CHANGING FACE OF MIGRAINE DURING CHILDHOOD DEVELOPMENT

PhD Thesis

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TABLE OF CONTENTS

ABBREVIATIONS

95% CI	95% confidence interval
CSD	cortical spreading depression
D	relative noise density
D_{min}	minimum value of *D*
DTI	diffusion tensor imaging
fMRI	functional magnetic resonance imaging
ICHD-II	International Classification of Headache Disorders, 2nd edition
IHS	International Headache Society
IHS-1	1st classification of headache disorders by the International Headache Society
IRR	incidence rate ratio
IT	inferior temporal cortex
MO	migraine without aura
M-pathway	magnocellular pathway
MT	middle temporal area
MWU	Mann-Whitney U-test
N.S.	not significant
OR	odds ratio
PAG	periaqueductal grey matter
P-pathway	parvocellular pathway
p value	probability value
r	Spearman's correlation coefficient
TGVS	trigeminovascular system
TTH	tension-type headache
V1	primary visual cortex
V2	parastriate cortex
V5	middle temporal area

SUMMARY

Background

Migraine headache poses an immense burden on both the individual and society. A better management necessitates a thorough knowledge of all aspects of the disease, including the magnitude of the problem and the pathophysiology.

Aims

We set out to estimate the prevalence of migraine in 7-18-year-old children and adolescents. We were additionally interested in whether there is any change in the prevalence of migraine and the frequency of its characteristic symptoms in this age group. Cortical areas involved in visual perception might be especially affected by the pathophysiological processes of migraine. In the second part of this work we compared the performance of migrainous children with that of their healthy peers in two psychophysical paradigms: contour integration capacity and motion coherence detection ability.

Subjects and methods

A cross-sectional school-based descriptive epidemiological study was performed by means of a questionnaire in the city of Szeged. The diagnosis of migraine was established according to the International Classification of Headache Disorders, 2nd edition. Contour integration capacity was assessed by means of a series of cards with a circular contour consisting of 12-14 Gabor patches embedded in a background of randomly placed patches (noise) of increasing density on the different cards. To evaluate visual motion processing ability, stimuli of random dot kinematograms with decreasing coherence rates were presented to the subjects on an LCD monitor.

Results

On the basis of the 7,361 responses returned, the estimated 12-month prevalence of migraine was 12.5% (9.2% in boys and 15.4% in girls). However, the prevalence decreased to 9.1% (7.3% in boys and 10.6% in girls) when criteria of the 1st classification of headache disorders by International Headache Society was applied. A steady increase in prevalence was found

from 7 up to 18 years in each gender. Moderate or severe pain intensity was unequivocally the most common migraine feature (99%), followed by phonophobia (88%) and photophobia (82%). The frequency and duration of headache were low in the youngest children and gradually became higher with advancing age. Nausea and vomiting displayed a decreasing tendency. With increasing age, a pulsating character became more prevalent in boys, while a uni/bilateral location, photophobia and phonophobia did so only in girls.

Contour detection thresholds of children with migraine without aura (MO) revealed no difference in the 6-9-year age groups, whilst the controls performed significantly better in the 10-14-year and 15-18-year cohorts. Young subjects performed poorer than older ones in both the MO and the control groups. A significant correlation between attack frequency and poor contour integration was revealed when the cohorts were taken together in a single migrainous or control group

8-17-year-old MO children had a higher threshold of visual motion processing than that of the controls. The control group performed at a constant level, regardless of age, while the motion coherence detection threshold of migraineurs was higher at younger ages, catching up with the controls by late puberty. Neither the duration of the disease nor the frequency of attacks exhibited a significant correlation with the performance.

Conclusions

The prevalence of migraine in Hungarian children fits well into the range found in similar studies in Europe. Further, our data correspond to the prevalence found among adults Hungary. It must be noted, however, that the strict use of the criterion of the minimally required headache duration results in undue findings in age-related prevalence. Hence, we suggest a more thorough tailoring of this criterion for migraine diagnosis in this age group.

The most common symptom was moderate or severe pain intensity, followed by phonophobia and photophobia, while vomiting presented the least commonly. Headache frequency and duration increased, whereas vomiting and nausea became less prevalent with advancing age. We found gender differences both in prevalence and in certain of the migraine features.

The visual contour integration capacity in migrainous children is poorer than that in their non-headache peers. Similarly, the perception of motion coherence is deficient in a wide age range of paediatric migraineurs. The difference in both tests is most marked at a young age and it

then decreases along with a delayed maturation by adolescence. A poor performance was found to correlate with the attack frequency in the first, but not in the second test in the setting used here.

In summary, several aspects of migraine change in parallel with brain maturation during childhood.

ÖSSZEFOGLALÁS

Háttér

A migrén jelentős terhet ró mind az egyénre, mind a társadalomra. A hatékonyabb kezelés szempontjából fontos a betegség valamennyi vonatkozásának, köztük az epidemiológiai adatok és a patofiziológiai folyamatok pontos ismerete.

Célkitűzések

Vizsgálataink célja a gyermek és serdülő kori migrén prevalenciájának valamint a prevalencia és a tünetek korosztályonkénti felmérése 7-18 éves korban. Klinikai és vizsgálati adatok szólnak amellett, hogy a migrénes folyamat különösen érinti a látás feldolgozásban fontos szerepet játszó agykérgi területeket. Munkánk második felében migrénes és fejfájásmentes gyermekek kontúr integrációs és mozgás-koherencia érzékelő készségét hasonlítottuk össze két pszichofizikai vizsgálatban.

Vizsgáltak és módszerek

Iskola-alapú, keresztmetszeti epidemiológiai vizsgálatunkban kérdőíves módszert alkalmaztunk 7-18 éves szegedi gyermekek és serdülők körében. A kontúr integrációs készség mérését fokozódó sűrűségű Gábor-foltokból álló zajba helyezett, azonos Gábor-foltokból álló kör kontúrt tartalmazó kártya sorozattal végeztük. A mozgás koherencia észlelési készség vizsgálatához randompont-kinematogramot alkalmaztunk. A migrén diagnózisát az International Classification of Headache Disorders 2. kiadása alapján állítottuk fel.

Eredmények

A beérkező 7.361 kérdőív alapján a migrén éves prevalenciája 12,5% volt (fiúknál 9.2%, lányoknál 15.4%). Azonban az International Headache Society első fejfájás klasszifikációs kritériumait alkalmazva a prevalencia csak 9,1%-nak bizonyult (fiúknál 7,3%, lányoknál 10,6%). 7 és 18 év között a prevalencia érték mindkét nemben folyamatosan emelkedett. A leggyakoribb migrén tünet egyértelműen fejfájás közepes és súlyos erőssége volt (99%), melyet a zajkerülés (88%) és a fénykerülés (82%) követett. A rohamgyakoriság és a fejfájás tartama alacsonyabb volt fiatal gyermek körében, majd ezek az értékek a korral fokozatosan

emelkedtek. A hányinger és hányás csökkenő gyakoriságot mutattak. Az emelkedő korral a fejfájás lüktető jellege fiúkon fokozatosan emelkedett, míg lányokon az egy- vagy kétoldali lokalizációval, a fénykerüléssel és zajkerüléssel tapasztaltuk ezt.

A kontúrérzékelési készség 6-9 éves korban nem mutatott különbséget aura nélküli (MO) migrénes és a kontrol gyerekek között, de a 10-14 és 15-18 éves korcsoportokban a kontroll vizsgáltak szignifikánsan jobban teljesítettek. A fiatalabbak teljesítménye mind a MO mind a kontroll csoportban rosszabb volt az idősebbekhez képest. Ha a migréneseket korcsoportonkénti bontás nélkül egy csoportban vizsgáltuk, a rohamgyakoriság és a gyenge kontúr integrációs készség között szignifikáns korreláció mutatkozott.

A 8-17 éves MO gyermekek mozgás koherencia érzékelése rosszabb volt a kontrollokénál. Utóbbiak kortól függetlenül egyenletes szinten teljesítettek, míg a fiatal migrénesek gyengébben, s csak késő serdülő korra érték utol fejfájásmentes társaikat. Sem a migrén fennállásának tartama sem a fejfájás gyakorisága nem mutatott korrelációt a teljesítménnyel.

Következtetések

A migrén gyermekkori prevalenciája jól illeszkedik a hasonló, Európában kapott eredményekhez. Hasonlóképpen ez az adat jól illeszkedik a hazánkban felnőtt korban észlelt migrén prevalenciához. Megjegyzendő azonban, hogy a fejfájás kritériumok között szereplő minimálisan elvárt roham tartam szigorú alkalmazása a korfüggő prevalencia indokolatlan csökkenéséhez vezet. Emiatt szükségesnek tartjuk ezen kritérium pontosítását ebben a korosztályban. További fontos megállapításunk, hogy a migrénes tünetek az életkorral, részben a nemektől is függően, fokozatosan változnak.

Migrénes gyermekeken mind a kontúr integrációs készség, mind a mozgás koherencia észlelés gyengébb, mint nem fejfájós társaikban. A különbség fiatalabb korban kifejezettebb, majd életkorral serdülő korra ez fokozatosan csökken. A kontúr integráció és a rohamgyakoriság között kapcsolat volt kimutatható, míg a mozgás koherenciával kapcsoltban az alkalmazott vizsgálati elrendezésekben ez nem állt fenn.

Összegezve: a migrén az életkorral - az agy érésével - párhozamosan számos szempontból változik.

1. INTRODUCTION

Migraine, one of the most common causes of headache, poses an immense burden on both the individual and society. The first step towards a better health care is the recognition of the magnitude of the problem in the hope that this will finally result in a proportional allocation of resources. Reliable and comparable epidemiological data can result only from correct diagnoses based on uniformly accepted and applied criteria. Though much is known about the pathophysiology of migraine, it is far from fully understood, and no reliable surrogate marker has been found. Thus, the diagnosis is still based on a set of characteristic clinical symptoms, generally considered sensitive and specific enough to establish a firm diagnosis [1].

A thorough knowledge of the pathophysiology is needed for certain other purposes, too. A better understanding of specific pain mechanisms, disease progression and potential complications holds the promise of the development of more specific and more efficient ways of prevention and therapy.

Childhood puts any disease into a special framework, especially if the brain is involved. The prevalence, symptoms, diagnostic approach and occasionally treatment may all differ from those in adults. Consequently, this age group demands special attention.

1.1 The burden of migraine

Headache is a complaint that most people experience on one or more occasions. In fact, a recent overview of epidemiological surveys published since 1988 in Europe established a 94.2% lifetime prevalence of any headache in adults [2]. In a World Health Organization-related comprehensive survey, the worldwide prevalence of tension-type (TTH) and migraine headaches proved to be 20.8% and 14.7%, respectively, ranking TTH as the second and migraine as the third most prevalent of the investigated 289 diseases and 1160 of their potential sequelae [3]. The same survey assessed the disability accompanying a severe migraine attack, and found it to be comparable to that of moderate multiple sclerosis, untreated spinal cord lesion, severe dementia or untreated epilepsy [4]. The 'years lived with disability', a measure taking into account the prevalence and the disability, but disregarding any potential fatal outcome, ranked migraine 8th [3].

Migraine headache may have an impact on the individual's life between attacks, too, as indicated by significantly lower Health Related Quality of Life measures [5]. Comorbidities, such as depression [6], and a complete or partial loss of ability to work or to participate in social, recreational, familial and other non-work activities are further contributors. On average, 2.2-5.7 working days per person are lost yearly due to migraine headache [7, 8] and more than half of the migraineurs reported adverse consequences of their disease regarding their family relationships [9].

