

REVIEW ARTICLE

Normal and abnormal development of visual functions in children

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ABSTRACT The human visual system goes through substantial changes during the first few months of postnatal life. The development of visual functions and structures occurs at different times and different rates. It has been a generally held belief that the development of visual functions and their critical period come to an end early in life. Most of the developmental data confirm this theory, although the findings sometimes are contradictory. Thus, our knowledge concerning visual development does not seem to be complete. The determination of exact timing of the different visual functions is relevant in children since a proved extended maturational timeframe can promote the trial of enhancement of visual abilities at a later age, up to puberty or beyond. There have already been suggestions for an extended developmental time span for some of the visual functions. Here we review the most relevant data with reference to the normal development of the eye, visual functions and visual pathways found in the literature and provide further evidence for the maturation and plasticity of visual functions after the age of 5 years.

KEY WORDS

visual development
critical period
contour-integration
amblyopia
plasticity

Acta Biol Szeged 45(1-4):23-42 (2001)

The need for understanding visual development has received increasing attention in the last four decades (Fiorentini 1984) since it is a system where work at behavioral, anatomical and physiological levels can be correlated to lead to study the basic mechanisms involved (Daw 1994).

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 who received the Nobel Prize in Medicine in appreciation of their work in 1981 (Hubel and Wiesel 1963a, b). Hubel and Wiesel deprived one or both eyes of visual impulses from birth in cats. They found more significant structural and morphological changes of the visual pathways during closure of one eye than during the closure of both eyes (Wiesel and Hubel 1965). 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 is susceptible to environmental influence as well as to abnormal visual experience (Hubel and Wiesel 1970; Barlow 1975; Wiesel

1982; Daw 1994). If stimulus deprivation occurs during this period, visual development will be impaired. Since the work of Hubel and Wiesel there has been an explosion of morphological, electrophysiological and behavioral experiments that studied how postnatal visual development occurs and whether and how it could be affected by early visual deprivation or by manipulations of the visual environment (Fiorentini 1984). Thus, the visual system has become the model for the understanding of plasticity (Daw 1994).

The study of vision in human infants has progressed considerably in parallel with the animal studies (Fiorentini 1984). It was shown that critical periods also exist in the visual development of humans. The clearest demonstration of this similarity, came out in studies on kittens and young monkeys with experimentally induced strabismus based on the pioneering work of Wiesel and Hubel (1963a, b).

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 (Atkinson 1984; Fiorentini 1984; Garey 1984). 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 (Conel 1939-1967; Harwerth et al. 1986; Daw 1994). Different functions may emerge at different times and develop at different rates (Levi

Accepted December 5, 2000

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and Carkeet 1993). The general belief that the critical period terminates by the end of the second year of life has been kept for long (Wright 1995). Most of the developmental data (see Normal visual development) until recently have confirmed this theory, although they are somewhat controversial. There are suggestions for an extended maturational time frame of some of the visual functions.

Therefore, the exact timing of the maturation of human visual functions and thus the length of plasticity and the so called critical period have remained to be a question. The accurate settling of the critical period would give the opportunity to more children for functional recovery, since impaired visual functions and developmental disorders e.g. amblyopia can be restored with a good chance before their critical period is over (Daw 1995). The lack of evidence in this field can be due to poor compliance of young children and the absence of standard and reliable evaluation as well as research methods for children.

In the view of the above mentioned notions the aim of our studies was two fold. On the one hand, to determine the length of the critical period in normal visual development by examining a less known visual function, namely, the spatial integration ability of children in different age groups through 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". On the other hand, 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 if it is worth performing late surgery at all and if we can expect functional changes besides cosmetical benefits.

Normal visual development

Substantial changes and rapid visual development occur during the first 6 months of postnatal life. Infants probably can discriminate between colors (Bornstein et al. 1976; von Noorden 1985; Burr et al. 1996), have preference for moving stimuli (Nelson and Horowitz 1987) and can process complex motion information (Kellman and Spelke 1983) by 3-4 months of age. Optokinetic nystagmus (OKN; Atkinson 1979, 1984; Nagele and Held 1982; Lewis et al. 1989; Eustis 1995), saccadic eye movements (McGinnis 1930; Barten et al. 1971; Atkinson 1984) and fixation are present from birth (Dayton et al. 1964b; Isenberg 1989; Eustis 1995) but become mature only by 6 months of age. Depth perception, discrimination (Aslin 1977; Braddick et al. 1980; Teller 1982; Atkinson 1984), smooth pursuit (Dayton and Jones 1964a; Atkinson 1984; Isenberg 1989; Johnson 1990) and eye alignment (Eustis 1995) 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 (Atkinson et al. 1981;

Atkinson 1984), they reach adult levels sometime between 1 and 5 years of age (McGinnis 1930; Dobson and Teller 1978; Gwiazda et al. 1980; Birch et al. 1983), 3 and 9 years of age (Romano et al. 1975; Braddick et al. 1980; Fox et al. 1980, 1986, Held et al. 1980; Birch et al. 1982) and by 2 to 5 years (Atkinson et al. 1981; Bradley and Freeman 1982) of age individually. Binocular vision and fusion also emerge around 1.5-4 months (Braddick et al. 1980; Petrig et al. 1981; Braddick and Atkinson 1983; Leguire et al. 1991) and mature between 1 to 7 years of age (Banks and Aslin 1975; Hohmann and Creutzfeld 1975). 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 (Marg et al. 1976; Eustis 1995). The visual field is supposed to reach adult values between 6 months (Mayer et al. 1988; Lewis and Maurer 1992) and 5 years (Lakowski and Aspinall 1969; Matsuo et al. 1974) depending on the technique and stimulus applied (Lewis and Maurer 1992; Sireteanu 1996a). Wilson et al. (1991), however, reported a much slower maturation that lasts through 10 years of age. A slower development of contrast sensitivity was found by Beazley et al. (1980) also up to early adolescence.

The ocular media are clear from birth (Atkinson 1984). The intraocular and orbital structures seem to be well developed at birth, however dramatic morphological, anatomical and physiological changes occur in them during infancy and continue in the first few years of life (Ozanic and Jakobiec 1985). 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 6-8 years of age while in the case of the eyeball it continues to mature until around 13 years of age (Blomdahl 1979; Swan and Wilkins 1984; Gordon and Donzis 1985).

