Lack of habituation causes high intensity dependence of auditory evoked cortical potentials in migraine

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Summary

Migraineurs are characterized interictally by lack of habituation, or even potentiation, of cortical evoked potentials during repetitive stimulation and by a strong intensity dependence of auditory evoked potentials (IDAP). To determine whether these two features of sensory processing are interrelated, we have studied them simultaneously on the same recordings of auditory evoked potentials (AEPs). AEPs were obtained at four different stimulation intensities in 14 patients suffering from migraine without aura (MO) and 14 healthy volunteers (HV). For each intensity, 120 trials were averaged off-line globally and over four sequential blocks of 30 trials. IDAP was expressed by the amplitude/stimulus intensity function (ASF slope) for global and block averages. Habituation was calculated as the percentage amplitude variation between the first and fourth blocks for each stimulus intensity. The IDAP slope for global averages was higher in MO (1.05 ± 0.27 μV/10 dB) than in HV (0.64 ± 0.45 μV/10 dB) (P = 0.008), but IDAP slopes for block averages were greater in MO only at the fourth block (P = 0.048). First block amplitudes tended to be lower in MO, except at 80 dB. There was a potentiation of AEP amplitudes at every stimulus intensity in MO, contrasting with habituation in HV. IDAP slopes were negatively correlated with mean habituation percentages in pooled data from patients and controls (r = −0.610; P = 0.0006). This study confirms that IDAP is higher in migraineurs than in healthy controls. It also shows that the AEP habituation is replaced by potentiation at all stimulus intensities. The negative correlation found between IDAP and habituation suggests that the latter is able to have a strong influence on the former and perhaps even lead to it. In migraine, the habituation deficit amplifies the IDAP and may thus be the causal functional abnormality. We propose that it is due to a decreased pre-activation level of sensory cortices, a hypothesis also supported in this study by the lower amplitude of first AEP blocks in patients.

Keywords: habituation; intensity dependence; auditory evoked potentials; migraine; cortical excitability

Abbreviations: AEP = auditory evoked potentials; HV = healthy volunteers; IDAP = intensity dependence of auditory evoked cortical potentials; MO = migraine patients; VEP = visual evoked potentials

Introduction

Migraine patients are characterized between attacks by a deficit of habituation, or even potentiation, of cortical evoked and event-related potentials (Schoenen et al., 1985, 1995; Maertens de Noordhout et al., 1986; Böcker et al., 1990; Kropp et al., 1993; Wang et al., 1995, 1999; Áfra et al., 1998; Wang and Schoenen, 1998; Ozkul and Uckardes, 2002).

Another interictal electrophysiological abnormality found in migraineurs is a marked intensity dependence of auditory evoked cortical potentials (IDAP) (Wang et al., 1996). In contrast to habituation which is measured during repetition of a stimulus at the same intensity, IDAP is obtained after stimulations of increasing intensities.

These two electrophysiological phenomena are thought to reflect different aspects of cortical information processing, and their impairment in migraine may be directly or indirectly related to decreased activity in the state-setting mono-
aminergic projections to the sensory cortices (Schoenen, 1998). It is not known if deficient habituation and increased IDAP are two independent dysfunctions with a possible common underlying cause, or whether the former may also be responsible for the latter. In a previous study where we compared IDAP and habituation of visual evoked potentials (VEPs) in the same migraine patients, we found no significant correlation between the two abnormalities (Áfra et al., 2000). On the other hand, both habituation and intensity dependence could be modulated simultaneously by changing synaptic efficiency in a neuronal network model (Thomas et al., 2002).

To explore the possibility of a causal link in a more adequate way, however, the golden standard is to analyse both phenomena in vivo during a unique recording with the same sensory modality and on the same signal.

We therefore have studied both phenomena simultaneously [i.e. habituation, evaluated by the changes of auditory evoked potential (AEP) amplitudes during repeated auditory stimulation, and intensity dependence of AEP] on the same recordings of AEPs, comparing patients suffering from migraine without aura with healthy volunteers.

