VISUAL DEVELOPMENT IN SCHOOL-AGE HEALTHY AND MIGRAINEOUS CHILDREN

Doctoral Thesis

Gábor Braunitzer, MA

Supervisors:
Prof. Dr. György Benedek
Prof. Dr. Márta Janáky

Department of Physiology

Faculty of Medicine, University of Szeged

Szeged, 2010

Table of contents

1. List of publications providing the basis and related to the topic of the thesis

I. Parallel development of contour integration and visual contrast sensitivity at low spatial frequencies
Benedek K, Janáky M, **Braunitzer G**, Rokszin A, Kéri Sz, Benedek Gy.
Neuroscience Letters 26: 175-178. (2010)
IF: 2.200

II. Is the development of visual contrast sensitivity impaired in children with migraine? An exploratory study
Braunitzer G, Rokszin A, Kóbor J, Benedek Gy.
Cephalalgia (under publication) doi:10.1177/0333102410363178 (2010)
IF: 3.686

III. Synchronized, oscillatory brain activity in visual perception
Braunitzer G
Ideggyogy Sz 61: 294-303. (2008)

FURTHER PUBLICATIONS RELATED TO DEVELOPMENTAL NEUROSCIENCE AND/OR VISION:

Spatio-temporal visual properties in the ascending tectofugal system.
Rokszin A, Márkus Z, **Braunitzer G**, Berényi A, Wypych M, Waleszczyk WJ, Benedek Gy, Nagy A.
Central European Journal of Biology, 5: 21-30. (2010)
IF: 0.662

Visual Pathways Serving Motion Detection in the Mammalian Brain.
Rokszin A, Márkus Z, **Braunitzer G**, Berényi A, Benedek Gy, Nagy A.
Sensors 10: 3218-3242. (2010)
IF: 1.800

A kognitív idegtudomány, idegélettan és a neveléstudomány kapcsolata – a társas viselkedés együttes vizsgálatának lehetőségei.
Braunitzer G, Kasik L, Benedek Gy. (2009)
Iskolakultúra 19: 58-75.

Életünk ritmusai.
Braunitzer G, Benedek Gy.
Orvostovábbképző Szemle 17: 1-7. (2010)

BOOK CHAPTER:

Benedek Gy, Braunitzer G (2010)**:** Az agressziótól a kooperációig: az együttműködési spektrum idegélettani alapjai. In: Zsolnai Anikó és Kasik László (eds.): *A szociális kompetencia fejlesztésének elméleti és gyakorlati alapjai.* Budapest: Nemzeti Tankönyvkiadó.

2. Introduction

2.1. General introductory remarks

Basic visual functions, such as flicker sensitivity, color and depth discrimination and visual acuity have traditionally been considered as reaching adult levels in the first few years of postnatal life, making the general impression that the postnatal development of human vision is finished early in life [1-4]. However, by today a vast body of evidence has emerged to suggest that certain aspects of human vision take definitely a long time to reach their functional maximum, as in, functioning as observed in healthy adults. Aspects developing beyond the second year of life include visual segmentation and form identification based on texture- [5;6], motion- [7;8], color- [9] and flicker contrast [10]. Visual spatial integration has been reported to show significant development until adolescence [11]. These tasks include processes that assemble local information across the visual field to a global representation of the spatially extended objects in the brain.

Such protracted development, of course, raises questions regarding the underlying anatomy. It seems logical to make the conjecture that the anatomical structures serving the above mentioned functions take longer to reach adult-like maturity, at least in the functional sense. An exact temporal assessment of the developmental course of these long-developing functions might allow one to draw conclusions regarding the developmental state of the underlying structures at different time points. First, however, one has to define which brain structures or functional systems are dealt with. Certainly, the local-to-global assembly requires the horizontal connections of the primary visual areas [12], possibly driven by both bottom-up and top-down signals [13]. To take a stand on this is one of the aims of this thesis.

More important, protracted development raises the possibility that chronic conditions might interfere with normal development, as it appears to be the case in schizophrenia [14], Williams syndrome [15] and autism [16]. However, if the observed alterations are caused by the actual condition or represent an endophenotype [17] is always difficult to tell- a factor always to be kept in mind when interpreting results of this nature.

Based on these premises we conducted three experiments providing the bulk of this thesis. Little was known about the developmental course of visual contrast sensitivity and contour integration between infancy and adulthood, so first of all, we sought to plot that course for both functions in healthy school- aged children through psychophysical tasks. Second, having thus obtained a representative control data base, we administered the same tasks to migraineurs of the same age cohort. Migraine was the disorder of choice because it is

chronic, comes in attacks with definite changes in cerebral blood flow and metabolism (thus having the potential to interfere with normal cerebral development), and alterations of visual perception in adult migraineurs have been described indeed [18-20]. Furthermore, to our knowledge, nobody before has examined visual development in relation to childhood migraine, and therefore such a project seemed to offer new insight into certain aspects of visual development both with and without migraine.

This thesis is a summary of our findings, and also an attempt to explain them in a way that anatomy and function fall into place.

2.2. On the functional anatomy of the visual brain

The mammalian higher visual system[1], as we know it today, consists of two major information processing streams, namely the dorsal and ventral streams. These streams are traditionally considered as systems responsible for the representation of ’where’ and ’what’ in the visual world, respectively [21]. Goodale and Milner [22] offer a somewhat different nomenclature, talking about the dimensions of ’action’ and ’perception’, thus emphasizing that the dorsal stream is not merely a functional system for the representation of location per se, but its most important role is to transfer and process visual information so as to foster visually guided actions.

As a rule of thumb, it might be said that the dorsal stream is principally concerned with location in space, while the ventral stream is responsible for the exact identification of what is seen. Such an assumption comes from the functional parameters of the two streams, as determined by physiological methods [23] . According to the classical view, the dorsal stream originates in the ’parasol’ ganglion cells of the retina, synaptizes in the magnocellular (M) layers of the lateral geniculate nucleus (LGN), to arrive at lamina 4Cα of the primary visual cortex (V1;Br. 17). From there on it runs on to laminae 4B and 6, and continues its way through the visual areas V2 and V3, to reach its destination in V5 and SMT in the parietal cortex.[2] The starting point of the system, ’parasol’ cells, possess large receptive fields, they are highly contrast sensitive, characterized by fast axonal conduction, and preference for low spatial and high temporal frequencies. The cortical center associated with the system, MT, is specialized for the analysis of motion and depth [24].

[1] That is, from the primary visual cortex (Brodmann 17) on, towards the associative areas.
[2] It was proposed by Rizzolatti and Matelli that this stream consists actually of two subcircuits which are relatively segregated. See: G. Rizzolatti, M. Matelli, Two different streams form the dorsal visual system: anatomy and functions, Exp Brain Res. 153 (2003) 146-157.

In contrast, the ventral stream has its origins in the ’midget’ cells of the retina, its fibers synaptize in the parvocellular (P) layers of LGN, to arrive at lamina 4Cβ of V1. From there it projects to the interblob regions of laminae 2 and 3 of V1, and passes through the visual areas V2 and V4 to arrive at the inferotemporal cortex (IT) [25]. Functionally, the ’midget’ cells are the opposites of the ’parasols’, as in, their receptive fields are small, their contrast sensitivity is low, they are characterized by slow axonal conduction, and they prefer high spatial and low temporal frequencies. Furthermore, the pathway arising from them carries color information, which is not characteristic of the pathway arising from the ’parasol’ cells [24]. Therefore, the dorsal and ventral (or magnocellular and parvocellular) streams are indeed well-suited for the representation of the features assigned to them –as described above. Furthermore, it is to be seen that the two streams are in a complementary relation, and therefore it is logical to assume that they co-operate in the process of building up a faithful visual representation of the perceived world. A third pathway deserving mention here is the koniocellular pathway. Starting out from the bistratified ganglion cells of the retina, the pathway synaptizes in the interlaminar layers of the LGN, and from V1 on it follows almost the same path as the parvocellular pathway, with the exception that this pathway projects into the blob regions in V1 laminae 2 and 3 before taking its way towards IT. However, the exact functions of this pathway remain unclear, while its anatomy suggests that it serves similar ends to those of the ventral stream [25]. For a schematic summary of these anatomical relations see Fig. 1.

It is important to emphasize that these pathways are not strictly segregated [26]. For instance, it was shown in studies conducted with macaque monkeys that inputs from the three pathways are definitely intermixed [27;28]. Other studies raise our attention to feedback (or top-down) connections within the individual pathways [29], while still other ones provide evidence for direct inter-pathway connections, as is the case with the parvocellular LGN input to MT [30;31]. Finally, Dacey [32] points out that in the primate at least seventeen anatomically distinct retinal ganglion cell types exist, thirteen of which project in parallel to the LGN. These data suggest that the student of vision faces considerable structural complexity- with relatively little knowledge of function. In the present work we make an attempt to explain our findings based on what is already established: the known functional characteristics of the dorsal and ventral streams.

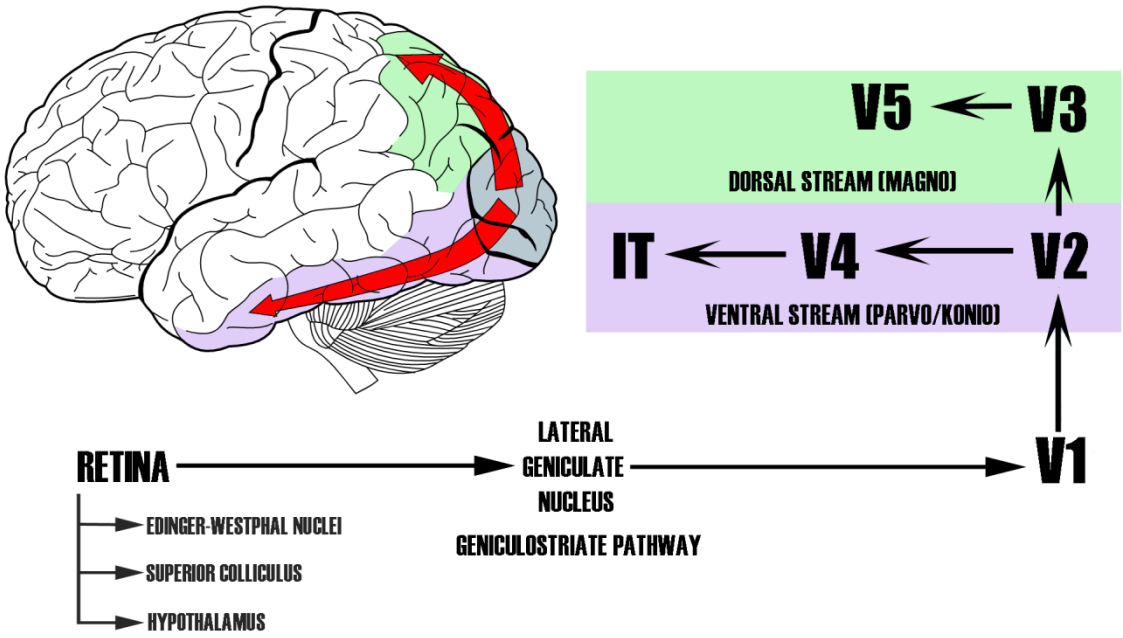

Figure 1. Schematic representation of the anatomy of the human visual brain as generally considered. Beyond the geniculostriate projection and the main cortical streams, the major extrageniculate projections are also indicated (without their extraretinal connections).

2.3. Developmental aspects

In fact, the question of which of the two main visual streams develops more quickly in postnatal life has generated some debate, especially that in the majority of cases observations were made with psychophysical methods, often complicated by the uncertainty about what brain areas are required by a particular task. We ourselves find it more proper to talk about the development of magnocellular and parvocellular visual functions, as defined by the functional characteristics traditionally associated with the related dorsal and ventral streams (see above). The exact developmental pattern of these functions is far from being clear. In this section we offer a brief summary of the available data on/attributed to the development of the two streams, without proposing our own theory at this point.

Proponents of the more protracted development of the parvocellular stream emphasize that preference for moving stimuli appears earlier in postnatal life than preference for visual details [33], that flicker sensitivity is near adult-like at the age of two months [34], that infants of four months of age are capable of processing complex motion information [2], while

grating acuity reaches an adult-like state only about two years of age [35], and Vernier acuity takes five years postnatally to reach full development. Visual evoked potential (VEP) studies are also available to support the slower maturation of the ventral stream [36;37]. Kovács [38] points out that studies performed on macaque monkeys corroborate the hypothesis by showing that in these primates the occipitotemporal (ventral) visual pathways exhibit slower development [39]. The thorough post mortem study of Burkhalter and colleagues [40] showed that the magnocellular - related local circuits of the primary visual cortex were mature 7 weeks postnatal, while the parvocellular - related ones emerged but 16 weeks postnatal and did not reach their mature form before 15 months of age. Based on the work of Pandya and colleagues [41] Kovács adds that the dorsal stream is phylogenetically older, and the information it carries (including movement information) may be enough for survival, while the same cannot be said about the ventral stream. Therefore she elegantly proposes that it is logical in an evolutionary sense that magnocellular functions should appear very early during the ontogenesis, while parvocellular ones take much longer to develop, especially that a sustained neural plasticity is necessary for the fine representations the latter is responsible for.