The financial burden of migraine too is enormously high. The direct costs of health care and indirect costs resulting from reduced work productivity amount to € 461 per migraineur per year in Western Europe [10]. Although per capita the cheapest, the € 43.5 billion global headache cost ranked 3rd of 11 purely neurologic disorders in a survey conducted by the European Brain Council in the EU [11].

A subgroup, maybe 14% of migraineurs, exhibits a progressing course, transforming into chronic migraine [12]. Furthermore, the risk of ischaemic stroke, myocardial infarction and claudication is increased in migraine [13-15]. It is tempting to conclude, that the optimal treatment of migraine would prevent these complications, but this remains to be proven.

1.2 The pathophysiology of migraine headache

Two major concepts of migraine pathophysiology have emerged, but both are surrounded by some controversy and inconsistency. One concept holds that pain is related to the activation of the trigeminovascular system (TGVS), this activation being is secondary to cortical spreading depression (CSD), a unique, apparently migraine-specific wave of excitatory cortical neural activity followed by a depressed state. Increased cortical excitability of the migrainous brain would serve as a basis for CSD. Others accept CSD only as the cause of migraine aura symptoms, but assume that the activation of the TGVS is not indispensable for pain generation. Instead, a dysfunction of the pain-processing structures in the brainstem, a ‘brainstem generator’ is considered responsible for the migraine attack.

Pain-sensitive structures in the skull, such as the large cerebral vessels, the venous sinuses and the dura mater, receive nociceptive sensory innervation from the ophthalmic branch of the trigeminal nerve. Their axons give collaterals to the neighbouring vessels, and release vasoactive mediators, resulting in vasodilation and plasma extravasation, and leading to

‘neurogenic inflammation’. Second-order neurons from the trigeminal nucleus ascend to the thalamus, and third-order neurons set out to various cortical areas. Second-order neurons give collaterals to the superior salivatory nucleus and to the ventrolateral periaqueductal grey matter (PAG), resulting in the release of further mediators and the modulation of pain inhibition, respectively.

A slowly spreading wave of neural depolarization followed by depressed neural activity, referred to as CSD, can be elicited in the visual cortex of rodents [16]. It is generally accepted that this is the electrophysiological correlate of the visual aura symptoms of human migraine. Similar events in relevant cortical areas are also postulated to be responsible for other kinds of aura symptoms. Chemicals capable of activating or sensitizing the perivascular nociceptive afferents are released into the cortical interstitial fluid during CSD. Some suggest that this is how migraine attacks start [17]. Although no aura symptom presents in 70% of migraine patients, such a pathophysiological event proceeding in clinically silent cortical areas cannot be excluded, however.

As an alternative explanation, abnormal brainstem activity has been suggested to act as a pain generator in migraineurs (brainstem generator). This is supported by the finding that electric stimulation of the PAG for pain control can elicit migrainous headache in non-migraineurs [18]. Those accepting this theory consider that activation of the TGVS is not necessary for headache.

Several lines of evidence indicate that cortical excitability is increased in migraineurs, which possibly provides the basis for CSD. Among others, psychophysical studies of the effects of physical stimulation on various processes of different types of sensation and perception confirm cortical hyperexcitability. It is of great interest that excitability demonstrates periodic changes, reaching its highest degree just before a migraine attack and normalizing during it, this phenomenon being termed ‘neurophysiological periodicity’ [19].

Any of the trigeminal afferent, second- or third-order pain-processing central neurons can become sensitized, and exhibit an increased responsiveness to stimuli. An example of the sensitization of trigeminal afferents (peripheral sensitization) is the increase in the degree of headache in response to physical exertion, a stimulus otherwise not causing pain. Allodynia, the painful experience of an otherwise indifferent stimulus from or even from outside a referred pain area is explained as sensitization of the second or the third-order neuron,

respectively. Some authors suggest that peripheral sensitization contributes to TGVS activation, while central sensitization may play a role in cortical hyperexcitability.

Genetic factors play an important role in migraine pathophysiology, as indicated by the apparent familial occurrence of migraine [20] and the mutations revealed in familial hemiplegic migraine [21].

1.3 Some special aspects of childhood related to the topic

Of all the organs, the brain undergoes the greatest rate of development during postnatal life, and more so as we go backwards in time towards birth, and beyond. Indeed, the International Headache Society (IHS) recognizes special childhood syndromes, such as cyclical vomiting, abdominal migraine and benign paroxysmal vertigo of childhood, as early precursors of a migrainous disorder, manifesting in the developing brain [1]. Thus, childhood puts investigations of this field in a special setting. Possible methodological differences are merely one example. A more important question is whether the prevalence and features of migraine do change across age cohorts. It is well established that the prevalence culminates at around the end of the 4^{th} decade of life [22], but little is known concerning the changes in prevalence, and much less about the possible changes in symptoms during childhood. Awareness of the characteristics of the whole age spectrum is important for a correct diagnosis both in epidemiological studies and in everyday clinical practice. Patient care, examinations, treatment planning, preventive measures and education should be carried out accordingly. Furthermore, the age-characteristic symptoms and the possible underlying alterations in the physiological processes may furnish information not only about migraine itself, but also about the functioning of the developing brain.

1.4 Visual information processing

Visual information processing is the most complex of all sensory modalities, involving at least 32 extrastriate areas and relating to over 50% of the neocortex in macaque monkeys [23]. Processing starts in the retina, from where information runs via the lateral geniculate nucleus in two major pathways, the M- (magnocellular) and P-pathways (parvocellular), to end in layers 4Cα and 4Cβ, respectively, of the primary visual cortex (V1). From there, the P-pathway projects via the parastriate cortex (V2) to the inferior temporal cortex (IT), forming

the ‘ventral pathway’ or ‘ventral stream’. This path receives a contribution from the M-pathway, too. The majority of the M-pathway extends from the V1 through the V2 to the middle temporal area (MT or V5), and then to the posterior parietal cortex, to form the ‘dorsal pathway’. Retinotopy is strictly preserved throughout [24]. Simple visual information on form and colour, necessary for further analysis, is conveyed by the P-pathway, whilst that on motion and depth is transmitted through the M-pathway. Perceptual organization of the form of objects starts in layers 4Cβ and 2/3 of the V1, and continues in the V2, and more complex forms are processed in the IT, supplied with information by the ventral pathway. Information on motion is processed mainly in the MT, based on data supplied by the dorsal pathway [25].
The bottom-up information processing relating to object recognition is facilitated by top-down influences from the prefrontal cortex and other cortical areas, therefore even details of visual perception are apparently a result more of a network program than of the activity of simple hierarchical systems [26].

2. AIMS OF THE STUDIES

1. Migraine frequency may vary in different geographical areas, therefore data on regional prevalence are needed for several purposes. As no such survey has been conducted in children in Hungary, we set out to establish the prevalence of migraine in a wide range of paediatric age groups in Szeged.
2. Both the prevalence and the symptoms of a disease may change with age. Our second major aim was to investigate how the prevalence and symptoms of migraine change with age in this population.
3. It is to believed that the cortical areas involved in visual perception may be especially affected by the pathophysiological processes of migraine. To assess whether alterations occur in migraine, we compared the performance of migrainous children with that of their healthy peers in two psychophysical paradigms: their contour integration capacity and motion coherence detection ability were tested.
4. With regard to the developing brain, we investigated whether changes occur in these psychophysical performances of migrainous children with increasing age.

3. PATIENTS AND METHODS

3.1 Epidemiological study

3.1.1 Study population

This cross-sectional school-based study was performed in the city of Szeged, the regional centre of South-Eastern Hungary, with 170,285 inhabitants. Of the total of 12,094 primary school pupils, all 9,234 attending one or other of the 21 municipality-maintained schools were invited to participate. High schools were selected by a two-stage stratified cluster sampling method, which resulted in a total of 6,178 pupils being invited to participate, i.e. 52% of the total.

3.1.2 Questionnaire

A questionnaire consisting of 37 questions was compiled. After questions relating to birth date and gender, the children were asked if they had ever had headaches more than one time, not connected with febrile illness or a head injury. Further questions concerning headache during the preceding 12 months involved the pain characteristics, so that a diagnosis of migraine could be established according to the International Classification of Headache Disorders, 2nd edition (ICHD-II).

Questions on nausea, vomiting, photophobia and phonophobia offered a 5-grade scale response based on frequency, ranging from 'always' to 'never', and we accepted the first 3 grades as positive. So as not to force any response, 'something else, namely:', 'I don't know' and 'I'm not sure' were options at most questions, and the latter two were evaluated as negation, just as when no answer was given. As headache features may vary from one attack to another, more than one answer was accepted in some cases and accepted as a migraine feature if there was a common characteristic amongst them.

The children took the questionnaires home to complete them together with their parents. Initially we distributed 124 questionnaires to randomly selected students to determine whether there was a need to make any changes, but we found that it was not necessary.

After approval had been granted by the city authorities, the school directors and the Ethical Committee of Szeged University, the study was performed in April and May, 2011.

3.1.3 Validation of the questionnaire

328 randomly selected parents and students were contacted via telephone, and the headache-related questions were asked again. This revealed 83.2% sensitivity, 92.6% specificity, and 85.5% positive and 91.3% negative predictive values of the questionnaire responses.

3.1.4 Data analysis

For the diagnosis of migraine, the ICHD-II criteria were strictly applied, with the single exception that a minimum of only 3 relevant headache episodes was required. A time limit of a minimum headache duration of 1 h was set for the 7-14-year-olds. For the 15-18-year age groups, the prevalence was calculated with a minimum duration of both 1 h and 4 h. No distinction was made between migraine with or without aura. In the calculations on the headache features, a diagnosis of migraine was accepted with a minimum headache duration of 1 h in all age groups.

For statistical analyses, SSPS for Windows (version 17.0) was used. The trends of the changes in the migraine prevalence data were assessed by Poisson regression (incidence rate ratio (IRR) and 95% confidence interval (95% CI)). For comparison with the results of other authors, we performed the same calculation when sufficient data were available. The trends in the changes in frequency of the various migraine features were estimated by using logistic regression (odds ratio (OR) and 95% CI), and those which demonstrated significant changes were further evaluated by multiple regression analysis. For the evaluation of changes in headache frequency and duration, Pearson's chi-square test was used.

3.2 Psychophysical studies

3.2.1 Selection of the participants

Consecutive children aged between 6 and 18 years with migraine without aura (MO), and with no other known neurological condition, were selected upon their first visit to our outpatient clinic. Migraine diagnosis was established according to the ICHD-II criteria [1]. No prophylactic migraine therapy had ever been administered to any participant before our measurements; the children had taken only over-the-counter painkillers before the study. Testing was performed interictally in all cases. Age- and sex-matched controls were recruited

from local schools in Szeged. All subjects, either healthy or migraineurs, had normal or corrected-to-normal (20/20) Snellen visual acuity, tested for both eyes separately. Children with extreme myopes, anisometropes or amblyopes were excluded from the study. Before each testing session, the children and their parents were provided with information on the aims and course of the procedure and they signed an informed participation consent form. The studies were approved by the Ethics Committee of the University of Szeged, and conformed to the tenets of the Declaration of Helsinki in all respects.

3.2.2 Visual contour integration study

Contour detection stimuli were presented on cards, at a distance of 0.5 m (size: 18 x 24.5 cm, subtending approximately 21° x 28°). On each card, a circular contour consisting of 12-14 Gabor patches was embedded in a background of randomly placed patches (noise) (reduced-size examples are illustrated in Figure 1). The task was to locate and indicate the contour. The cards were presented in a sequence of increasing difficulty. Contour visibility (difficulty) was varied by manipulating the relative noise density (*D*). The *D* value was defined as the ratio of the average noise spacing over the 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. At $D>1$, the contour elements were closer to each other than the noise elements. However, at $D<1$, this cue was not available, and it was impossible to detect the contour without orientation-specific long-range interactions.