At birth the human visual system is immature at the level of retina, lateral geniculate nucleus (LGN), and visual cortex, too (Garey 1984). The retina develops intensively during the first 6 months of life and comes to its full maturity around age 1-4 years (Abramov et al. 1982; Hendrickson and Yuodelis 1984; Yuodelis and Hendrickson 1986). The LGN reaches adult volume by the end of the first 6 months (de Courten and Garey 1982; Huttenlocher et al. 1982; Garey and de Courten 1983), but the morphological maturation and the development of different visual functions occur between 8 months to 2 years (Hickey 1981; Huttenlocher et al. 1982; Garey and de Courten 1983; Garey 1984).

The primary visual pathway becomes functional around the age of 2-3 months (Bronson 1974, 1982). Recent data by Sloper and Collins (1998), however, demonstrated that the central visual pathways continue to mature after the age of 5. The myelination of the optic nerve lasts until 2 years of age (Marg et al. 1976; Fox et al. 1980; Johnson 1990). Some of the extrastriatal visual areas and intracortical interneurons probably have a much longer myelination period (Yakovlev and Lecours 1967; Atkinson 1984).

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 (Shankle et al. 1998a). This can imply a prolonged structural maturation of the human visual cortex. At about 4 months of age the primary visual cortex (V1) reaches adult volume, much earlier than the brain as a whole (Lemire et al. 1975; Garey and de Courten 1983; Garey 1984; Huttenlocher and de Courten 1987). Adult values of synaptic density are reached at the age of 4 years in the primary, while at the age of 11 years (Huttenlocher 1994; Huttenlocher and Dabholkar 1997) 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 (Chugani et al. 1987; Giedd et al. 1996; Sowell et al. 1999). 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 (Gollin 1960) as well as in visual integration and form identification when it is based on contrasts in texture (Atkinson and Braddick 1992; Sireteanu and Rieth 1993), motion (Hollants-Gilhuijs et al. 1998a) or color (Hollants-Gilhuijs et al. 1998b).

Spatial integration

Spatial integration is our ability to segment the visual image and to perceive contours and borders of objects by the integration of the local features such as orientation, depth, color etc., across the visual field (Field et al. 1993; Kovács and Julesz 1993; Kovács et al. 1996a; Kovács 1996b; Dakin and Hess 1998; Penefather et al. 1999). The efficiency of the integrating mechanism can be estimated psychophysically in a contour detection task that employs orientational noise (Field et al. 1993; Kovács and Julesz 1993; Kovács 1996b; Dakin and Hess 1998).

The world around us at a certain moment is very complex; it 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 (Kohler 1967): objects are grouped together, because they are close (proximity), have similar features (similarity), they follow the same direction (good continuation), 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 (Sireteanu and Fronius 1981; Schiffman 1996).

Contour integration is part of the segregation process. The Gestalt laws that are mostly influence contour integration are good continuation (Field et al. 1993; isolinear paths of Gabor patches are easier to detect) and closure (Kovács and Julesz 1993). It is easier to detect a contour when it follows these laws. Pettet et al. (1998) reported that in addition to closure and good continuation, the geometric properties, e.g. alignment, were also substantial in contour detection.

Anatomical data show that the neuronal connections that give rise to this integration process are probably the long-range interactions (Mitchinson and Crick 1982; Nelson and Frost 1985; Ts'o and Gilbert 1988; Gilbert 1998). 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 interactions 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 Gabor Dennis, roughly model the receptive field structure of simple cells in V1 (Jones and Palmer 1987). Therefore, they are appropriate stimuli for the examination of these small spatial filters and their interactions in V1. Gabor patches are the products of a sine wave multiplied by a smooth bell shaped (Gaussian) envelope (Bruce et al. 1996). 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 (Field et al. 1993) as well as on the parameters of Gabor patches. The contour and its surroundings also appear to influence contour detection (Bruce et al. 1996).

Long-range interactions probably refine postnatally in an experience-dependent fashion (Callaway and Katz 1990). 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.

Burkhalter et al. (1993a) found that long-range interactions within layer 2/3 of the primary visual cortex 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 (Callaway and Katz 1990; Burkhalter 1993a; Polat and Sagi 1994). 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 (Burkhalter et al. 1993a). There is also some psychophysical indication that the development of these connections in humans lasts longer — until around school age (Sireteanu and Rieth 1993) — than the development of other primary functions in infancy (Atkinson and Braddick 1992), but the exact age has not been determined yet.

Thus, it is essential to study contour detection developmentally. Work with infants may provide insight into mechanisms of cortical development. To study the human developmental pattern of spatial integration between orientation selective cells of the primary visual cortex we used a card test version (Kovacs et al. 1996a; Pennefather et al. 1999) of a contour detection task in children (5-14 years) with normal vision. These developmental results will be reported below in details (see Maturation of visual spatial integration in children).

Abnormal visual development: amblyopia

Visual experience during development is necessary for normal vision. If visual experience early in life is abnormal a disorder called amblyopia develops. 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 (Vaegan and Taylor 1979; Sanke 1988; Daw 1995). Amblyopia together with strabismus is the most common functional visual disorders in early childhood (Levi and Carkeet 1993). Amblyopia is generally defined as reduced visual acuity — for diagnostic purposes at least 2 Snellen lines difference between the eyes (Kushner 1988) — 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. It has two horizontal types: esotropia (inward deviation) and exotropia (outward deviation). Esotropia is not controlled by fusional mechanisms and can lead to amblyopia if not treated properly (Hecht et al. 1996). 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 (von Noorden 1985). From the aspect of our study acquired esotropia developed together with amblyopia will be in focus.

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%; von Noorden 1985) as well as to its detrimental, long term effect on personality (Asbury and Burke 1995) and occupation of the amblyopes (Reinecke 1978). Amblyopia accounts for more cases of vision impairment than all other causes (ocular diseases and trauma) combined (von Noorden 1985, 1996). In those with strabismus or anisometropia, 40-60% develops amblyopia. Children with esotropia show an approximately four times greater incidence of amblyopia than those with exotropia (Costenbader et al. 1948).

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 sees very little." (von Noorden 1996). Many different definitions have 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 (Ciuffreda et al. 1991; von Noorden 1996; Kushner 1998). When strabismus and amblyopia develop together a condition called strabismic amblyopia occurs. The notion that amblyopia is a developmental disorder was first expressed 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.

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, Kiorpes and Movshon (1996a) have found that the neural basis of amblyopia begins but does not end in V1. The primary effects may involve extrastriate visual areas, too (Kiorpes et al. 1996b).