At the same time, some VEP studies seem to indicate that it is actually the dorsal stream that takes longer do reach maturity [42], and the up-to-adolescence maturation course of scotopic dynamic visual contrast sensitivity at low spatial frequencies [43] undoubtedly indicates the same. There seems to be slightly more direct (anatomical/imaging) evidence for this theory- a thorough study of the human lateral geniculate nucleus examining 31800 cells [44] showed that cells in the parvocellular layers reached their adult size quite rapidly, while for those in parvocellular layers it took two years. Furthermore, magnocellular-related parietal lobe gray matter seems to develop until about 6 years of age [45;46].

It is to be seen that data regarding the development of the two visual streams are quite contradictory, which is possibly a result of methodological differences, but it also raises the possibility that there might be other, unconsidered factors at play, as it will be put forward in this thesis.

For the purposes of this thesis we chose an intriguing observation of ours as a starting point: in two independent studies [11;43] our group found that visual contour integration (requiring integration of local details into a global shape - a task seemingly heavily dependent on parvocellular input) and contrast sensitivity at low spatial frequencies, and especially in scotopic and dynamic conditions (indicating predominantly magnocellular input) exhibited parallel development in healthy children between 5 and 14 years of age. Therefore, the first study we conducted was aimed at a direct comparison of performance on these two tasks in

the same population of healthy school-age children to enable us to apply the findings and conclusions to the other two studies with a migrainous population of the same age cohort. McKendrick and Sampson [47] have recently criticized traditional contrast sensitivity measurement methodology for not being able to properly dissociate the dorsal and ventral streams. That criticism we have taken into consideration when designing our experiments and explaining our findings.

2.4. Migraine: definition and brief pathophysiology

The International Headache Society classifies 19 altered health states as migraine (including complications and probable forms). Following the 2nd revised edition of the IHS International Headache Classification [48] and for the purposes of this thesis we define migraine as migraine without aura, that is, a primary headache coming in attacks of 1-72 hours in duration, characterized by at least two of the following: unilateral or bilateral location, pulsating quality, moderate or severe pain intensity and aggravation by or causing avoidance of routine physical activity, and during headache at least two of the following: nausea and/or vomiting, photophobia or phonophobia. It is important to point out that migraine without aura reaches a peak of incidence during the school years [49]. The other common form, migraine with aura (focal neurological symptoms preceding the headache) - being less prevalent, especially in the examined age cohort - is outside the scope of this thesis.

A universal trigger that leads to the actual migraine attack has not been identified so far [50], however, quite much is known about the pathophysiology of the aura and headache phases, and about the interictal period as well. The two main theories of migraine are the neuronal (concentrating on peripheral nerve sensitization) and the vascular (concentrating on the role of vessel tone) theories [51], most likely representing two sides of a single neurovascular theory.

Although it is often mentioned in connection with the aura phase, it is not unequivocally proven that the characteristic cortical spreading depression (CSD) [52] is a trait of migraine with aura only. This disturbance of cerebral cortical function is associated with considerable metabolic and haemodynamic changes. Electrophysiologically speaking, the process begins with depolarization associated with an increase in extracellular potassium, followed by a short-lasting depression of electrical activity. At the biochemical level, glutamate seems to play a key role through NMDA (*N*-methyl-D-aspartate) receptors [53]. Glutamate increase is caused by a K^+ -induced removal of the voltage-sensitive Mg^{2+}

blockade of NMDA receptors. This, in turn, induces a Ca^{2+} -influx, accompanied by increased nitric oxide synthesis. This also shows that glia is indeed a factor in migraine, as proposed by Bartley [54], given that glial cells are the major scavengers of extracellular potassium, and therefore their dysfunction might lead to an increased susceptibility to CSD. Associated haemodynamic changes include an early and short-lasting vasoconstriction with consequent reduction in regional cerebral blood flow, followed by a transient increased cortical flow lasting 1-2 min, and in the later stages a persistent flow reduction and hypoperfusion of variable duration [55].

The headache phase is related to the large cerebral vessels, pial vessels, large venous sinuses and dura mater as pain sensitive structures and the trigemino-cervical complex (TCC) innervating them in the form of a plexus of largely unmyelinated fibers. This plexus originates in the ophthalmic division of the trigeminal ganglion and in the upper dorsal cervical roots of the spinal cord [50]. A central event in the headache phase is a neurogenic vasodilation of the intracranial vessels, initiated by Calcitonin Gene Related Peptide (CGRP) from the trigeminal ganglion. This brings about a kind of ‘sterile inflammation’, coming with plasma protein extravasation and sensitization of the sensory nerve endings. Simultaneously, mast cell degranulation (serotonine release) [56] and platelet aggregation [57] also occur. Serotonine release is a direct link between the neurogenic and vascular theories, the latter postulating that the starting point of migraine is in fact pathological serotonine release, followed by vasoconstriction and compensatory vasodilation causing the actual painful sensation. It has recently been pointed out that the neurotransmitter systems involved in this general process are largely modulated by sex hormones [58], giving rise to a sex-influenced trait model [59]. Migraine has also been proposed to be a channelopathy, most likely a disorder of the Ca^{2+} P/Q channel, however, this has been proven only in the case of the relatively rare Familial Hemiplegic Migraine [51]. An alternative ocular theory of migraine has been proposed by Gupta [60], but that theory possibly fails to account for the general picture.

Interictally the most obvious findings are lowered ionized magnesium levels in the serum [61] and lack of habituation at the cortical level [62], both pointing to a hyperexcitability of the cortex.

It is to be seen that a migraine attack is a considerably serious insult to the cerebral circulation and ion homeostasis, and we propose that repeated attacks might interfere with the development of the visual brain. However, this question is largely undecided, and we do not fail to mention that any functional alteration observed in migraineurs’ vision might as well be a genetic trait, part of an endophenotype, having nothing to do with the actual attacks.

3. Aims of the study

The aims of our study were:

- to describe the development of visual contrast sensitivity as compared to the development of visual contour integration in healthy school-age children to see if any correlation is present beyond the two functions apparently developing parallel;
- to describe the development of the above functions in migraineous children from the same age cohort;
- to compare the healthy and migraineous development courses to tell if any aspect of migraine might interfere with performance on the tested functions and if the interference - if it exists - causes significant developmental difference between the two tested groups;
- should such a difference exist, to describe it; and finally
- to give a reasonable explanation of our findings.

4. Materials and methods

4.1. Subjects

The 152 healthy volunteers, aged between 5 and 30 years, were divided into four groups: 5-8 years (n=50), 9-11 years (n=41), 12-14 years (n=43), 18-30 years (n=18). The physiological background of dividing the participants into these cohorts was that the maturation of the human visual system is not a fully linear process, as revealed by our previous studies [11;43]. The 48 migraineurs, aged between 6 and 18 years were all patients of our outpatient clinic, and their diagnosis was established on the basis of the latest edition of the International Headache Society (IHS) criteria [48]. Recruitment took place upon the first visit to the clinic, and measurements were carried out before the prescription of any anti-migraine medication. Only migraineurs with no other known neurological condition were eligible for the study. The migraine group was divided into corresponding age cohorts to those described above, except for 18-30 years. Migraineurs participated in two studies, one for contour integration and one for contrast sensitivity. For the general characteristics of the studied migraineurs see Table 1.[3] It is to be seen that in the migraine studies we had to rely on a small number of participants, which was partly due to a strict following of the inclusion criteria, but because of the limited availability of clinical cases as well. Furthermore, we usually could not include participants of the first study (contour integration) in the second study (contrast sensitivity), because their interval therapy started in the meantime in most of the cases. However, this relatively small number of cases was a strict safeguard of validity at the same time, as in, any effect is to be robust enough to prove significant in small samples.

All subjects, either healthy or migraineur had normal or corrected-to-normal (20/20) Snellen visual acuity, tested for both eyes separately. Extreme myopes, anisometropes or amblyopes were not included in the study. Our studies were approved of by the Ethics Committee of the University of Szeged, and conformed to the tenets of the Declaration of Helsinki in all respects. Before each testing session, children and their parents were provided with information on the course and aims of the procedure in both oral and written form. To testify that they gave their informed consent to the participation of their children, parents were asked to sign an informed consent sheet.

[3] Please note that because of the limitations of the clinical sample, the cohorts do not exactly match, but care was taken that the migraine cohorts represent the same developmental stages.

Cohort (age)	Number of participants	Disease history (years, average)	Days elapsed since last attack on the day of measurement (days, median)	Average duration of attacks (hours, mean)	Number of attacks/month (months,median)
~ 5-8 years	CS: 6 CI: 12	0.9	2.5	1.4	1.5
~ 9-11 years	CS: 6 CI: 11	1.8	4	1.8	2
~ 12-14 years	CS: 6 CI: 7	2.3	2	1.6	2.2

Table 1. General characteristics of the 48 studied migraineurs. Tilde indicates that in the actual studies there might be deviations from the exact limits given, however, within the same developmental stage. CS and CI refer to the contrast sensitivity and contour integration studies, respectively.

4.2. Methods I.: Contour Integration

Contour detection stimuli were presented on cards (size: 18 x 24.5 cm). On each card, a circular contour consisting of 12 Gabor patches was embedded in a background consisting of randomly placed patches (Fig. 2). The cards were presented at a 0.5 m distance. The task was to identify the location of the contour and its trace. The cards were presented in an increasing order of difficulty. Contour visibility (difficulty) was varied by the manipulation of relative noise density (*D*). The *D*-value was defined as the ratio of average noise spacing over contour spacing. We used a set of 10 cards in which *D* ranged between 1.1 and 0.65 and was varied with a step size of 0.05. When $D>1$, the contour elements are closer to each other than the noise elements. However, when $D<1$, this cue is not available, and it is impossible to detect the contour without orientation-specific long-range interactions. The dependent measure was the *D* min-value, which was the value of *D* in the last correctly identified card.

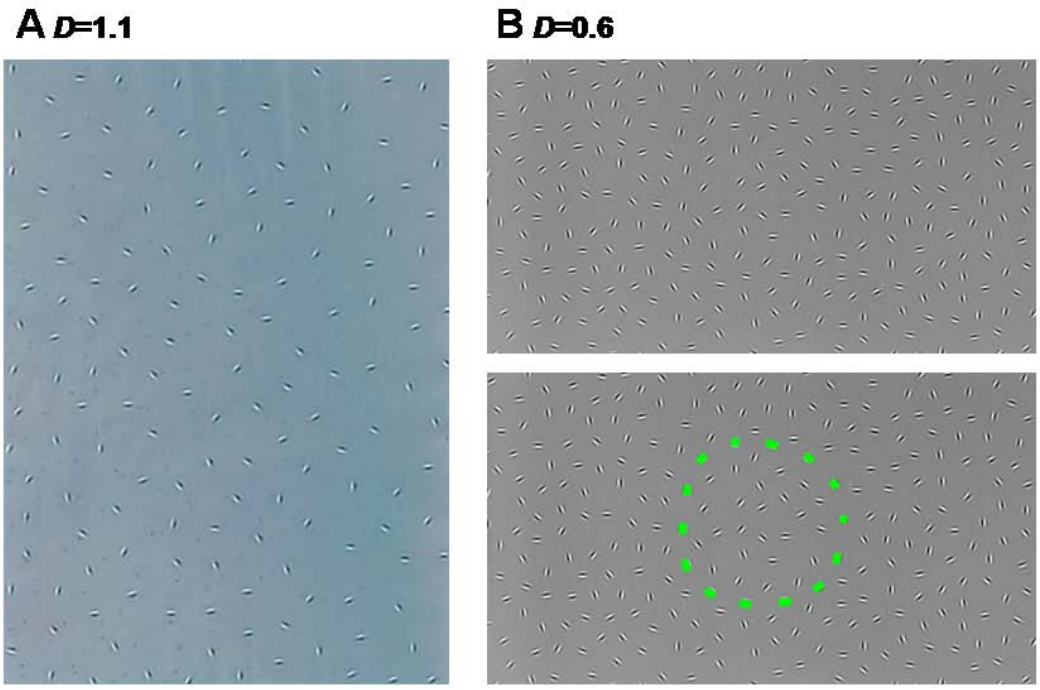

Fig. 2. Example of stimuli used in the contour integration test. (A) In the easy condition (*D*=1.1), the circle can be readily detected among noise patches. (B) In the difficult condition (near threshold in adults, *D*=0.6), the circle is difficult to detect. In the bottom part of figure B, green dots show the circle for illustrative purposes in order to ease its recognition in the upper part of the figure (during the experiment such cues were not presented).

