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What is This?
Event-Related Potentials to Emotional Stimuli in Migrainous Children

Giulia Buodo, PhD¹, Michela Sarlo, PhD¹, Pier Antonio Battistella, MD², Cristiano Naccarella, MD², and Daniela Palomba, MD¹

Abstract
The present preliminary study was aimed at investigating the electrocortical correlates of attentional allocation toward emotional stimuli in children and adolescents with migraine by means of the event-related potentials. The electroencephalogram was continuously recorded in 7 migrainous children and 8 healthy controls while they were looking at a series of pleasant, neutral, and unpleasant pictures. The mean amplitude of the Negative Central component of the event-related potentials was computed as an index of the allocation of attentional resources to the presented stimuli. Relative to controls, children with migraine displayed reduced fronto-central negativity and larger posterior positivity in response to emotional pictures. This effect was already evident, overall, in a time window preceding the Negative Central component. The smaller cortical negativity in response to emotional stimuli suggests reduced attentional engagement toward emotionally relevant stimuli, or might be interpreted in terms of advanced brain maturation in migraine children.

Keywords
migraine without aura, event-related potentials, childhood, emotional pictures, affective processing

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In both adults and children with migraine, repeated attacks can occur as a result of physiological or environmental factors, such as rest or sleep deprivation, dietary factors, fasting, bright or flickering light, loud noises, barometric pressure changes, strong odors, and rapid temperature changes.¹

Besides physiological and environmental triggers, there is evidence that some psychological conditions can precipitate or increase the frequency and severity of migraine attacks in both adult and young patients. In children and adolescents who have a predisposition for migraine headaches, negative emotional events, such as problems at school or in the family, emotional upset, and stress have been shown to play a relevant role in precipitating attacks or in increasing migraine activity.²–⁵ Moreover, children and adolescents with headache report more anxiety, depression, and somatization symptoms than healthy peers, and show high levels of emotional, conduct, and inattention-hyperactivity problems.⁶–⁸ Emotional flatness and rigidity, inhibition in emotionally intense situations, and the tendency to limit the expression of anger and aggression have been indicated as personality traits of young migraineurs.⁹

Thus, research literature strongly suggests that negative emotions and maladaptive coping strategies do play a role in triggering or aggravating migraine headache in young patients. On the other hand, systematic research about the impact of pleasant emotions and events on migraine intensity and frequency is lacking. There are some indications that, whereas adult patients with tension-type headache react more selectively to negative emotions (anger, anxiety), subjects with migraine report a more uniform distribution of attacks across different emotional precipitants.¹⁰ This evidence suggests that the high emotional relevance of a situation, rather than unpleasantness only, might represent a potential precipitant of migraine attacks.

To date, the event-related potentials have not been used to assess the processing of affective stimuli in either adult or child patients with migraine. A slow negative component labeled Negative Central, located primarily over frontal and central cortical areas, is observed in the event-related potentials of infants and preadolescents 400–800 milliseconds after the onset of stimuli that selectively capture attention. This broad negativity, in which earlier components appear to be embedded, can still be present after 300 milliseconds up to

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adolescence and is thought to be an index of allocation of attentional resources to unexpected, infrequent, salient or task-relevant visual or auditory stimuli.\textsuperscript{11} Cortical negativity has been found to be reduced in children high in shyness/behavioral inhibition as compared with healthy controls,\textsuperscript{12} and, therefore, can be relevant to the study of children with migraine who exhibit similar traits. Although cortical negativity largely predomnates in infants and children, positive-going deflections with the largest amplitude in the parietal areas, such as the Late Positive Complex, are also detectable in children. Positive components of the event-related potentials increase with cerebral maturation, and their functional meaning is thought to be related to updating of representations in working memory.\textsuperscript{13}

Some research findings suggest that brain maturation is advanced in children with migraine with respect to some functions and normal for others,\textsuperscript{14,15} but no study so far has addressed the issue of brain maturation in children with migraine with regard to the processing of emotional stimuli. It would be interesting to assess whether the amplitude of positive components of the event-related potentials in response to emotional stimuli is increased in children with migraine with respect to controls, independent of their valence.