Treatment

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 paper by Sireteanu et

al. (1984), however, suggests a very unique and interesting finding that patching 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 (Simon and Calhoun 1998). This finding also confirms the notion that critical period for cure of amblyopia lasts longer than the critical period for its creation (Daw 1995). The general rule of thumb is that every child under 9 years of age should undergo a trial of amblyopia therapy (Mitchell and Timney 1984; Greenwald and Parks 1990; Wright 1995).

The first step in treatment is the correction of any significant refractive error that may be present in the amblyopic eye (Reinecke 1978; Kushner 1998) 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 (Simon and Calhoun 1998). Penalization, Cambridge vision stimulator (CAM) and pleoptics are alternatives to occlusion but do not work better than patching (Greenwald and Parks 1990). Other nonsurgical treatments of amblyopia include orthoptics and neurotransmitter, e.g. levodopa replacement (Pettigrew 1982; Gottlob and Stangler-Zuschrott 1990; Leguire et al 1992; von Noorden 1996). 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 (Lam et al. 1993). The aim of strabismus surgery is not only cosmetic but also has functional benefits, such as development of binocularity, reestablishment of the fusion reflex and prevention of sensor 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 (Reinecke 1978). By age 8, the sensory status is generally so fixed that it cannot be effectively influenced by treatment (Asbury and Burke 1995).

Visual functions

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. The spatial visual performance of the amblyopic eyes resembles the performance of both immature and peripheral visual systems (Kiorpes 1992a; Levi and Carkeet 1993; Kiorpes and Mov-

shon 1996a; Kiorpes et al. 1996b). 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 (Sireteanu and Fronius 1981). When tested through the amblyopic eye, amblyopes also have decreased contrast sensitivity at high spatial and low temporal frequencies in the central visual field (Wali et al. 1991) and decreased visual discrimination ability (Vernier acuity or positional acuity; Eggers 1993; Levi and Carkeet 1993; von Noorden 1996). The grating acuity deficit is relatively small compared to Vernier acuity (Hess et al. 1990; Daw 1995; Kiorpes and Movshon 1996a). Dark adaptation in all (Hess et al. 1990) and color vision (Levi and Carkeet 1993; von Noorden 1996) in most of the amblyopic eyes are normal. Strabismic amblyopes appear to have an additional loss of positional uncertainty often accompanied by aberrations of space perception (mislocalize targets), and spatial distortion.

Binocular interactions are also abnormal in amblyopia. When amblyopia occurs early in life it can even 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 (Mitchell and Timney 1984). Fusion is an acquired reflex (Aslin 1977; Starger and Birch 1986). The potential advantages of fusion include improved stereoacuity, improvement in the development of fine motor skills (Rogers et al. 1982) and stability of ocular alignment (Arthur et al. 1989; Morris et al. 1993). It is widely believed that the development of fusion is rare if ocular alignment does not occur or is not stable enough during the critical period of development for binocular vision (Leguire et al. 1995).

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 (Hohmann and Creutzfeld 1975; Braddick et al. 1980; Petrig et al. 1981). If strabismus occurs during maturation it can lead to poor binocular vision (Mitchell and Timney 1984), but it has very little effect on binocularity after 6 to 8 years of age (Banks and Aslin 1975). 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; Roelfsema et al. 1994). Though there is no agreement about the exact timing of maturation it seems that binocular vision has the longest critical period (Konig et al. 1993; Simmers and Gray 1999), and the critical period of development is prolonged when amblyopia is present (Ciuffreda 1986).

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 (Lam et al. 1993). The later a squint is acquired the more likely it is that binocular vision will be restored after a successful operation (Epelbaum et al. 1993; Kushner 1994;

Wright 1996; Kraft 1998). 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 (Lam et al. 1993). 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 unfavorable 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 unfavorable complications and to return the eyes as quickly as possible to a position where fusion and fusion reflex can be reestablished.

Here we report our results on the effect of late strabismic surgery on binocularity and on pattern reversal visual evoked potentials (VEPs) in children suffering from acquired esotropia (see Effect of late strabismus surgery in children with acquired esotropia).

Visual evoked potentials

Most of our knowledge of amblyopia has been gained through subjective psychophysiological techniques and objective electrophysiological methods carried out on human amblyopes (Cibis 1975). Electrophysiological methods such as VEPs can differentiate more easily between abnormalities in retinal and cortical functions than psychophysical methods do. VEP is a gross electrical signal generated at the occipital cortex in response to visual stimulation (Phelps 1976; Carr and Siegel 1982). The electrical activity is recorded by scalp electrodes, which are usually placed midoccipitally (O₂, 10-20 system) about 1-3 cm above the inion (Carr and Siegel 1982). 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 (Bodis-Wollner et al. 1986). These consist of light and dark checks, that reverse periodically from black to white and back at a selected alternation rate while maintaining a constant mean luminance on the retina (Carr and Siegel 1982; Fishman and Sokol 1990). The field size, retinal location and specific stimulus parameters, such as pattern size, contrast, and rate of presentation of pattern stimuli can be varied (Fishman and Sokol 1990). Within the central

region, the fovea and the parafovea can be stimulated differentially by varying check size. Bodis-Wollner et al. (1986) pointed out that checks of 10-15 minutes stimulate the fovea optimally, while larger checks, such as 50 minutes, stimulate parafoveal regions. (Fishman and Sokol 1990). 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.

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; Fig. 1). 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 (Zhang et al. 1993). During maturation the N1-P1 amplitude becomes higher and P1 latency becomes shorter for all check sizes (Uysal et al. 1993). 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 (Fiorentini and Trimarchi 1992). 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 3-4 months) (Moskowitz and Sokol 1983; Harding et al. 1989; Zhang et al. 1993). 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 (Zhang et al. 1993). 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 (Atkinson 1984), which is due to the fact that binocular input to cortical neurons is not found until about 13 weeks on average (Braddick and Atkinson 1983; Braddick et al. 1986).

The P100 component is the most frequently studied component of the VEP. It is of macular origin (Halliday et al. 1979; Zhang et al. 1993; Crognale et al. 1997) and its amplitude and latency are frequently measured parameters in clinical studies at various spatial frequencies (check sizes) (Bodis-Wollner et al. 1981; Sokol 1983; Fishman and Sokol 1990). The latency improves while the amplitude decreases with increasing check size (Roy et al. 1995). Thus, the P100 component can be best elicited by small size checks (Bodis-Wollner et al. 1986) and seems to be the best indicator of binocular interaction. Shawkat et al. (1998) showed that the P100 component especially of the reversal VEP is also the most useful tool to differentiate normals from amblyopes. Differences between amplitude rates of amblyopes and normals decrease with increasing check size and a 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 (Arden et al. 1974; Sokol 1980, 1983; Fishman and Sokol 1990). The VEP amplitude of the first major positive wave (P1) in the amblyopic eye is reduced compared to the normal eye (Arden et al. 1974; Bodis-Wollner et al. 1986; Henc-Petrinovic et al. 1993), but the latency values are normal or only slightly increased (Sokol and Dobson 1976; Arden et al. 1979; Sokol 1980, 1983; Fishman and Sokol 1990). Accordingly, latency is not as sensitive a marker of amblyopia as that of amplitude (Fishman and Sokol 1990).