4.3. Methods II.: Contrast Sensitivity

Dynamic CS was measured in photopic condition at nine spatial frequencies (0.5, 1.2, 1.9, 2.9, 3.6, 4.8, 5.7, 7.2 and 14.3 cycles/degree (c/d)) in migraineurs and at six spatial frequencies (0.5, 1.2, 1.9, 5.7, 7.2 and 14.3 c/d) in controls with a computerized test (Venus, NeuroScientific Corporation, USA). Stimuli were luminance-contrast gratings with a sinusoidal luminance profile (Fig. 3). Contrast was defined according to the Michelson formula (C= (L_{max}-L_{min})/(L_{max}+L_{min})). The pattern was reversed at an 8 Hz rate. The display subtended a visual angle of 13x13and was viewed from a distance of 1m. The maximum contrast was 70.7%. For the measurement of the contrast threshold at each spatial frequency, we used a method of adjustment. First, the contrast was set at 15 dB above the mean normal

value. If the participant was unable to detect the grating at this contrast level, the contrast was further increased until they were able to detect the stimulus. The contrast level was then decreased stepwise by 3 dB every 5 s until the subject reported that the stimulus disappeared (descending method). Next, contrast was set at 15 dB below the threshold, and the contrast was increased stepwise by 3 dB every 5 s until the subject was able to detect the stimulus (ascending method). Left and right eyes were tested separately. The whole procedure was repeated three times for both eyes to obtain a mean contrast threshold at a particular spatial frequency. CS was defined as the reciprocal of the contrast threshold.

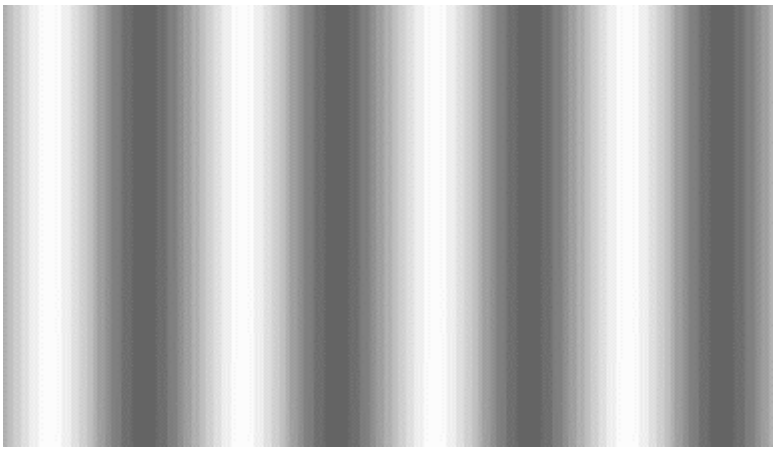

Fig. 3. Luminance contrast grating with a sinusoidal luminance profile

4.4. Statistical analysis

In the case of healthy volunteers visual contrast sensitivity and contour integration data were entered into analyses of variance (ANOVAs). Tukey HSD tests were used for post-hoc comparisons. Pearson's correlation coefficients were calculated between contrast sensitivity and contour integration data. The level of significance was set at alpha<0.05.

In the case of migraineurs, given the small number of cases, we applied the nonparametric Mann-Whitney U test for the pairwise comparison of the individual groups. The level of significance was set at alpha<0.05.

Data analysis was performed with Statistica for Windows (StatSoft, Tulsa, OK, USA). In the migraineur vs. healthy comparisons we always applied age- and sex-matched controls.

5. Results

5.1. Development of contour integration and contrast sensitivity in healthy children

The ANOVA conducted on the contrast sensitivity data revealed a significant main effect of age ($F(3,148)=19.16$, $p<0.001$) and spatial frequency ($F(5,740)=425.34$, $p<0.001$). Most importantly, there was significant interaction between age and spatial frequency ($F(15,740)=8.32$, $p<0.001$) indicating that development was not equal for the six spatial frequencies tested. As shown in Fig. 4, the development of contrast sensitivity was the most pronounced at the three lowest spatial frequencies (0.5, 1.2, and 1.9 c/d), whereas this effect was less marked at the three highest spatial frequencies (5.7, 7.2, and 14.4 c/d). The significant interaction between age and spatial frequency was due to this differential effect of age on lower vs. higher spatial frequencies. The largest developmental step was seen when the 5-8-year-old children were compared with the 9-11-year-old children (Tukey HSD, $p<0.01$).

The one-way ANOVA conducted on the contour integration data revealed a significant main effect of age ($F(3,148)=16.52$, $p<0.001$) (Fig. 5). Similarly to the contrast sensitivity data, the most pronounced developmental step was observed when the 5-8-year-olds were compared with the 9-11-year-olds (Tukey HSD, $p<0.01$). There was a spatial frequency-specific correlation between contrast sensitivity and contour integration: *D* threshold values correlated with contrast sensitivity at 0.5 c/d ($r=-0.56$), 1.2 c/d ($r=-0.51$), and 1.9 c/d ($r=-0.49$) when all age groups were combined. At higher spatial frequencies, we found no evidence for correlation between contrast sensitivity and contour integration ($r<0.1$). Similarly, there were significant correlations between age and contrast sensitivity at lower spatial frequencies (0.5 c/d: $r=0.68$, 1.2 c/d: $r=0.71$, 1.9 c/d: $r=0.67$, 5.7 c/d: $r=0.48$), but not at the two highest spatial frequencies ($r<0.2$).

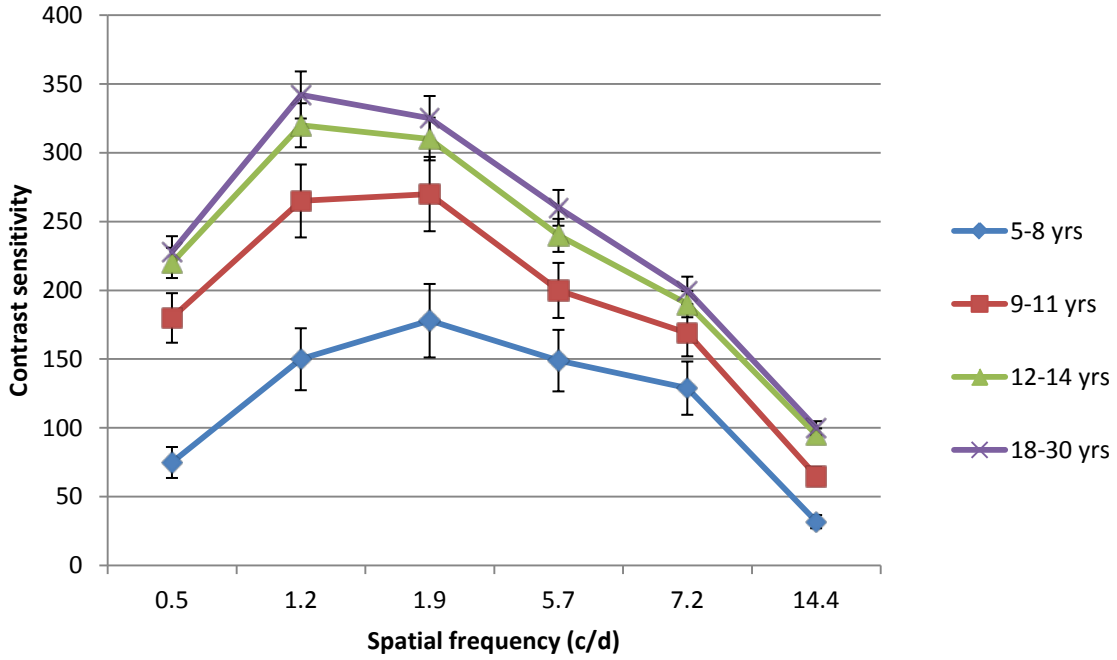

Fig.4. Visual contrast sensitivity results from the different age groups of healthy subjects. Note the difference between the junior (5-8 years) and the (pre)adolescent (12-14 years) cohorts, indicating considerable development during the elementary school years. CS results at the different spatial frequencies are represented as mean ± S.E.M.

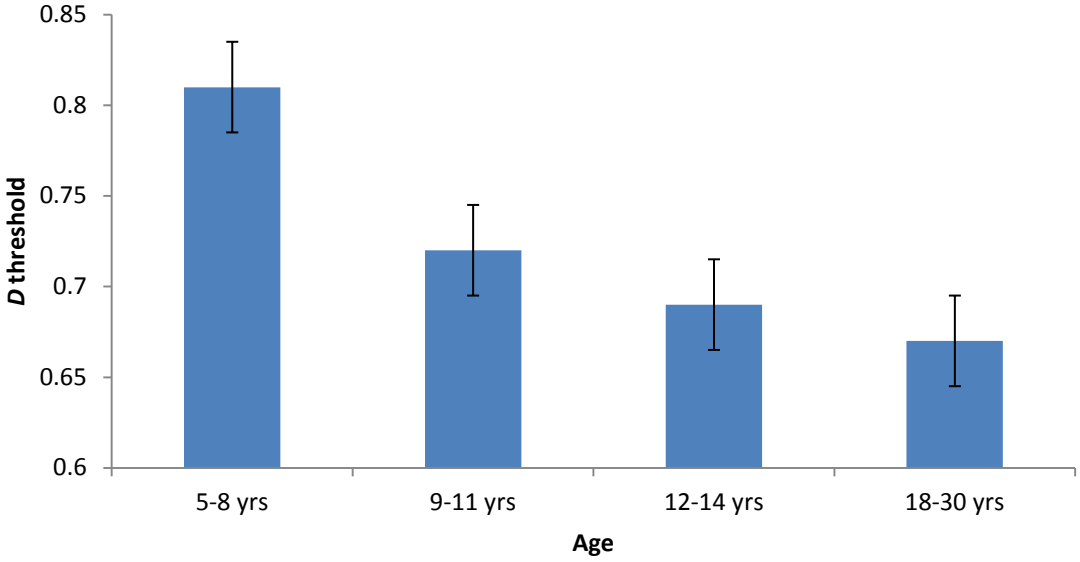

Fig. 5. Contour integration results from the different age groups of healthy subjects. Results are represented as mean *D* ± S.E.M. (Note: higher *D* values signify poorer performance.)

5.2. Development of contour integration in migraineous children and matched controls

The exact age grouping for this study was as follows: 7-9 years, 10-12 years, and 13-16 years. Within-group and between-group comparisons were performed.

Development-wise the largest step in the migraine group was observed when comparing the youngest and the eldest cohorts (MWU= 7, n_1=12, n_2=7, $p<0.001$, two-tailed). Somewhat less pronounced, but still significant development was seen when comparing 10-12-year-olds with the eldest cohort (MWU= 16, n_1=11, n_2=7, $p<0.05$, two-tailed). However, the remarkable development one would expect based on the study conducted with healthy subjects between ~5-7 and ~9-11 years did not appear (MWU= 55.5, n_1=12, n_2=11, $p=0.53$, two-tailed). Spearman's R for the total development between 7 and 16 years: 0.51 ($p<0.05$).

The same comparisons were performed for the cohorts of age- and sex-matched controls as well, yielding the following results: 7-9 years vs. 10-12 years (MWU= 8, n_1=12, n_2=11, $p<0.05$, two-tailed); 10-12 years vs. 13-16 years (MWU= 4.5, n_1=11, n_2=7, $p<0.001$, two-tailed); 7-9 years vs. 13-16 years (MWU= 6, n_1=12, n_2=7, $p<0.001$, two-tailed).

Between - group comparisons by cohort turned up the following results: 7-9 years (MWU= 56, n_1= n_2=12, $p=0.4$, two-tailed); 10-12 years (MWU= 38.5, n_1= n_2=11, $p=0.2$, two-tailed); 13-16 years (MWU= 9, n_1= n_2=7, $p<0.05$, two-tailed). Spearman's R for the total development between 7 and 16 years: 0.65 ($p<0.05$).

In summary, both groups exhibited significant age-related development, the migraineur group lagging somewhat behind both in general and in the cohort-wise comparison. It is also to be mentioned that the gap in the performance of the two groups is obviously widening with age. Results are summarized in Fig.6.

