Subjects were recruited by advertisement, and the experiments were carried out at day-care centers, schools, and colleges of Szeged.

In the *learning study* we employed a training paradigm and determined D_{\min} in a group of 60 adults (19-35 years) and in 60 (5-6 years) children on three consecutive days. We tested whether learning was specific for the stimulus dimensions of orientation and color in the contour-detection task. Equal number of subjects was divided randomly into four groups ('orientation', 'color', 'color-to-orientation', 'orientation-to-color'). Both orientation- and color-defined cards were applied depending on the groups. The 'orientation' group was tested with orientation-defined cards while the 'color' group with color-defined cards on three consecutive days. Before testing with the color-defined cards the color vision of the subjects was assessed by using Ishihara plates. To test whether the improvement transfers from color to orientation, we had a group of subjects

that practiced with color-defined cards for two days and with orientation-defined cards on the third day ('color to orientation' group). The fourth group of subjects practiced with the orientation-defined cards for two consecutive days and was examined with the color cards on the third day ('orientation to color' group). The *eye-specificity* of learning was studied with orientation-defined cards on a different group of 10 (5-6 years) children by practicing the right eye on two consecutive days, and testing the left eye on the third day.

In the third '*spatial range study*' we investigated the spatial range of long-range horizontal interactions. Only orientation-defined cards were used. One set with increased ($\lambda = 9$) (λ is the wavelength of the Gabor patch), one with decreased ($\lambda = 4.5$) and another with the original ($\lambda = 7$) spacing among contour elements while keeping the relative noise level constant. We tested 54 naive adults (19-30 years) and 30 naive children (5-6 years) children with the three sets of cards in one session. In order to eliminate the effect of practice, we used a counterbalanced design for the order of presentation of the three sets. Statistical analysis was performed by using two-tailed t-test. The performance of the different groups was compared to one another in each study.

RESULTS

In our main study we found a significant deficit in the spatial integration ability of 5-14 year old children compared to adults, using a contour detection paradigm (120). 5-6 year old children missed the contours on about half of the cards ($D_{\min} < 0.9$) ($D_{\min} = 0.84$). They could recognize the contour when the D value of the card equaled to or was less than 0.9. As the value of D decreased, the performance of the children also decreased. the performance of the children also decreased. When older children were examined the performance got better. Children in the 13-14 year old group were able to see most of the contours ($D_{\min} < 0.7$) ($D_{\min} = 0.7$) and had similar performance to adults. Although the largest improvement seemed to occur between the 5-6 and 6-7 year old ($D_{\min} = 0.79$) groups, there was a tendency for gradually increasing performance in the other age groups as well: in the 9-10 year old group $D_{\min} = 0.76$, in the 10-11 year old group $D_{\min} = 0.72$. The difference in contour-integration performance between the 5-6 and 13-14 year-age groups is significant (two-tailed t test: $p < 0.005$). There is a slight improvement even after adolescence: $D_{\min} = 0.67$ in the 19-30 year old group. The results of the two eyes were similar. There was no significant effect of eye and gender with respect to contour-detection performance ($p > 0.05$).

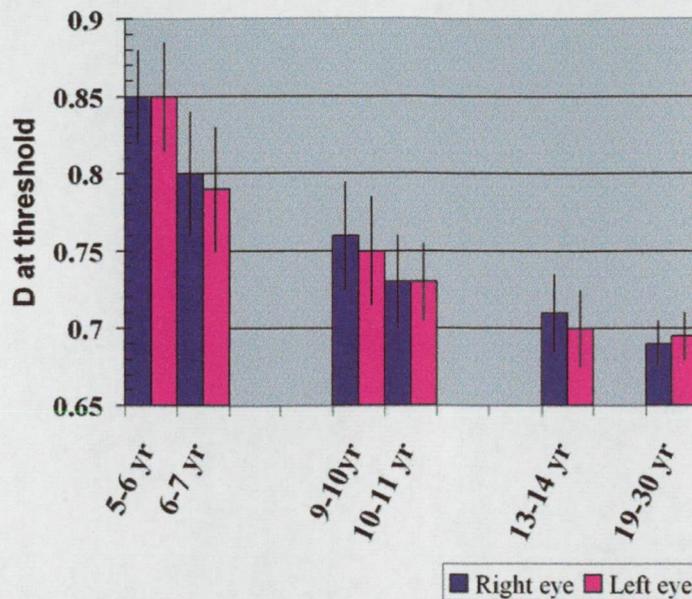


Figure 2. Contour-integration performance of 5-14 year old children compared to adults

We conducted two further experiments (see below) to determine whether the significant age-effect was purely due to the maturation of the primary visual cortex (lower-level visual factors) or to higher-level cognitive developmental (such as search strategies) or motivational factors (such as perseverance in completing a difficult task).

CUE SPECIFIC LEARNING IN THE CONTOUR INTEGRATION TASK

In the ‘orientation’ group tested with the new set of orientation-defined cards on consecutive days, we found significantly improved performance by the third day of practice (Figure 3). The improvement was more evident in children (1st and 3rd day performances compared: two-tailed t-test: $p < 0.01$,) than in adults ($p < 0.05$). Learning in the ‘color’ group was similar to learning in the ‘orientation’ group both in children (1st and 3rd day performances compared : $p < 0.01$) and in adults ($p < 0.05$). We found that experience with color cards did not significantly improve performance with orientation-defined cards, and vice versa.