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 (Taylor and McCulloch 1992; Henc-Petrinovic et al. 1993).

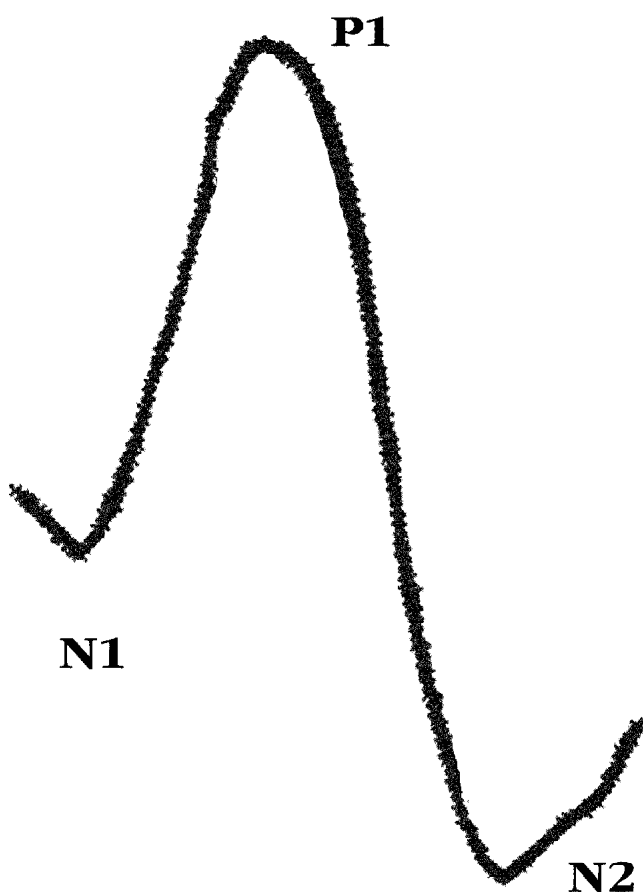


Figure 1. A VEP response. N1= negative peak 1; P1= positive peak 1 (P 100); N2= negative peak 2

Materials and Methods

Maturation of visual spatial integration in children

Three different experiments were conducted within this study. 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 in the “spatial range study”.

Stimuli

Two different sets of cards were used: orientation- and color-defined (Fig. 2). The cards were generated on a Silicon Graphics Indy R4000 computer. Both the orientation-defined cards and the color-defined cards were printed on an Epson Stylus Color 800 printer. Gabor patches were used as 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) (Fig. 2a, b).

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 spacing. 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 were 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 ($7l$, where l = wavelength of Gabor patches) with increasing background density across the cards. The value of D (relative noise density), where D = noise spacing/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 because the contour elements were closer to each other than the noise elements (Fig. 2a). However, when $D \leq 1$, this cue was not available and it was impossible to detect the contour without orientation specific long-range interactions (Fig. 2b). 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 the 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 lumi-

nance contrast. Thirteen percent of all dots were red and 87% were green across the cards. The contour locations were equivalent to those 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. 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 (1996a), 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. The value of D also ranged between 1.2-0.5 in the color-defined set.