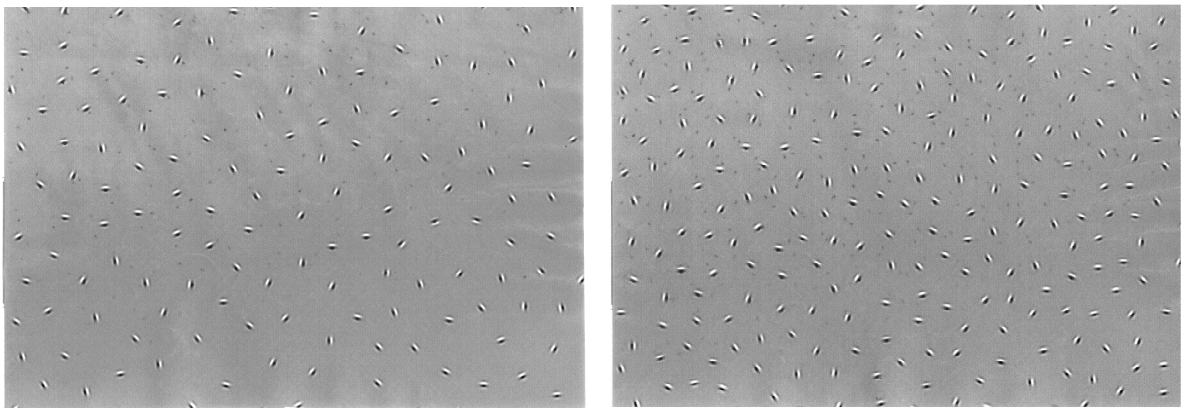

Figure 1. Examples of cards with Gabor patches forming circles or acting as noise (size reduced at a 1:2.8 ratio). Left: $D=1.15$, right $D=0.85$ (right).

3.2.2.1 Data analysis for visual contour integration study

Participants were assigned to age cohorts reflecting the normal healthy developmental steps of this function, as found by Benedek et al. [27], i.e. 6-9 years, 10-14 years, and 15-18 years. The dependent variable was the minimum value of D (D_{min}), reflecting the subject's absolute detection threshold.

As our data did not follow a normal distribution, and since splitting of the total number of participants into three cohorts left us with a relatively small number of elements for each particular comparison, we applied non-parametric analyses. For the between-group comparisons, i.e. migraineurs vs. controls, by age cohort, we used the Wilcoxon matched pairs test at a significance level of $p<0.05$, while for the within-group comparisons, i.e. the comparison of the age cohorts within the migraineur and control groups, the Mann-Whitney U-test (MWU) was applied, after the Bonferroni correction at $p<0.017$. The MWU at the same level of significance was also performed in both groups for all cohorts to establish whether the gender causes any significant variance in D_{min}. For a better characterization of developmental tendencies, Spearman's correlation coefficient (r) was computed for cohort-wise comparisons in both groups, and to reveal whether there was a significant correlation between attack frequency and D_{min}.

3.2.3 Study of the development of visual motion processing

Stimuli were generated with Psychophysics Toolbox Version 3 (http://psychtoolbox.org/), under MatLab (MathWorks, Inc.) on a PC, and presented on a 24-inch LCD monitor at a resolution of 1920 by 1200 pixels and at a 60 Hz refresh rate. Stimuli were random dot kinematograms with variable coherence rates (Figure 2). Stimuli consisting of 100 moving dots were presented on a neutral grey background in a centred rectangular stimulation field occupying 60% of the whole screen. At a viewing distance of 0.5 m, the stimulation field subtended an area of 35.74° by 22.34°. The diameter of each dot was 10 pixels (~3 mm), subtending ~0.34°. In each trial a given percentage of the dots moved coherently to the right or to the left, while the rest moved in random directions. After each trial, movement starting points were regenerated so that subjects would avoid using the movement of one dot as a clue. One trial lasted approximately 0.8 s (50 consecutive frames), during which each dot travelled 38.4 mm at a speed of 48 mm/s. The path of movement therefore, subtended a visual angle of

4.4° for each dot. The task of the subjects was to indicate whether the coherently moving dots moved to the left or to the right, by pressing the appropriate cursor button on a computer keyboard. The absolute coherence threshold was determined via the QUEST adaptive threshold seeking algorithm [28] (Figure 2).

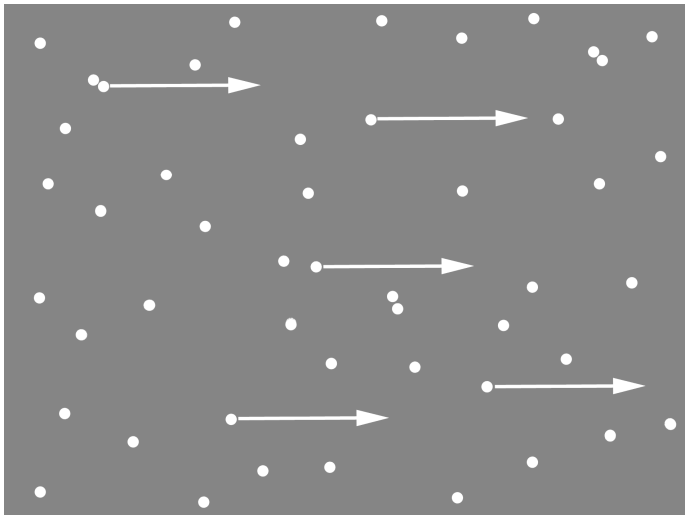

Figure 2. A static illustration of the applied stimulus. In each trial a given percentage of the dots moved coherently to the right or to the left (targets), while the rest moved randomly (noise). Here a 10% condition is shown with a total of 50 dots, 5 of which belong in the coherently moving group (arrows). During the actual measurements, 100 dots were used, according to the same principles as described here. For the stimulus details, see the text.

3.2.3.1 Data analysis for study of the development of visual motion processing

For the statistical analysis, we used Statistica for Windows 9 (StatSoft, Inc.). Because of the relatively low number of participants, we did not divide the groups into cohorts by age. However, we ensured that the demographic characteristics of the migraineurs and the controls would be as similar as possible (see Table 1), so that the comparisons would be valid. In consequence of the lack of normal distribution in both the migraineur group (Shapiro-Wilk W=0.94, p=0.44) and the control group (Shapiro-Wilk W=0.92, p=0.07), we chose the non-parametric MWU for the comparisons. Correlations (Spearman's r) between task performance and certain migraine characteristics (such as a positive family history and attack frequency) were also calculated.

4. RESULTS

4.1 Epidemiological study

A total of 15,412 questionnaires were distributed, and 7,361 that were appropriate for evaluation were returned. The overall response rate was 48%, 56.3% from primary school pupils, most of them under 15, and 34.6% from high school pupils. 3,465 (47.1%) of the respondents were boys and 3,896 (52.9%) were girls. Their ages varied between 6 years 9 months and 23 years 9 months. The 20 pupils younger than 7 years were grouped together with the 7-year-olds, and those over 18 years among the 18-year-old students (Table 1). As the overall response rate was relatively low, we compared the prevalence of migraine in the 8 primary schools with the highest response rate (70%) with that for all of the pupils of the same age: 9.3% and 9.2%, respectively (p=0.84).

Age (years)	**All respondents**			**Migraine pupils (duration >1 h in all age groups)**				**Migraine pupils (duration >4 h over 15 years)**			
	Boys + Girls (*n*)	**Boys (*n*)**	**Girls (*n*)**	**Boys + Girls (%)**	**Boys (%)**	**Girls (%)**	***p* value**	**Boys + Girls (%)**	**Boys (%)**	**Girls (%)**	***p* value**
7	557	249	308	3.6	3.2	3.9	0.27	3.6	3.2	3.9	0.27
8	657	333	324	5.2	3.3	7.1	<0.001[a]	5.2	3.3	7.1	<0.001[a]
9	701	348	353	6.6	7.5	5.7	0.20	6.6	7.5	5.7	0.20
10	728	391	337	10.3	9.0	11.9	0.022[a]	10.3	9.0	11.9	0.022[a]
11	663	328	335	10.0	9.5	10.4	0.27	10.0	9.5	10.4	0.27
12	656	332	324	11.9	11.1	12.7	0.19	11.9	11.1	12.7	0.19
13	698	334	364	12.8	9.0	16.2	<0.001[a]	12.8	9.0	16.2	<0.001[a]
14	565	273	292	12.6	11.7	13.4	0.20	12.6	11.7	13.4	0.20
7-14	5,225	2,588	2,637	9.2	8.1	10.2	<0.001[a]	9.2	8.1	10.2	<0.001[a]
15	607	249	358	18.5	13.3	22.1	<0.001[a]	6.6	5.2	7.5	<0.001[a]
16	506	211	295	17.2	9.5	22.7	<0.001[a]	8.1	3.3	11.5	<0.001[a]
17	421	171	250	21.6	11.1	28.8	<0.001[a]	9.5	5.3	12.4	<0.001[a]
18	602	246	356	24.6	14.6	31.5	<0.001[a]	11.3	6.1	14.9	<0.001[a]
15-18	2,136	877	1,259	20.5	12.3	26.2	<0.001[a]	8.8	5.0	11.5	<0.001[a]
Total	**7,361**	**3,465**	**3,896**	**12.5**	**9.2**	**15.4**	**<0.001[a]**	**9.1**	**7.3**	**10.6**	**<0.001[a]**

Note: n: number of respondents; %: prevalence of migraineur pupils; p value: statistical difference in migraine prevalence between boys and girls in the individual age and gender groups; [a]: statistically significant.

Table 1. Prevalence of migraine overall and in the individual age and gender groups.

4.1.1 Prevalence of migraine headache

With a minimum headache duration of 1 h, we found 917 migrainous pupils in the overall population: 318 boys and 599 girls. The overall 12-month prevalence was 12.5%: 15.4% among girls and 9.2% among boys. Migraine was more common among the high-school pupils (20.5%) than in the 7-14-year age group (9.2%).

In contrast with ICHD-II, where no age limit but 'childhood' was applied for a headache duration of 1 h [1], the 1st classification of headache disorders by the IHS (IHS-1) accepted a duration of 2 h for migraine diagnosis only 'under the age of 15' [29]. Calculation with this second approach, i.e. applying a 4-h limit over the age of 15, but accepting a duration of only 1 h under that age, resulted in a significant decrease in the number of migraineurs to 668, yielding an overall prevalence of 9.1% (7.3% in boys and 10.6% in girls). With this approach, the 15-18-year-olds were less commonly migrainous (8.8%) than the younger pupils (9.2%).

4.1.2 Age and gender-related prevalence

Girls suffered from migraine more commonly in all but the 9-year age group, though the gender difference was significant in only 3 of the 8 age groups under 15 (Table 1). A steady increase in prevalence was found from 7 up to 18 years, both overall (IRR: 1.15, 95% CI: 1.13-1.18, $p<0.001$), and in each gender, at a higher rate in girls (IRR: 1.20, 95% CI: 1.17-1.23, $p<0.001$) than in boys (IRR: 1.07, 95% CI: 1.04-1.11, $p<0.001$) (Table 1).

With the use of a minimum headache duration of 4 h for the diagnosis of migraine over the age of 14, the continuous rise in the yearly prevalence dropped abruptly at the age of 15 years, and then resumed at the previous rate (IRR: 1.16, 95% CI: 1.03-1.21, $p=0.007$).