### Material and methods

#### Subjects

Fourteen patients suffering from migraine without aura according to the diagnostic criteria of the International Headache Society (1988) (MO; IHS code 1.1; mean age: 31.2 ± 12.9 years, range 19–62; nine women, five men; attack frequency: 3.1 ± 2.2/month) were enrolled for this study and compared with 14 healthy volunteers (HV; mean age: 35.2 ± 14.7 years, range 20–63; 10 women, four men).

Subjects were devoid of any other medical condition detectable by history and clinical examination; none was taking drugs on a regular basis, nor had taken any drug within 3 days before the recordings. Healthy volunteers had no personal or familial history of recurrent headaches. Migraineurs were recorded at least 3 days after the last and before the next attack. Occurrence of the latter was checked by a telephone call 4 days after the recording. The study was conducted with the approval of the Ethics Committee of the Faculty of Medicine, University of Liège and with the understanding and consent of each participant.

#### Evoked potential recordings

Recordings were performed in an electrically shielded, dimly lit room. Subjects were seated comfortably in a reclining chair and asked to fix a target in front of them in order to limit ocular artefacts. The EEG was recorded with an active electrode placed at Cz and linked mastoids as reference. EEG signals (band pass filters = 0.001–1000 Hz) were amplified by CED™ 1902 pre-amplifiers and recorded by a CED™ 1401 device (Cambridge Electronic Design Ltd, Cambridge, UK). All recordings were averaged off-line using the Signal™ software package version 1.88 (CED Ltd). Single trial files were unlabelled, in order to keep the operator unaware of the diagnosis.

AEPs were elicited by 1000 Hz tones (duration = 4 ms) delivered binaurally by earphones with a Medelec ST5 Stimulator (Oxford, UK) (repetition rate = 0.474 Hz) at four different intensities (50, 60, 70 and 80 dB) above sensation level in a pseudo-randomized order. For each intensity, 120 trials were collected with the following settings: sampling frequency 4000 Hz; sweep duration 400 ms, 50 ms before and 350 ms after the auditory stimulus. Visual inspection was used to identify trials contaminated by ocular, muscle and movement artefacts. This inspection was performed separately by two researchers (A.A. and P.R.), and only trials considered non-artefact-contaminated by both examiners were averaged.

A first off-line averaging was performed on the total number of artefact-free recordings (‘global averages’). In a second off-line step, the recordings were partitioned in four sequential blocks of 30 trials, among which at least 25 artefact-free trials were averaged (‘block averages’). Although this number of trials was low, the amplitudes of the evoked potential signals were sufficient to secure an acceptable signal to noise ratio, which depends both on the signal amplitudes and on the square root of the number of trials. The number of rejected artefact-contaminated trials was comparable in the four consecutive blocks for healthy volunteers and migraineurs (Table 1).

After identification of the AEP components N1 (between 60 and 150 ms post-stimulus) and P2 (between 120 and 200 ms), we measured peak-to-peak the N1–P2 amplitude for each stimulus intensity. The IDAP was expressed by the amplitude/stimulus intensity function (ASF slope) in µV/10 dB for both global and block averages. Habituation was

