Somatosensory evoked high-frequency oscillations reflecting thalamo-cortical activity are decreased in migraine patients between attacks

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Summary
A deficit of habituation in cortical information processing, including somatosensory evoked potentials (SSEPs), is the most consistent neurophysiological abnormality in migraine patients between attacks. To explore further the mechanisms underlying this interictal neural dysfunction, we have studied the high-frequency oscillations (HFOs) embedded in SSEPs because they are thought to reflect spike activity in thalamo-cortical cholinergic fibres (early HFOs) and in cortical inhibitory GABAergic interneurons (late HFOs). Untreated migraine patients with (MA) and without (MO) aura were recorded during (n = 13: nine MO, four MA) and between attacks (n = 29: 14 MO, 15 MA) and compared with healthy volunteers. SSEPs were filtered off-line (digital band-pass between 450 and 750 Hz) to extract the two HFO bursts from the broad-band contralateral N20 somatosensory cortical response obtained by median nerve stimulation. In both migraine groups, amplitudes and latencies of conventional broad-band SSEPs recorded interictally from cervical and parietal active electrodes were not significantly different from those found in healthy volunteers. In contrast, maximum peak-to-peak amplitude and area under the rectified curve of the early HFO burst were significantly smaller in both MA and MO patients than in healthy volunteers. There was no significant difference in the later HFO burst between migraineurs and healthy volunteers. During attacks, all electrophysiological measurements in migraineurs were similar to those found in healthy volunteers. Thalamo-cortical activation, as reflected by the early SSEP HFO burst, may thus be reduced in migraine interictally, but normalizes during an attack, whereas intracortical inhibition, as indexed by the late HFO burst, is normal at any time. This supports the hypothesis that the habituation deficit in migraineurs is due to a reduced pre-activation level of sensory cortices and not to increased cortical excitability or reduced intracortical inhibition.

Keywords: high-frequency oscillations; somatosensory evoked potentials; habituation; migraine; cortical excitability

Abbreviations: HFO = high-frequency oscillation; MA = migraine with aura; MO = migraine without aura; SSEP = somatosensory evoked potential


Introduction
The best reproducible interictal electrophysiological abnormality in migraine patients with (MA) or without aura (MO) is lack of habituation (or even potentiation) of evoked and event-related cortical potentials during repetition of the same stimuli (see review by Schoenen et al., 2003). Such a habituation deficit was also reported for somatosensory evoked potentials (SSEPs; Ozkul and Uckardes, 2002). It is most probably responsible for the strong intensity dependence of auditory evoked cortical responses (IDAP) found in migraineurs between attacks (Ambrosini et al., 2003) and for the increased amplitude of evoked potentials reported in some studies (Gawel et al., 1983; Schoenen et al., 2003). Moreover, it has a familial character (Sándor et al., 2002).
The underlying cause of the habituation deficit in cortical information processing is still under debate. In theory, it could be due to increased cortical excitability (and homosynaptic facilitation) or to decreased intracortical inhibition (heterosynaptic inhibition) (Stanley, 1976), both of which have been proposed in migraine following transcranial magnetic stimulation (Aurora et al., 1998; Aggugia et al., 1999; Mulleners et al., 2001; Battelli et al., 2002; Young et al., 2004) and psychophysical studies of the visual cortex (Chronicle and Mulleners, 1994; Wray et al., 1995). Conversely, both methods have also provided results favouring hypoexcitability of the visual cortex and normal function of inhibitory cortical interneurons (Áfra et al., 1998; Shepherd, 2001; Shepherd et al., 2001; Bohotin et al., 2002, 2003). We have therefore hypothesized, in line with the ‘ceiling theory’ (Knot and Irwin, 1973), that an interictal reduction of the pre-activation level of sensory cortices could be the culprit in migraine. It could indeed explain the low amplitudes found in the first blocks of evoked responses and the lack of habituation in subsequent blocks since it would offer a larger range for suprathreshold cortical activation up to the ‘ceiling’ where habituation starts (Schoenen, 1996). The pre-activation excitability level of sensory cortices is set by activity in thalamo-cortical loops and aminergic, in particular serotonergic and noradrenergic, projections from the upper brainstem (Mesulam, 1990; Hegerl and Juckel, 1993).