Thus, learning seemed specific for the cue used for practice. It meant that there was no substantial transfer across the different visual cues of color and orientation. The transfer was completely absent in adults in both the ‘color to orientation’ and the ‘orientation to color’ groups (Figure 4). There was a slight but not significant tendency for transfer in children in the ‘color to orientation’ group (1st day ‘orientation’ and 3rd day ‘color to orientation’ performances were not significantly

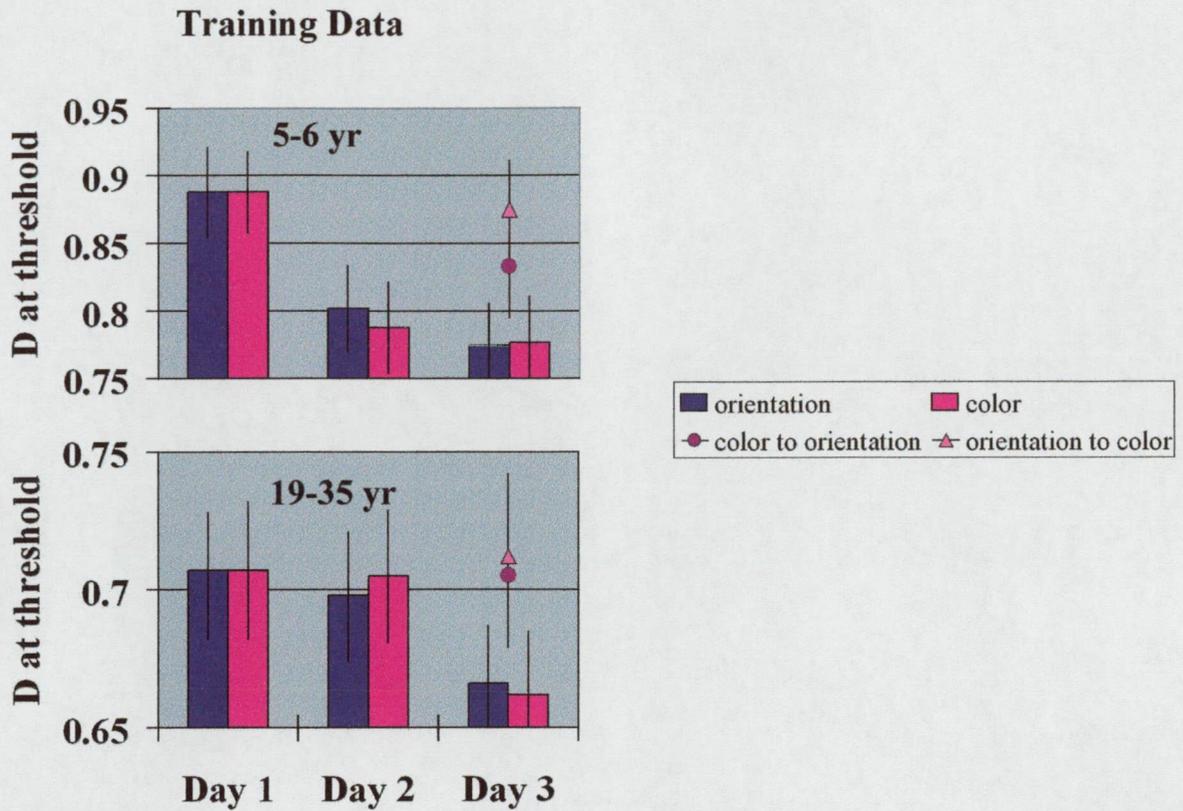


Figure 3.

different: $p = 0.073$; 3rd day 'orientation' and 3rd day 'color to orientation' performances were significantly different: $p < 0.05$). While testing transfer across eyes we found complete interocular transfer $D_{\min} = 0.70$ on the third day of practice.

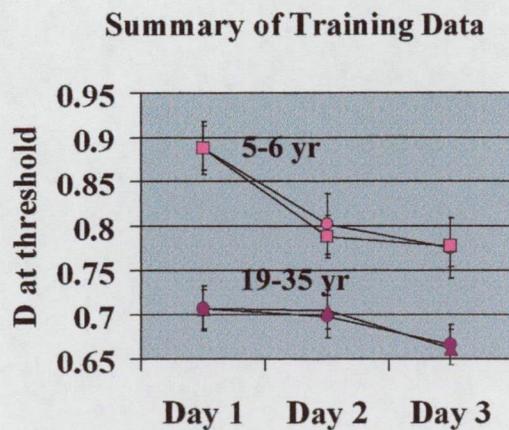


Figure 4.