### Table 1 Percentage of artefact-contaminated trials excluded during off-line averaging

<table>
<thead>
<tr>
<th>Stimulus intensities</th>
<th>Global averages</th>
<th>First block averages</th>
<th>Second block averages</th>
<th>Third block averages</th>
<th>Fourth block averages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HV</td>
<td>MO</td>
<td>HV</td>
<td>MO</td>
<td>HV</td>
</tr>
<tr>
<td>50 dB</td>
<td>9.6 ± 2</td>
<td>10.2 ± 2.4</td>
<td>9.4 ± 1.9</td>
<td>9.8 ± 2.3</td>
<td>10 ± 2.2</td>
</tr>
<tr>
<td>60 dB</td>
<td>10.1 ± 1.4</td>
<td>11.1 ± 2.1</td>
<td>10.4 ± 0.9</td>
<td>11 ± 2.3</td>
<td>10.6 ± 1.3</td>
</tr>
<tr>
<td>70 dB</td>
<td>9.9 ± 2.1</td>
<td>9.4 ± 2.8</td>
<td>10.8 ± 1.2</td>
<td>8.8 ± 2.7</td>
<td>9.2 ± 2.3</td>
</tr>
<tr>
<td>80 dB</td>
<td>10.3 ± 1.8</td>
<td>11.2 ± 1.7</td>
<td>10.3 ± 1.7</td>
<td>11.4 ± 1.4</td>
<td>10.2 ± 1.8</td>
</tr>
</tbody>
</table>

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in blocks 1 (MO, 0.93; HV, 0.54) and 3 (MO, 0.94; HV, 0.68) 

Results

**IDAP**

On global averages, N1–P2 amplitudes were comparable between migraineurs and healthy volunteers for all stimulus intensities (Table 2). The IDAP slope was steeper in migraineurs (1.05 ± 0.27 μV/10 dB) than in healthy volunteers (0.64 ± 0.45 μV/10 dB) (P = 0.008) (Fig. 1).

No significant N1–P2 amplitude difference was found in the fourth block averages between the two groups of subjects at any stimulus intensity (Table 2). The data in Table 2 show, nevertheless, that N1–P2 amplitudes of migraine patients were always below those of healthy controls, except in the fourth block of averagings for all intensities and in the first block at 80 dB.

IDAP slopes calculated on block averages were significantly different between patients and controls only for the fourth block (MO, 1.17 ± 0.51; HV, 0.55 ± 0.68; P = 0.048). In blocks 1 (MO, 0.93 ± 0.54; HV, 0.60 ± 0.95), 2 (MO, 0.94 ± 0.48; HV, 0.59 ± 0.87) and 3 (MO, 0.73 ± 0.48; HV, 0.64 ± 0.87), there was no difference between groups.

**Habituation**

In migraine patients, there was a clear amplitude increase, i.e. potentiation, of the AEP N1–P2 component between the first and fourth block. This potentiation was similar at all

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**Table 2 N1–P2 amplitudes (μV; mean ± SD) in global averages and sequential block averages as well as habituation (%; mean ± SD) at increasing stimulation intensities in healthy volunteers (HV) and migraine patients (MO)**

<table>
<thead>
<tr>
<th>Stimulation intensity</th>
<th>N1–P2 amplitudes</th>
<th>HV</th>
<th>MO</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Global averages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 dB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 1</td>
<td>6.49 ± 1.99</td>
<td>5.41 ± 1.50</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Block 2</td>
<td>7.07 ± 2.34</td>
<td>5.60 ± 2.03</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Block 3</td>
<td>7.08 ± 2.90</td>
<td>5.85 ± 2.48</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Block 4</td>
<td>6.41 ± 2.80</td>
<td>6.44 ± 1.31</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Habituation (%)</td>
<td>-0.02 ± 32.97</td>
<td>+22.75 ± 24.82</td>
<td></td>
<td>P = 0.049</td>
</tr>
<tr>
<td>60 dB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 1</td>
<td>7.14 ± 2.46</td>
<td>6.70 ± 1.50</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Block 2</td>
<td>7.34 ± 2.72</td>
<td>6.75 ± 1.88</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Block 3</td>
<td>7.09 ± 3.30</td>
<td>6.91 ± 1.89</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Block 4</td>
<td>6.74 ± 2.93</td>
<td>7.43 ± 1.46</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Habituation (%)</td>
<td>-4.65 ± 23.27</td>
<td>+13.40 ± 20.85</td>
<td></td>
<td>P = 0.04</td>
</tr>
<tr>
<td>70 dB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 1</td>
<td>8.19 ± 3.02</td>
<td>7.48 ± 1.94</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Block 2</td>
<td>7.59 ± 2.52</td>
<td>7.49 ± 2.49</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Block 3</td>
<td>7.77 ± 2.51</td>
<td>7.13 ± 2.26</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Block 4</td>
<td>7.62 ± 3.27</td>
<td>8.01 ± 1.73</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Habituation (%)</td>
<td>-7.39 ± 18.52</td>
<td>+11.33 ± 27.06</td>
<td></td>
<td>P = 0.042</td>
</tr>
<tr>
<td>80 dB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 1</td>
<td>8.13 ± 3.09</td>
<td>8.24 ± 2.07</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Block 2</td>
<td>8.94 ± 3.78</td>
<td>8.50 ± 1.38</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Block 3</td>
<td>9.00 ± 3.62</td>
<td>8.20 ± 1.80</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Block 4</td>
<td>7.93 ± 3.35</td>
<td>9.63 ± 1.75</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Habituation (%)</td>
<td>-1.91 ± 15.77</td>
<td>+19.77 ± 19.24</td>
<td></td>
<td>P = 0.013</td>
</tr>
</tbody>
</table>