The present study is a preliminary attempt to assess the electrocortical correlates of attentional allocation toward emotional stimuli in children and adolescents with migraine by means of the event-related potentials. Self-reported emotional reactivity (subjective ratings of pleasantness and arousal) was also assessed. The stimuli used were selected from a large set of standardized, emotionally evocative color pictures that includes a wide range of semantic contents encountered in everyday life or in the media. The picture-viewing methodology has been widely used in emotion research,\textsuperscript{16} and has been more recently extended to investigate children’s individual differences in affective processing and emotional modulation.\textsuperscript{17}

Because young patients with migraine are thought to be particularly sensitive to negative emotional events, it was hypothesized that children with migraine would allocate more attentional resources to unpleasant emotional stimuli as compared with healthy controls. This would be reflected in larger amplitude of the Negative Central component than controls in response to unpleasant pictures. Furthermore, patients with migraine were hypothesized to rate unpleasant pictures as more unpleasant and arousing than controls.

**Methods**

**Participants**

Seven patients (4 males, 3 females) participated in the study. All the participants were outpatients of the Department of Pediatrics, University of Padova. The mean age of the patients was $10.7 \pm 1.2$ (range, 9–13 years). Physicians experienced in juvenile headache diagnosis had documented the patients were affected by migraine without aura according to the diagnostic criteria of the International Headache Society.\textsuperscript{18} Inclusion criteria were: at least 1 migraine episode per month, at least 6 months’ illness duration, and last migraine episode at least 3 days before investigation. Neurological examination had excluded the presence of any neurological disorder. In patients, mean illness duration was 3.2 years (SD = 1.5; range = 13 months to 5 years) and mean number of attacks per month was 2 (SD = 2; range = 1–8). Intensity of attacks was severe for 5 patients and moderate for 2 patients. The duration of a single attack was 1–6 hours for 5 patients and 7–12 hours for 2 patients.

At the time of investigation, no patients were taking any prophylactic medication or receiving nonpharmacological treatments. Their participation in the study took place on a symptom-free day. None of the patients reported a migraine attack in the 72-hour period following participation in the study, as ascertained by telephone interview.

The control group included 8 healthy participants (4 males, 4 females), mainly recruited in local schools and sport/leisure centers. They had no recurrent headache episodes, or first-degree relatives affected by migraine. Mean age for this group was $9.9 \pm 1.2$ (range, 8–12 years).

All the participants were treated in compliance with the ethical standards of the Declaration of Helsinki and of the Ethical Committees of the Departments of Pediatrics and General Psychology, University of Padova.

**Stimulus Material**

Thirty-six digitized color pictures were chosen from the International Affective Picture System,\textsuperscript{19} showing pleasant, neutral, and unpleasant contents. These pictures represented a wide range of contents, including flowers, food, candies, puppies, household objects, neutral people, aggressive animals and humans, and are included in a subset of the International Affective Picture System for which normative valence and arousal ratings\textsuperscript{19} have been obtained from groups of children aged 7–9, 10–12, and 13–14 years. Twelve pictures were presented for each valence category.

**Procedure**

Written informed consent was obtained after the nature and aim of the study had been fully explained to the parents of the children. Assent was obtained orally by the children after the procedure and goal of the study were explained with age-appropriate language.

Participants were seated in a comfortable armchair in a quiet, light-attenuated room. They were asked to pay attention to the pictures, while keeping their eyes on the center of the screen and limiting body movements and blinking during each picture presentation. Total task duration was approximately 30 minutes.

Two semi-randomized picture orders were arranged, so that no 2 pictures with the same valence were presented in succession. Each picture in the sequence was presented 3 times. Picture duration was 6 seconds, and the intertrial interval varied between 8 and 12 seconds.

After picture viewing, the participants were asked to rate the 36 pictures using a computerized version of the Valence and Arousal 1–9 point scales of the Self-Assessment Manikin.\textsuperscript{19}

The task was presented using a 486 IBM-compatible computer with a 17-inch monitor. The computer monitor was placed at a distance of approximately 1 meter from the subject and picture resolution was 1024 × 768 pixels. Picture presentation was accomplished by MEL 2.0 software (Micro Experimental Laboratory, Psychology Software Tools, Inc., Pittsburgh, PA).\textsuperscript{20}
ERP Recording and Measurement

The electroencephalogram was recorded from Fz, Cz, and Pz according to the International 10-20 System with 3 surface silver-silver chloride electrodes referred to linked mastoids. The ground electrode was placed midway between Fz and Cz. Electrode impedance was kept below 5 kilo-ohm. Vertical and horizontal eye movements were recorded with electrodes placed above and below the left eye and on the outer canthi of both eyes. High-pass and low-pass filters were set at 0.16 Hz and 40 Hz, respectively. The sampling rate was 500 Hz. Signals were filtered and amplified by a SynAmps unit amplifier (Neuroscan, Inc., Compumedics, Ltd, El Paso, TX).

The electroencephalogram was corrected for blink artifacts using a regression-based weighting coefficients technique, as implemented in the SCAN 4.1 software (Edit module; Neurosoft, Inc.).