Most of the published studies that used the IHS-1 or ICHD-II criteria revealed a steady increase in the age-specific prevalence data (Figure 3) [30-42].

Poisson regression analysis of the data inferred from those publications demonstrated a rate of increase similar to that which we observed [30, 33, 38, 39], though higher rates too occurred [32, 34, 41]. When the genders were evaluated separately, the boys showed a significant increase in 3 [30, 33, 34] and no statistically significant change in 3 other studies [31, 40, 41]. Among the girls, the prevalence of migraine increased in 4 surveys [30, 34, 40, 41] and exhibited no statistically significant change in 3 others [31, 33, 43] (Table 2). Only one study

[31] did not note a continuous elevation in either gender, but an increase from 11 to 12 years only, in girls.

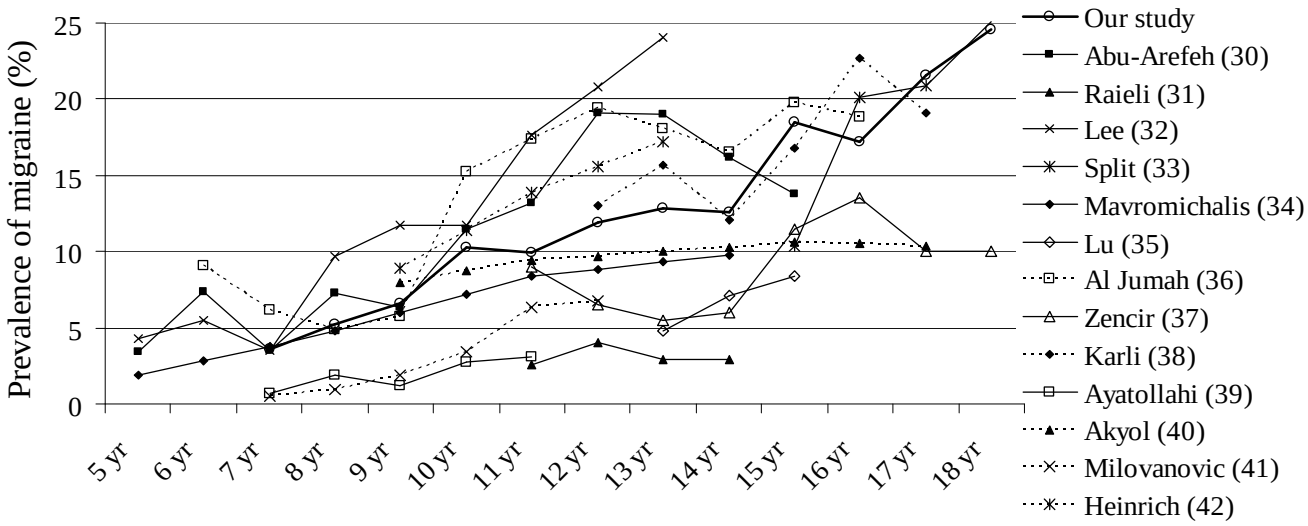

Figure 3. Changes in prevalence rates (%) of migraine across various childhood age groups in different studies. References in parentheses.

4.1.3 Prevalence of migraine symptoms

Of all the major migraine features, moderate or severe pain intensity was unequivocally the most common, presenting in 99% of the migraineurs, in all age groups and both genders. Phonophobia (88%) and photophobia (82%) followed (Figure 4). A high frequency of headache (OR: 1.652717, 95% CI: 1.2017-2.273007, p=0.002), a uni/bilateral location (OR: 1.460619, 95% CI: 1.05892-2.014702, p=0.021), phonophobia (OR: 1.860171, 95% CI: 1.313793-2.633776, p<0.001) and photophobia (OR: 1.822099, 95% CI: 1.212395-2.738417, p=0.004) were reported significantly more commonly, whereas vomiting presented much more rarely (OR: 0.6620754, 95% CI: 0.4610252-0.9508023, p=0.026) in girls than in boys. In general, vomiting was the least common symptom in both genders (22% in boys, 14% in girls).

Study	Age	Gender	Change in prevalence	IRR [95% CI]	*p* value
Our study	7-18 yr	boys+girls	↑	1.15 [1.13-1.18]	<0.001[a]
		boys	↑	1.07 [1.04-1.11]	<0.001[a]
		girls	↑	1.20 [1.17-1.23]	<0.001[a]
Abu-Arafeh [30]	5-15 yr	boys+girls	↑	1.16 [1.10-1.23]	<0.001[a]
		boys	↑	1.13 [1.04-1.22]	0.002[a]
		girls	↑	1.20 [1.11-1.29]	<0.001[a]
Raieli [31]	11-14 yr	boys+girls	N.S.	1.01 [0.75-1.35]	0.963
		boys	N.S.	0.71 [0.46-1.12]	0.138
		girls	N.S.	1.39 [0.93-2.10]	0.111
Lee [32]	5-13 yr	boys+girls	↑↑	1.27 [1.20-1.35]	<0.001[a]
Split [33]	15-19 yr	boys+girls	↑	1.10 [1.02-1.18]	0.017[a]
		boys	↑↑	1.30 [1.09-1.56]	0.004[a]
		girls	N.S.	1.07 [0.99-1.16]	0.109
Mavromichalis [34]	4-15 yr	boys+girls	↑↑	1.58 [1.35-1.84]	<0.001[a]
		boys	↑↑	1.33 [1.05-1.68]	0.018[a]
		girls	↑↑	1.77 [1.45-2.17]	<0.001[a]
Karli [38]	12-17 yr	boys+girls	↑	1.10 [1.04-1.17]	0.001[a]
Ayatollahi [39]	6-11+ yr	boys+girls	↑	1.44 [1.14-1.81]	0.002[a]
	11-17+ yr	girls	N.S.	0.94 [0.84-1.05]	0.267
Akyol [40]	9-17 yr	boys+girls	N.S.	1.04 [1.00-1.08]	0.057
		boys	N.S.	0.98 [0.92-1.04]	0.508
		girls	↑	1.09 [1.03-1.15]	0.002[a]
Milovanovic [41]	7-12 yr	boys+girls	↑↑	1.63 [1.31-2.02]	<0.001[a]
		boys	N.S.	1.38 [0.99-1.92]	0.060
		girls	↑↑	1.80 [1.35-2.40]	<0.001[a]
Heinrich [42]	9-14 yr	boys+girls	↑↑	1.38 [1.24-1.54]	<0.001[a]
		boys	↑↑	1.37 [1.17-1.59]	<0.001[a]
		girls	↑↑	1.40 [1.20-1.62]	<0.001[a]

Note: ↑: increasing prevalence at a rate similar to ours; ↑↑: increasing prevalence at a rate higher than ours; N.S.: no significant change in prevalence rate; [a]: statistically significant.

Table 2. Poisson regression analysis of trends of changes in the prevalence of migraine across ages and genders.

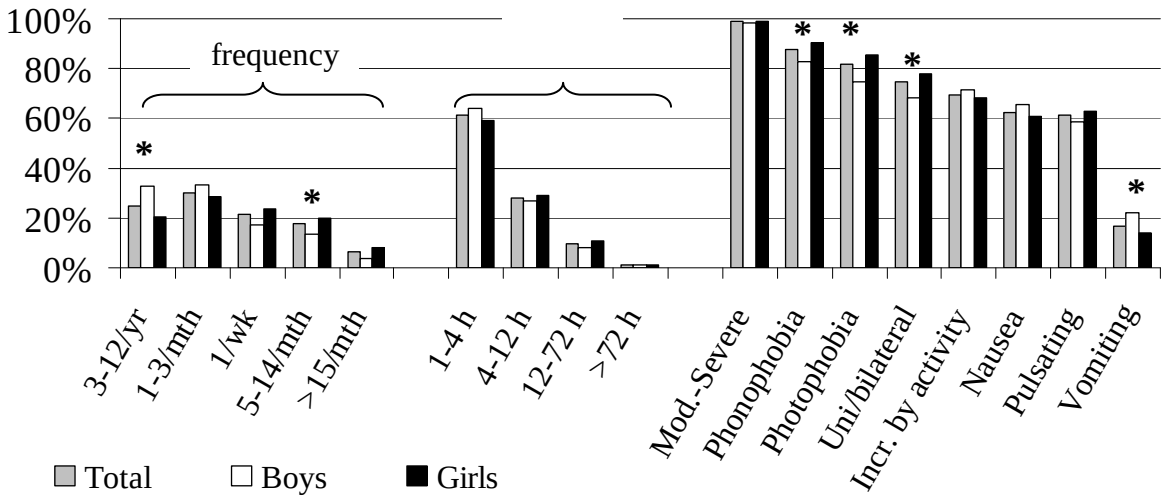

Figure 4. Prevalence of frequency, duration and symptoms of migraine attacks in the overall population. *: statistically significant difference between boys and girls.

4.1.4 Change in migraine symptom prevalence across age groups

The frequency and duration of headache were low in the youngest children and gradually became higher with advancing age (Figure 5), in both boys and girls. Nausea and vomiting displayed a decreasing tendency. With increasing age, a pulsating character became more prevalent in boys, while a uni/bilateral location, photophobia and phonophobia did so only in girls. All these changes proved significant in logistic regression analysis, and the changes in frequency, uni/bilaterality, nausea (only in boys), vomiting (only in girls) and phonophobia remained significant in multiple regression analysis (Table 3).

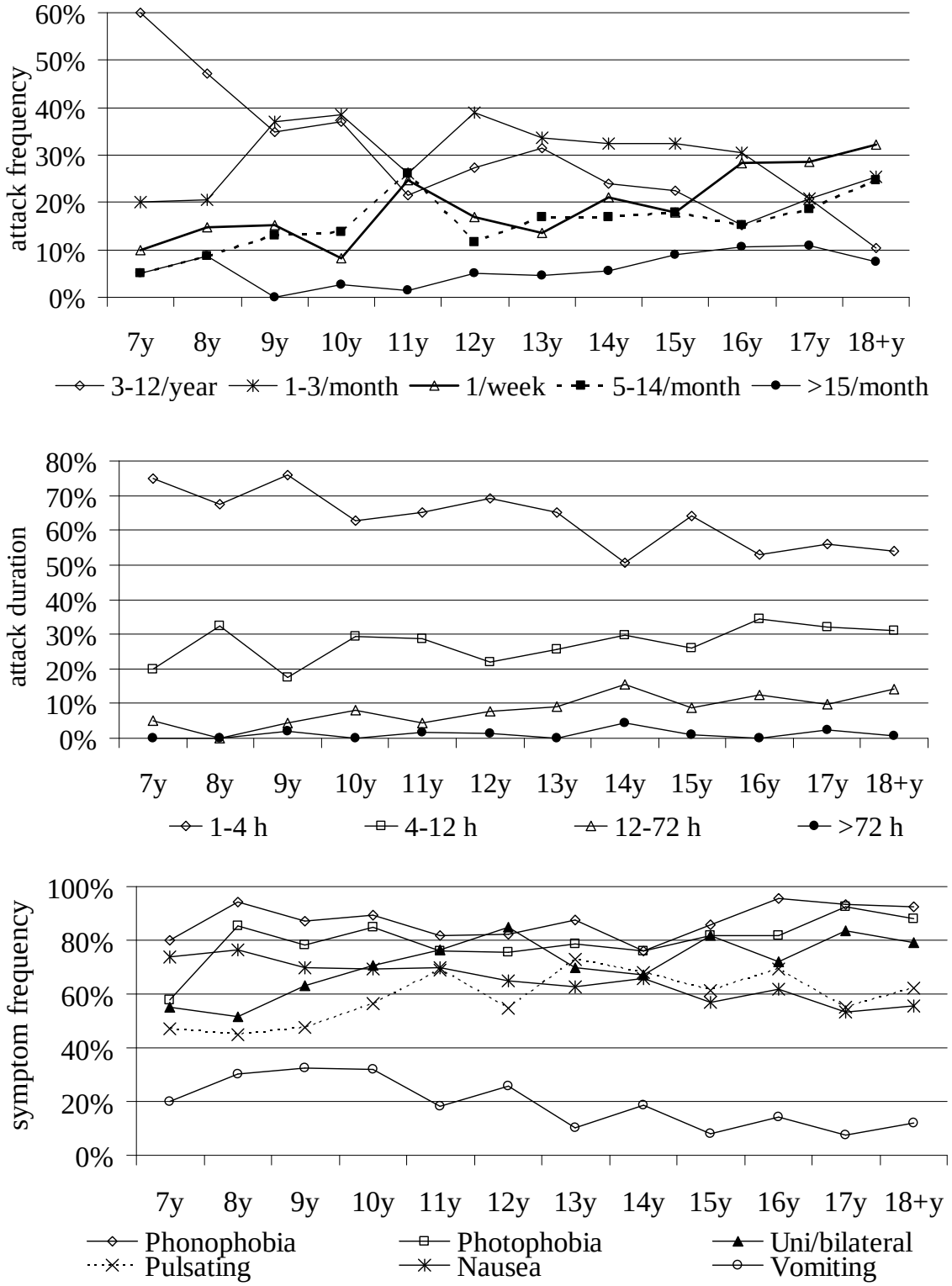

Figure 5. Changes in migraine attack frequency, duration and some other symptoms across age groups.