Negative percentage values indicate habituation, whereas positive values indicate potentiation.
stimulation intensities. In contrast, N1–P2 decreased, i.e. habituated, or was stable in healthy controls (Fig. 2). Consequently, there was a significant difference in the habituation pattern between migraineurs and healthy volunteers at all stimulation intensities (Table 2).

Correlations
There was a moderate, though non-significant, trend for a negative correlation between IDAP slopes and mean habituation percentages, when migraineurs \(r = -0.428; P = 0.12\) or controls \(r = -0.492; P = 0.07\) were considered separately. This negative correlation became significant, however, when both subject groups were combined \(r = -0.610; P = 0.0006\), suggesting that IDAP increases when habituation decreases.

Discussion
In this study, we confirm in different groups of subjects our previous AEP findings. Intensity dependence of the long latency N1–P2 component is significantly increased (Wang et al., 1996) in migraine patients between attacks. Moreover, we extend our preliminary finding of reduced N1–P2 habituation (Wang et al., 1996) by showing that over all stimulus intensities (50, 60, 70 and 80 dB), habituation is lacking in migraine patients and in most instances replaced by potentiation of the cortical responses.

The major objective of the present study, however, was to explore the possible correlation in migraine without aura between lack of habituation and elevated intensity dependence for the auditory sensory modality. The question arises of whether these two different electrophysiological abnormalities are independent from each other and due to different pathophysiological mechanisms, or separate consequences of a common defect, or if one is causing the other. Our results show that AEP habituation taken globally over all stimulus intensities is inversely correlated with IDAP. This correlation is significant if the data from healthy volunteers and migraine patients are pooled, suggesting that it is a general phenomenon, not specific to migraine. Habituation thus seems to condition the degree of intensity dependence. In healthy volunteers, it is normal, though moderate, at every stimulation intensity. In contrast, it is replaced by potentiation at all intensities in migraineurs, which contributes to the progressive increase of the N1–P2 amplitude with increasing stimulation intensities, resulting in a steep amplitude–stimulus slope of IDAP (see Table 2).

Habituation of compound AEP is well known in normal volunteers (Lutzenberger et al., 1979). Only two studies, however, have explored AEP habituation in migraine. In the first one (Wang et al., 1996), performed on a small number of subjects, we found that habituation was replaced by potentiation during the 70 dB, but not during the 40 dB stimulation. In the second study (Sand and Vingen, 2000), no significant habituation deficit was found in migraineurs at 40, 55 and 70 dB. One reason for this difference may be that Sand and Vingen (2000) assessed habituation on only two sequential block averages of 80 trials, whereas in the present study we used four blocks of 30 responses, which is a more sensitive method.

