Cortical excitability in patients with migraine with aura and depressive symptoms: a visual evoked potentials study

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ABSTRACT

Introduction

Migraine is a complex brain disorder characterized by the cyclical recurrence of headache attacks and a variable length of interictal pain-free phase.

It is commonly accepted that endogenous and environmental factors influence this cyclical repetition of attacks. Among the internal influencing factors, emotional comorbidities may play an important role. Emotional distress is commonly recognized as a migraine trigger (1), and anxiety and depressive feelings are highly associated with migraine, as their prevalence increases with the frequency of migraine episodes (2). Altered neurochemical monoaminergic activity may be involved in the mechanisms of psychopathology bidirectional comorbidity with migraine. In support of this view is the evidence that migraine can be treated with drugs acting on the serotonin system, such as triptans, ditans, and tricyclic antidepressants. The most frequently reported cortical abnormality in migraine between attacks, the lack of sensory habituation, was found to be under the influence of serotonin and other monoamines, like norepinephrine (3-5). Intercital migraine is also characterized by a tendency to be significantly higher in MA patients than in HV (STAI-HV 33.1±7.6, MA 39.5±10.0, F=4.94, p=0.03; BDI HV 1.4±1.6, MA 3.7±3.2, F=8.69, p=0.006). We obtained analyzable electrophysiological tracings from all study-included participants. The mean age between the groups was comparable [healthy volunteers (HV) 27.2±7.2, patients 28.4±9.1, p=0.638], as well as sex distribution (χ²=0.771, p=0.680).

Psychometric tests. State Anxiety Inventory (STAI) showed only a tendency to be significantly higher in MA patients than in HV (HV 29.6±5.6, MA 35.1±11.3, F=3.78, p=0.06) (Figure 1).

Trait STAI and BDI values were significantly higher in MA patients than in HV (STAI-HV 33.1±7.6, MA 39.5±10.0, F=4.94, p=0.03; BDI HV 1.4±1.6, MA 3.7±3.2, F=8.69, p=0.006).

Visual evoked potentials. ANOVA showed a significant difference in the degree of habituation between the 2 groups (MA and HV). Both the regression line between the 6 blocks (HV -0.17±0.18, MA 0.06±0.25, F=10.13, p=0.003) and the percentage change in amplitude between the first and sixth blocks (HV -0.17±0.18, MA 0.06±0.25, F=10.13, p=0.003). These results highlight a link between the level of brain responsiveness and depressive symptoms in patients with MA. Further research is required to confirm whether the same correlations exist in patients with other headache disorders.

Results

Conclusions: These results highlight a link between the level of brain responsiveness and depressive symptoms in patients with MA. Further research is required to confirm whether the same correlations exist in patients with other headache disorders.

Key words: neurophysiology, emotional distress, habituation, cortical disexcitability, comorbidity.

Methods: Visual evoked potentials from monocular stimulation were recorded in 16 patients with migraine with aura (MA) and 22 healthy volunteers (HV). The visual stimulus consisted of a full-screen black-and-white checkerboard pattern with a reversal rate of 1.55 Hz, 600 consecutive traces were collected and divided into six sequential blocks of 100 sweeps. Before the recording session, both MA patients and HV completed the Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory (STAI). Pearson’s correlation test was used to find correlations between electrophysiological and psychometric variables in HV and MA patients.

Results: Compared to HV, MA patients showed a significant difference in the degree of habituation to repeated visual stimulation between the two groups, resulting in a habituation deficit. Psychometric test results showed that trait STAI and BDI values were significantly higher in MA patients. In the MA group, BDI correlated negatively with the amplitude of the habituation (HV -0.17±0.18, MA 0.06±0.25, F=10.13, p=0.003) and the percentage change in amplitude (HV -0.17±0.18, MA 0.06±0.25, F=10.13, p=0.003).

Conclusion: These results highlight a link between the level of brain responsiveness and depressive symptoms in patients with MA. Further research is required to confirm whether the same correlations exist in patients with other headache disorders.

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References

-8.3±13.9, MA 22.4±34.3, F=13.82, p=0.001) showed a deficit in habituation to repeated visual stimulation in MA patients.

Statistical analysis did not show any significant differences between the 2 groups for the amplitude values of the first and sixth blocks of 100 responses (first: HV 5.5±2.3, MA 5.1±2.4, F=0.20, p=0.657; sixth: HV 4.9±2.2, MA 5.8±2.4, F=1.23, p=0.275).

**Correlation between neurophysiological and psychometric variables.** Within the group of patients, there was a negative correlation between BDI and the amplitude of the first block (r=-0.547, p=0.028) (Figure 2). Additionally, there was a positive correlation between BDI and the degree of habituation, but only when expressed as the percentage changes between the first and last block of VEP amplitude (r=0.628, p=0.009) (Figure 3), rather than as the slope of the linear regression (r=0.339, p=0.199). No significant correlation was found between BDI and neurophysiological variables in the healthy volunteers group.