SPATIAL RANGE OF INTERACTIONS IN CHILDREN AND IN ADULTS

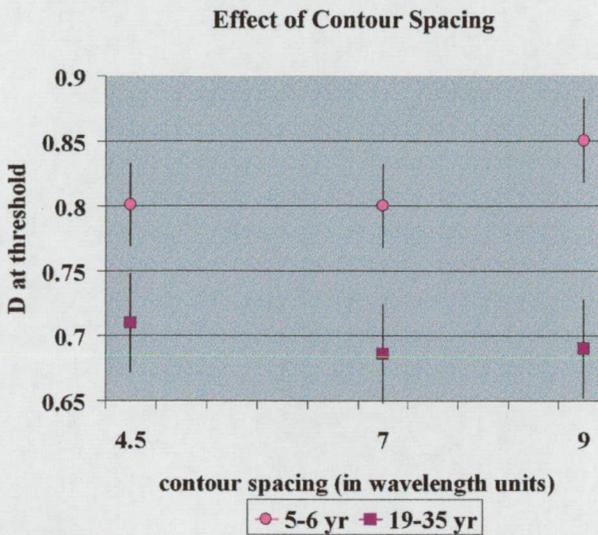


Figure 5.

We found better performance when testing with smaller contour spacings in children (Figure 5). At 9λ contour spacing, performance was poorer than at 4.5λ ($p < 0.01$, two-tailed t-test), or at 7λ ($p < 0.01$). Unlike in children D_{\min} in adults is independent of contour spacing. The difference between children and adults in contour detection performance is bigger at larger contour spacings.

DISCUSSION

Classically, visual development has been assumed to be complete early in life to give way to cognitive development after the basic visual functions are established in infancy. Although, behavioral studies of human visual development beyond the second year of age are rare, there is indication that children may encounter problems in tasks involving integration of information across the visual field for object representation (visual segmentation and form identification based on texture (10,188), motion (96) or color-contrast (97); recognition of incomplete objects (74)). Our result also provides evidence for late maturation of visual functions: contour detection performance shows significant development in children between ages 5-14 years. To test the contribution of low-level visual mechanisms and higher level cognitive factors in our contour-detection task, we looked at the effect of practice and the specificity of learning in the contour-integration performance of 5-6 year-old children and adults by employing a learning paradigm. Performance in various low-level visual tasks has been shown to significantly improve with practice (e.g., hyperacuity (162), visual discrimination (62), pop-out (108), and visual search tasks (186)). Although these tasks involve a variety of visual stimuli, most of them seem to be specific for stimulus parameters (62,108,162), and some of them even for retinal location (62,108). We found significant improvement with practice in both age groups similar to other low level visual tasks (62,108,162,186). This shows that, the strength of interactions can be extended even with a short training in children with normal vision, however a good night's sleep is necessary for such interactions to improve (probably consolidating the effect) (96). The improvement was specific for



the visual cue defining the task. The slight, but not significant tendency for transfer in children in the 'color to orientation' group might indicate that the contribution of cognitive/motivational factors is present in children to a certain extent, however, it does not explain our data. The results show a significant age-effect, but there is no significant difference between eyes and gender. The similar trends found in adults and children suggest that the same mechanisms might be responsible for the performance in both groups. A high degree of stimulus specificity usually suggests that the plastic neuronal changes of learning took place at early cortical levels where the basic stimulus dimensions are still separable. This implies that the reduced contour integration performance of 5-14 year old children is a perceptual effect and cannot be explained by high-level cognitive developmental factors, such as less efficient search strategies (187); or by non-visual factors, such as less motivation. The transfer found across eyes indicates that learning must have occurred in the cortex at a level where information from the two eyes is combined, and the contribution from subcortical structures is insubstantial. And it also implies that a relatively long consolidation period might be necessary for the learning effect to occur.

Based on our two further experiments, we believe that the age effect can be explained at the level of long-range spatial interactions. Integration of orientation information across space in the contour-detection task has been related to long-range facilitatory interactions between orientation tuned spatial channels (48,61,115,118,119,157). We assumed that the analysis of the actual spatial ranges of interactions in children and in adults might give some explanation of the developmental effect. We found that contour integration performance depends on absolute contour spacing in children and not on the level of noise or signal-to-noise ratio per se. However, the performance of adults in the tested range is limited only by display parameters (signal-to-noise ratio) and not by the absolute range of cortical interactions (the range of contour spacings that can be tested at all is limited: above 9λ spacing the number of contour elements would be too small to provide comparable conditions). The results suggests that long-range spatial interactions - although probably present at an early age - might not be functioning at an adult level in terms of their spatial range.

There exist psychophysical indications that the development of orientation based segmentation in humans lasts longer than the development of luminance or motion based segmentation (10,188). The intrinsic horizontal connections of the primary visual cortex (72,166) are assumed to provide the anatomical substance for long-range interactions. There are also anatomical data showing that long-range spatial interactions subserving contour integration, and segmentation (73,147,152), develop at various times in different layers of the primary visual cortex. They seem to be immature

even at 5 years of age in layer 2/3 of the human visual cortex (36). The plasticity of the long-range interactions was demonstrated in psychophysical studies where the spatial range of the interactions was extended in adult human subjects (163). Let us also mention that similar, horizontally connected V1 circuits might be behind the integration of color information (205). On the other hand, in addition to these lateral connections the role of higher level processing such as modulatory feedback connections of extrastriate origin and/or participation of 'intermediate' level cortical areas (V4) cannot be excluded (115,219). High-level perceptual interpretations function to make sense of the stimulus and it might well be that young children cannot generate and apply these interpretations that easily. Interestingly, a delayed postnatal development of feedback connections between V2 and V1 has also been indicated in humans (39). More recent studies raise the possibility of a significant increase in the number of cortical cells between birth and six years of age (176), implying a strikingly extended structural maturation of the human cortex, including the early visual areas (177). The cue specificity of learning found in our studies supports the idea that our subjects' task performance above all depended on the state of development of their low-level perceptual mechanisms. In the light of these results, the question arises whether the maturation of human vision really comes to an end early - by the first or second year of life.