Using digital high-pass filtering (>400 Hz), it was shown in recent years that high frequency (>600 Hz) oscillations (HFOs) of low amplitude are superimposed on the N20 component of median nerve SSEPs. Two bursts of HFOs have been identified in animals (Ikeda et al., 2002; Baker et al., 2003), and with depth ( Klostermann et al., 1998, 1999) as well as scalp recordings in humans (Gobbelé et al., 1998, 1999, 2003; Hashimoto et al., 1999; Halboni et al., 2000; Haueisen et al., 2001). Early HFOs are thought to be generated by thalamo-cortical afferents, and late HFOs by inhibitory interneurons in parietal area 3b. A study of SSEP HFOs in migraine may thus shed some light on the neurophysiological causes of the interictal habituation deficit found in evoked cortical responses, as it explores simultaneously thalamo-cortical activation and intrinsic inhibition of the parietal cortex. We reasoned that on the one hand the early burst of HFOs would be increased if migraineurs have cortical hyperexcitability between attacks, but decreased if thalamo-cortical pre-activation is reduced. On the other hand, defective intracortical inhibition would result in a decrease of late HFOs.

**Material and methods**

**Subjects**

We recorded 42 migraine patients: 19 MA [International Classification of Headache Disorders, II (ICHD-II), Headache Classification Committee of the International Headache Society (2004) code 1.2; mean age: 31 ± 11 years; 11 women, eight men] and 23 MO (ICHD-II code 1.1; mean age: 30.0 ± 10; 17 women and six men). They were compared with 15 healthy volunteers of comparable age and gender distribution (healthy volunteers; mean age 29 ± 7; eight women and seven men) without personal or familial history of migraine and devoid of any detectable medical condition. Subjects taking any medication on a regular basis except for the contraceptive pill were excluded.

We analysed separately the recordings from two groups of patients. In the first (interictal) group (n = 29; 15 MA, 14 MO, 17 females, 12 males), we included only data from patients who had an interval of at least 3 days between the recording and their last or their next migraine attack. The second group (n = 13; 4 MA, 9 MO, 11 females, two males) was composed of subjects in whom the recordings were made within a time range of 12 h before or after the beginning of an attack.

All participants gave informed consent in accordance with the Declaration of Helsinki and the study was approved by the Ethics Committee of the Faculty of Medicine, University of Liège.

**Data acquisition**

SSEPs were elicited after electrical stimulation of the right median nerve at the wrist using a constant current square wave pulse (0.2 ms width, cathode proximal) and a stimulus intensity set at twice the motor threshold. One series of 500 sweeps was collected and averaged at a repetition rate of 4.4 Hz. The active electrodes were placed over the contralateral parietal area (C3, 2 cm posterior to C3 in the international 10–20 system) and on the fifth cervical spinous process (C5v), both referenced to Fz; the ground electrode was on the right arm. The evoked potential signals were amplified by CED™ 1902 pre-amplifiers and recorded by a CED™ 1401 device (Cambridge Electronic Design Ltd, Cambridge, UK). Subjects were seated relaxed on a comfortable chair in an illuminated room and asked to stay with their eyes opened and to fix their attention on the wrist movement. Forty milliseconds of the post-stimulus period were sampled at 5000 Hz to collect a wide range of frequencies. All recordings were averaged off-line using the Signal™ software package version 2.14 (CED Ltd).

**Data analysis**

**Wide-band somatosensory evoked potentials**

For wide-band unfiltered SSEPs (0–2500 Hz), we have identified the various components according to their respective latencies. Thereafter we have measured peak-to-peak amplitudes of the N13 cervical component under the Cv5 active derivation and of N20onset–N20peak, N20peak–P25, P25–N33 under the active C3’ left-sided scalp electrode.