Intensity dependence of evoked potentials, which is comparable with the ‘augmenting–reducing’ response (Buchsbaum and Silverman, 1968), has been investigated extensively in relation to personality traits, diagnostic categories of psychiatric disorders and biochemical variables (reviewed by Hegerl and Juckel, 1993). Converging evidence from human studies and animal experiments suggests that a pronounced IDAP, i.e. an ‘augmenting’ pattern, indicates low central serotonergic transmission (Hegerl and Juckel,
Low activity in raphe–cortical serotonergic pathways is thought to be responsible for a low pre-activation level of auditory cortices, in particular of the primary auditory cortex, where N1–P2 is predominantly generated (Hegerl et al., 1994), which may explain the increased intensity dependence.

Habituation, i.e. amplitude reduction of a cortical response to a sustained stimulus of equal intensity, is considered to reflect an adaptive cortical mechanism protecting from sensory overstimulation (reviewed by Thompson et al., 1979) and lactate accumulation (Sappey-Marinier et al., 1992). In the Aplysia gill-withdrawal reflex, habituation is controlled by serotonergic neurons (Kandel, 1991). Although habituation of long latency cortical evoked responses in the human brain is likely to have more complex underlying molecular mechanisms, there are some arguments suggesting that it might be inversely related to serotonin activity. In migraineurs, the interictal habituation deficit of VEPs disappears during treatment with fluoxetine, the specific

**Fig. 2** Left: illustrative traces of global averaged trials at the different stimulation intensities in a healthy volunteer and a migraine patient. Right: block averages at the 50 and 80 dB stimulation intensities in the same subjects.
serotonin reuptake blocker (Ozkul and Bozlar, 2002). Moreover, Evers et al. (1999) have shown in migraineurs that habituation, assessed by a latency increase of the event-related visual P300 response, varies inversely with platelet serotonin content; in particular, it augments, i.e. normalizes, during the attack in parallel with a decrease in platelet serotonin. Normalization of amplitude habituation during the attack was also found for VEPs (Judit et al., 2000) and contingent negative variation (Kropp and Gerber, 1995). Interestingly, on the basis of biochemical studies in peripheral blood, migraine is thought to be characterized between attacks by a low serotonin disposition, which partially reverses during the attack (Anthony et al., 1969; Sicuteri et al., 1972; Ferrari, 1992).

Taken together, these data suggest that habituation and intensity dependence vary in parallel and that they may be controlled by similar neuronal networks. Our study demonstrates for the first time that for the same sensory modality, there is a strong link between the two phenomena and that the habituation deficit is most likely to be responsible for the high intensity dependence in migraineurs between attacks. The lack of habituation, although similar at all stimulation intensities, will indeed lead to a proportionally greater global averaged response at high intensities, because first block amplitude is greater at high than at low intensities, hence amplifying the intensity dependence (see Table 2). Consequently, we propose that serotonin modulates IDAP (Hegerl and Juckel, 1993) through an effect on AEP habituation. This would explain why IDAP is not significantly different between controls and migraineurs in the first blocks of averagings.

A final result from our study worth discussing is the AEP amplitude in first blocks of averages, i.e. after a small number of stimulations. According to the ‘ceiling’ theory of Knott and Irwin (1973), habituation is negatively correlated to the pre-activation level of sensory cortices. We have shown previously (Áfra et al., 2000) that for pattern-reversal VEPs, habituation is inversely correlated to amplitude in the first block of 50 averaged trials. Our present findings for the auditory modality are in line with these results. First block N1–P2 amplitudes seem indeed to be lower in migraineurs than in healthy volunteers, except for the 80 dB stimulus intensity where they are almost equal (see Table 2). If migraine were to be characterized interictically by hypereexcitability of the auditory cortex, which in physiological terms would produce a greater response to a low number of suprathreshold stimuli, one would expect first block amplitudes to be higher in patients than in healthy controls, i.e. the exact opposite. Together with our results on VEPs (Áfra et al., 2000) and their modulation by repetitive transcranial magnetic stimulations (Bohotin et al., 2002), the present data therefore favour the view that the cerebral cortex of migraineurs is characterized interictically by a reduced pre-activation excitability level causing the habituation deficit, and not by hypereexcitability.

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