In both HV and patients with MA groups, state and trait STAI did not correlate with the amplitude of the first block of VEPs (healthy volunteers: state STAI: r=-0.257, p=0.249, trait STAI: r=-0.419, p=0.052; patients: state STAI: r=-0.446, p=0.08; trait STAI: r=-0.366, p=0.163). No correlation was found between state and trait STAI and the degree of habituation in the 2 groups of subjects (state STAI: healthy volunteers r=-0.047, p=0.838, patients r=0.368, p=0.161; trait STAI: healthy volunteers r=-0.167, p=0.470, patients: r=-0.365, p=0.164).

**Discussion**

Our results confirmed once more that patients with MA fail to reduce the amplitude of cortical evoked responses during the interictal period, i.e., they have a habituation deficit to repetitive visual stimulation (10).

The main findings of our study can be summarized as follows:

- The BDI score negatively correlated with the first VEP N1-P1 amplitude block in MA patients but not in HV.
- The BDI score positively correlated with the habituation deficit in MA patients.
- While within the range of normality, MA patients had significantly higher BDI scores than HV.

Then, the higher the depressive symptoms, the lower the initial activation of the visual cortex and, therefore, the more deficient the habituation to repeated stimuli.

Several observations help explain why VEP amplitude and habituation correlated in MA patients.

In humans, the aminergic systems of the brainstem are responsible for regulating the processing of sensory information in cortical and thalamocortical neurons. The excitability level of the sensory cortex is set by projections of monoamines, particularly serotonin, from the upper brainstem (11,12). In the animal model, serotonin is capable of influencing thalamus neuronal excitability, and similar results, with lower activity, were also highlighted for noradrenergic transmission as to emphasize a redundant and shared system between the two neurotransmitters (13). Serotonin activity on thalamic neurons is largely mediated by mechanisms that increase depolarization, i.e., thalamic neurons excitation (14). Notably, the serotonergic (serotonin, 5-HT) pathway from the brainstem raphe nucleus has been most strongly linked to migraine pathogenesis among the various neurotransmitters in the brain (15). In migraine patients, PET studies with receptor ligands 5-HT radio-labeled have revealed a possible role of serotonin in the genesis of migraine. Some authors have demonstrated that during a migraine attack, there is an increase in the availability of the 5-HT1A receptor in the pontine nuclei (16). On the other hand, during the interictal period, there

![Figure 1. Bar graph showing the results from the Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory (STAI-S and STAI-T respectively), in healthy volunteers (HVs) and migraine with aura patients (MA). STAI-S values were not significantly higher in MA patients than in HVs, while STAI-T and BDI values were significantly higher in MA patients than in HVs.]

![Figure 2. Graph showing Beck Depression Inventory (BDI) negative correlation with the 1st block amplitude in migraine with aura patients (MA). No statistically significant correlation was found between BDI and the 1st block amplitude in healthy volunteers (HVs).]

![Figure 3. Graph showing Beck Depression Inventory (BDI) positive correlation with the degree of habituation deficit in migraine with aura patients (MA). No statistically significant correlation was found between BDI and the degree of habituation deficit in healthy volunteers (HVs).]
is a decrease in the binding of the 5-HT1B receptor in cortical areas responsible for processing pain (17). Lack of habituation to brainstem-related repetitive stimuli-evoked potentials and event-related cognitive potentials has been correlated with platelets serotonin content during the migraine cycle (3,18). Moreover, the slope of intensity-dependent auditory evoked potentials (IDAP), known to be inversely linked to serotonin released at the synaptic level in the central nervous system (12), has been reported to be steeper in the inter-critical phase of migraine than healthy controls (19), suggesting a major grade of habituation deficit. In an electrophysiological study, an increase in serotonin firing, as indexed by a flattening of IDAP slope, was associated to a reduction of migraine days after successful treatment with greater occipital nerve block (20).

It is possible to hypothesize that a state of reduction in serotonin levels can lead to an increase in thalamic neuronal polarization, which can cause a general decrease in the activity of neurons in between migraine attacks. This could indirectly explain the present observation of an inverse correlation between the initial excitability level of the visual cortex (1st VEP amplitude block) and the BDI scale score. This interpretation fits well with the so-called thalamocortical dysrhythmia (TCD) model, frequently employed to explain certain neurological conditions. TCD is characterized by the shift from a synchronized to a desynchronized oscillatory pattern between the activity of the thalamus and cortex and can be observed both in patients suffering from migraine and mood disorders (21, 22). According to the TCD theoretical model, the lack of input due to an anatomical or functional disconnection of the thalamus from its controlling inputs (e.g., aminergic brainstem nuclei), can thus favor low-frequency activity. Low-frequency activity reduces cortical lateral inhibition and enhances high-frequency discharges in cortical networks of inhibitory interneurons, leading to a low pre-activation level and possibly a lack of response habituation (23, 24).