Taken together, we found significant improvement in children between ages 5 to 14 years in visual spatial integration using a contour-detection task. Our results in accordance with those Sireteanu & Rieth (188), and Atkinson & Braddick (10) may indicate a very late maturation of long-range spatial interactions subserving the integration of orientation information across the visual field. We hypothesize that long-range spatial interactions might have a shorter spatial range in children than in adults since search deficiency (187) should result in an opposite tendency (improving performance with decreasing number of distractors). The span of these interactions can be enhanced by learning. Performance in the task improves in a cue-specific manner with practice, which indicates the involvement of fairly low-level perceptual mechanisms. The observed handicap in children is probably truly perceptual because motivational factors (such as perseverance in completing a difficult task) or cognitive mechanisms (such as search strategies) would not be expected to generate different tendencies among children and adults in terms of contour spacing. In other words, visual integration carried out by long-range spatial interactions may require an extended maturational period, which can be strongly affected by visual experience. The long-range connections of the visual cortex are assumed to intervene contextual effects in perception (72,73,115,116,119,205). There is behavioral evidence that these contextual effects might be largely mediated by the occipitotemporal (or ventral) visual stream (75,76,83,139). Thus,

our result further suggest the different maturational rate of the two major subsystems of vision, namely the dorsal (occipitoparietal) stream and the ventral (occipitotemporal) stream that are going to be discussed in more details in the General Discussion session. Our study is the only developmental study to date assessed contour detection in human children, varying the ratio of spacing between noise elements and contour elements.

STUDY II:

EFFECT OF LATE STRABISMUS SURGERY ON PATTERN REVERSAL VISUAL EVOKED POTENTIALS OF CHILDREN SUFFERING FROM ACQUIRED ESOTROPIA

SUBJECTS AND METHODS

Ten (6 female and 4 male) consecutive 5-6 year-old pre-school children with acquired esotropia admitted to the Department of Ophthalmology, Albert Szent-Györgyi Medical University, Szeged, Hungary for late strabismic surgery were examined (*strabismic group*). The late surgery of the children was first and foremost due to late referrals or consecutive ongoing treatment of amblyopia. The children received conservative therapy until there was no further improvement in their visual acuity. Hence, most of them were at most mild amblyopic (visual acuity better than 20/40) (124) at the time of surgery (although we will refer to the former amblyopic eye also as amblyopic in the course of this paper). Three children with a history of prematurity or strabismus surgery or other ophthalmological diseases were excluded from this study at the start. The onset of strabismus ranged from 1.5 to 4 years (mean: 2.6 years). To study the effect of surgical intervention visual evoked potentials to pattern reversal stimulation were recorded one day before and at least 3 months after surgery. Prior to their VEP recording visual acuity, stereovision and the angle of deviation were assessed. The angle of strabismus was measured by alternate prism and cover test by fixating to a light source at distance (5 m), and to a small object at near (33 cm). The stereoacuity was obtained by Randot test. Following surgery all the previously used tests were performed again and the degree of binocularity was also assessed by synoptophore. Clinical data obtained by synoptophore were correlated with VEP amplitude values following surgery. Seven healthy, age-matched children with normal binocular vision and visual acuity of 1.0 (20/20) or better served as controls (*control group*) for VEP recordings.

VEPs were recorded from an active scalp electrode placed at the O_z (10-20 system). The left earlobe was used for placement of the system reference electrode. The impedance was kept under 5 k Ω . Single channel recording was used. Recordings were done in a well-insulated darkened room with no windows. Subjects were seated on a height-adjustable revolving chair with arm- and headrest one meter from the monitor. The session lasted 1 hour or somewhat longer. A fixation point was used and the attention of the children was drawn and kept by tales. A pattern-reversal checkerboard stimulus was used for testing. Each check subtended 80', 40', 20' and the entire stimulus field was 15.64 degrees by 11.31 degrees of visual angle. The frequency of the stimulation was 1.8 Hz. Monocular- and binocular stimulation were performed while the subjects wore appropriate correction for refractive errors. The amplitude and latency values of the P100 component were measured and one hundred responses were averaged. During surgical intervention recession was performed on all the patients, but one underwent also a resection of the lateral rectus muscle. One eye was operated on in 3 patients, and both eyes in 7 subjects. Statistical analysis was performed using three-way ANOVA and Student t-test. Eyes, check-sizes, and timing were compared within and between the strabismic and control groups.