Electroencephalographic epochs of −200 to 1500 milliseconds post-stimulus, baseline corrected by subtraction of the average prestimulus voltage, were averaged separately for each valence category. Trials with signal amplitude exceeding ±120 microvolts in any recording channel were excluded from averaging. The mean number of trials that remained after artifact rejection was 25.63 for Unpleasant pictures (range, 18–36).

The mean number of trials that remained after artifact rejection was 25.63 for Unpleasant (range, 19–35), 23.89 for Neutral (range, 18–35), and 25.03 for Pleasant pictures (range, 18–36).

Two time intervals for the Negative Central component were chosen based on the pre-existing literature and visual investigation of individual participants’ data, namely the 400–600 and the adjacent 600–800 milliseconds time windows. Furthermore, the time window between 200 and 400 milliseconds was measured to check for possible differences between groups in event-related potentials preceding the Negative Central component. Mean window amplitudes were computed as the mean of all data points within the selected window.

An independent sample t test for age was performed to elucidate whether age differences between groups were present. The t test was not significant [t(13) = −1.22; P = .24; Cohen’s d = 0.6]. However, the observed power for this test was low (≈.18), making inferences about the result difficult. Migraineurs were, on average, almost 1 year older than Controls. Because age differences might account for group differences in the event-related potentials, particularly during childhood, separate analyses of covariance with age as covariate, a between-subject factor (Group: Migraineurs and Controls) and 2 within-subject factors (Valence: Pleasant, Neutral, Unpleasant; Site: Fz, Cz, and Pz) were used to analyze the 3 selected time windows.

For subjective ratings of valence and arousal, separate 2 (Group: Migraineurs and Controls) × 3 (Valence: Pleasant, Neutral, Unpleasant) analyses of variance were performed.

Significant main effects and interactions (P < .05) were followed by Newman-Keuls post hoc comparisons to identify specific differences.

Statistical analyses were performed using Statistica 6.1 (StatSoft Inc., Tulsa, OK) and SPSS 15.0 (SPSS Inc., Chicago, IL) software.

Results

Event-Related Potentials

Figures 1 and 2 show the grand averages for pleasant, neutral and unpleasant pictures in Migraineurs and Controls, respectively.

200- to 400-Millisecond Window

Whereas Controls showed larger negativity to emotional pictures than to neutrals, Migraineurs showed the opposite pattern, that is, they displayed smaller negativity in response to emotional as compared with neutral pictures (Group × Valence interaction; \[F(2,24) = 3.56; P = .044; \text{partial } \eta^2 = .23; \text{observed power } = .60\]). Migraineurs differed significantly from Controls as to their response to both pleasant (P < .0001) and unpleasant (P < .0001), but not to neutral pictures (P = .24). Overall, in Migraineurs only unpleasant pictures differed significantly from neutral (P = .042). In Controls the responses to pleasant, unpleasant and neutral pictures did not differ significantly from each other.

400- to 600-Millisecond Window

The Group × Valence × Site interaction proved to be significant \[F(4,48) = 2.66; P = .043; \text{partial } \eta^2 = .18; \text{observed power } = .70\]. At Fz, post hoc tests did not yield any significant differences within and between groups. At Cz, within-group differences were not significant in any of the 2 groups. However, Migraineurs showed significantly lower negativity compared with Controls in response to pleasant (P < .004) and unpleasant (P < .002), but not to neutral pictures (P = .1). At Pz, Controls displayed larger negativity in response to emotional as compared with neutral pictures, but differences among picture contents were not significant. In contrast, Migraineurs showed obvious positivity in response to emotional pictures (pleasant versus neutral P = .03; unpleasant versus neutral P = .004; pleasant versus unpleasant P = .23). Migraineurs displayed larger positivity than Controls in response to pleasant (P = .01), neutral (P = .01) and unpleasant pictures (P = .01).

600- to 800-Millisecond Window

The Group × Valence × Site interaction proved to be significant \[F(4,48) = 6.44; P = .0001; \text{partial } \eta^2 = .36; \text{observed power } = .99\]. At Fz, Migraineurs responded with significantly reduced negativity compared with Controls to pleasant (P = .029) and neutral (P = .011), but not to unpleasant (P = .71) pictures. In neither group were the differences among picture contents significant.

At Cz, differences among picture contents were not significant in either group. However, Migraineurs showed significantly lower negativity compared with Controls in response to pleasant (P = .007), neutral (P = .046) and unpleasant pictures (P = .045).