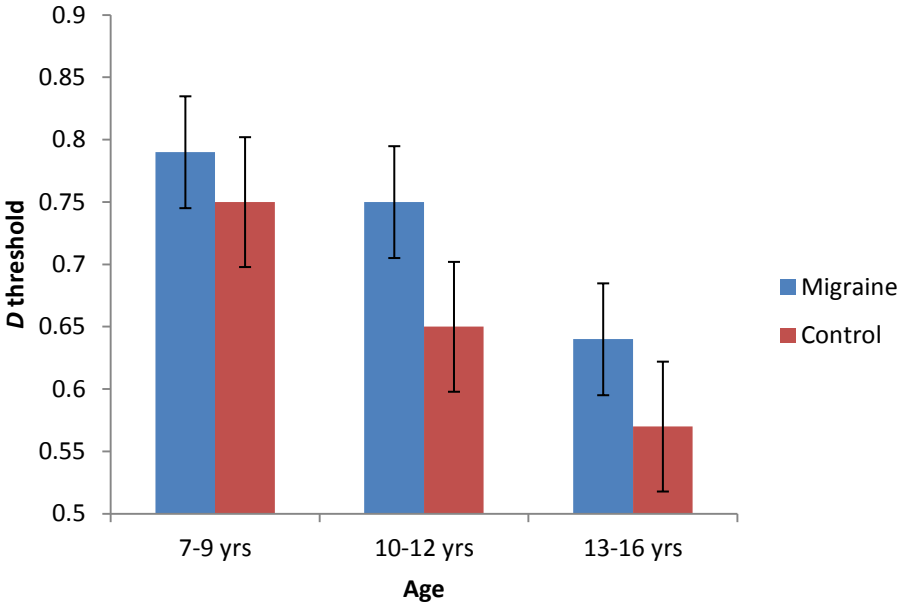

Fig.6. Contour integration performance of migraineurs and controls compared. Note the difference between the two groups in the two elder cohorts, indicating the poorer performance of migraineous subjects.

5.3. Development of contrast sensitivity in migraineous children and matched controls

The exact age grouping for this study was: 6-10 years, 10-12 years and 12-14 years. Within-group and between-group comparisons were performed.

Development-wise in the control group we found that between the 6-10 year cohort and the 10-12 year cohort significant development occurred at 0.5 c/d (MWU=4, n_1= n_2=6, $p<0.05$, two-tailed), while no such development was to be seen at any of the tested spatial frequencies when comparing the 10-12 year cohort with 12-14-year-olds. However, a comparison of the youngest cohort with the eldest one (overall development) revealed significant development at 0.5 c/d (MWU= 0, n_1= n_2=5, $p<0.05$, two-tailed), 1.2 c/d (MWU= 4, n_1= n_2=6, $p<0.05$, two-tailed), 2.9 c/d (MWU= 2, n_1= n_2=6, $p<0.05$, two-tailed) and 3.6 c/d (MWU= 2, n_1= n_2=6, $p<0.05$, two-tailed)(See Fig.7.).

Migraineurs exhibited no significant inter-cohort development at any of the tested spatial frequencies, but in an overall-comparison (the youngest vs. the eldest). However, even there only at 7.2 c/d (MWU= 5, n_1= n_2=6, p<0.05, two-tailed).

The results of between-groups comparisons are illustrated in Fig.8. As can be seen, we found no significant differences between migraineurs and controls for either of the tested spatial frequencies in the first age cohort (6-10 years). It was first in the second age group (10-12 years) that significant differences were found by diagnosis, for two frequencies: 1.2 c/d (MWU= 3.5, n_1=n_2=8, p< 0.05, two-tailed) and 1.9 c/d (MWU= 1.5, n_1=n_2=8, p< 0.01, two-tailed). Analysis of the third age group (12-14 years) yielded similar results. Statistically significant difference was found at: 1.2 c/d (MWU= 2.5, n_1=n_2=8, p< 0.05, two-tailed) and 1.9 c/d (MWU= 2.5, n_1=n_2=8, p< 0.05, two-tailed). Age of healthy participants proved to be significantly correlated with the above mentioned spatial frequencies of interest in controls (1.2 c/d R= 0.6; 1.9 c/d R=0.54), while this relationship did not reach statistical significance in migraineurs (1.2 c/d R= 0.46; 1.9 c/d R =0.4) (Spearman's R).

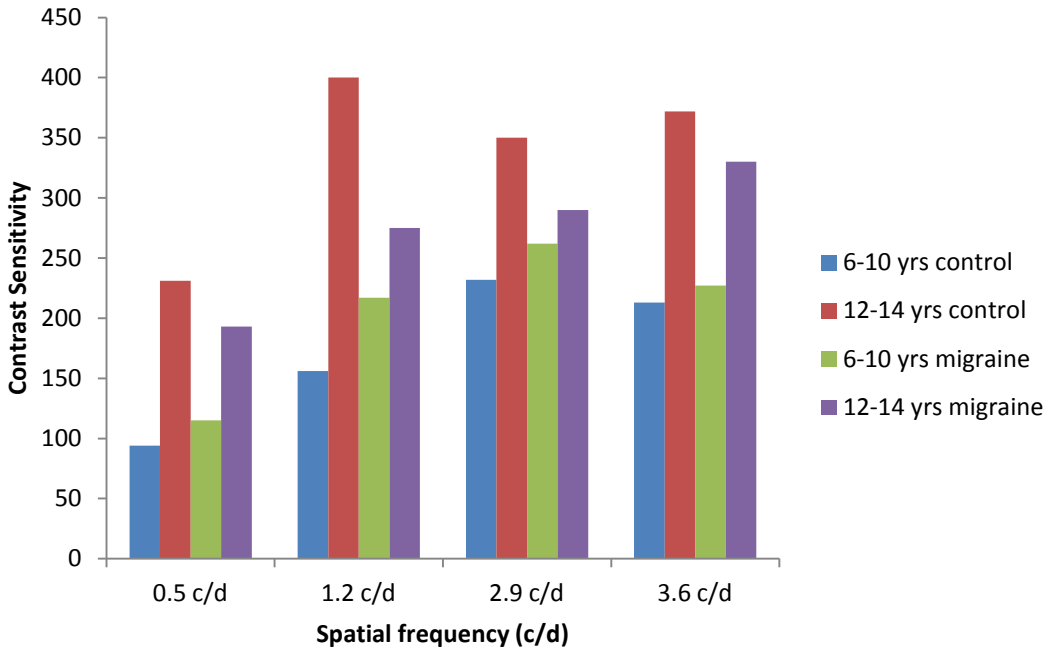

Fig.7. Overall development of contrast sensitivity. Comparison of controls and migraineurs at the spatial frequencies having exhibited significant overall development in controls. Note that no statistically significant development does not mean no development at all, and also that it is characteristically a low frequency (1.2 c/d) that shows the biggest differences.

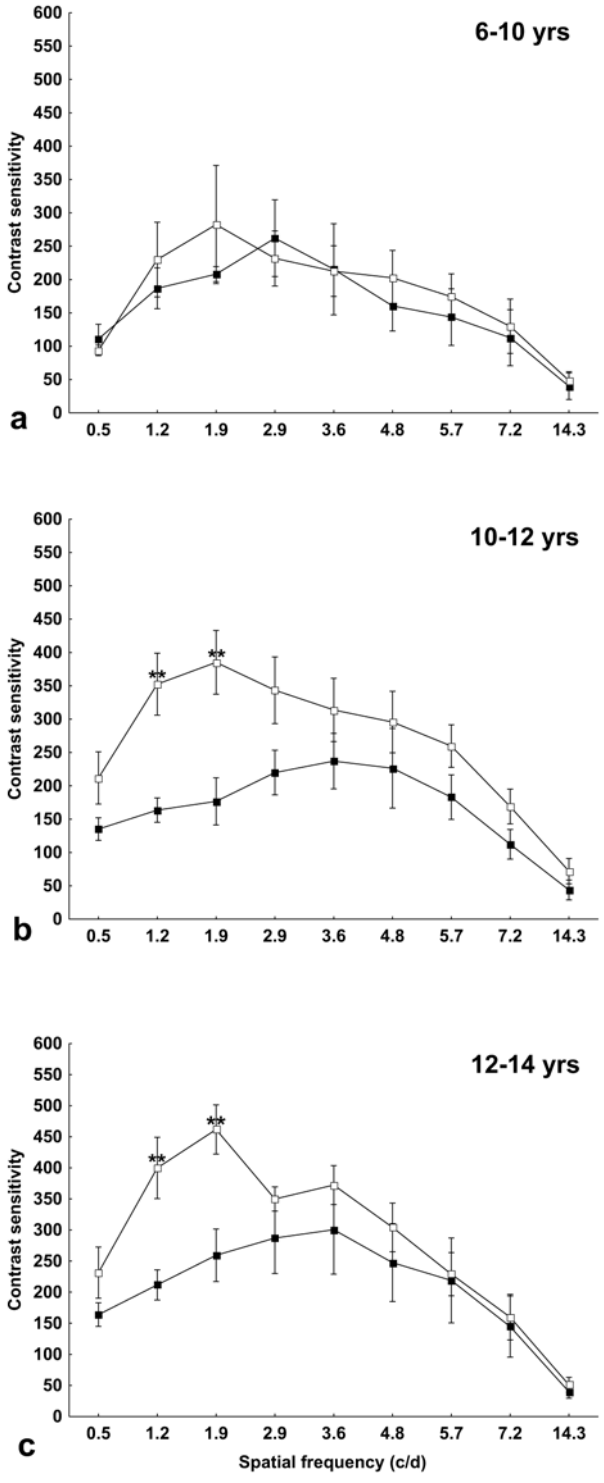

Fig. 8. Photopic-dynamic spatial contrast sensitivity functions of migraine patients and control subjects by age groups: (a) 6-10 years; (b) 10-12 years; (c) 12-14 years. Asterisks (*) mark significant differences at the probability level of 0.05. Temporal frequency of pattern reversal was 8Hz at all nine tested spatial frequencies. Values are shown as mean ± S.E.M.

5.4. A synopsis of results

In summary, the findings we were to provide a satisfactory explanation for are as follows:

- The development of performance on contour integration and contrast sensitivity tasks appear to be related in healthy subjects, especially when considering contrast sensitivity at lower spatial frequencies (0.5, 1.2 and 1.9 c/d).
- Healthy subjects also exhibit a period of massive development between 5 and 14 years of age in both contour integration and contrast sensitivity tasks.
- Such a period of remarkable development appears to be lacking in migraineurs of the same age range in both contour integration and contrast sensitivity tasks, and specifically:

- Migraineurs between 10 and 14 years of age perform significantly poorer than controls in the contrast sensitivity task, especially at lower spatial frequencies (1.2 and 1.9 c/d).
- In terms of contour integration, migraineurs of all cohorts are lagging behind controls, the difference being the most pronounced in the two elder cohorts (covering the range of 10 to 16 years of age).

6. Discussion

6.1. Structure and function

To see what our findings may tell us about how the visual brain develops in healthy children and in migraine, we have to link the studied functions to brain structures first. Of the two functions, contour integration is the more complex one, while contrast sensitivity is rather an elementary visual capability, characteristic of both of the major visual pathways (magnocellular and parvocellular, that is) in a spatial frequency and condition[4]-dependent manner. What follows is an attempt to show how the development of the related brain structures might shed light on the meaning of our findings. The analysis concentrates on contour integration as the basis of form perception, while contrast sensitivity results are used in a somewhat ancillary manner, to support our assumptions on the underlying functional systems.

6.1.1. Contour integration – a traditional view and questions left unanswered

Gestalt psychology, flourishing in the thirties of the twentieth century, suggested that contour perception is basically carried out via the integration of local contour elements [63]. Evidently, our task requiring the subject to identify a circular shape made up of Gabor patches placed at a distance from one another necessitates a shape perception system capable of just such an integration, with the extra requirements that it has to be able to solve the task of bridging the gaps between the individual elements and that it has to be able to overcome contextual noise.

The first reasonable physiological cues concerning the nature of contour/shape perception came in the 1960s, from the pioneering experiments of Hubel and Wiesel [64;65], supporting the gestaltist insight by the demonstration of cellular level orientation preference in the primary visual cortex of both cats and monkeys. For our explanation the group of cells later named ‘simple cells’ in the 4Cβ layer of the primary visual cortex[5] is of importance. These cells, acting as local filters, fire the most vigorously when their receptive field is matched by a line of their preferred orientation. It is easy to see that such simple cells are fit to process fine detail, and indeed, V1 4Cβ is the primary cortical receptive layer of parvocellular geniculostriatal input [24]. Linking local filters and bridging gaps (even in

[4] i.e. photopic or scotopic
[5] henceforth: V14Cβ

noise) is possibly carried out via an intrinsic plexus of horizontal connections in V1 4Cβ [12;40;66;67]. That is, perception of a shape, a contour might be interpreted as cells with receptive fields of the proper orientations responding simultaneously, linked by their horizontal connections. Indeed, a whole ‘ventral stream theory’ has been built up around this interpretation, implicitly defining shape perception as the product of a serial, bottom-up functional system starting at the retina and ending in the inferior temporal cortex, with the orientation-sensitive cells of the primary visual cortex and their lateral connections as its core. (The very method of testing contour integration with Gabors emerged as a result of looking for the most ideal stimuli for the simple cells of the primary visual cortex [68].) In short, the theory suggests that while structures and functions considered as linked to the dorsal stream develop rapidly during the ontogenesis, those related to the ventral stream take much longer to reach maturity [38]. This seems to be supported by anatomical studies on the monkey brain [39;69]. As far as human observations are concerned, Káldy and Kovács [70] compared children’s and adults’ performance on a size contrast illusion (the Ebbinghaus illusion, see Fig.9.), and found that the magnitude of the illusory effect was significantly smaller in preschool children, which the authors put down to immature ‘context integration’ as related to immature local cortical circuits. Kovács and colleagues [11] discuss their findings on the late (up to 14 years of age) maturation of human integration of Gabors in similar terms.