**High-frequency oscillations**

Digital zero-phase shift band-pass filtering between 450 and 750 Hz (Barlett-Hanning window, 51 filter coefficients) was applied off-line in order to extract the HFOs superimposed on the N20 left parietal component of the SSEP. In the majority of recorded traces, we were able to identify two separate bursts of HFOs: the first, early burst occurred in the latency interval of the ascending slope of the conventional N20 component, and the second, late burst in the time interval of the descending slope of N20, sometimes extending into the ascending slope of the N33 peak. In general, the frequency of oscillations was higher in the first than in the second HFO burst,
and in between the first and the second burst there was a clear frequency and amplitude decrease, which allowed separation of the two bursts. In recordings in which a clear distinction between the two components was not possible, we considered as first burst HFOs occurring before the N20 peak and as second burst those after the N20 peak.

After elimination of the stimulus artefact, we have measured the latency of the negative oscillatory maximum, the intra-burst frequency, the number of negative peaks, the maximum peak-to-peak amplitude and the area under the rectified curve (AUC), computed using an interval of ±1.17 ms around the maximum peak to provide stability against noise (see Gobbelé et al., 1998). All measurements were performed separately on the two HFO bursts.

Finally, since the recorded signal was short (50 ms) and contained high-frequency oscillations that varied with time, we have used a short-time Fourier transform spectrum (STFT) to obtain an indication of the time–frequency properties. This method offers the advantage of visualizing the power (z-axes) of a two-dimensional signal represented by time (x-axes) and frequency (y-axes).

The difference between each group of migraine patients and healthy volunteers was evaluated by one-way analysis of variance (ANOVA), and a \( P < 0.05 \) was considered significant.

### Results

All the measured components, for both wide-band and HFO SSEPs, were clearly identified in all examined subjects. Tables 1 and 2 show synoptically mean values ± SD and levels of significance found for the various measures taken in healthy volunteers, in interictal recordings from MA and MO patients and in ictal recordings.

#### Intercital recordings

##### Broad-band SSEPs

In the MO and the MA groups, peak-to-peak amplitudes and latencies recorded from the cervical and parietal active electrodes were not significantly (\( P > 0.05 \)) different from those of healthy volunteers.

##### High-frequency oscillations in SSEPs

Maximum peak-to-peak amplitude and area under the rectified curve of the first burst of HFOs were significantly smaller in MO \( [F(1,27) = 4.822, \ P = 0.037 \text{ and } F(1,27) = 5.456, \]
Healthy volunteer

Migraine without aura

Migraine with aura

Fig. 1 Illustrative a traces of a (A) broad-band SSEPs, (B) HFO SSEPs and (C) three-dimensional short-time Fourier transform spectrum in a healthy volunteer, a MO and a MA patient.

Fig. 2 Grand average of all traces for the healthy volunteer (HV) group, MO and MA patients group for (A) broad-band SSEPs and (B) HFO SSEPs.

$P = 0.027$, respectively] and MA patients [$F(1,28) = 7.358$, $P = 0.011$ and $F(1,28) = 7.067$, $P = 0.013$] than in healthy volunteers.

In contrast, there was no significant difference between healthy volunteers and patients in amplitude or AUC of the second HFO burst.

Latency of the negative oscillatory maximum, intra-burst frequency and number of negative peaks for both early and late HFO bursts were similar between the three subject groups.

Ictal recordings

In the 13 migraineurs recorded during an attack or in the immediate peri-attack phase, measurements performed on both broad-band and HFOs SSEPs were not significantly different from those of our healthy volunteer group.

Discussion

In accordance with previous studies (Firenze et al., 1988; de Tommaso et al., 1997), we found no significant difference between migraineurs recorded outside of an attack and healthy volunteers for broad-band conventional SSEPs. This suggests that the somatosensory signal is normally conducted along the dorsal columns up to the contralateral somatosensory cortex. In contrast, after band-pass filtering, the first early burst of high-frequency oscillations embedded in the
N20 component of the SSEP was significantly reduced in both MA and MO subjects compared with healthy volunteers, while the second late HFO burst was normal.

To the best of our knowledge, our study is the first to apply the rather recent methodology of SSEP HFOs to research on brain physiology in migraine patients. The results have to be interpreted in the light of available, still incomplete and partially contradictory knowledge on the neural generators involved in HFOs.