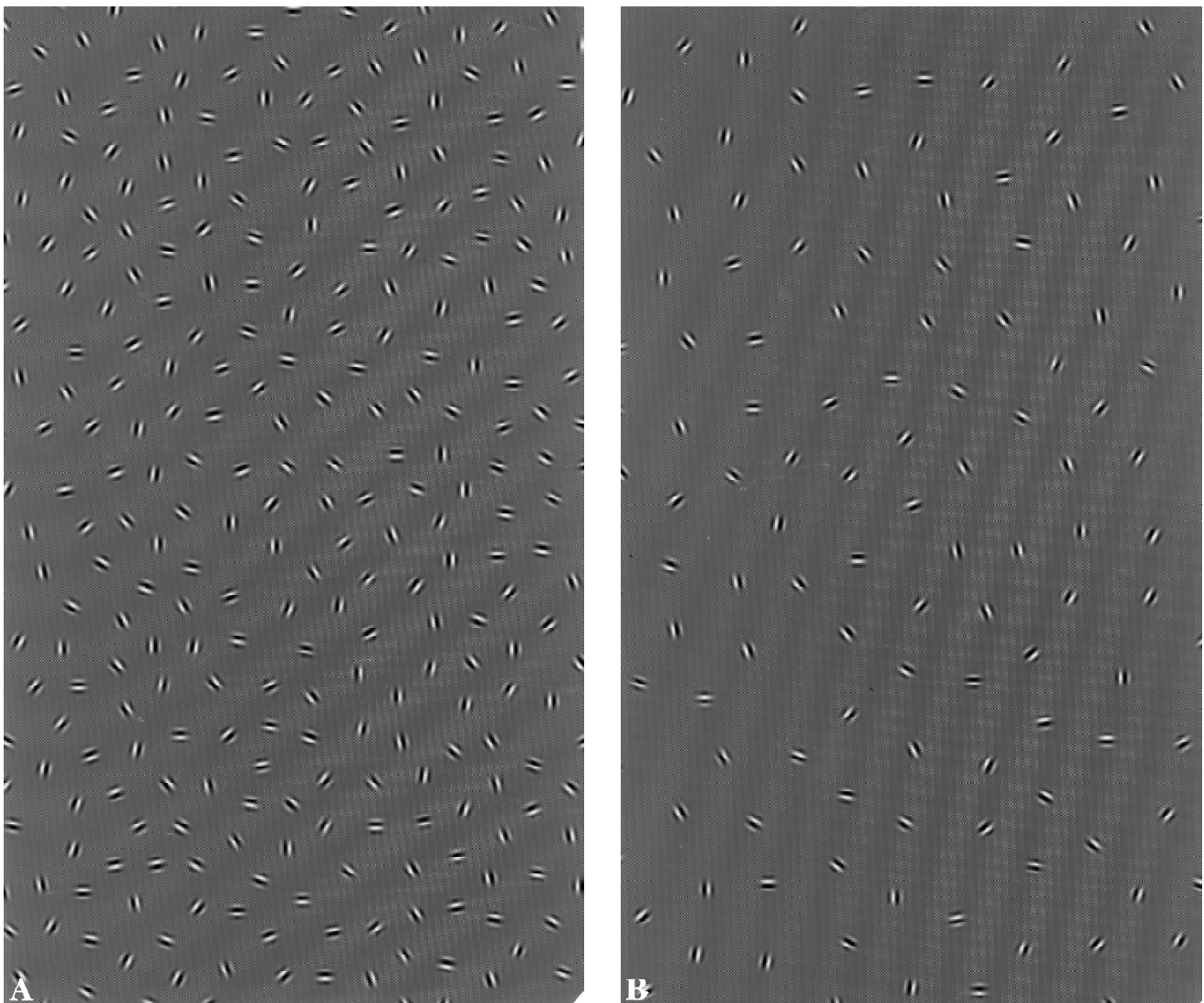


Figure 2. Two samples of the orientation-defined cards with **A.** a small ($D = 0.65$) and **B.** a high ($D = 1.1$) D value.

Procedure

The subjects were tested by using contour detection paradigm (Field et al. 1993; Kovács and Julesz 1993). 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; approximately 18 subjects in the entire sample) and those with lack of compliance (5 in the entire sample) had been 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 (Kovács et al. 1996a; Hess et al. 1997; Pennefather et al. 1999). 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 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 used 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 had been recruited by advertisement, and the experiments were carried out at daycare centers, schools, and colleges of Szeged, Hungary.

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 numbers of subjects were divided randomly into four groups (“orientation”, “color”, “color-to-orientation”, “orientation-to-color”). Both orientation- and color-defined cards were used 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. We tested whether the improvement transferred from color to orientation on 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 presented. One set with increased ($l = 9$; l is the wavelength of the Gabor patch), one with decreased ($l = 4.5$) and another with the original ($l = 7$) spacing of contour elements was used, while keeping the relative noise level constant. We tested 54 naive adults (19-30 years) and 30 naive children (5-6 years) 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 a two-tailed t-test. The performance of the different groups was compared to one another in each study.

Effect of late strabismus surgery in children with acquired esotropia

Subjects

We examined 10 (6 female and 4 male) 5-6 year old preschool children with acquired esotropia. Children were admitted to the Department of Ophthalmology, University of Szeged, Szeged, Hungary, for late strabismic surgery (strabismic group). The late surgery of the children was due to late referrals or ongoing treatment of amblyopia. The children received conservative therapy until there was no further improvement in their visual acuity. Therefore most of them had a visual acuity better than 20/40 (mild amblyopia; Kushner 1988) at the time of surgery (we will refer to the former amblyopic eye also as amblyopic). Three children were excluded from this study due to a history of prematurity, strabismus surgery and other ophthalmological diseases. Seven healthy, age-matched children with visual acuity of 1.0 (20/20) or better and normal binocular vision served as controls (control group).

Methods

During orthoptic examination the visual acuity of children was assessed using E cards. Their stereoacuity was obtained by Randot test and 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 (0.33 m). Subsequently, visual evoked potentials to pattern reversal stimulation were recorded. Orthoptic examination and recordings were performed one day before and at least 3 months after surgery. Following surgery the degree of

binocularity was also assessed by synoptophore. Clinical data obtained by synoptophore were correlated with VEP amplitude values following surgery.

VEPs were recorded from an active scalp electrode placed midoccipitally (O_z in the 10-20 system). The system reference electrode was located on the left earlobe. The impedance was kept under 5 kW. Single channel recording was used. Subjects were seated on a height-adjustable revolving chair with arm- and headrest one meter from the monitor in a well-insulated darkened room with no windows. A fixation point was used and the attention of the children was drawn and kept by tales during the one hour session. Pattern reversal checkerboards with 80', 40', 20' check-sizes were used as stimulus for testing. The entire stimulus field subtended 15.64 degrees by 11.31 degrees of visual angle. The frequency of the stimulation was 1.8 Hz. The subjects wore appropriate correction for refractive errors. Monocular and binocular stimulation was performed. The amplitude and latency values of the P100 component were measured and one hundred responses were averaged. Further data of the strabismic group is indicated in Table 1. Statistical analysis was performed using three-way ANOVA and Student's t-test. We compared eyes, check-sizes, and timing within and between the strabismic and control groups.

Results

Maturation of visual spatial integration in children

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 (Fig. 3; Kozma et al. 1997). Five-six year old children could recognize the contour when the D value of the card equaled to or was less than 0.9 ($D_{min} < 0.9$; $D_{min} = 0.84$). As the value of D decreased, the performance of the children also decreased. Children missed the contours on about half of the cards. 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. There was no significant effect of eye and gender with respect to contour-detection performance ($p > 0.05$).

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. The improvement was more obvious 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 orien-

Table 1. Summary data of children

onset of strabismus		1.5 months-4 years
type of operation	recession	9 cases
	resection	0 "
	both	1 "
number of eyes operated on	one eye	3 cases
	both eyes	7 "

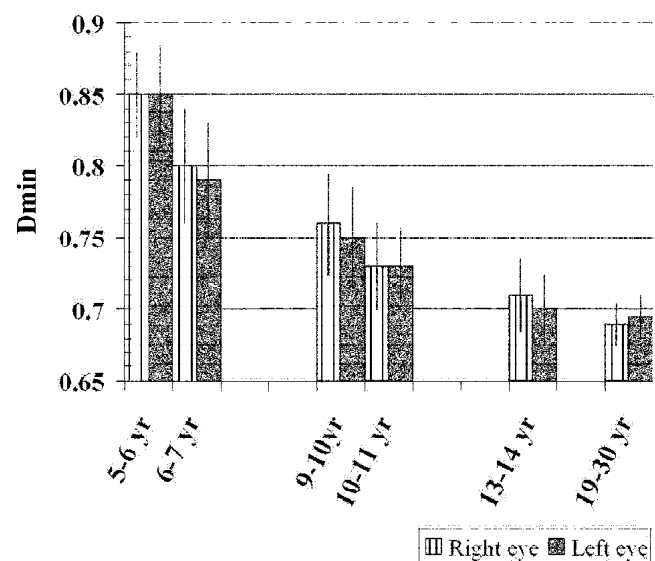


Figure 3. Contour-integration performance of 5-14 year old children and adults

tation” and the “orientation to color” groups. 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 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.