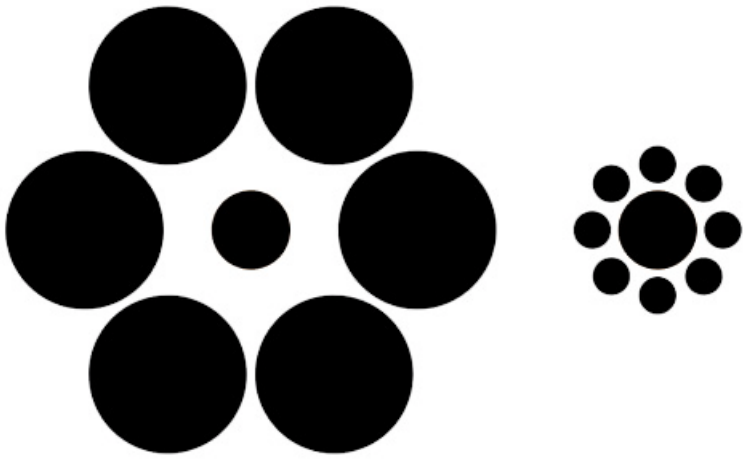

Fig.9. The Ebbinghaus illusion, demonstrating the effect of context on visual perception. The inner circles are of the same size, yet, because of their different context they seem to differ. This illusion is most likely to be the result of a simple local modulatory effect, restricted to the primary visual cortex.

Such a theory implies that our contours composed of Gabors and embedded in Gabor-noise is processed in a serial manner in the visual brain, along the retino-geniculo-striatal pathway. In the primary visual cortex the local elements are identified by simple cells, bound together by the lateral connections of these cells, and then they possibly serve as convergent input for higher processing areas until reaching the inferior temporal cortex, where shape identification can occur. Furthermore, it is also suggested that the protracted development of this integrative function reflects the protracted development of horizontal connections within V1 4Cβ / V1 2/3 [38]. Simple and elegant as it may sound, this interpretation fails to explain a number of observations, both task-specific and general.

First of all, Burkhalter and colleagues [40] established in their post mortem study that horizontal connections within V1 4Cβ / V1 2/3 are structurally adult-like by the age of 15 months. This early development makes complete sense, given the hierarchical nature of neocortical development [71], progressing from the primary sensory areas toward the association areas, which Flechsig was among the first to point out, as early as in 1920 [72]. Accordingly, functionality in terms of contour detection appears quite early: at three months of age it is not yet to be seen [73], but six-month-old babies perform well over chance level, even if their noise tolerance is quite limited [74]. Taken together, this rather makes the impression of mature primary cortical circuits without fully effective filtering mechanisms than primary cortical circuits at the beginning of a decade-long developmental path.

Second, such a serial, bottom-up model does not give a satisfactory explanation for noise suppression. The Ebbinghaus illusion, used by Kovács to support her argument on the immaturity of horizontal connections, shows that the primary visual cortex is indeed of key importance in terms of contour detection; however, it also shows how much noise can interfere with the process at this level, and, therefore, how much noise suppression is necessary for the system to work properly. Taken that example into consideration, it is to be seen that based purely on a V1-centered bottom-up interpretation it cannot be satisfactorily explained how the actual contour elements are segregated from noise, even at fairly high noise densities. Should that ability be served by the primary visual cortex alone, six-month-olds should not be limited by noise. Still, they are, which is another piece of evidence against the primacy of the primary visual cortex in terms of contour integration.

Third, there is a number of everyday phenomena that in themselves make up an argument against a serial model, as pointed out by Hochstein and Ahissar [75]. Maybe the

most remarkable of these is our ability to capture the conceptual gist of an image extremely rapidly without encoding its details. A serial model presupposes that the whole is built up of its parts, and without the parts the whole cannot be put together. Real world experience does not support this. Instead, argue the authors, explicit visual perception begins when processing reaches high cortical areas, and proceeds in top-down fashion to encompass detailed information from more peripherical cortical areas as needed. Electrophysiological studies support such a 'reverse hierarchy'- theory [76-78], implying pathways fast enough to convey information to those high cortical areas ahead of bottom-up processing, and possibly taking different routes as well.

Finally, in terms of the different streams, it must be seen that proponents of the 'dorsal theory' (that is, that the dorsal visual stream develops slower) have their pieces of evidence too, post mortem [44], electrophysiological [42;79], psychophysical [80] and imaging [45;46] as well.

Taken all this together, what is clear is that the exclusively serial and bottom-up interpretation of contour/shape perception cannot be defended for a few simple reasons. Furthermore, though both ventral and dorsal theorists have valid points to make, neither of these interpretations is able to give a satisfactory account of all observations in itself. We propose that an integrated model, observing the real complexity of anatomy and the possibilities that complexity provides is fit to give a satisfactory explanation for both the unanswered questions mentioned above and our findings regarding developmental issues.

6.1.2. Contour integration updated – bidirectional parallel processing

Perhaps the most trivial and – by until recently – most overlooked argument against an unidirectional processing of visual information in the brain is, as Kveraga et al. [13] put it, is that 'the human brain is not a passive organ simply waiting to be activated by external stimuli.' Indeed, we normally do not spend our lives in an everlasting re-sampling of the world around us, like patients suffering from anterograde amnesia do. Unless things go wrong, we are able to generate categories from a limited amount of samples, and then, having stored them in our memory, we use them to behave in an economical and highly efficient way. After an optimal amount of sampling, familiar objects, persons, or situations are processed almost unconsciously, in a way that all potentially significant connotations are at

our disposal in a fraction of a second, for any response we might intend to give. Such efficiency presupposes that

a) there is a way in which memory stores (higher cortical areas) may obtain quickly accessible clues regarding what is actually perceived, to be able to select the most relevant stored information, and
b) there is a way in which the higher areas can send this pre-selected information toward the primary areas to enhance recognition, either by excitation or inhibition.

Based on such premises have Moshe Bar and Kestutis Kveraga developed a theory of visual object recognition, which they have elaborated in a series of articles from 2003 on [13;81-83]. The theory –supported by magnetoecephalographic experiments- states that a low spatial frequency representation of the input image is projected rapidly from early visual cortical areas to the orbitofrontal cortex, in parallel to the systematic and relatively slower propagation of information along the ventral visual pathway. The coarse, low spatial frequency representation serves the purpose of activating a minimal set of the most probable interpretations of the input, which are, then, compared with information coming from the bottom-up stream. In addition, Kveraga [83] explicitly argues that it is the dorsal stream through which the transmission of the coarse image happens, though he never goes into detail regarding the exact pathways. We find that our findings do support such an interpretation of object recognition. However, before putting that into more detail, we have to briefly address the anatomical framework for the Bar-Kveraga hypothesis.

A closer look at the anatomy of the primate visual brain[6] corroborates the suspicion that interpreting vision as a one-way process is gross oversimplification (Fig.10.). In fact, the majority of the structures building up both the cortical and subcortical visual system are connected by massive parallel and feedback connections, beyond the feed-forward ones [84-88]. The Bar-Kveraga hypothesis implies that for orbitofrontal cortical activity to precede inferotemporal activity by 50-80 ms within the usual 150-200 ms of object recognition [83] visual information has to take a shortcut from lower areas toward the orbitofrontal cortex, possibly bypassing the V1-route; furthermore, if it is in fact the orbitofrontal cortex that supports visual recognition, a feedback projection upon the ventral stream, most likely on the inferotemporal cortex, should exist.

[6] Data presented here are based on studies on the Macaca mulatta, unless indicated otherwise.

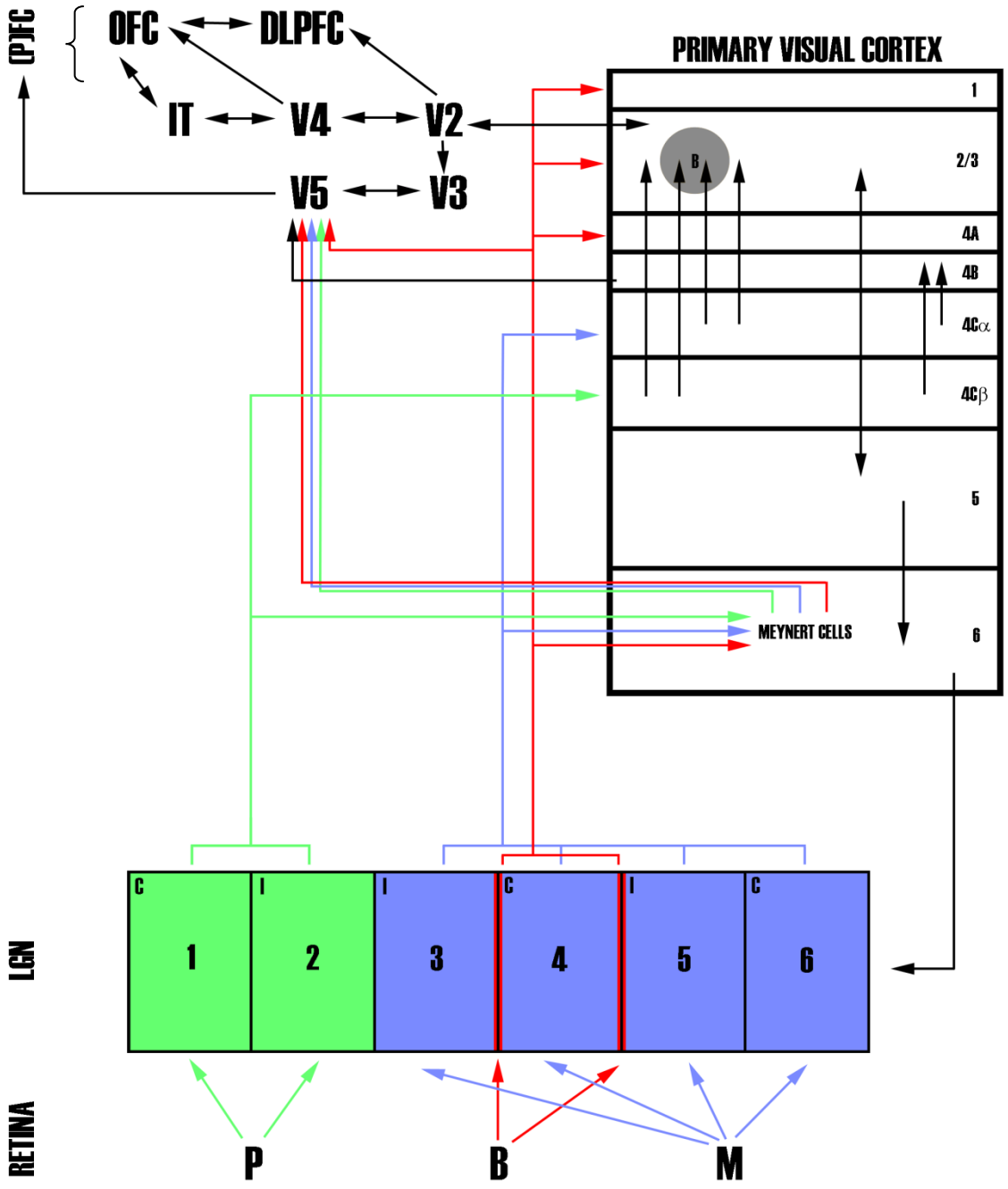

Fig.10. A scheme of connections between anatomical structures of primate visual perception, including the main retinal ganglion cells, the lateral geniculate nucleus of the thalamus (LGN), the primary visual cortex and the extrastriate visual structures. P,B,M = parasol, bistratified and midget cells of the retina; B = blob area in V1 2/3; OFC = orbitofrontal cortex; DLPFC = dorsolateral prefrontal cortex. Green, red and blue arrows indicate the parvocellular, koniocellular and magnocellular pathways, respectively. Based on [24;30;31;89].