Logistic regression analysis

	Boys+Girls			Boys			Girls		
	OR	***p* value**	**95% CI**	**OR**	***p* value**	**95% CI**	**OR**	***p* value**	**95% CI**
frequency	1.18	<0.001[a]	1.12-1.23	1.14	0.001[a]	1.05-1.24	1.17	<0.001[a]	1.10-1.25
duration	1.08	0.001[a]	1.03-1.13	1.08	0.037[a]	1.01-1.17	1.07	0.011[a]	1.02-1.13
uni/bilateral	1.09	<0.001[a]	1.04-1.15	1.04	0.359	0.96-1.12	1.11	0.001[a]	1.04-1.18
non-pulsating	0.96	0.09	0.92-1.01	0.91	0.012[a]	0.84-.98	1.00	0.981	0.95-1.06
physical activity	0.98	0.40	0.93-1.03	0.98	0.727	0.90-1.08	0.98	0.542	0.92-1.05
severe	1.02	0.84	0.85-1.23	0.96	0.774	0.72-1.28	1.04	0.737	0.81-1.34
nausea	0.92	<0.001[a]	0.88-0.96	.90	0.006[a]	0.83-0.97	0.94	0.018[a]	0.89-0.99
vomiting	0.86	<0.001[a]	0.82-0.91	.90	0.019[a]	0.82-0.98	0.86	<0.001[a]	0.80-0.92
photophobia	1.09	0.002[a]	1.03-1.14	1.05	0.300	0.96-1.14	1.08	0.026[a]	1.01-1.16
phonophobia	1.07	0.024[a]	1.01-1.14	1.00	0.948	0.91-1.10	1.10	0.027[a]	1.01-1.20

Multiple regression analysis

	Boys+Girls			Boys			Girls		
	OR	***p* value**	**95% C]**	**OR**	***p* value**	**95% CI**	**OR**	***p* value**	**95% CI**
frequency	1.43	<0.001[a]	1.26-1.62	1.36	0.010[a]	1.08-1.71	1.43	<0.001[a]	1.23-1.67
duration	1.11	0.32	0.90-1.37	1.10	0.645	0.74-1.63	1.09	0.505	0.85-1.41
uni/bilateral	1.61	0.006[a]	1.15-2.26	-	-	-	1.58	0.035[a]	1.03-2.43
non-pulsating	-	-	-	0.70	0.199	0.41-1.21	-	-	-
nausea	0.90	0.52	0.64-1.25	0.47	0.010[a]	0.26-.083	1.01	0.947	0.68-1.52
vomiting	0.44	<0.001[a]	0.29-0.68	0.75	0.428	0.37-1.53	0.41	0.002[a]	0.23-0.71
photophobia	1.23	0.36	0.79-1.90	-	-	-	0.93	0.814	0.52-1.67
phonophobia	1.55	0.10	0.92-2.59	-	-	-	1.97	0.049[a]	1.00-3.88

[a]: statistically significant increase in symptom frequency through ages

Table 3. Trends in changes of frequency of migraine features from 7 through 18 years.

4.2 Psychophysical Studies

4.2.1 Visual contour integration

48 MO children, aged between 6 and 18 years, and 48 age-matched controls with no headache participated in this case-control study. The most important migraine-related and demographic characteristics and major migraine symptoms of this population are summarized in Table 4.

	Number of participants (girls/boys) (*n*)	**Mean age** (years)	**Average migraine history** (years)	**Mode of days since last attack** (days)	**Average attack duration** (hours)	**Monthly number of attacks** (mode (range))
6-9 years	8 (5 / 3)	7.8	0.8	3	1.5	1 (1-3)
10-14 years	21 (12 / 9)	12.2	1.7	2	2	2 (2-5)
15-18 years	19 (13 / 6)	17.1	2.2	3	2	2 (2-5)
	Unilateral location (%(*n*))	**Pulsating quality** (%(*n*))	**Severity: severe** (%(*n*))	**Aggravated by exercise** (%(*n*))	**Nausea/ vomiting** (%(*n*))	**Photophobia/ phonophobia** (%(*n*))
6-9 years	25 (2)	75 (6)	100 (8)	38 (3)	100 (8)	100 (8)
10-14 years	71 (15)	90 (19)	95 (20)	90 (19)	71 (15)	48 (10)
15-18 years	84 (16)	100 (19)	89 (17)	74 (14)	84 (16)	63 (12)

Table 4. Characteristics of cohorts of migraineurs participating in visual contour integration study.

The comparison of the contour detection thresholds (D_{min}) of the migraineurs and the controls (between-group comparisons) by cohort revealed no difference in the 6-9-year age groups ($n_{1,2}$=8, p=1.0), while the controls performed significantly better in the 10-14 year ($n_{1,2}$=21, p<0.05); and 15-18 year cohorts ($n_{1,2}$=19, p<0.05); Wilcoxon matched pairs test. For the exact p values, see Table 5.

The results of the within-group cohort-wise comparisons for the migraine group, in the order of significance, were as follows: the 6-9-year group performed poorer than the 15-18-year group (MWU 7, n_1=8, n_2=19, p<0.001, two-tailed); and so did the 10-14-year group vs. the 15-18-year group (MWU 16, n_1=21, n_2=19, p=0.044, two-tailed), but the difference between

the 6-9-year and 10-14-year groups was not significant (MWU 55.5, n_1=8, n_2=21, p=0.53, two-tailed). Spearman's r coefficient for the total development between 6 and 18 years was 0.51 (p<0.05).

The analogous comparisons for the cohorts of the age- and sex-matched controls, yielded significant differences in all comparisons, with the following results: the 6-9-year group vs. the 10-14-year group (MWU 8, n_1=8, n_2=21, p=0.043, two-tailed); the 10-14-year group vs. the 15-18-year group (MWU 4.5, n_1=21, n_2=19, p<0.001, two-tailed); and the 6-9-year group vs. 14-18-year group (MWU 6, n_1=8, n_2=19, p<0.001, two-tailed). Spearman's coefficient r for the total development between 6 and 18 years was 0.65 (p<0.05).

Between-groups: migraineurs vs. controls Wilcoxon matched pairs test		**Within-group: migraineurs** Mann-Whitney U-test		**Within-group: controls** Mann-Whitney U-test	
M1 vs C1	p=1.0	**M1 vs M2**	p=0.5321	**C1 vs C2**	p=0.0433
M2 vs C2	p=0.0036*	**M2 vs M3**	p=0.0441	**C2 vs C3**	p<0.0001*
M3 vs C3	p=0.0042*	**M1 vs M3**	p=0.0007*	**C1 vs C3**	p<0.0001*

Table 5. Significance values for the within-group and between-group comparisons of average D_{min} values of age groups. M and C denote migraineurs and controls, respectively, and the index numbers indicate the age cohorts as follows: 1: 6-9 years; 2: 10-14 years; 3: 15-18 years. M1 vs. M2, for instance means a comparison between the 6-9 and 10-14-year-old migraineurs. * denotes significant values.

No significant difference between genders was measured in any age cohort either among the migraineurs or among the controls: migraineurs: 6-9-year group (MWU 7, n=8, p=1.0, two-tailed); 10-14-year group (MWU 51, n=21, p=0.86, two-tailed); 15-18-year group (MWU 37.5, n=19, p=0.9, two-tailed); and controls: 6-9-year group (MWU 6.5, n=8, p=0.79, two-tailed); 10-14-year group (MWU 40, n=21, p=0.35, two-tailed); 15-18-year group (MWU 37, n=19, p=0.9, two-tailed).

Spearman's coefficient r for attack frequency vs. D_{min} revealed no significant difference by cohort: 6-9-years group: 0.52 (N.S.); 10-14-year group: 0.33 (N.S.), 15-18-year group: 0.17 (N.S.); but did so when the cohorts were taken together in a single migrainous or control group: 0.31 (p<0.05). All results are summarized in Figures 6, 7 and 8.

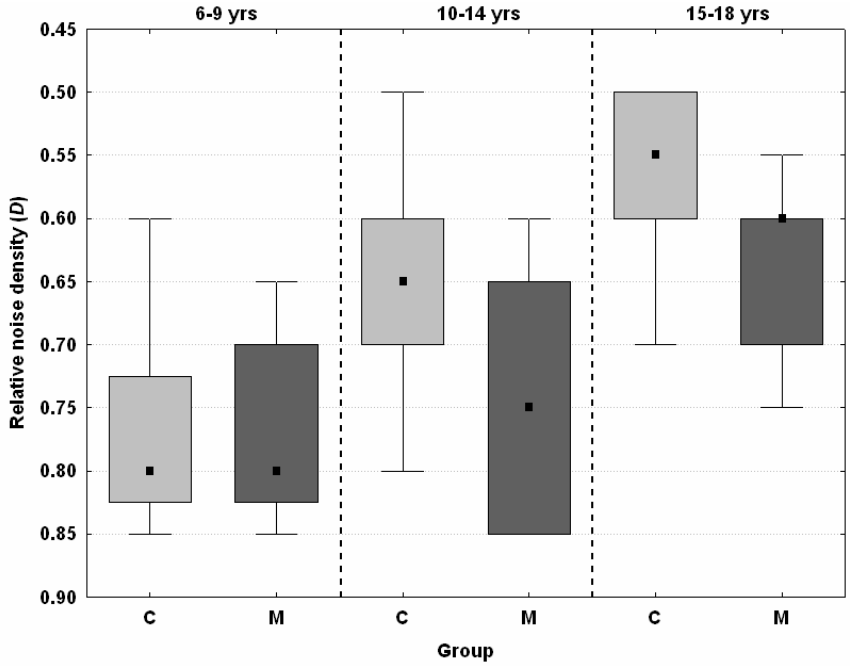

Figure 6. A group- and cohort-wise summary of performance. The small solid squares indicate the median value of D_{min} in the given group. Boxes indicate 25-75 percentiles, and whiskers the non-outlier range.