Spatial range of interactions in children and adults

When testing with smaller contour spacing the performance of the children was better. At 9 contour spacing, performance was poorer than at 4.5 ($p < 0.01$, two-tailed t-test), or at 7 ($p < 0.01$). 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 spacing.

Effect of late strabismus surgery in children with acquired esotropia

The data of 10 children with treated strabismic amblyopia were analyzed. The mean corrected monocular visual acuity was 0.935. Six children had a monocular visual acuity of 1.0 for both eyes preoperatively. In one child 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. Occlusion had to be reinstated in one child because of an impairment in visual acuity in all other cases no changes were detected. The orthoptic findings of the children are indicated in detail in Table 2.

Prior to the operation, the mean angle of strabismus was 14.25 degrees at distance and 21.45 degrees at near. Preoperatively, the pattern evoked potential amplitude of the fellow eye was consistently higher than that of the amblyopic eye, but the binocular response was generally similar to that observed when stimulating the non amblyopic fellow eye.

The largest response was found on binocular stimulation (Kozma et al. 2001). Significant interocular differences were

not detected in the control group (t-test: 80’: $p = 0.994$; 40’: $p = 0.698$; 20’: $p = 0.734$). Differences for the P100 amplitude between the amblyopic and the fellow eye were significant by ANOVA analysis in the strabismic group ($F = 4.553$; $df = 2,14$; $p < 0.05$). The largest response was usually recorded on stimulation with the 80’ check-size. There was a tendency for slightly longer latency values in the amblyopic eyes compared to the fellow eyes, however, the difference was not statistically significant ($p > 0.05$).

Visual evoked potentials showed clear changes under the effect of the surgery (three-way ANOVA: $F = 4.903$; $df = 2,14$; $p < 0.05$). Postoperatively, the amplitude values of P100 component increased significantly ($p < 0.05$), while no significant changes were seen in the latencies ($p > 0.05$; Fig. 4).

The most prominent changes were observed upon binocular stimulation at 80’ and 40’ checksize. Binocular fusion measured by synoptophore improved similarly after surgery, however, no correlation was found when comparing postoperative electrophysiological data on binocular stimulation and the synoptophore findings (Table 3).

Statistical analysis also showed a significant increase in VEP amplitude at 80’ and 40’ check-size for both the amblyopic and the fellow eyes (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: $F = 2.986$; $df = 4,36$; $p < 0.01$).

There were significant differences between the P100 amplitudes of the strabismic and the control group in relationship to check-size and eye (eyes: $F = 153.029$; $df = 5,20$; $p < 0.001$; between eyes and check-size: $F = 2.595$; $df = 10,40$; $p < 0.05$). Although amplitude values of the strabismic group were larger following the intervention, the differences observed between strabismics 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

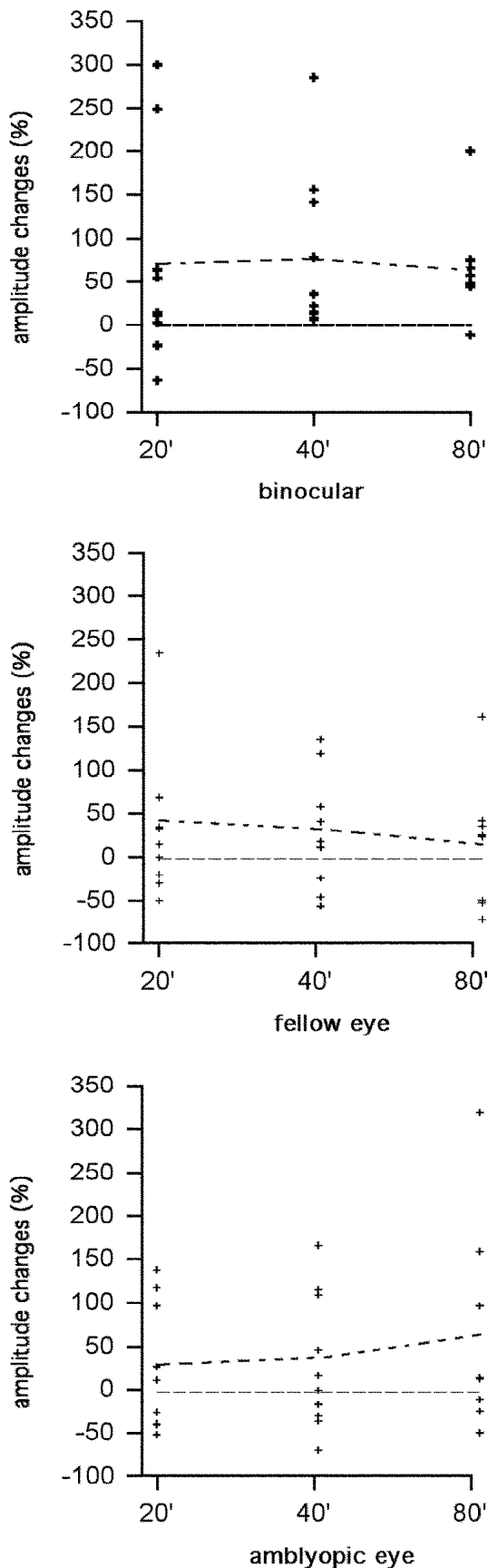
Maturation of visual spatial integration in children

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 have problems in tasks involving integration of information across the visual field (visual segmentation and form identification based on texture; Atkinson and Braddick 1992; Sireteanu and Rieth 1993), motion (Hollants-Gilhuijs 1998a) or color-contrast (Hollants-Gilhuijs 1998b); recognition of incomplete objects; Gollin 1960). Our result also confirms the late maturation of a visual function: contour detection performance shows significant development in

Table 2. Orthoptic findings of children before and after surgery

corrected monocular visual acuity	before surgery		0.6-1.0
	after surgery		0.25-1.0
angle of strabismus	before surgery	D	4-22°
		N	15-25°
	after surgery	D	0-7°
		N	3-6°
stereopsis	before surgery		-
	after surgery		-

D: at distance, N: at near



children between ages 5-14 years. The results indicate a significant age-effect, but there is no significant difference between eyes and gender.

It has been shown that low-level visual tasks significantly improve with practice (e.g. hyperacuity; Poggio et al. 1992), visual discrimination (Fiorentini and Berardi 1980), pop-out (Karni and Sagi 1993), and visual search tasks; Sireteanu and Rettenbach 1995) and seem to be specific for stimulus parameters and some of them even for retinal location. Therefore, we tested the contribution of low-level visual mechanisms to our developmental effect by employing a learning paradigm in children and in adults (“learning study”). We found significant improvement with practice and the improvement was specific for the visual cue defining the task in both age groups similar to other low-level visual tasks. Our findings demonstrate that the strength of interactions can be extended even with a short training in children with normal vision; however, a relatively long consolidation period might be necessary for such interactions to improve (Hollants-Gilhuijs 1998a).