Depression and anxiety disorders are often characterized by abnormally low activity in the monoaminergic, especially serotonin (SHT), neurotransmitter systems (25). Twenty-five percent of migraine patients have a mood disorder, and more than 50 percent have an anxiety disorder (26). Features of anxiety and depression, such as irritability and difficulty concentrating, are significantly more frequent in migraineurs than in healthy subjects (27).

Considering these neurobiological observations, we propose that the positive correlation found between BDI and VEP N1-P1 amplitude habituation strongly supports that interictal migraine, an electrophysiological phenomenon not concerning from migraine and mood disorders (21, 22). According to the TCD model, the lack of input due to an anatomical or functional disconnection of the thalamus from its controlling inputs (e.g., aminergic brainstem nuclei), can thus favor low-frequency activity. Low-frequency activity reduces cortical lateral inhibition and enhances high-frequency discharges in cortical networks of inhibitory interneurons, leading to a low pre-activation level and possibly a lack of response habituation (23, 24).

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Considering these neurobiological observations, we propose that the positive correlation found between BDI and VEP N1-P1 amplitude habituation strongly supports that interictal migraine, an electrophysiological phenomenon not confirmed by all research groups (28). It has been observed that this is not a static phenomenon but a plastic, continuously changing process that depends on many factors, such as stress, sun irradiance, family history of migraine, the point where the patient is in the migraine cycle, and drugs used as preventives (4, 24, 29-31). Here, we showed that the level of depressive symptomology can be an additional influencing factor of the habituation level in migraine with aura patients between attacks.

These findings provide evidence of a bidirectional relationship between psychopathology and cortical excitability in migraine.

Conclusions

The results of the present study show a close relationship between depressive symptoms and the degree of brain responsiveness in patients with MA. This relationship may be supported by a common pathophysiological substrate, with brainstem monoaminergic activity playing a primary role.

Further studies in a larger cohort of patients are needed to verify whether the same correlations are also present in patients with migraine without aura and in chronic migraine, where the level of psychological distress is at higher levels.

Materials and Methods

Subjects. Patients attending the neurology service at the headache clinic of Sapienza University of Rome, Polo Pontino, Latina, Italy were prospectively included. We initially recruited 20 patients who met the International Classification of Headache Disorders (ICHD-3) (32) criteria for the diagnosis of MA (ICHD-3 code 1.2.1) and had filled a headache diary for at least 1-month without having migraine attacks in the 3 days to the enrollment. All patients had a varying combination of attacks with or without aura. Patients who had an alternative diagnosis of headache or were using migraine prophylactic therapies were not recruited. If the patient developed a migraine attack in the 3 days after the enrollment, this would be considered a reason for exclusion. Of the 20 patients initially recruited, 4 were excluded because they had migraine in the 3 days after the enrollment, resulting in a final analysis of 16 included patients (mean age 28.4). For comparison, we included a group of 22 healthy volunteers (HV, mean age 27.2), primarily recruited from medical students and healthcare professionals (Table 1). The exclusion criteria for them included having migraine or a family history of migraine. Patients and healthy volunteers with any manifest systemic and cerebral disorder other than migraine or the inability to achieve visual acuity of 8/10 were excluded. All participants (MA and HV) were blinded to the study protocol objectives. All study participants gave written informed consent to participate, which was approved by the local ethics committee.

Visual evoked potentials. VEP recordings were conducted on the same day of the screening visit. Subjects were seated in an acoustically isolated room with subdued lighting, facing a monitor surrounded by a uniform lighting field of 5 cd/m². To achieve adequate pupillary diameter, each subject was allowed to adapt to the room’s light for 10 minutes before VEP recording. VEPs were derived from right monocular stimulation. The visual stimulus consisted of a full-screen black-and-white checkboard pattern (80% contrast) generated by a PC monitor, with a reversal rate of 3.1 Hz. At a visual distance of 114 cm, individual checks had a visual angle of 15 minutes, and the checkboard had a visual angle of 23°. To maintain stable fixation during the recording session, subjects were