As for the shortcut, two pathways are proven to exist in primates that are potential candidates. The first one is a direct input from the lateral geniculate nucleus of the thalamus to the extrastriate visual area V5 [31]. This is primarily a parvocellular/koniocellular input, in contradiction with the original assumption of the hypothesis, which, however, does not exclude its participation in an 'early signaling network.' A more likely candidate for a key role in the early signaling process is the pathway starting from the Meynert cells of the sixth layer of V1. The Meynert cells receive input from all the three main geniculostriate pathways, and project directly upon V5, bypassing other V1 layers and extrastriate visual areas [30]. It is to be seen (as indicated in Fig.10.) that input to V5, even though it is traditionally known as a movement-related area [90] , is not restricted to movement-related information. Rather, V5 seems to be situated ideally to be a common relay station for various types of visual information. More importantly, V5 also projects upon the dorsolateral prefrontal areas, which, in turn, are in a reciprocal connection with the orbitofrontal cortex. Therefore, we hypothesize that it might be this pathway that carries quickly accessible, coarse information to the orbitofrontal cortex, which, in turn, helps inferotemporal object identification by reducing the number of potentially valid guesses. The lateral geniculate nucleus – V5 connection might serve some sort of amplification or modulation purpose.

The existence of a direct connection between the orbitofrontal cortex and the inferotemporal cortex has also been established, and it was found to be bidirectional [89;91]. Bar et al. [82] found that the activity of this connection, as detectable in human subjects by magnetoencephalograpy, is influenced by the spatial frequencies of the input image, especially by low spatial frequencies. We assume that it is this connection through which supporting information from the orbitofrontal cortex is transmitted to the inferotemporal cortex.

Although the exact organization of these pathways in humans is not yet known, their existence is made obvious by phenomena like blindsight [92;93], the ability to learn even complex patterns of visual motion after V1 damage [94] or to detect motion direction while V1 processing is being functionally 'minimized' by a flash stimulus [95].

6.2. Explanation of results within the proposed framework

6.2.1. Contour integration in migraineurs and controls

The first and possibly most important result to be explained is that contour integration shows massive development between 5 and 14 years of age. It has previously been established that the development of the primary visual cortex per se cannot be the reason for this pattern. At the same time, we proposed a prefrontal, top-down system as the key element of successful shape recognition.

The literature of cortical development unequivocally considers the frontal/prefrontal cortical areas as being among the last to maturate [71;96-99]. It is important to mention that this late maturation refers both to internal and external connections, and myelination as well. From an ontogenetic point of view, this makes complete sense, considering the complex functions these cortical areas are assumed to perform. For instance, the orbitofrontal cortex, also playing a central role in our explanation, is considered to be of a pivotal role in social adaptation, through the inhibition of maladaptive behavioral responses [100-102]. The functional repertoire of the orbitofrontal cortex includes such functions as self-evaluation [103] and risk-based decision-making [104] as well. It cannot be overlooked that these are all functions that include some sort of comparison, and indeed, the orbitofrontal cortex is turning out to be a modality-independent intergrative structure, possibly comparing (or supporting the comparison of) stored memories with the actual input [105].

In terms of our findings, however, the exact developmental studies have the highest explanatory power. Kanemura et al. [106] examined the development of the prefrontal cortex in children in a three-dimensional volumetric MRI study, and found that this cortical area reaches its final, adult-like size by the age of 18, with a period of rapid growth between the ages of 8 and 14. Furthermore, Fornari [107] examined the relationship between the total amount of white matter and performance on a spatial integration task, and found that there is a linear relationship between age and white matter volume between the ages 7 and 13, also reflected by improving performance. Finally, Olesen et al. [108], in a combined DTI[7]-fMRI study showed that the myelination of long-range cortical connections and the activation of their target areas are associated between the ages 8 and 18.

Therefore, we conclude that the developmental spurt we observed in our study between 5 and 14 years of age is likely to be associated with myelination and the activation of

[7] Diffusion Tensor Imaging tractography

prefrontal cortical inhibitory areas. This also explains the ‘noise-problem’ mentioned under 5.1.1. That is, it is possibly the top-down inhibitory (filtering) mechanism that is gradually reaching full efficiency in the examined period, and this is what makes children capable of suppressing increasing amounts of noise with age.

Aging studies with spatial integration tasks provide further support to our assumption. It is known that frontal cortical areas are the most sensitive to aging [109;110], and accordingly, performance on visual spatial integration tasks show deterioration with aging [111;112].

Second, the most pronounced development in both the contour integration and contrast sensitivity tasks was observed at low spatial frequencies. Furthermore, the biggest developmental difference between migraineurs and controls was seen at the same frequencies. What this finding tells us is that, as predicted by the Bar-Kveraga hypothesis, the magnocellular system may really play an important role in contour/form perception. Although there are authors who claim that the magnocellular system might be activated by spatial frequencies as high as 12 c/d [113], and that recent criticism has questioned the validity of the present methods of psychophysics in telling magnocellular from parvocellular [47], it is relatively well established that the dividing line in terms of psychophysical testing is approximately 1.5 c/d [114;115]. That is, test results below 1.5 c/d reflect the performance of the magnocellular system, while results above that value characterize the functioning of the parvocellular system. Naturally, considering the individual variability, deviations from the 1.5 c/d line may occur; testing the two systems without overlap is still an unresolved problem, especially that these functional systems of vision do not work independently of each other. However, the application of dynamic stimuli (moving gratings) might at least partially have made up for that uncertainty, given that (as mentioned in 2.2.) processing of high temporal frequencies is dominantly carried out by the magnocellular system. We found that the development was most pronounced at 0.5 c/d, 1.2 c/d and 1.9 c/d, which, therefore, seems to indicate the protracted development of the magnocellular system. At the same time, the finding that the same frequency range appears to be affected in development of migraine, points to the protracted vulnerability of the system, corroborating its late maturation from another point of view.

In summary, these findings fit with the idea that what is reflected in the late maturation of the contour integration function is the protracted myelination of the (probably magnocellular) pathways that link early visual cortical areas with the prefrontal cortical areas in a way to bypass primary processing. However, the top-down inhibitory system serving to

enhance signal/noise differentiation cannot work at full efficiency until that process has finished, which is observable as gradually improving task performance. Thereby we also propose that in migraine it is the retarded development of those pathways (due to their developmental vulnerability) that prevent migraineurs from performing at the level of controls.

6.2.2. Contrast sensitivity in migraineurs and controls

To our knowledge, our study is the first to suggest that the contrast sensitivity deficit described in adult migraineurs [19] is to be observed in childhood, and especially at low spatial frequencies.

The finding that significant differences between the two groups were first to be seen in the 10–12-year-old age group came as no surprise, given that this is consistent with the finding that in healthy children the first significant developmental step in terms of low spatial frequencies occurs between the ages of 5 and 10 [43]. Why in the age group of 6–10-year-olds we found no significant differences might be due to a number of possible reasons. First, although migraine does exist in such a young age [116-118], the diagnosis poses challenging dilemmas [119], even following the IHS criteria as closely as possible. Thus, it cannot be ruled out that 'false positives' were included in the sample, and in turn, an existing but not robust difference was rendered insignificant, given the small number of observations.

Another factor is disease duration, which was quite short in the first cohort (~0.9 years). We do not find it likely that such a short exposure to migraine attacks should result in significant deterioration. However, this is not to say that repetitive migraine attacks themselves offer the ultimate explanation for the described contrast sensitivity deficits, as there is some evidence indicating that the length of migraine history is a factor [19].

The results for the two older age groups are less ambiguous. That migraineurs are lagging behind at low spatial frequencies is obvious. However, it must be noted that even if statistically significant difference characterizes only two frequencies in both groups, robust differences are to be seen over a wide range of frequencies. Why 1.2 c/d and 1.9 c/d are affected the most we consider a theoretically unimportant problem; possibly, this is an epiphenomenon of our measurement, reflecting a broader tendency of lower spatial frequencies in general being affected, as we found no reference in the literature indicating such specific differences.

What, then, might be the explanation for the deficit found in our study? Known evidence suggests a genetically determined vulnerability model. Repeated migraine attacks seem to interfere with contrast sensitivity in a progressive manner [120]. This is corroborated by the finding that stimulation of the Gasserian ganglion results in morphological changes at the level of perivascular nerve terminals [121]. That is, migraine, perhaps via the chemical mediators that are released in the process, does have the capacity to bring about permanent changes, possibly in a progressive or cumulative manner.

However, as migraine is known to be a familial disease, it is possible that the explanation for the early appearance of this contrast sensitivity difference is that it reflects an endophenotype. Di Clemente et al. [122] make a similar argument in connection with the interictal habituation deficit of the nociceptive blink reflex in migraineurs. However, even if we consider the deficit described here as reflecting an endophenotype, it remains an open question whether increased vulnerability to insults or a relatively stable (low) degree of contrast sensitivity decrease constitutes that endophenotype. The former scenario, of course, predicts that the longer the migraine history is, the more pronounced the contrast sensitivity deficit, which, despite the relative paucity of research in this direction, seems to be the case indeed. Therefore, we propose that migraineurs might be extremely vulnerable to the neurovascular challenge posed by the attacks, and that this vulnerability might be genetically determined. Of course, if migraine attacks can bring about a progressive deterioration in adult contrast sensitivity performance (indicating at least some functional damage to the underlying neural structures), they must also interfere with the development of the immature visual system. Indeed, our results show a weaker age-performance correlation in migraineurs than in controls, suggesting greater variability and a less homogenous developmental pattern.

As explicated under 5.2.1., based on the affected spatial frequencies, we assume that the the migrainous process interferes primarily with the development of the magnocellular visual system.

7. Summary

In this study we have compared contour integration and contrast sensitivity in school-age healthy and migrainous children, based on data we have gathered through psychophysical methods. We have established that the development of performance on contour integration and contrast sensitivity tasks are related in healthy subjects, especially when considering contrast sensitivity at lower spatial frequencies (0.5, 1.2 and 1.9 c/d). Healthy subjects also exhibit a period of massive development between 5 and 14 years of age in both contour integration and contrast sensitivity tasks.

It has also been found that the period of remarkable development observed in healthy subjects appears to be lacking in migraineurs of the same age range in both contour integration and contrast sensitivity tasks. Migraineurs between 10 and 14 years of age perform significantly poorer than controls in the contrast sensitivity task, especially at lower spatial frequencies (1.2 and 1.9 c/d). Furthermore, migraineurs of all cohorts are lagging behind controls, the difference being the most pronounced in the two elder cohorts (covering the range of 10 to 16 years of age).

To explain these findings we proposed a theoretical framework, the key element of which is a top-down inhibitory feedback from the orbitofrontal cortex toward the inferotemporal cortex. This feedback builds on shape-related memory information, and is activated by an early signaling pathway, which conveys coarse visual information of low spatial frequency bypassing detailed primary cortical processing, so that the coarse information can reach the orbitofrontal cortex well ahead of information arriving at the inferotemporal cortex along the ventral stream. This way, memories supporting efficient contour detection may be activated right in time. The protracted development of task performance on both tasks we explained with the long maturation of the pathways and structures necessary for the above explicated process, instead of with the long maturation of either the dorsal or ventral stream, in an isolated manner, like earlier theories did. At the same time we acknowledge that the magnocellular system may play a key role in contour processing, as indicated by the most markedly developing / most affected spatial frequencies in our contrast sensitivity task. Following from this, we assume that migraine, most likely through a genetically determined vulnerability, affects the development of the magnocellular visual system the most.

8. Acknowledgments

First of all, I wish to express my deepest gratitude to Professor György Benedek and Professor Márta Janáky for having trusted and supported me all along the way, in spite of my original background – I think their having done so is an example to anybody believing in a society based on knowledge and life-long learning. I would also like to express my gratitude to Professor Gábor Jancsó for having given me the chance to participate in the Neuroscience Ph.D. program, making a dream come true, and also bearing out the idea that one's first degree is not necessarily one's fate. Not less grateful am I to Professor Benő Csapó who first suggested that I should deal with research.

A distinguished place among those to be honored goes out to László Újvári, my first high school teacher of English, for the language he gave me. I hope that this thesis, should he happen to read it, will reach his standards.

A hearty thank you goes out to my colleagues, Dr. Zita Márkus, Dr. Alice Rokszin, Dr. Zsuzsanna Paróczy, Dr. Antal Berényi, Dr. Attila Nagy and Péter Gombkötő. Beside that they are great people who have been fun to work with, they gave me the chance to face the gaps in my knowledge every now and then- the only key do development.

I am also indebted to Dr. Krisztina Benedek, Dr. Szabolcs Kéri, Dr. Zsigmond Tamás Kincses, Professor László Sztriha, Dr. Jenő Kóbor, Kati Majer and Gabriella Dósai Molnár for their professional cooperation of the highest standard, and to all my colleagues at the Department of Physiology for the friendly and inspiring atmosphere. Special thanks to Anikó Jász, for always having been a partner in my bureaucratic and financial struggles.