The slight but not significant tendency for transfer in children in the “color to orientation” group might indicate that cognitive/motivational factors cannot be excluded completely in children, but do not explain our data. The similar trends found in adults and children imply 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. 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. Consequently, our result implies that the reduced contour integration performance of 5-14 year old children is a low-level perceptual effect and cannot be explained by high-level cognitive developmental factors or by non-visual factors.

As mentioned before, long-range interactions might subserve the integration process (Mitchinson and Crick 1982; Nelson and Frost 1985; Ts’o and Gilbert 1988; Gilbert 1998). The possible anatomical substrate of the long-range interactions is the intrinsic horizontal connections of the primary visual cortex (Rockland and Lund 1982; Gilbert and Wiesel 1983). The plasticity of these interactions was demonstrated in psychophysical studies where the spatial range of the interactions was extended in adult human subjects (Polat and Sagi 1994). Therefore, 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. In the “spatial range study” we found that contour integration

Figure 4. Amplitude values under the effect of surgery

performance depends on absolute contour spacing in children and not on the level of noise or signal-to-noise ratio per se. On the contrary, 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 spacing that can be tested at all is limited: above 9° spacing the number of contour elements would be too small to provide comparable conditions). The results suggest 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.

Let us mention that, in addition to these lateral connections, higher level processing such as modulatory feedback connections of extrastriate origin and/or participation of “intermediate” level cortical areas (V4) might also play some role (Kovacs and Julesz 1993; Wilson and Wilkinson 1998). 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, Callaway and Katz (1990) indicated a delayed postnatal development of feedback connections between V2 and V1 in humans. More recent studies raise the possibility of a significant increase in the number of cortical cells between birth and six years of age (Shankle et al. 1998a), showing an extended structural maturation of the human cortex, including the early visual areas (Shankle et al. 1998b).

In summary, we found significant improvement in children between ages 5 to 14 years in visual spatial integration using a contour-detection task. We hypothesize that long-range spatial interactions might have a shorter spatial range in children than in adults since search deficiency (Sireteanu and Rettenbach 1996b) should result in an opposite tendency (improving performance with decreasing number of distractors). Learning can enhance the span of these interactions. Cue-specific learning indicates the involvement of fairly low-level perceptual mechanisms. Therefore, the observed lag in children is probably truly perceptual because motivational factors or cognitive mechanisms would not be expected to generate different tendencies among children and adults in terms of contour spacing. Our results are in accordance with

recent anatomical (Burkhalter et al. 1993a) and psychophysical (Atkinson and Braddick 1992; Sireteanu and Rieth 1993) findings and indicate that the orientation-based segmentation carried out by long-range spatial interactions may have an extended maturational period (Kovacs et al. 1999).

The long-range connections of the visual cortex are also assumed to take part in contextual effects in perception (Gilbert and Wiesel 1983; Ts'o and Gilbert 1988; Kovacs and Julesz 1993, 1994; Kovacs 1996b; Gilbert 1998). There is behavioral evidence that these contextual effects might be largely mediated by the occipitotemporal (or ventral) visual stream (Goodale and Haffenden 1998a; Goodale and Humphrey 1998b; Haffenden and Goodale 1998; Marotta et al. 1998). Thus, our result further suggests 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 Discussion section.

Effect of late strabismus surgery in children with acquired esotropia

The proper timing of surgery and its functional consequences in acquired esotropia, unlike infantile esotropia, have not been studied extensively because those suffering from it have a better chance for functional recovery (Birch et al. 1990).

Leguire et al. (1991) studied pre- and postoperative binocular summation of pattern visual evoked response in 9 early onset esotropic (1-58 months old) children. They found a significant difference between binocular and monocular amplitudes in accordance with 64% increase in the binocular and a 28% decrease in the monocular amplitude postoperatively. We studied 5-6 year old children with acquired esotropia several years beyond the end of the classical critical period. Our results also showed a significant improvement of the amplitude of pattern-visual evoked potentials after surgical intervention. 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'). In the view of the classical developmental theory this considerable increase of evoked potentials in children

Table 3. Comparison of electrophysiological and synoptophore data

binocular interaction on VEP	before surgery	binocular summation	6 cases
		binocular facilitation	1 "
		binocular inhibition	3 "
	after surgery	binocular summation	10 "
		binocular facilitation	0 "
		binocular inhibition	0 "
synoptophore	after surgery	HRC	3 cases
		NHRC	3 "
		CS	4 "

(Summation index introduced by Apkarian et al. (Apkarian et al. 1981b) and modified by Nuzzi and Franchi (1983): HRC: Harmonic Retinal Correspondence, NHRC: Non-harmonic Retinal Correspondence, CS: peripheral fusion with central suppression (von Noorden 1985)

following corrective surgery for acquired strabismus was an unexpected finding. Similarly good binocular fusion was observed in 6 cases (60%) and peripheral fusion in 4 cases (40%) by synoptophore following surgery.

Unlike Amigo et al. (1978) we observed no correlation between the strength of binocular summation (Apkarian et al. 1981b; Nuzzi and Franchi 1983) on the VEP and the degree of binocularity obtained by clinical evaluating method after surgery (Table 3). Besides, Amigo et al. (1978) noted that binocular VEP summation in stereodeficient adults is extremely variable. Postoperatively we noticed VEP summation in most cases and found no facilitation for reversal stimulation in amblyopes which is in agreement with the findings of Shawkat and Kriss (1997), but contrary to the findings of Apkarian et al. (1981a). Shawkat and Kriss (1997) had found that reversal P100 component showed the greatest difference between normals and amblyopes for small (12') and moderate sized checks (20', 50'). Similarly, we also observed the most pronounced binocular enhancement for the moderate check-size. Our finding supports earlier results (Nuzzi and Franchi 1983, Shea et al. 1987) despite of slight differences in the different studies.