At Pz, Migraineurs showed significantly larger positivity in response to unpleasant than to pleasant (P < .004) and neutral pictures (P = .0001), whereas no difference was observed between pleasant and neutral pictures (P = .075). No significant differences were found among picture contents within Controls. Migraineurs displayed larger positivity compared with Controls to pleasant (P = .013) and unpleasant (P = .0001) but not neutral pictures (P = .58).
Mean component amplitudes and standard deviations in the 3 time windows (200–400, 400–600, and 600–800 milliseconds) for Migraineurs and Controls as a function of recording site and picture valence are reported in Table 1.

Subjective Ratings
No differences between groups in valence and arousal ratings were found. The highest valence ratings were attributed to pleasant pictures (7.96), followed by neutral (5.87) and unpleasant (3.40) (Category main effect; $F(2,26) = 44.65; P = .0001$). Each category differed significantly from the other 2.

Discussion
Considering that negative emotions are major precipitants of migraine attacks in young migraineurs, we made a preliminary attempt to investigate whether the Negative Central component, a negative component of the event-related
Table 1. Mean Event-Related Potentials Amplitude (and Standard Deviations) in the 3 Time Windows for Migraineurs and Controls, as a Function of Recording Site and Picture Content

<table>
<thead>
<tr>
<th></th>
<th>200-400 Milliseconds</th>
<th>400-600 Milliseconds</th>
<th>600-800 Milliseconds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fz</td>
<td>Cz</td>
<td>Pz</td>
</tr>
<tr>
<td>Migraineurs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleasant</td>
<td>-7.97 (7.59)</td>
<td>-7.14 (6.58)</td>
<td>2.8 (8.92)</td>
</tr>
<tr>
<td>Neutral</td>
<td>-10.86 (9.37)</td>
<td>-12.68 (8.18)</td>
<td>-0.71 (5.06)</td>
</tr>
<tr>
<td>Unpleasant</td>
<td>-8.6 (5.12)</td>
<td>-8.03 (5.12)</td>
<td>2.98 (5.4)</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleasant</td>
<td>-13.4 (9.27)</td>
<td>-15.86 (10.54)</td>
<td>-8.56 (9.57)</td>
</tr>
<tr>
<td>Neutral</td>
<td>-13.65 (8.06)</td>
<td>-12.83 (10.35)</td>
<td>-3.6 (12.41)</td>
</tr>
<tr>
<td>Unpleasant</td>
<td>-11.57 (7.64)</td>
<td>-14.39 (9.66)</td>
<td>-9.9 (8.62)</td>
</tr>
</tbody>
</table>

Values are expressed in microvolts.
traits in children with primary headache. Indeed, individual inhibition, flatness or rigidity as peculiar personality toward emotionally relevant stimuli, which would be consistent view as a manifestation of reduced attentional engagement response to emotional stimuli in young migraineurs can be viewed as a manifestation of reduced attentional engagement toward emotionally relevant stimuli, which would be consistent with literature findings of shyness, avoidant behavior, emotional inhibition, flatness or rigidity as peculiar personality traits in children with primary headache. Indeed, individual differences in such temperamental traits as behavioral inhibition and shyness have been found to predict, at least in part, cortical responses to affective stimuli in children. In particular, smaller negative potential at a latency of approximately 400 milliseconds in response to some emotional facial expressions was obtained in children high in shyness/behavioral inhibition as compared with healthy controls. This finding has been interpreted as decreased cortical activity in brain areas involved in high-order emotional evaluative processes, possibly co-occurring with heightened activation of phylogenetically older subcortical structures involved in the recognition of dangerous, novel, or ambiguous stimuli. Further research is needed to elucidate the nature of a potential association between temperamental traits, migraine, and emotional reactivity in children.

Along this line, interesting findings have been provided by recent studies that explored the relationship between picture viewing and pain experience. Reduced amplitude of the Late Positive Potential to both pleasant and unpleasant pictures in adult migraine patients as compared with healthy controls has been observed. In this study, the event-related potentials to affective pictures were recorded while participants were administered painful laser stimuli. As reported by the Authors, participants were warned of the presentation of pain stimuli during picture viewing and, therefore, painful stimulation can have resulted in reduced attentional engagement toward concurrent emotional stimulation. Our finding possibly suggests that reduced attentional engagement toward emotional stimuli is a general mechanism that extends to pain-free conditions and begins in migraine patients during childhood.