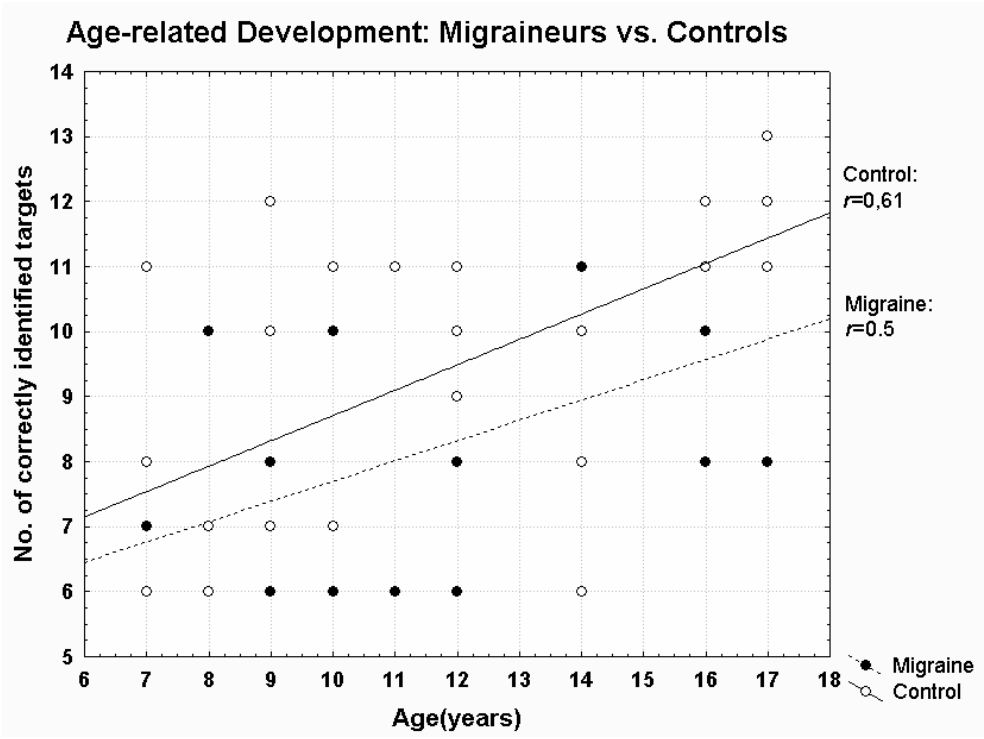

Figure 7. Comparison of age-dependent development of contour detection in migrainous and control children. Dashed line/full circles: migraineurs; continuous line/empty circles: controls. As several circles represent more than one child, their number is less than that of the participants.

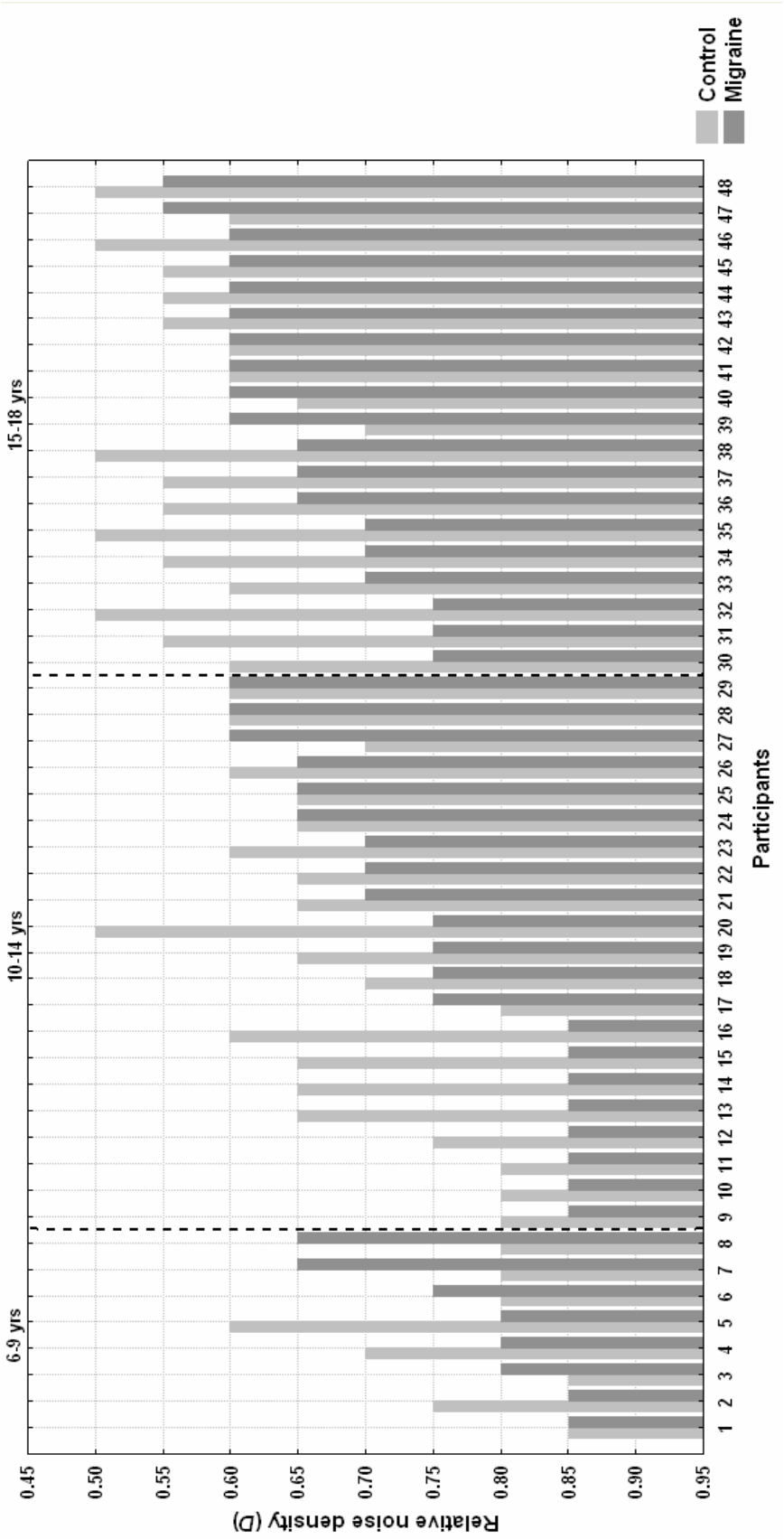

Figure 8. A plot of individual performance. D_{min} values of each migraineur-control pair are given. Light-grey bars indicate controls, and dark-grey bars indicate migraineurs. Data have been ordered according to the performance of the migraineurs in each cohort. Numbers on the lower horizontal axis refer to pairs, not individuals. C: controls, M: migraineurs.

4.2.2 The development of visual motion processing

Visual motion processing was investigated in 14 MO children and 21 controls, aged between 8 and 17 years. Their age data and most important migraine-related characteristics are presented in Table 6.

The comparison of the two groups revealed a significant difference in motion coherence detection threshold, the control group having a lower threshold (MWU=62.5, n_1=14, n_2=21, p<0.05, two-tailed; control: median (range) 0.2 (0.18-0.23), migraineurs: median (range) 0.32 (0.14-0.56)). The difference between the two groups seemed to be more pronounced for girls (MWU=14.5, n_1=10, n_2=7, p<0.05, two-tailed) than for boys (MWU=18.5, n_1=7, n_2=11, p=0.07, two-tailed). No significant gender-related difference in performance was found within the groups: (MWU=18.5, n_1=7, n_2=7, p=0.07, two-tailed, migraineurs) and (MWU=41.5, n_1=10, n_2=11, p=0.35, two-tailed, controls).

	Number of participants (girls/boys) (*n*)	**Age mean (range)** (years)	**Average migraine history** (years)	**Mode of days since last attack** (days)	**Migraine in linear relatives** (*n*)	**Monthly number of attacks** (mode (range))
Migraineurs	14 (7 / 7)	13 (8-17)	2.13	4	8	2 (1-4)
Controls	21 (10 / 11)	12.4 (8-17)	-	-	3	-
	Unilateral location (%(*n*))	**Pulsating quality** (%(*n*))	**Severity: severe** (%(*n*))	**Aggravated by exercise** (%(*n*))	**Nausea/ vomiting** (%(*n*))	**Photophobia/ phonophobia** (%(*n*))
Migraineurs	71 (10)	100 (14)	86 (12)	71 (10)	43 (6)	57 (8)
Controls	-	-	-	-	-	-

Table 6. Characteristics of migraineurs and controls participating in the study of the development of visual motion processing.

A more detailed analysis of the age dependence of the motion detection threshold revealed that the control group performed at a constant level, regardless of age, while the motion coherence detection threshold of the migraineurs was higher at younger ages, but caught up with that of the controls by late puberty (Figure 9). In statistical terms: the regression coefficients differed significantly ($\beta_{migraine}$=-0.3; $\beta_{controls}$=-0.001, t=-5.68, p<0.001). This was

also reflected in the correlation coefficients (threshold vs. age): r=0.685, p<0.05, migraineurs; r=0.064, N.S., controls.

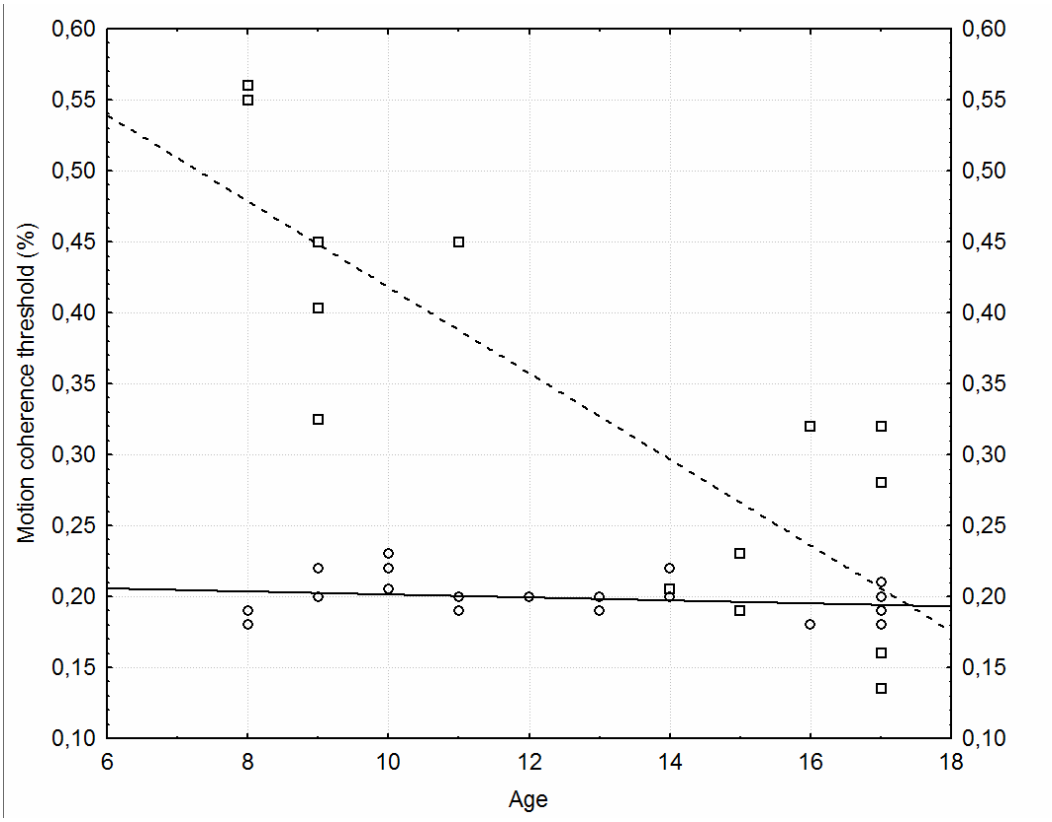

Figure 9. Age-dependent comparison of the visual motion detection thresholds of the migraineurs and the controls. Dashed line: migraineurs; continuous line: controls. Squares represent migraineurs and full circles control participants. At the age of 8 a robust difference is seen, but by the age of 17 this difference has disappeared. The performance of the migraineurs caught up with that of the controls by the age of 17, in terms of the motion detection threshold.