Achievement of fusion (O'Keefe et al. 1996; Willshaw and Keenan 1991) is the main goal of strabismus surgery both in children and in adults (Hohmann and Creutzfeld 1975; Kraft 1998). Fusion is thought to be an acquired reflex (Aslin 1977; Starger and Birch 1986), hence can be regained when it is lost. Previous fusional ability present before the onset of strabismus can probably be reestablished by surgery involving at least some binocular neurons in the visual cortex (Hohmann and Creutzfeld 1975; Morris et al. 1993; Wright 1996). The marked postoperative changes in the visual evoked potential to binocular stimulation in the strabismic group therefore are probably due to the attainment of fusional mechanisms. Patients with acquired esotropia were shown to have a better chance for binocularity than patients with infantile esotropia (Kushner 1994). Even adults with no previous alignment have the potential for peripheral fusion after strabismus surgery (Morris et al. 1993). Alignment of the eyes and binocular fusion is the prerequisite of stereopsis, although it also largely depends on visual acuity (Daw 1995). Reduction in acuity can lead to degraded stereopsis even in normal people. Unfortunately there is no chance to regain it when it was impaired within the first 18 months (Sloper and Collins 1998). Our subjects had no detectable stereopsis neither before nor after operation, thus probably lost their stereopsis within its critical period and could not regain it.

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 (Roelfsema et al. 1994). The significantly reduced amplitude values of the fellow eyes even with good visual acuity in the amblyop group can

probably be explained by the presurgical occlusion therapy applied to all children (Arden and Barnard 1979; Barnard and Arden 1979; Wilcox and Sokol 1980; Leguire et al. 1995; Shawkat et al. 1998). It appears that the amblyopic eye influences the fellow eye through interocular interactions (Sclar et al. 1986; Wali et al. 1991) Our finding is in agreement with that of previous groups, and indicates that despite of good visual acuity (20/20) the fellow eyes of the amblyopes are not functionally normal (Kandel et al. 1976,1980; Rentschler and Hilz 1979; Leguire et al. 1990).

The postoperative improvement of amplitude values of both amblyopic and fellow eyes observed during the 3-month follow up cannot be attributed to physiological rate of cortical maturation in these children (see the introductory paragraphs). Although the role of discontinuation of occlusion therapy, increase of visual field (Bowering et al. 1997; Hohmann and Creutzfeld 1975; Wortham and Greenwald 1989; Kushner 1994), changes in the organization of afferent inputs as well as in the intracortical interactions (Konig et al. 1993) cannot be excluded entirely.

In conclusion, our results provide evidence about enhancement in binocular function after strabismus surgery, even if performed years beyond the end of the classical critical period. Since no correlation was determined between the amount of improvement in the VEP and in the synoptophore findings, the VEP results could also reflect the epiphenominal nature of our finding besides improved binocular function. However, good ocular alignment itself can also enhance the signals coming from the two eyes without any substantial changes in the brain.

Conclusions

Much of our knowledge of the external world is gained through the visual system. As we have seen in the previous sections the visual system is immature at birth and is relatively mutable and plastic as it develops in infancy (Fiorentini 1984; Daw 1994). Looking for timing is relevant since 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 (Banks and Aslin 1975; Marg et al. 1976; Huttenlocher et al. 1982) or continues through puberty (Vaegan and Taylor 1979; Daw 1994, 1995). Hormonal changes around puberty might determine the end of plasticity (Daw et al. 1991). 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 through adolescence in our spatial integration study. The improvement in spatial integration with practice and with age was considered to be due to plasticity and 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 our second study. This also provides evidence for the plasticity of visual functions years beyond infancy.

Based upon our results the question arises 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. Due to scientific and methodological development the interpretation of different definitions has also undergone some changes. Hence, what previously had been considered to be the critical period seems to be only the first part of it. The visual system, however, could retain plasticity for a longer time and this involves a prolonged 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. As also mentioned before, we suppose that our findings can be further related to the different maturational time frame of the two parallel visual pathways, namely, the dorsal and the ventral streams (Ungerleider and Mishkin 1982) 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 online control of goal directed actions (Ungerleider and Mishkin 1982; Goodale and Milner 1992; Milner and Goodale 1995). The color sensitive parvo- (P) and the motion and luminance sensitive magnocellular (M) retinocortical pathways (Livingstone and Hubel 1988) do not project separately to the ventral and the dorsal streams (Livingstone and Hubel 1988; Shapley 1990; Wright 1995). 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 (Milner and Goodale 1995). The ventral pathway gets at least as much input from the magno as it does from the parvo system (Stoner and Albright 1993; Milner and Goodale 1995; Sawatari and Callaway 1996; Neville and Bavelier 2000).

Concerning their developmental pattern, not many studies are available and the findings are controversial. Global models of visual development have occasionally been proposed in which the P pathway precedes the M pathway in development or vice versa (Teller 2000). 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 (Bachevalier et al. 1991, Distler et al. 1996). Neville and Bavelier (2000), on the other hand, suggest that the dorsal visual pathway has a more prolonged maturational time course.

Dobkins et al. (1999) and Teller (2000), in accordance with others (LeVay et al. 1980, Livingstone and Hubel 1988) propose a precocious development of the M pathway according to their human psychophysical findings. Tassinari et al. (1994) also provide evidence for a later development of the M fibers of the optic tract compared to the P-fibers. The larger cells in the M-layers of the corpus geniculatum laterale also have a longer period of susceptibility than the small cells in the P-layers (Hickey 1977; Wiesel 1982). The rapid growth ends at around 6 months for the small cell type and at around 12 months for the larger cell type (Hickey 1977).

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 (Wright 1995). Kiorpes et al. (1996b) found some deficit in the middle temporal area of the visual system of the amblyopic monkeys, that is part of the dorsal stream. Thus, the situation is not quite clear in amblyopia, either.

What can explain the extended time frame of plasticity concerning the amblyopic visual system? It was found that amblyopia only slows down the development and causes relative immaturity (Kiorpes 1992b; Kiorpes and Movshon 1996a). 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 (Ciuffreda et al. 1991). The findings of Kiorpes et al. (1996b) 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; von Noorden 1961) suggest that higher levels of the visual system are probably also involved in amblyopia. As we have seen earlier, higher levels keep plasticity for a longer span than lower levels (Daw 1995). It is probable that these factors might all contribute to the prolonged plasticity in amblyopes to some extent.

In conclusion, contrary to the theory that visual functions mature by 2 years of age, we have shown that the maturation of at least some visual functions and the plasticity of the visual cortex last 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.

Acknowledgments

We wish to thank Drs. Andrea De k and M rta Jan ky for their help and advice. We are further grateful to Dr. Krisztina Boda for her assistance in statistical analysis. This work was supported by Soros Grants: 222/3588, 222/3/3745, by the J.S. McDonnell Foundation Grant 9560 and by the Hungarian National Research Found (OTKA, Hungary) Grants 016959, 29817 as well as the ETT Grant (Hungary) 57404.

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