Table 1. Clinical and demographic characteristics of healthy volunteers and migraine with aura patients. Data are expressed as means ± standard deviation.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HVs (n=22)</th>
<th>MA (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Age, years</td>
<td>27.2±7.3</td>
<td>28.4±9.1</td>
</tr>
<tr>
<td>STAI-S</td>
<td>29.6±5.6</td>
<td>35.1±11.3</td>
</tr>
<tr>
<td>STAI-T</td>
<td>33.1±7.6</td>
<td>39.5±10.0</td>
</tr>
<tr>
<td>BDI</td>
<td>1.4±1.6</td>
<td>3.7±3.2</td>
</tr>
<tr>
<td>Duration of migraine, years</td>
<td>15±10.7</td>
<td></td>
</tr>
<tr>
<td>Attack frequency/month, n</td>
<td>2.1±1.6</td>
<td></td>
</tr>
<tr>
<td>Attack duration, hours</td>
<td>24.5±21.2</td>
<td></td>
</tr>
</tbody>
</table>

HVs, healthy volunteers; MA, migraine with aura patients; STAI-S and STAI-T, State-Trait Anxiety Inventory Scale; BDI, Beck Depression Inventory.
instructed to fixate a red dot at the center of the screen with their right eye while a patch covered the contralateral eye. VEPs were recorded from the scalp using silver/chloride cup electrodes placed at Oz (active electrode) and Fz (reference electrode). A grounding electrode was placed on the right forearm.

Signals were amplified by Digitimer\textsuperscript{TM} D360 (Digitimer Ltd, Welwyn Garden City, UK; bandwidth 0.05-2000 Hz, gain 1000) and recorded using a CED\textsuperscript{TM} power 1401 device (Cambridge Electronic Design Ltd, Cambridge, UK). 600 consecutive traces, each lasting 200 msec, were collected and sampled at 4000 Hz. The cortical responses were divided into 6 sequential blocks of 100, consisting of at least 95 artifact-free traces. Offline averaging of the responses in each block ("block averages") was performed using Signal\textsuperscript{TM} software version 4.10 (CED Ltd). Artifacts were automatically removed using Signal\textsuperscript{TM}’s artifact rejection tool only if the signal amplitude exceeded 90 percent of the analog-to-digital conversion range, which was further checked through visual inspection. The EP signal was corrected off-line for DC deviations, eye movements, and blinking.

VEP components were identified according to their laten- cies: N1 was defined as the major negative peak between 60 and 90 msec, and P1 was the major positive peak following N1 between 80 and 120 msec. We measured the peak-to-peak amplitude of the N1-P1 complex (in mV).

Habituation was defined as the slope of the linear regres- sion line for the 6 blocks and as the change expressed as a per- centage between the first and last VEP blocks. Positive values indicate a lack of amplitude habituation, whereas negative values indicate a more significant amplitude habituation.

All recordings were collected by the researchers, who had not met the participants before the examination and were not involved in recruiting and including the subjects. All recordings were numbered anonymously and analyzed off-line blinded by a researcher, who was not blinded to the order of the blocks.

Psychometric tests. Immediately before the recording session, on the same day, we administered state and trait anxiety and depression self-rating scales to all study participants to test how subjective perception of psychopathological comorbidity affects cortical excitability. Both migraine patients and healthy volunteers completed the following psychometric tests: the BDI and the STAI.

The first (33) is a depression measure consisting of 21 items. Each item is rated on a 4-point Likert scale, with higher scores representing greater severity of depressive symptomatology. The second (34) is a psychological index based on a 4-point Likert scale and consists of 40 questions on a self-report basis. The STAI measures two types of anxiety: state anxiety, anxiety about an event, and trait anxiety, the level of anxiety as a personal characteristic.

All patients and healthy volunteers completed the scales by answering the paper-based questions independently and without being instructed on the clinical implications of their answers.

Statistical analysis. For all statistical analyses, we used SPSS software for Windows version 21. An independent operator carried out the statistical analyses. The Kolmogorov-Smirnov test was used to check for normal distribution, and all the consid- ered variables displayed a normal distribution. Clinical, electro- physiological, and psychometric variables were compared between groups using an ANOVA analysis using the factor group as the independent variable. We used Pearson’s correla- tion test for relationships between the clinical, psychometric, and electrophysiological variables. A p < 0.05 was considered significant.

References


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Conflict of interest: the authors declare no conflict of interest.
Contributions: FC and CDL, conceptualization; CDL and MS, methodology; ADR, software; formal ADR, analysis; GS, CA, EC and VP, investigation; FC, data curation; FC, writing original draft preparation; CDL, writing review and editing. All authors have read and agreed to the published version of the manuscript.
Ethical approval and consent to participate: not applicable.
Availability of data and material: data and materials are available by the authors.
Acknowledgments: the contribution of the G.B. Bietti Foundation in this paper was supported by the Italian Ministry of Health and Fondazione Roma.

Received: 24 March 2024. Accepted: 7 May 2024.
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Confinia Cephalalgica 2024; 1:15764. doi:10.4081/cc.2024.15764
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