It was further found that migraineurs with direct line relatives suffering from migraine seemed to exhibit a poorer performance: (MWU=6.0, n_1=6, n_2=8, p<0.05, two-tailed). Neither the length of the disease history nor the frequency of the attacks exhibited a significant correlation with the performance: r=0.46, N.S.; and r=0.27, N.S., respectively.

5. DISCUSSION

5.1 Epidemiological study

Recurrent headache, the most common of all neurological complaints, poses a great burden on both the affected individual and society. An awareness of the epidemiological parameters is of importance for better patient care planning, and from this respect abundant data have been published from around the world [44].

A study in Hungary in 2000 revealed a migraine prevalence of 9.6% in adults [45] but no data on migraine have been published as concerns Hungarian children. The present school-based large-scale questionnaire study demonstrated an overall prevalence of migraine with or without aura in the age group 7-18 years of 12.5%, a level situated in the higher range of the results reported from similar surveys [44, 46]. We found that migraine headache was more common in girls, at a ratio of 1:1.67. The response rate in this population was relatively low. Although no difference emerged in the response rate-related prevalence of migraine in the 7-14-year-old pupils, such a bias can not be excluded among the adolescents.

The steady rise in the prevalence of migraine, peaking at the end of the 4th decade of life, is well established [20] and increases from young childhood to adulthood have also been demonstrated [30, 32-34, 36-39, 41, 47, 48]. We confirmed this finding in both boys and girls. Studies involving both children and adults tend to apply an identical minimum required duration of headache for all ages: those focusing on adults commonly stipulate 4 h [49-52], whilst those few that relate mostly to children and adolescents, but which include a proportion over the age of 18, apparently uniformly accept a 1 or 2-h limit (for adult migraineurs too) [33, 53]. The prevalence in childhood is underestimated by the previous approach, whilst that in adults is overestimated by the latter approach. Surveys based on the IHS-1 criteria, including children both under and over 15 years of age, commonly do not specify whether any distinction was made in the minimally required duration of headache [36, 37, 43, 54]. Strict adherence to this criterion as suggested by IHS-1 or ICHD-II would probably result in a drop in the age-related prevalence at the age of 15, or in adulthood, as noted in our study. Most published adult surveys indicated a 1.2-1.4 times higher prevalence of migraine when a 1 h

limit or no limit was applied, as compared with the prevalence based on a 4-h limit. With the requirement of a 4-h duration for adolescents, we observed the much lower prevalence of 8.8%, a value in accord with the rate of 9.6% found in Hungarian adults in 2000 [45].
Some authors have suggested the elimination of any time limit for the diagnosis of migraine during childhood [48, 55], which may question the need for a longer or any time limit for adults. Another option would be to apply a 2-h limit for those aged 15-18 years, while keeping a 1-h limit under the age of 15 and a 4-h limit over the age of 18 years. This approach would be in line with the experience that the duration of migraine episodes increases through childhood. However, this would make the diagnostic system somewhat more complicated.

Overall, the prevalence of migraine depends on a number of things. Inherent patient-related factors, such as the genetic background, gender and age, and environmental effects, such as an increasing level of stress, changes in alimentary habits, etc., may well play a role. However, methodological variances in epidemiological studies may cause undue differences. The most widely criticized point has been the minimally required headache duration. An increase in migraine duration with advancing age, as demonstrated here and by others, serves as the basis for the application of different time limits for children and adults in migraine diagnosis, as recognized by IHS-1 [29] and more so by ICHD-II [1]. However, this excludes those (whose numbers probably decrease with age) who experience shorter attacks with migraine characteristics, as discussed previously. A further problem is that the increase of the limit from 1 h to 4 h for adults causes an excessive drop in the estimated prevalence, and further modification of this criterion appears to be needed. Without this, in studies on a paediatric population with a broad age range, or in those equally comprising children, adolescents and adults, the further use of 'loose' diagnostic criteria can be expected, a practice resulting in data that are difficult to compare.

The most common migraine symptom in our study population was moderate or severe pain, followed by phonophobia and photophobia. This parallels the findings of numerous authors on paediatric populations of various ages [32, 39, 40, 48, 55-60]; only a few publications have reported appreciably different findings [54, 61, 62]. Apart from the latter studies, nausea and especially vomiting are generally regarded as the least common symptoms. The relatively

high frequency of a characteristic migraine headache location in our study may be related in part to the fact that here we accepted bilateral headache too, as suggested by ICHD-II.
The gender differences included higher rates of headache frequency, a uni/bilateral location, photophobia and photophobia in girls, and vomiting was more common in boys. Ando et al. [63] and Karli et al. [58] published similar findings from children aged 12-15 and 12-17 years, respectively. In 9-17-year-old students, Akyol et al. [40] observed slightly higher rates of a pulsating character, photophobia or phonophobia in boys and higher rates of nausea and/or vomiting in girls, though the differences were not significant. Vomiting and phonophobia were more common in boys in the study by Wöber-Bingöl et al. [61], while girls complained more commonly of the aggravating effect of physical activity.

Age-related differences in migraine headache location and duration are recognized by both IHS-1 and ICHD-II. Changes in the prevalence of other symptoms as a function of age have been investigated by only a few authors. It was our experience that the frequency and duration of the attacks increase with advancing age, whereas vomiting and nausea become less prevalent. Uni/bilaterality, photophobia and phonophobia increased significantly in prevalence only in girls, while a pulsating character did so only in boys. Hershey et al. [64] observed virtually the same findings among 3-18-year-old migraineurs, and Eidlitz-Markus et al. [65] did so as concerns the frequency, duration and vomiting in a 6-18-year-old paediatric population. Winner et al. [57] and Karli et al. [58] compared the trends between 12-14 and 15-17-year age groups, and reached similar conclusions to ours in respect of photophobia, phonophobia, nausea and vomiting; Karli et al. [58] additionally observed an increasing trend of a pulsating character and a unilateral location, though the extents of the changes were statistically significant for only localization, nausea and vomiting. In a comparison of migraine groups aged 3-10 and 10-14 years, Gherpelli et al. [55] detected a significant increase only in the pulsating character. No gender differences were investigated in these studies. In 2007, Özge et al. [66] found a significant increase of a pulsating character in both boys and girls among 8-12-year-old schoolchildren, and an increasing trend of phonophobia only in girls. They might have experienced significant changes in a larger number of features if had studied through a wider age range, including adolescent students. In contrast, Wöber-Bingöl et al. [61, 67] experienced a decreasing tendency of vomiting in both boys and girls

among 3-19-year-old children, and a similar trend of nausea only in boys and of aggravation by physical activity, photophobia and phonophobia only in girls. The same research group reported changes in symptoms that were nearly identical with those we experienced in the much wider age range of 3-69-year-old female migraineurs [68]. All these results reveal a fairly congruent tendency of the changes in the prevalence of migraine features in children.

In summary, increasing age in childhood (probably in part through the ongoing maturation of the nervous system) and gender (through hormonal differences) influence not only the prevalence and the duration of migraine, but also the frequencies of other features. These changes have much less effect than the minimum required duration of headache on the estimated prevalence, as they do not act as individual, i.e. obligatory requirements, but merely feature among the optional migraine criteria, and the diagnosis of migraine can be established even if one or other of them is not yet present. Nevertheless, the changing features make childhood migraine more heterogeneous as compared with that in adulthood, a fact that should be an essential consideration in studies on this age group.

5.2 Psychophysical studies

As indicated by the facts that increased visual discomfort, a decreased threshold for phosphene generation and photophobia are all common features of migraine, or that visual sensations are the most common of all aura symptoms, the visual cortex seems to occupy an outstanding position in the migrainous process, and therefore deserves great attention in migraine research. In the second part of our work, we performed two psychophysical studies on two distinct processes of visual perception in migrainous children and compared their performance with that of headache-free age- and sex-matched controls.

First we assessed the contour integration ability of 6-18-year-old migraineurs in three age cohorts. The performance was characterized by the absolute detection threshold of the participants, expressed as the lowest value of relative noise density (D_{min}) at which they were still able to identify the target contour. Between-group comparisons revealed that the children with migraine exhibited a poorer performance than the controls in all three studied cohorts, the difference reaching the level of statistical significance in the 10-14 and the 15-18-year-old

groups. As for the within-group (cohort-wise) comparisons, the largest difference was observed in the migraine group when the youngest and the oldest cohorts were compared. A somewhat less, but still significant degree of development was seen in the comparison of the 10-14-year-olds with the oldest cohort. However, the pronounced development between 6-9 and 10-14 years that might be expected on the basis of a study of a large number of healthy subjects [27] did not appear. The controls exhibited significant development in all of these comparisons, as reflected by the stronger correlation of age and D_{min} in the controls than in the migraineurs when the performance of all 48 subjects was considered. The correlation between attack frequency and D_{min} was significant only when it was computed for all 48 subjects. Gender did not seem to have a significant effect on performance in this type of contour integration test.

This study has corroborated our hypothesis based on our previous findings: if children with migraine exhibit contrast sensitivity deficits [63], they will also exhibit contour integration deficits.

Probably the most important finding is that the marked development observed in healthy subjects between 6 and 14 years of age [27], and appearing in the controls in our own study, is not seen in migraineurs. This finding correlates well with that of our previous study [70], where we detected the same pattern for contrast sensitivity at low spatial frequencies in migrainous children. The plexus of horizontal connections between the direction-sensitive cells of the primary visual cortex is considered to be of key importance in a Gabor-based contour integration task. Could it be that migraine, and specifically its pathophysiological process, interferes with the development of these connections? Such an interpretation, no matter how appealing it sounds, fails to explain a number of observations alone.