RESULTS

The data of 10 children with treated strabismic amblyopia were included in the analysis. The corrected monocular visual acuity ranged between 0.6 to 1.0 before surgery (mean: 0.935). Preoperatively, the monocular visual acuity was 1.0 for both eyes in 6 children. In one case the difference between the visual acuity in the amblyopic and fellow eye was two lines and in three cases it was only one line on the Snellen eye chart. No significant change in the visual acuity was observed in most of the cases after surgery, although occlusion had to be re-instituted in one child because of a slight impairment in visual acuity.

Prior to the operation, the angle of strabismus ranged between 4 and 22 degrees (mean: 14.25 degrees) at distance, and between 15 and 25 degrees (mean: 21.45 degrees) at near. The angle of deviation ranged between 0 to 7 degrees at distance, and 3 to 6 degrees at near after surgery. Postoperatively, good binocular fusion (210) was found in 6 cases with synoptophore. (Harmonic Retinal Correspondence (HRC) in 3 children and non-harmonic RC (NHRC) in another 3 children). Only peripheral fusion (besides central suppression (CS)) was seen in the rest of the children. No stereopsis was detected by Randot test.

Before surgery, the pattern evoked potential amplitude of the amblyopic eye was consistently smaller than that of the fellow eye and the binocular response was generally similar to that

observed when stimulating the non-amblyopic fellow eye. P100 amplitude values of the age-matched control group are shown in Table 1 for comparison to that of the strabismic group.

		Binocular (μV)			Monocular I. (μV)			Monocular II. (μV)		
		80'	40'	20'	80'	40'	20'	80'	40'	20'
strabis- mic group	before surgery	11.094 ± 3.267	13.943 ± 6.71	12.824 ± 5.91	10.218 ± 4.386	11.074 ± 3.513	9.303 ± 3.903	12.688 ± 5.347	13.699 ± 3.755	11.288 ± 5.271
	after surgery	21.567 ± 10.658	21.486 ± 10.184	19.056 ± 11.124	16.602 ± 9.375	14.322 ± 9.037	10.773 ± 6.527	16.207 ± 10.026	17.465 ± 9.058	15.156 ± 7.924
control group		24.784 ± 8.23	25.233 ± 11.743	23.856 ± 15.314	24.313 ± 11.786	23.913 ± 12.623	19.151 ± 10.925	24.366 ± 12.549	26.912 ± 15.435	21.594 ± 15.044

Table 1. P100 amplitude values of the strabismic and control group. Monocular I. indicates the amblyopic, while Monocular II. indicates the fellow eye in the strabismic group and right and left eyes separately in the control group.

No significant interocular difference was found in the control group (t-test: 80': $p = 0.994$; 40': $p = 0.698$; 20': $p = 0.734$). However, ANOVA analysis showed significant differences for the P100 amplitude between the amblyopic and the fellow eye ($F = 4.553$; $df = 2,14$; $p < 0.05$). The largest response was usually recorded on stimulation with the 80' check-size (Figure 1).

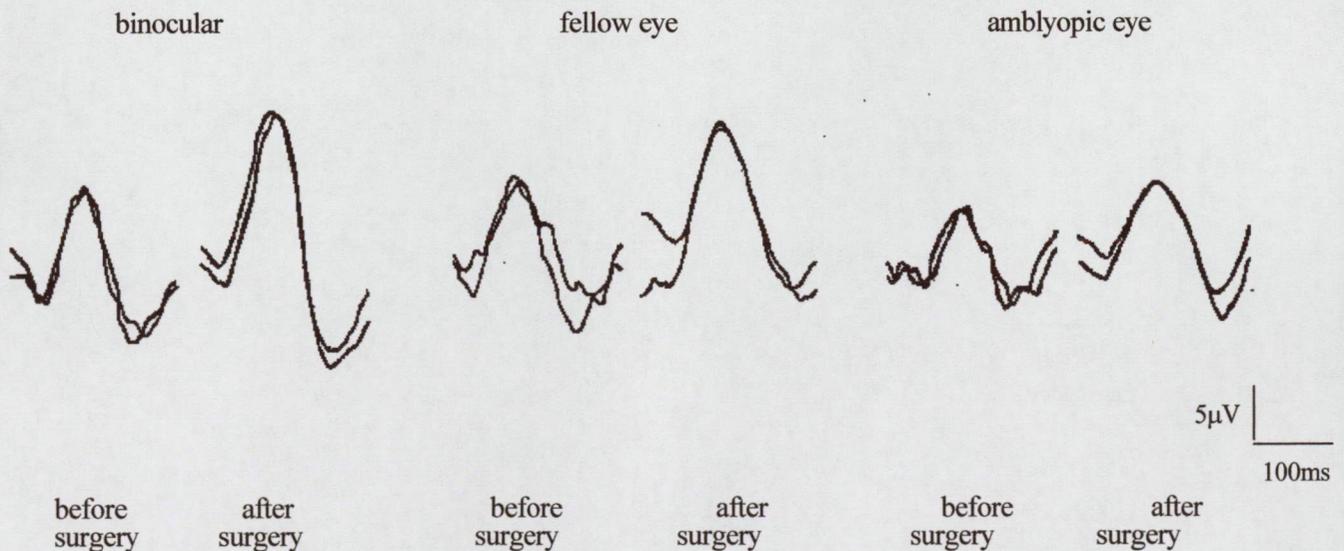


Figure 1. Effect of strabismus surgery on the VEP

The latency values from amblyopic eyes were commonly slightly longer than those from the fellow eye, although the difference was not statistically significant ($p > 0.05$).