Personally I would like to express my deepest thanks to those who have been with me, supported me, or inspired me during the last five years; first of all, my mother, Edit Horváth, who has done her best as a mother. My friends, Ádám Botyánszki, Tamás Nagy, Emília Róza Barna, Steve Swindelli, Angéla Horváth, Dániel Molnár, Adrienn Kurtai, Péter Hertelendy, Tivadar Csányi, Szabolcs Sántha and Péter Palásti have done their best to support me throughout the ups and downs of my personal life. Special thanks to Tamás Fülöp and Dániel 'Nemsokmit' Fórizs for all I may be especially thankful for.

9. References

[1] D.M.Regal, Development of Critical flicker frequency in human infants, Vision Res. 21 (1981) 549-555.

[2] P.J.Kellman, E.S.Spelke, Perception of partly occluded objects in infancy, Cogn Psychol. 15 (1983) 483-524.

[3] O.Braddick, J.Wattam-Bell, J.Day, J.Atkinson, The onset of binocular function in human infants, Hum. Neurobiol. 2 (1983) 65-69.

[4] D.Y.Teller, M.A.McDonald, K.Preston, S.L.Sebris, V.Dobson, Assessment of visual acuity in infants and children: the acuity card procedure, Dev. Med. Child Neurol. 28 (1986) 779-789.

[5] J.Atkinson, O.Braddick, Visual segmentation of oriented textures by infants, Behav. Brain Res. 49 (1992) 123-131.

[6] C.Rieth, R.Sireteanu, Texture segmentation and 'pop-out' in infants and children: the effect of test field size, Spat. Vis. 8 (1994) 173-191.

[7] D.Giaschi, D.Regan, Development of motion-defined figure-ground segregation in preschool and older children, using a letter-identification task, Optom. Vis. Sci. 74 (1997) 761-767.

[8] M.A.Hollants-Gilhuijs, J.M.Ruijter, H.Spekreijse, Visual half-field development in children: detection of motion-defined forms, Vision Res. 38 (1998) 651-657.

[9] M.A.Hollants-Gilhuijs, J.M.Ruijter, H.Spekreijse, Visual half-field development in children: detection of colour-contrast-defined forms, Vision Res. 38 (1998) 645-649.

[10] N.Barnard, S.G.Crewther, D.P.Crewther, Development of a magnocellular function in good and poor primary school-age readers, Optom. Vis. Sci. 75 (1998) 62-68.

[11] I.Kovacs, P.Kozma, A.Feher, G.Benedek, Late maturation of visual spatial integration in humans, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 12204-12209.

[12] C.D.Gilbert, J.A.Hirsch, T.N.Wiesel, Lateral interactions in visual cortex, Cold Spring Harb. Symp. Quant. Biol. 55:663-77. (1990) 663-677.

[13] K.Kveraga, A.S.Ghuman, M.Bar, Top-down predictions in the cognitive brain, Brain Cogn. 65 (2007) 145-168.

[14] N.Revheim, P.D.Butler, I.Schechter, M.Jalbrzikowski, G.Silipo, D.C.Javitt, Reading impairment and visual processing deficits in schizophrenia, Schizophr. Res. 87 (2006) 238-245.

[15] M.Palomares, B.Landau, H.Egeth, Orientation perception in Williams Syndrome: discrimination and integration, Brain Cogn. 70 (2009) 21-30.

[16] F.Pei, S.Baldassi, G.Procida, R.Igliozzi, R.Tancredi, F.Muratori, G.Cioni, Neural correlates of texture and contour integration in children with autism spectrum disorders, Vision Res. 49 (2009) 2140-2150.

[17] S.Keri, A.Must, O.Kelemen, G.Benedek, Z.Janka, Development of visual motion perception in children of patients with schizophrenia and bipolar disorder: a follow-up study, Schizophr. Res. 82 (2006) 9-14.

[18] R.Oelkers-Ax, K.Schmidt, S.Bender, I.Reimer, E.Mohler, E.Knauss, F.Resch, M.Weisbrod, Longitudinal assessment of response preparation and evaluation in migraine gives evidence for deviant maturation, Cephalalgia. 28 (2008) 237-249.

[19] K.Benedek, J.Tajti, M.Janaky, L.Vecsei, G.Benedek, Spatial contrast sensitivity of migraine patients without aura, Cephalalgia. 22 (2002) 142-145.

[20] K.Shibata, K.Yamane, K.Otuka, M.Iwata, Abnormal visual processing in migraine with aura: a study of steady-state visual evoked potentials, J. Neurol. Sci. 271 (2008) 119-126.

[21] L.G.Ungerleider, J.V.Haxby, 'What' and 'where' in the human brain, Curr. Opin. Neurobiol. 4 (1994) 157-165.

[22] A.D.Milner, M.A.Goodale, Two visual systems re-viewed, Neuropsychologia. 46 (2008) 774-785.

[23] Smith,V.C. and Pokorny,J., Psychophysical Correlates of Parvo- and Magnocellular Function. In: J.D.Mollon, J.Pokorny, K.Knoblauch (Eds.), Normal and Defective Colour Vision, Oxford University Press, 2003, pp. 91-107.

[24] J.J.Nassi, E.M.Callaway, Parallel processing strategies of the primate visual system, Nat. Rev. Neurosci. 10 (2009) 360-372.

[25] Mason,C. and Kandel,E., Central Visual Pathways. In: E.R.Kandel, J.H.Schwartz, T.M.Jessell (Eds.), Principles of Neural Science, Elsevier, 1991, pp. 420-439.

[26] L.C.Sincich, J.C.Horton, The circuitry of V1 and V2: integration of color, form, and motion, Annu. Rev. Neurosci. 28:303-26. (2005) 303-326.

[27] T.A.Nealey, J.H.Maunsell, Magnocellular and parvocellular contributions to the responses of neurons in macaque striate cortex, J. Neurosci. 14 (1994) 2069-2079.

[28] J.G.Malpeli, P.H.Schiller, C.L.Colby, Response properties of single cells in monkey striate cortex during reversible inactivation of individual lateral geniculate laminae, J. Neurophysiol. 46 (1981) 1102-1119.

[29] J.M.Hupe, A.C.James, B.R.Payne, S.G.Lomber, P.Girard, J.Bullier, Cortical feedback improves discrimination between figure and background by V1, V2 and V3 neurons, Nature. 20;394 (1998) 784-787.

[30] L.C.Sincich, K.F.Park, M.J.Wohlgemuth, J.C.Horton, Bypassing V1: a direct geniculate input to area MT, Nat. Neurosci. 7 (2004) 1123-1128.

[31] J.J.Nassi, D.C.Lyon, E.M.Callaway, The parvocellular LGN provides a robust disynaptic input to the visual motion area MT, Neuron. 20;50 (2006) 319-327.

[32] D.M.Dacey, Physiology, morphology and spatial densities of identified ganglion cell types in primate retina, Ciba Found. Symp. 184:12-28; discussion 28-34, 63-70. (1994) 12-28.

[33] Nelson,C.A. and Horowitz,F.D., Visual motion perception in infancy: a review and synthesis. In: P.Salapatek, L.Cohen (Eds.), Handbook of infant perception, Academic, New York, 1987, pp. 123-153.

[34] D.M.Regal, Development of Critical flicker frequency in human infants, Vision Res. 21 (1981) 549-555.

[35] E.B.Ciner, E.Schanel-Klitsch, C.Herzberg, Stereoacuity development: 6 months to 5 years. A new tool for testing and screening, Optom. Vis. Sci. 73 (1996) 43-48.

[36] B.Hammarrenger, F.Lepore, S.Lippe, M.Labrosse, J.P.Guillemot, M.S.Roy, Magnocellular and parvocellular developmental course in infants during the first year of life, Doc. Ophthalmol. 107 (2003) 225-233.

[37] M.Madrid, M.A.Crognale, Long-term maturation of visual pathways, Vis. Neurosci. 17 (2000) 831-837.

[38] I.Kovacs, Human development of perceptual organization, Vision Res. 40 (2000) 1301-1310.

[39] C.Distler, J.Bachevalier, C.Kennedy, M.Mishkin, L.G.Ungerleider, Functional development of the corticocortical pathway for motion analysis in the macaque monkey: a 14C-2-deoxyglucose study, Cereb. Cortex. 6 (1996) 184-195.

[40] A.Burkhalter, K.L.Bernardo, V.Charles, Development of local circuits in human visual cortex, J. Neurosci. 13 (1993) 1916-1931.

[41] Pandya,D.N., Seltzer,B. and Barbas,H., Input-output organization of the primate cerebral cortex. In: H.D.Steklis, J.Erwin (Eds.), Comparative Primate Biology.Neurosciences., Vol. 4, Wiley-Liss, New York, 1988, pp. 39-80.

[42] J.Langrova, M.Kuba, J.Kremlacek, Z.Kubova, F.Vit, Motion-onset VEPs reflect long maturation and early aging of visual motion-processing system, Vision Res. 46 (2006) 536-544.

[43] G.Benedek, K.Benedek, S.Keri, M.Janaky, The scotopic low-frequency spatial contrast sensitivity develops in children between the ages of 5 and 14 years, Neurosci. Lett. 345 (2003) 161-164.

[44] T.L.Hickey, Postnatal development of the human lateral geniculate nucleus: relationship to a critical period for the visual system, Science. 198 (1977) 836-838.

[45] O.Braddick, J.Atkinson, J.Wattam-Bell, Normal and anomalous development of visual motion processing: motion coherence and 'dorsal-stream vulnerability', Neuropsychologia. 41 (2003) 1769-1784.

[46] N.Gogtay, J.N.Giedd, L.Lusk, K.M.Hayashi, D.Greenstein, A.C.Vaituzis, T.F.Nugent, III, D.H.Herman, L.S.Clasen, A.W.Toga, J.L.Rapoport, P.M.Thompson, Dynamic mapping of human cortical development during childhood through early adulthood, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 8174-8179.

[47] A.M.McKendrick, G.P.Sampson, Low spatial frequency contrast sensitivity deficits in migraine are not visual pathway selective, Cephalalgia. 29 (2009) 539-549.

[48] Headache Classification Subcommittee of the International Headache Society, The International Classification of Headache Disorders. 2nd Edition (2005) http://www.i-h-s.org

[49] Tajti,J. and Vécsei L., Migrén. In: L.Vécsei (Ed.), Fejfájás. Válogatott fejezetek., B+V Lap- és Könyvkiadó, 2001, pp. 13-51.

[50] P.J.Goadsby, A.R.Charbit, A.P.Andreou, S.Akerman, P.R.Holland, Neurobiology of migraine, Neuroscience. 161 (2009) 327-341.

[51] A.A.Parsons, P.J.Strijbos, The neuronal versus vascular hypothesis of migraine and cortical spreading depression, Curr. Opin. Pharmacol. 3 (2003) 73-77.

[52] A.Mayevsky, A.Doron, T.Manor, S.Meilin, N.Zarchin, G.E.Ouaknine, Cortical spreading depression recorded from the human brain using a multiparametric monitoring system, Brain Res. 740 (1996) 268-274.

[53] M.Lauritzen, A.J.Hansen, The effect of glutamate receptor blockade on anoxic depolarization and cortical spreading depression, J. Cereb. Blood Flow Metab. 12 (1992) 223-229.

[54] J.Bartley, Could glial activation be a factor in migraine?, Med. Hypotheses. 72 (2009) 255-257.

[55] Seri,S. and Cerquiglini,A., Neurophysiology. In: V.Guidetti, G.Russell, M.Sillanpaa, P.Winner (Eds.), Headache and Migraine in Childhood and Adolescence, Martin Dunitz Ltd., 2002, pp. 11-17.

[56] V.Dimitriadou, M.G.Buzzi, M.A.Moskowitz, T.C.Theoharides, Trigeminal sensory fiber stimulation induces morphological changes reflecting secretion in rat dura mater mast cells, Neuroscience. 44 (1991) 97-112.

[57] V.Dimitriadou, M.G.Buzzi, T.C.Theoharides, M.A.Moskowitz, Ultrastructural evidence for neurogenically mediated changes in blood vessels of the rat dura mater and tongue following antidromic trigeminal stimulation, Neuroscience. 48 (1992) 187-203.

[58] S.Gupta, S.Mehrotra, C.M.Villalon, M.Perusquia, P.R.Saxena, A.MaassenVanDenBrink, Potential role of female sex hormones in the pathophysiology of migraine, Pharmacol. Ther. 113 (2007) 321-340.

[59] X.P.Wang, J.M.Liu, Y.B.Zhao, Migraine: sex-influenced trait model?, Med. Hypotheses. 71 (2008) 14-21.

[60] V.K.Gupta, Migrainous scintillating scotoma and headache is ocular in origin: A new hypothesis, Med. Hypotheses. 66 (2006) 454-460.