First of all, Burkhalter et al. [71] established in a post mortem study that the horizontal connections within the 4Cb and 2/3 layers of the primary visual cortex are structurally adult-like by the age of 15 months. This early development fits in with the hierarchical nature of neocortical development [72], progressing from the primary sensory areas towards the association areas, pointed out by Flechsig as early as 1920 [73]. Accordingly, functionality in terms of contour detection appears quite early: at 3 months of age it is not yet seen [74], but 6-month-old babies perform well over the chance level, even if their noise tolerance is quite limited [75]. Overall, this gives the impression of mature primary cortical circuits without

fully effective filtering mechanisms, rather than of primary cortical circuits at the beginning of a decade-long developmental path. We propose, therefore, that the observed deficit of contour integration in paediatric migraine cannot be approached exclusively from the malfunctioning of the primary visual cortex, even if it is of central importance in such a task. A better explanation necessitates the identification of structures whose development is well established and fits in with our findings. The literature on cortical development unequivocally considers that the frontal/prefrontal cortical areas are among the last to mature [72, 76-79]. In relation to our findings, two particular developmental studies deserve special attention. Kanemura et al. [80] investigated the development of the prefrontal cortex in children in a three-dimensional volumetric magnetic resonance imaging 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. Fornari et al. [81] examined the relationship between the total amount of white matter and the performance in a spatial integration task, and observed a linear relationship between age and white matter volume between the ages of 7 and 13, also reflected by improving performance in psychophysical tasks. It can be seen that the age ranges strikingly resemble the range in which the most significant differences were found in our study. We therefore propose that the frontal/prefrontal areas and their connectivity might offer an insight into why contour integration develops rapidly in healthy subjects between 6 and 14 years of age, and why it fails to do so in migraineurs. We suggest, as a possible explanation, that the bottom-up visual connections of the frontal/prefrontal cortical areas fail to develop at a normal rate due to the repeated migrainous attacks, and this brings about a slightly delayed development of the related cortical parts, and in turn results in a deficient top-down inhibition. Our results fit in well with the theory of Bar et al. [26], who concluded from a number of magnetoencephalography studies that the orbitofrontal cortex is a structure of key importance in object recognition. Accordingly, on the basis of our findings and the literature data, we assume that it is not the contour or shape perception per se that is deficient in paediatric migraine, but rather visual noise suppression by a top-down influence. This assumption is supported by a number of imaging studies. Schmitz et al. showed that the impaired executive function in migraine can be linked to a decreased frontal and parietal grey matter density in adult migraineurs [82]. Rocca et al. [83] and Ruscheweyh et al. [84]

similarly came to the conclusion that the frontal areas are especially vulnerable to migraine and chronic pain in general, respectively.
A possible explanation as to why we did not find a significant difference between migraineurs and controls in the cohort of 6-9-year-olds is that at this really young age the disease history is too brief to result in a level of deterioration sufficient to be detected by our method.

In the second psychophysical study, we assessed visual motion coherence processing, a function thought to depend on the activity of cortical area V5/MT. We compared the performance of 14 MO children with that of 21 age- and gender-matched controls. Because of the relatively low number of participants, they were not divided into cohorts by age.
A reduced motion coherence processing capacity was found in the children with migraine. Further, we demonstrated a delayed development of visual motion processing in the age range 8-17 years, as young migraineurs performed poorer than older ones. The poorer performance was more pronounced in girls than in boys when the migraineurs and the controls were compared in the separate genders. No significant gender-related difference in performance was found within the groups, however. A further finding was that MO children with direct-line migrainous relatives exhibited a poorer performance, but neither the duration of the disease nor the frequency of attacks correlated significantly with the performance.

Similarly to our findings, Antal et al. [85] demonstrated a higher threshold of coherent motion perception in an incoherent environment in adult migraineurs. They attributed their findings to an altered signal-to-noise ratio, caused by increased cortical excitability, resulting in decreased motion-discrimination [86]. An increased visual cortical excitability in young migraineurs is also corroborated by a recent transcranial magnetic stimulation study that found reduced phosphene thresholds in both the interictal and the pre- and post-headache periods [87]. Thus, hyperexcitability might also affect the function of the V5/MT in children directly. However, in a different paradigm Webster et al. [88] concluded that the motion coherence processing deficit in migraine is independent of a generalized increase in internal noise. Instead, they raised the possibility that the loss of motion coherence sensitivity may be a result of structural cortical differences in the V5/MT of migraineurs, as was evidenced by a

diffusion tensor imaging (DTI) study [89], leading to a less efficient extraction of the global motion signals from the noise**.**

As a further alternative, it must be considered that the changes causing the altered motion processing in children with migraine might not take place directly in the V5/MT. It has been demonstrated that the processing of special features of visual stimuli can be modulated by another top-down effect: attention [90]. Similarly, primate studies [91] and functional magnetic resonance imaging (fMRI) investigations [92, 93] revealed the attentional modulation of motion processing, i.e. attention-related modulatory influences from a wide network in the frontal and parietal cortices can increase the responsiveness of the motion-selective cortical area V5/MT. The developmental difference observed in our study may therefore alternatively be associated with the delayed maturation of these modulatory connections.

Mention must be made here of an apparent contradiction. Whereas Antal et al. [85] and Webster et al. [88] observed a poorer performance in adult migraineurs, we did so only in young children, and the performance had seemingly normalized by the age of 18. We regard this as a methodological issue. The cited authors applied a different motion perception paradigm, which might be more sensitive in detecting smaller, but still significant differences in adulthood.

In summary, we investigated two separate processes of visual perception. Both the contour integration and the coherent motion detection capacity were poorer in migrainous children than in age-matched controls: the younger the participant, the greater the deficiency documented. As an explanation, we speculate that the cause of these dysfunctions may be an alteration in the high-level, top-down influence on visual processing.

What exactly causes the observed impairments in both the contour detection and motion coherence ability of migrainous children remains unclear. One point for consideration is the role of the attacks. Although cohort-wise computation on the contour integration task did not reveal a significant correlation between the monthly attack frequency and D_{min}, the correlation was weak, but nevertheless significant when all subjects were included. The lack of a correlation in the cohort-wise comparisons may be a statistical issue resulting from the

relatively small number of subsample participants, and the same may apply to the lack of a correlation between the performance and the attack frequency in the motion coherence assessment, too.

It is likely that a larger sample would have resulted in a significant correlation, just as was the case when all migraineurs, considered as a single group, were assessed in the contour integration task. In other words, we assume that the attacks do have a role in bringing about the pattern of dysfunction we found in contour integration and motion coherence, even though these particular samples are possibly not optimal for the demonstration of this.

As migraine is known to be a familial disease, it is possible that the early appearance of the differences described here between migraineurs and controls is part of an endophenotype. Di Clemente et al. [94] put forward a similar argument in connection with the interictal habituation deficit of the nociceptive blink reflex in migraineurs. However, even if we regard these deficits as endophenotypic features, the question remains open as to whether this involves an increased vulnerability to insults or whether these are relatively static deficits, inherent to the migrainous process. The former option predicts that, the longer the migraine history, the more pronounced the deficits become. In spite of the relative paucity of research in this field, the lack of development of contour integration in migraineurs between 6 and 14 years (an age range of outstandingly rapid development under normal circumstances), and the correlation between the attack frequency and D_{min} when computed for all 48 migraineurs, this does seem to be the case. The markedly decreased spatial contrast sensitivity in migraine patients may be considered to be further support [95], for this function probably involves pathways similar to those of contour integration. Similarly as in our second psychophysical study, however, other authors [85, 96] found no correlation between the duration of migraine and the impairment in visual processing, which argues against the direct role of headache attacks. A further interesting question is whether this assumed vulnerability is merely part of the migrainous endophenotype or is a more general feature. Recent evidence [97] argues in favour of the latter option. The magnocellular pathway deserves special consideration, as the results of our previous study [70] on the contrast sensitivity of child migraineurs also suggested a magnocellular deficit.

What might the underlying cellular mechanism of all these changes be?

Extensive brain development takes place in the foetus, but it continues well after birth, up to adolescence. Structural changes (though to a lesser degree and at a slower pace) are seen even later, in relation with learning or, in a broader sense, adaptation processes, or with many pathological conditions. Post-mortem studies have shown that, during the first 2 years of postnatal life, there is an excessive overproduction of synapses, and this is followed by a longer period of activity-dependent pruning of synaptic connections [98]. This pruning is accomplished by mid-adolescence in the motor system, but earlier in the visual system [99]. Another process that occurs during childhood and adolescence is myelination [77]. Apart from the earlier-mentioned studies of Kanemura et al. [80] and Fornari et al. [81] on the development of the prefrontal cortex and the white matter volume, respectively, the study by Olesen et al. should be cited here [100]. Their combined analysis of DTI and fMRI demonstrated that the processes of myelination of long-range cortical connections and the activation of their target areas are associated between the ages of 8 and 17. All these findings reflect a prolonged period of development, probably with increased vulnerability.

A likely candidate as concerns interference with the normal development of visual perception in migraine is CSD [101], which might trigger or by itself may be the harmful event by causing neuroinflammation [102-104] and possibly cellular damage. Repeated attacks of CSD in migraine can selectively damage GABAergic inhibition [105]. An excessive release of glutamate, even between attacks [106, 107], may be the final pathway to induce excitotoxicity and cell damage [108]. An increased level of matrix metalloproteinase activity has recently been detected in migraineurs [109], possibly bringing about leakage of the blood-brain barrier and also leading to an inflammatory response and neuronal damage [110]. Similarly, Yilmaz et al. [111] found increased ictal levels of S100B and neuron-specific enolase, markers of glial and neuronal damage, respectively, in migraineurs without aura.

As the maturation of the nervous system during development is activity-dependent [100], it may be hypothesized that the altered cortical excitability and the repetitive painful episodes might modify the normal development in children through a mechanism of maladaptive plasticity. This would slow down the maturation considerably, potentially resulting in a delayed development of certain visual functions in migraine.

6. CONCLUSIONS

1. Our large-scale, school-based epidemiological study, carried out with the strict use of the ICHD-II criteria, revealed that the 12-month prevalence of migraine in 7-18-year-old Hungarian children and adolescents is 12.5%. The prevalence is 9.2% in boys and 15.4% in girls, i.e. girls suffer from migraine 1.7 times more frequently than boys. These values fit well into the range reported from similar studies in Europe. Further, these data on paediatric migraine prevalence in Hungary accord well with the prevalence observed among Hungarian adults.

2. It must be noted, however, that the literature data demonstrate a great inconsistency in the use of migraine criteria, especially as regards the minimally required headache duration. Moreover, the strict use of this criterion results in undue findings in age-related prevalence data. In view of this changing characteristic, we suggest a more thorough tailoring of the headache duration requirement for migraine diagnosis in this rapidly developing age group.

3. Our survey indicates that the most common of the symptoms featuring among the ICHD-II criteria was moderate or severe pain intensity, followed by phonophobia and photophobia, whilst vomiting presented least often in this population. In terms of gender differences, girls exhibited a higher headache frequency and higher rates of a uni/bilateral location, photophobia and photophobia, whereas vomiting was more common in boys.

4. The frequency and duration of headache increased with advancing age, while vomiting and nausea became less prevalent between the ages of 7 and 18 years. Uni/bilaterality, photo- and phonophobia increased significantly only in girls, and a pulsating character did so only in boys.

5. The visual contour integration capacity in migrainous children is poorer than that in their non-headache peers. The difference is most marked at around 6 years, but subsequently decreases in association with a delayed maturation until adolescence.

6. Another dorsal stream-related function, the perception of motion coherence in noise, is similarly deficient in a wide age range of paediatric migraineurs, relative to age and sex-matched controls. Again, the performance was poorer in the younger cohorts.

7. The psychophysical performance was found to correlate with the attack frequency in the contour detection within the overall group of migraineurs, but not in the individual age groups, and not at all in the motion coherence study. This lack of a correlation may have been reflection of a sample-related bias.

7. NEW OBSERVATIONS

1. The 12-month prevalence of migraine in 7-18-year-old Hungarian children and adolescents is 12.5%, 9.2% in boys and 15.4% in girls.
2. The prevalence of migraine shows a steady and significant increase from the age of 7 to 18 years.
3. A more thorough tailoring of the headache duration requirement is needed for migraine diagnosis in this rapidly developing age group.
4. The most common of the symptoms of migraine is moderate or severe pain intensity, followed by phonophobia and photophobia, whilst vomiting presents least often in the 7-18-year-old population.
5. Features of migraine show changes with advancing age between the ages of 7 and 18 years.
6. The visual contour integration capacity in migrainous children is poorer than that in their non-headache peers. The difference decreases until adolescence.
7. The perception of motion coherence is also deficient in paediatric migraineurs, relative to age and sex-matched controls. The performance is poorer in the younger cohorts.
8. The contour detection performance correlates with the attack frequency.

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