Visual evoked potentials showed clear changes under the effect of the surgery (Three-way ANOVA: $F = 4.903$; $df = 2,14$; $p < 0.05$). The amplitude values of P100 component increased significantly after surgery ($p < 0.05$), while no significant changes were seen in the latencies ($p > 0.05$) (Figure 2).

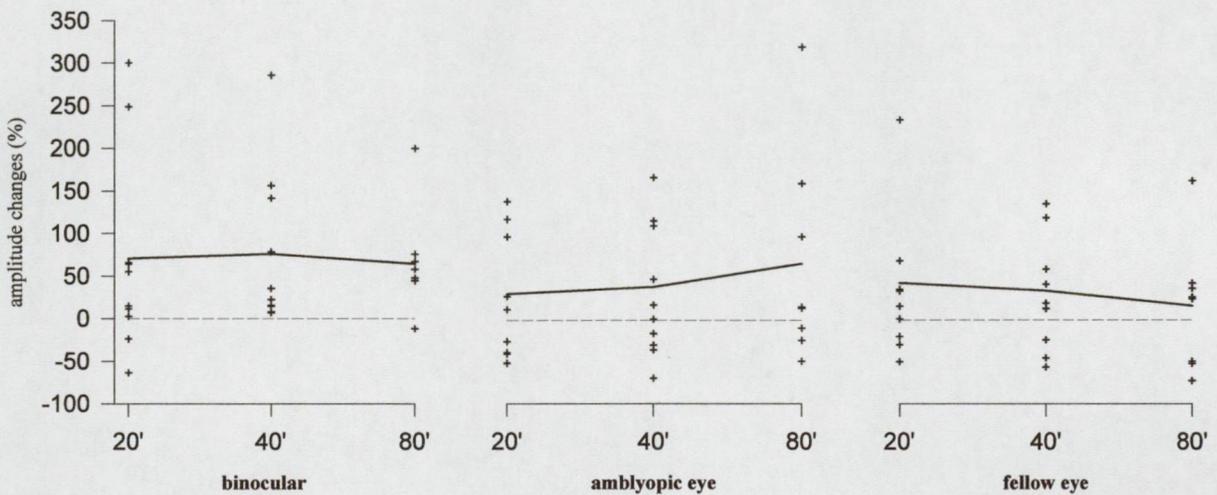


Figure 2. Effect of strabismus surgery on the amplitude values

The VEP changes were most prominent upon binocular stimulation at 80' and 40' checksizes. Binocular summation (summation index introduced by Apkarian et al. (4) and modified by Nuzzi and Franchi: $2MM > \text{binocular amplitude} > \text{mean MM}$; MM: monocular amplitude) (154) was noticed in every case after surgery, while it appeared only in 60% of the cases prior to surgical intervention. Before surgery 3 subjects showed binocular inhibition, while binocular facilitation was detected in one case by VEP. Binocular fusion measured by synoptophore showed similarly considerable improvement after intervention, however, no correlation was found when comparing postoperative electrophysiological data on binocular stimulation and the synoptophore findings (Table 2).

subjects	degree of stereopsis (synoptophor)	level of binocular interaction (VEP)
1.	HRC	+
2.	HRC	+
3.	NHRC	+
4.	NHRC	+
5.	HRC	+
6.	CS	+
7.	CS	+
8.	CS	+

Table 2. Comparison of clinical (synoptophor) and electrophysiological (VEP) data. Abbreviations see in text.

There was a significant increase in VEP amplitude at 80' and 40' check-size for each stimulated eye shown by statistical analysis (main effect of surgery: 80': $F = 4.839$; $df = 2,14$; 40': $F = 5.453$; $df = 2,18$; relationship between eyes postoperatively: $F = 16.565$; $df = 2,18$; interaction between eyes and check-size postoperatively: $F = 2.986$; $df = 4,36$; $p < 0.01$).

A comparison between the pre-surgery values of the strabismic group and those of the control group indicated significant differences between the P100 amplitudes in relationship to check-size and eye (eyes: $F = 153.029$; $df = 5,20$; $p < 0.001$; between eyes and check-size: $F = 2.595$; $df = 10,40$; $p < 0.05$). Though, amplitude values of the strabismic group were larger after surgery, the differences observed between patients and controls were still significant (eyes: $F = 51.581$; $df = 5,30$; $p < 0.001$; between eyes and check-size: $F = 4.007$; $df = 10,60$; $p < 0.001$).

DISCUSSION

The proper timing of surgery and its functional consequences in acquired esotropia, unlike infantile esotropia (22), has never been a primary focus and has not been studied by many groups partly because those suffering from it having a better chance for functional recovery.