[61] S.Soriani, C.Arnaldi, C.L.De, D.Arcudi, D.Mazzotta, P.A.Battistella, S.Sartori, V.Abbasciano, Serum and red blood cell magnesium levels in juvenile migraine patients, Headache. 35 (1995) 14-16.

[62] G.Coppola, F.Pierelli, J.Schoenen, Habituation and migraine, Neurobiol. Learn. Mem. 92 (2009) 249-259.

[63] Wertheimer M, Laws of organization in perceptual forms, Harcourt, London, 1983.

[64] D.H.Hubel, T.N.Wiesel, Receptive fields of single neurones in the cat's striate cortex, J. Physiol. 148 (1959) 574-591.

[65] D.H.Hubel, T.N.Wiesel, Receptive fields and functional architecture of monkey striate cortex, J. Physiol. 195 (1968) 215-243.

[66] K.S.Rockland, Anatomical organization of primary visual cortex (area 17) in the ferret, J. Comp Neurol. 241 (1985) 225-236.

[67] C.D.Gilbert, T.N.Wiesel, Intrinsic connectivity and receptive field properties in visual cortex, Vision Res. 25 (1985) 365-374.

[68] S.Marcelja, Mathematical description of the responses of simple cortical cells, J. Opt. Soc. Am. 70 (1980) 1297-1300.

[69] M.J.Webster, L.G.Ungerleider, J.Bachevalier, Connections of inferior temporal areas TE and TEO with medial temporal-lobe structures in infant and adult monkeys, J. Neurosci. 11 (1991) 1095-1116.

[70] Z.Kaldy, I.Kovacs, Visual context integration is not fully developed in 4-year-old children, Perception. 32 (2003) 657-666.

[71] R.W.Guillery, Is postnatal neocortical maturation hierarchical?, Trends Neurosci. 28 (2005) 512-517.

[72] Flechsig,P.E., Anatomie des Menschlichen Gehirn und Rückenmarks auf Myelogenetischen Grundlage, G.Thieme, 1920.

[73] P.Gerhardstein, I.Kovacs, J.Ditre, A.Feher, Detection of contour continuity and closure in three-month-olds, Vision Res. 44 (2004) 2981-2988.

[74] T.J.Baker, J.Tse, P.Gerhardstein, S.A.Adler, Contour integration by 6-month-old infants: discrimination of distinct contour shapes, Vision Res. 48 (2008) 136-148.

[75] S.Hochstein, M.Ahissar, View from the top: hierarchies and reverse hierarchies in the visual system, Neuron. 36 (2002) 791-804.

[76] A.Martinez, L.Anllo-Vento, M.I.Sereno, L.R.Frank, R.B.Buxton, D.J.Dubowitz, E.C.Wong, H.Hinrichs, H.J.Heinze, S.A.Hillyard, Involvement of striate and extrastriate visual cortical areas in spatial attention, Nat. Neurosci. 2 (1999) 364-369.

[77] P.R.Roelfsema, V.A.Lamme, H.Spekreijse, Object-based attention in the primary visual cortex of the macaque monkey, Nature. 395 (1998) 376-381.

[78] A.C.Nobre, T.Allison, G.McCarthy, Modulation of human extrastriate visual processing by selective attention to colours and words, Brain. 121 (1998) 1357-1368.

[79] G.Tassinari, D.Campara, G.Balercia, M.Chilosi, G.Martignoni, C.A.Marzi, Magno- and parvocellular pathways are segregated in the human optic tract, Neuroreport. 5 (1994) 1425-1428.

[80] G.Benedek, K.Benedek, S.Keri, M.Janaky, The scotopic low-frequency spatial contrast sensitivity develops in children between the ages of 5 and 14 years, Neurosci. Lett. 345 (2003) 161-164.

[81] M.Bar, A cortical mechanism for triggering top-down facilitation in visual object recognition, J. Cogn Neurosci. 15 (2003) 600-609.

[82] M.Bar, K.S.Kassam, A.S.Ghuman, J.Boshyan, A.M.Schmid, A.M.Dale, M.S.Hamalainen, K.Marinkovic, D.L.Schacter, B.R.Rosen, E.Halgren, Top-down facilitation of visual recognition, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 449-454.

[83] K.Kveraga, J.Boshyan, M.Bar, Magnocellular projections as the trigger of top-down facilitation in recognition, J. Neurosci. 27 (2007) 13232-13240.

[84] J.Bullier, L.G.Nowak, Parallel versus serial processing: new vistas on the distributed organization of the visual system, Curr. Opin. Neurobiol. 5 (1995) 497-503.

[85] J.Bullier, J.M.Hupe, A.C.James, P.Girard, The role of feedback connections in shaping the responses of visual cortical neurons, Prog. Brain Res. 134(2001) 193-204.

[86] N.L.Rempel-Clower, H.Barbas, The laminar pattern of connections between prefrontal and anterior temporal cortices in the Rhesus monkey is related to cortical structure and function, Cereb. Cortex. 10 (2000) 851-865.

[87] H.Nakamura, R.Gattass, R.Desimone, L.G.Ungerleider, The modular organization of projections from areas V1 and V2 to areas V4 and TEO in macaques, J. Neurosci. 13 (1993) 3681-3691.

[88] L.J.Porrino, A.M.Crane, P.S.Goldman-Rakic, Direct and indirect pathways from the amygdala to the frontal lobe in rhesus monkeys, J. Comp Neurol. 198 (1981) 121-136.

[89] M.L.Kringelbach, E.T.Rolls, The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology, Prog. Neurobiol. 72 (2004) 341-372.

[90] A.Kaas, S.Weigelt, A.Roebroeck, A.Kohler, L.Muckli, Imagery of a moving object: the role of occipital cortex and human MT/V5+, Neuroimage. 49 (2010) 794-804.

[91] C.Cavada, T.Company, J.Tejedor, R.J.Cruz-Rizzolo, F.Reinoso-Suarez, The anatomical connections of the macaque monkey orbitofrontal cortex. A review, Cereb. Cortex. 10 (2000) 220-242.

[92] P.Stoerig, Cueless blindsight, Front Hum. Neurosci. 3:74. (2010) 74.

[93] D.Seifert, C.Falter, H.Strasburger, M.A.Elliott, Bandpass characteristics of high-frequency sensitivity and visual experience in blindsight, Conscious. Cogn. 19 (2010) 144-151.

[94] K.R.Huxlin, T.Martin, K.Kelly, M.Riley, D.I.Friedman, W.S.Burgin, M.Hayhoe, Perceptual relearning of complex visual motion after V1 damage in humans, J. Neurosci. 29 (2009) 3981-3991.

[95] M.A.Schoenfeld, H.J.Heinze, M.G.Woldorff, Unmasking motion-processing activity in human brain area V5/MT+ mediated by pathways that bypass primary visual cortex, Neuroimage. 17 (2002) 769-779.

[96] B.A.Brody, H.C.Kinney, A.S.Kloman, F.H.Gilles, Sequence of central nervous system myelination in human infancy. I. An autopsy study of myelination, J. Neuropathol. Exp. Neurol. 46 (1987) 283-301.

[97] Yakovlev,P.I. and Lecours,A.R., The myelogenetic cycles of regional maturation of the brain. In: A.Minkowski (Ed.), Regional Development of the Brain In Early Life, Blackwell, Oxford, 1967.

[98] Fuster,J.M., The Prefrontal Cortex - anatomy, physiology and neuropsychology of the frontal lobe, Lippincott-Raven, Philadelphia, 1997, 6-11 pp.

[99] M.G.Cunningham, S.Bhattacharyya, F.M.Benes, Amygdalo-cortical sprouting continues into early adulthood: implications for the development of normal and abnormal function during adolescence, J. Comp Neurol. 453 (2002) 116-130.

[100] G.Schoenbaum, M.R.Roesch, T.A.Stalnaker, Y.K.Takahashi, A new perspective on the role of the orbitofrontal cortex in adaptive behaviour, Nat. Rev. Neurosci. 10 (2009) 885-892.

[101] P.Pietrini, M.Guazzelli, G.Basso, K.Jaffe, J.Grafman, Neural correlates of imaginal aggressive behavior assessed by positron emission tomography in healthy subjects, Am. J. Psychiatry. 157 (2000) 1772-1781.

[102] J.Decety, P.L.Jackson, J.A.Sommerville, T.Chaminade, A.N.Meltzoff, The neural bases of cooperation and competition: an fMRI investigation, Neuroimage. 23 (2004) 744-751.

[103] J.S.Beer, M.V.Lombardo, J.P.Bhanji, Roles of Medial Prefrontal Cortex and Orbitofrontal Cortex in Self-evaluation, J. Cogn Neurosci. 19 (2009) Ahead of print.

[104] J.R.St Onge, S.B.Floresco, Prefrontal Cortical Contribution to Risk-Based Decision Making, Cereb. Cortex. (2009) Ahead of print.

[105] G.Schoenbaum, G.R.Esber, How do you (estimate you will) like them apples? Integration as a defining trait of orbitofrontal function, Curr. Opin. Neurobiol. (2010) Ahead of publication.

[106] H.Kanemura, M.Aihara, S.Aoki, T.Araki, S.Nakazawa, Development of the prefrontal lobe in infants and children: a three-dimensional magnetic resonance volumetric study, Brain Dev. 25 (2003) 195-199.

[107] E.Fornari, M.G.Knyazeva, R.Meuli, P.Maeder, Myelination shapes functional activity in the developing brain, Neuroimage. 38 (2007) 511-518.

[108] P.J.Olesen, Z.Nagy, H.Westerberg, T.Klingberg, Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network, Brain Res. Cogn Brain Res. 18 (2003) 48-57.

[109] D.Yanase, I.Matsunari, K.Yajima, W.Chen, A.Fujikawa, S.Nishimura, H.Matsuda, M.Yamada, Brain FDG PET study of normal aging in Japanese: effect of atrophy correction, Eur. J. Nucl. Med. Mol. Imaging. 32 (2005) 794-805.

[110] R.A.Hawkins, J.C.Mazziotta, M.E.Phelps, S.C.Huang, D.E.Kuhl, R.E.Carson, E.J.Metter, W.H.Riege, Cerebral glucose metabolism as a function of age in man: influence of the rate constants in the fluorodeoxyglucose method, J. Cereb. Blood Flow Metab. 3 (1983) 250-253.

[111] E.Roudaia, P.J.Bennett, A.B.Sekuler, The effect of aging on contour integration, Vision Res. 48 (2008) 2767-2774.

[112] M.M.Del Viva, R.Agostini, P.C.Tumeh, A.Alavi, M.Houseni, A.Greenfield, T.Chryssikos, A.Newberg, D.A.Torigian, G.Moonis, Visual spatial integration in the elderly
Structural and functional imaging correlates for age-related changes in the brain, Semin. Nucl. Med. 37 (2007) 69-87.

[113] J.Stein, V.Walsh, To see but not to read; the magnocellular theory of dyslexia, Trends Neurosci. 20 (1997) 147-152.

[114] G.E.Legge, Sustained and transient mechanisms in human vision: temporal and spatial properties, Vision Res. 18 (1978) 69-81.

[115] D.J.Tolhurst, Reaction times in the detection of gratings by human observers: a probabilistic mechanism, Vision Res. 15 (1975) 1143-1149.

[116] U.Balottin, F.Nicoli, G.Pitillo, G.O.Ferrari, R.Borgatti, G.Lanzi, Migraine and tension headache in children under 6 years of age, Eur. J. Pain. 8 (2004) 307-314.

[117] C.F.Barlow, Migraine in the infant and toddler, J. Child Neurol. 9 (1994) 92-94.

[118] M.L.Chu, S.Shinnar, Headaches in children younger than 7 years of age, Arch. Neurol. 49 (1992) 79-82.

[119] D.W.Lewis, Pediatric migraine, Pediatr. Rev. 28 (2007) 43-53.

[120] A.M.McKendrick, D.R.Badcock, Contrast-processing dysfunction in both magnocellular and parvocellular pathways in migraineurs with or without aura, Invest Ophthalmol. Vis. Sci. 44 (2003) 442-448.

[121] E.Knyihar-Csillik, J.Tajti, S.Mohtasham, G.Sari, L.Vecsei, Electrical stimulation of the Gasserian ganglion induces structural alterations of calcitonin gene-related peptide-immunoreactive perivascular sensory nerve terminals in the rat cerebral dura mater: a possible model of migraine headache, Neurosci. Lett. 184 (1995) 189-192.

[122] C.L.Di, G.Coppola, D.Magis, A.Fumal, P.De, V, P.Di, V, J.Schoenen, Interictal habituation deficit of the nociceptive blink reflex: an endophenotypic marker for presymptomatic migraine?, Brain. 130 (2007) 765-770.

APPENDIX

I.

II.

III.