Reduced electrocortical reactivity to emotional stimuli seems at odds with the large body of evidence suggesting that cortical hypersensitivity is the constitutional basis for the development of migraine and is a prerequisite under which external and/or internal stimuli trigger the attacks. However, recent electrophysiological investigations of interictal cortical activity in migraine indeed point out that some processes and/or response systems might be characterized by hypo- rather than hyperactivation. The increased evoked- and event-related potentials amplitudes found in many studies might not be due to cortical hyperexcitability as such, but to deficient habituation of the responses during repeated stimulation, due to decreased preactivation of cortical excitability. An interpretation of our results based on these considerations would suggest that cortical excitability in children with migraine is reduced in response to emotional stimuli. Future research should clarify whether habituation to repeated emotional stimulation is also deficient in these patients.

An alternative interpretation of our results is related to the issue of brain maturation during childhood. Maturation of information processing can be identified in age-related changes in the event-related potentials. With increasing age, the amplitude of negative components decreases, whereas positive potentials increase. The prevalence of cortical negativity during infancy and childhood reflects the high cortical excitability necessary for facilitation of information processing at an early ontogenetic stage. Indeed, several studies indicate that brain maturation is altered in children with migraine for special sub-functions and quite normal for others. In particular, the maturation pattern of some Visual Evoked Potentials components appears to be advanced in children with migraine as compared with age-matched controls. Along the same line, our finding of smaller negativity (and, more specifically, parietal positivity) in children with migraine as compared with controls in response to affectively relevant stimuli could be interpreted as advanced brain maturation. In fact, research on emotional processing on adult healthy individuals has repeatedly highlighted that affectively intense pictures, both pleasant and unpleasant, prompt larger late positivity of the event-related potentials as compared with neutral pictures. It has been hypothesized that such long-lasting positivity reflects the deployment of attentional resources to affective contents that engage motivational circuits in the brain. The smaller negativity in response to affective than to neutral pictures in young patients with migraine does resemble the pattern of affective modulation displayed by adults and contrasts with the opposite pattern observed in age-matched healthy controls, thus possibly indicating advanced maturation of affective processing.

A further consideration is that the time window of the Negative Central component overlaps with the Late Positive Complex, which is largest in posterior areas and is related to the engagement of processing resources toward relevant stimuli. Therefore, our finding of larger late positivity in children with migraine as compared with healthy controls in response to emotional pictures could reflect a difference in the Late Positive Complex rather than in the Negative Central component. This again would suggest that children with migraine display increased, and not reduced, attention toward emotional stimuli.

It should be noted that at Pz in the 400–600 milliseconds window and at Cz in the 600–800 milliseconds window children with migraine exhibited larger positivity than controls in response to all picture contents, including neutral. This
suggests that, in children with migraine, the faster maturation of attentional circuits could be reflected in the allocation of greater attentional resources toward visual stimuli in general, and not only emotionally relevant contents.

Of interest, subjective ratings of valence and arousal in young migraineurs were comparable to those reported by healthy controls. This suggests that, although subjective indices of emotional reactivity might be similar in children with and without migraine headache, electrophysiological measures do highlight different processing of emotionally relevant stimuli.

At present, the question as to whether different precipitants cause headache through a final common physiological pathway or whether they activate several different mechanisms is still a matter of debate. Further research is needed to clarify how emotional processing abnormalities are implicated in migraine.

Considering that research has mainly focused on the role of negative emotional states and events in precipitating migraine attacks in adults and children, the preliminary findings of the present study rather suggest a broader association between migraine headache and altered processing of emotional stimuli in general. Thus, greater attention should be paid to the cognitive impact of pleasant stimuli and to the role of affective relevance as a potential trigger factor of migraine attacks in migraine sufferers.

Our data add to the extant literature on emotional functioning in migraine patients, which is relatively scarce and mainly based on self-report measures, by providing preliminary information on the electrophysiological correlates of emotional processing in young patients.

We acknowledge that the small size of the participants samples, and their heterogeneity in relation to sex and age, are major limitations of the present study. Further research should be undertaken with much larger and homogeneous groups to ascertain the generalizability of the findings.

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Author Contributions
Giulia Buodo: conception and design of the study, collection of data, analysis and interpretation of data, drafting of the article; Michela Sarlo: study supervision, analysis and interpretation of data, critical revision of the article for important intellectual content; Pier Antonio Battistella: study supervision, provision of study patients, interpretation of data, critical revision of the article for important intellectual content; Cristina Naccarella: provision of study patients, critical revision of the article for important intellectual content; Daniela Palomba: conception and design of the study, study supervision, interpretation of data, critical revision of the article for important intellectual content.

Declaration of Conflicting Interests
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Ethical Approval
The study was approved by the Ethical Committees of the Departments of Pediatrics and General Psychology, University of Padova.

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