Leguire et al. (130) studied binocular summation of pattern visual-evoked response in 9 early-onset esotropic (1-58 months old) children pre- and postoperatively and reported a 64% increase in the binocular VEP amplitude and a 28% decrease in the monocular amplitude after surgery. They also found a significant difference between binocular and monocular amplitudes following surgery. We studied 5-6 year old children because they can be examined without parental control

and they are several years beyond infancy, and the end of the classical critical period. Our results also showed a significant enhancement of the amplitude of pattern-visual evoked potentials after surgical correction of strabismus in these children. The most consistent increase was found in the amplitude values of the P100 component to binocular stimulation especially with a moderately large check-size (40'). This considerable increase of evoked potentials in children following corrective surgery for acquired strabismus was an unexpected finding. Parallel to the electrophysiological findings we also detected good binocular fusion in 6 cases (60%) and peripheral fusion in 4 cases (40%) on clinical examination by synoptophore after surgery.

However, unlike Amigo et al. (2) no correlation was determined between the strength of binocular summation (the index introduced by Apkarian et al. (4) and modified by Nuzzi & Franchi (154)) on the VEP and the degree of binocularity obtained by clinical evaluating method after surgery. Amigo et al. claimed that binocular VEP summation in stereodeficient adults is extremely variable (2). Contrary to the findings of Apkarian et al. (3), but similar to that Shawkat et al. (180) we noticed VEP summation in most cases and found no facilitation for reversal stimulation in amblyopes. Binocular enhancement was most pronounced for the moderate check-size that is in agreement with the study of Shawkat and Kriss who found that reversal P100 component showed the greatest difference between normals and amblyopes for small (12') and moderate sized checks (20', 50') (180). Despite of slight differences in the groups of subjects and VEP stimulations used in the different studies, our finding supports earlier results (154,181). Our study is unique in regard to the fact that former groups were not studying P100 VEP amplitude values and their correlation to clinical measures of binocularity in relation to surgery in 5-6 year old children.

Achievement of fusion (155,218) is the main goal in the surgical treatment of esotropia both in children and in adults (95,121). Fusion is considered to be an acquired reflex (9,197), hence its development or regain is probably allowed by the previous fusional ability present before the onset of strabismus, allowing the development of at least some binocular neurons in the visual cortex (95,148,222). Patients with acquired esotropia have been reported to have a better chance for binocularity than patients with infantile esotropia (123). Morris et al. (148) suggested that even adults with no previous alignment have the potential for peripheral fusion after strabismus surgery. It thus appears that the marked changes in the visual evoked potential to binocular stimulation following surgical intervention are due to the attainment of fusional mechanisms. Alignment of the eyes and binocular fusion is the prerequisite of stereopsis (51). No stereopsis was found in our subjects on clinical examination neither before nor after operation. Stereopsis largely depends on visual acuity. If there is a reduction in acuity it can lead to degraded stereopsis even in normal

people. But there is no chance to regain it when it was impaired within the first 18 months (191). Our subjects probably lost their stereopsis within its critical period, and the reestablishment of good visual acuity could not lead to the recovery of stereopsis.

Late or prolonged maturation in strabismics (95-97,117,148,182,), the discontinuation of occlusion therapy and the increased field of vision (27,95,123,221), the organization of afferent inputs as well as possible changes in the intracortical interactions (114) following surgery might also play some role in the improvement of amplitude values of both amblyopic and fellow eye. The reduced amplitude values of the amblyopic eye compared to the fellow eye can be due to the stronger synchronization of the neurons' responses driven by the normal than by the amblyopic eye (167).

The changes observed during 3-month interval cannot be attributed to physiological rate of cortical maturation in these children (see Chapter Amblyopia and VEP). Alternatively, the significantly reduced amplitude values of the fellow eyes even with good visual acuity compared to the normal control group can be attributed to the protracted effect of occlusion therapy in both the deprived and the fellow eyes (6,17,129,179,217). It is possible that the amblyopic eye influences the fellow eye through interocular interactions (174,212) thus leading to reduced amplitude values. In our study, all children had pre-surgical occlusion therapy that was terminated with the exception of one case, after the operation. This finding is in agreement with that of previous groups, who suggested that the fellow eyes of the amblyopes are not functionally normal, although their visual acuity is generally good (20/20) (106,107,128,165).

In conclusion, our results provide evidence about improvement in binocular function following strabismus surgery, even if performed years after infancy beyond the end of the classical critical period. We found a significant increase in the P100 amplitude of the binocular VEP and most children also had improved binocular fusion as measured on a synoptophore. However there was not good correlation between the amount of improvement from VEP and synoptophore testing. Thus, our VEP result could be indicative of improved binocular function but could also reflect the epiphenominal nature of our finding. In addition it might indicate some processes not shown by other evaluation methods. It is also conceivable that good ocular alignment can itself enhance the signals coming from the two eyes on the VEP and thus result in increased amplitude values without any substantial changes in the brain. Our study is the only study to date that examine P100 VEP amplitude values and their correlation to clinical measures of binocularity in relation to surgery in 5-6 year old children.

GENERAL DISCUSSION

„Children are not little adults.’

- Unknown

Much of our knowledge of the external world is gained through the visual system. As we have seen in the previous chapters the visual system is immature at birth and is relatively mutable and plastic as it develops in infancy (50,64). Looking for timing is relevant in the development of the nervous system, since changes can occur only at specific, genetically predetermined times and thus it is an important question when plasticity comes to an end? The onset of critical periods and duration of plasticity for different visual functions in humans are not understood precisely. Some begin by few months of age and some may last 5 or 7 years (15,100,138) or continues well into puberty (50,51,208). Hormonal changes around puberty might determine the end of plasticity (49). The development of visual functions usually correlates well with the morphological changes detected in the visual cortex. In the face of the uncertainty concerning the onset and length of the critical periods and plasticity it is very timely and worthwhile to study various visual functions in extended populations but in more specific age groups.

Both of our studies were unique of their kind and both focused on the maturation and plasticity of visual functions in children after the age of 5 years. We found significant changes in a visual function up to adolescence in *Study 1*. The improvement in spatial integration with practice and with age was considered to be due to the plasticity and to at least functional immaturity of horizontal connections in the visual cortex. We similarly noticed significant functional changes after surgery beyond the end of the classical critical period in the amblyopic or formerly amblyopic visual system in *Study 2*. This also provides evidence for the plasticity of visual functions years beyond infancy.

Based upon our results the question raises why researchers and clinicians did have a theory of a shorter span (by 2 years of age) of maturation of visual functions? The answer to this question is not easy since the whole picture of development is not yet known. The different methodology, the bad cooperation of children at certain ages and the distinct explanation of definitions clearly played an important role. However, due to scientific and methodical development the interpretation of different definitions has also undergone some changes. Thus, what previously had been considered to be the critical period seems to be only the first part of it. The visual system could retain plasticity, nevertheless, for a longer time and this yields in a susceptibility to abnormal stimuli and responsiveness to treatment. The second reason why these phenomena of late visual

maturation have not been described could be the historical fact that the classical description of the visual development in children had been completed before the discovery of the parallel visual streams. Thus, no special attention has been paid to the reinvestigation of all visual developmental phenomena. We suppose now that our findings can be related to the different maturational time frame of the two parallel visual pathways, namely the dorsal and the ventral streams (206), that subserve different aspects of vision.

The occipitotemporal or ventral stream is involved in more refined perceptual categorization, object recognition and mediates contextual effects. The occipitoparietal or dorsal stream is concerned with the on-line control of goal-directed actions (77,145,206). The color sensitive parvo- (P) and the motion and luminance sensitive magnocellular (M) retinocortical pathways (136) do not project separately to the ventral and the dorsal streams (136,178,223). It is suggested, that the ventral and dorsal streams both receive inputs from the M and P pathways, although most of the input to the dorsal stream is magno in origin (145). The ventral pathway gets at least as many inputs from the magno as from the parvo system (145,153,172,198).

Concerning their developmental pattern, not many studies are available. Global models of visual development have occasionally been proposed in which the P pathway precedes the M pathway in development or vica versa (204). It is very likely that each pathway and their function develops at different rates. There is little if any neuroanatomical evidence in humans about the time span of the development of the two streams. According to anatomical studies in macaque monkeys, the dorsal pathway matures earlier, than the ventral stream (14,55). Neville and Bavelier (153), on the other hand suggest that the dorsal visual pathway has a more prolonged maturational time course. Dobkins et al. (56) and Teller (204) in accordance with others (132,136) propose a precocious development of the M pathway according to their human psychophysical findings. Tassinari et al. also provide evidence for a later development of the M fibres of the optic tract compared to the P-fibres (200). The larger cells in the M-layers of the CGL also have a longer period of susceptibility than the small cells in the P-layers (93,216). The period of susceptibility extends and the rapid growth ends around 6 months for the small cell type and at around 12 months for the larger cell type (93).

Concerning the maturation of the two visual streams in amblyopia, it is widely accepted that amblyopes have impaired form vision that is strongly related to the P system. Abnormal P-cell development, however was found predominantly only in cases of pattern deprivation amblyopia while M-neuron maldevelopment was reported mainly in cases of strabismus or severe monocular blur. Maldevelopment of M-cells might also explain motor abnormalities in amblyopia (223).

Kiorpes et al. (111) found some deficit in the middle temporal (MT) area of the visual system of the amblyopic monkeys, that is part of the dorsal stream. Thus, the situation is also not quite clear in amblyopia.

What can explain the plasticity concerning the amblyopic visual system? It was found that amblyopia only slows down the development and causes relative immaturity (110,113). Thus, it is not surprising that the visual system is more plastic, and remains plastic for a prolonged period of time when amblyopia is present (43). The findings of Kiorpes et al. (111) and the notion that the VEP latency is considerably less prolonged in amblyopes than the reaction time (the time required to produce a motor response to a visual stimulus) (211) suggest that higher levels of the visual system are probably also involved in amblyopia. As we have seen in previous chapters, higher levels keep plasticity for a longer span than lower levels (51). It is probable, that these factors might all contribute to the prolonged plasticity in amblyopes to some extent.

In conclusion, we regard as our main findings that contrary to the theory that visual functions mature by 2 years of age our results suggest, that the maturation of at least some visual functions and the plasticity of the visual cortex lasts much longer than it was indicated before. This notion has a considerable theoretical importance and practical benefit in clinical efforts aiming at the enhancement of visual abilities in children. It raises the possibility of functional improvement at a later age and promotes the trials for treatment up to the puberty or even later.

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