As mentioned, the late burst of HFOs is thought to have a postsynaptic cortical origin, probably reflecting the activity of intracortical GABAergic inhibitory interneurons (Hashimoto et al., 1996; Mochizuki et al., 2003). Presynaptic subcortical activity, most probably repetitive action potentials along the terminal segment of thalamocortical fibres, is on the contrary responsible for the early burst of HFOs (Gobbelé et al., 1998, 2003; Ikeda et al., 2002; Mochizuki et al., 2003). Multichannel scalp recordings and dipole source analysis in normal subjects have shown that both the thalamic and the cortical components of the early presynaptic component of SSEP HFOs were reduced in amplitude during non-rapid eye movement (REM) sleep with partial recovery during REM sleep, while the later HFO bursts were unchanged or rather enhanced (Halboni et al., 2000). Furthermore, the amplitude of the thalamic component and of the cortical tangential source activity of HFOs was significantly greater with eyes open than with eyes closed (Gobbelé et al., 2000). After administration of the central acetylcholinesterase inhibitor rivastigmine, Restuccia et al. (2003) found an increase in amplitude of the cortical HFO component in the 18–28 ms latency range and concluded that cortical HFOs are generated mainly by specialized pyramidal neurons. Considering that cholinergic systems play a pivotal role in sleep–wake cycle and arousal (Mesulam, 1995), cholinergic reticulothalamic pathways could be crucial for the generation of SSEP HFOs.

Our finding of a reduced activity of the early HFO burst in migraineurs between attacks suggests, therefore, that migraine is associated with hypofunction in thalamo-cortical excitatory cholinergic afferents. By the same token, the normal second HFO burst indicates that the late generators function normally, be they cortical inhibitory interneurons (Hashimoto et al., 1996; Mochizuki et al., 2003) or pyramidal chattering cells (Restuccia et al., 2003).

As mentioned in the Introduction, controversy has arisen about the excitability status of the cerebral cortex in migraineurs between attacks. Intuitively, some clinical features of migraine such as hypersensitivity to light or noise, and the aura symptoms suggest that the cerebral cortex is hyperexcitable. In the physiological sense, however, hyperexcitability would mean that the brain responds to a subliminal stimulus or that its response to a supraliminal stimulus is increased in amplitude. These two abnormalities have never been demonstrated precisely in migraineurs. Increased amplitudes of psycho-physical (Wray et al., 1995) or cortical evoked responses (Gawel et al., 1983) were reported by some, but these studies are based on the use of repetitive stimuli and we and others have shown that the lack of habituation of an initial low amplitude response during stimulus repetition is responsible for the net increase in averaged responses (Schoenen et al., 2003). Unfortunately, transcranial magnetic stimulation of the visual cortex in migraineurs has provided contradictory results (see the review by Schoenen et al., 2003).

We have therefore hypothesized that the finding of reduced habituation of evoked responses in migraine is probably not due to hyperexcitability and homosynaptic facilitation as such, nor to lack of heterosynaptic inhibition, but to a reduced pre-activation excitability level of sensory cortices (Schoenen, 1996). According to the ‘ceiling theory’ (Knott and Irvine, 1973), this can explain the low response amplitude for a single or a few stimuli and its marked increase (potentiation) or lack of decrease, i.e. habituation, because it allows a wider range of suprathreshold activation before reaching the ‘ceiling’ and initiating habituation of the response. Our finding of reduced early HFO bursts in SSEPs, and thus reduced thalamo-cortical activation is in agreement with this hypothesis and can hardly be explained by increased cortical excitability. Similarly, the normal late SSEP HFO suggests that intracortical inhibition is normal in migraine.

Interestingly, cortical evoked potentials habituate normally just before and during a migraine attack (Áfra et al., 2000) which suggests, according to the previous ‘ceiling’ hypothesis, that cortical excitability increases to normal levels. As expected, the early HFO burst was within normal values in migraineurs recorded during an attack, which probably reflects an increase in thalamo-cortical activation. Whether such an increase could be induced by the ictal activation of the dorsal rostral brainstem (Welller et al., 1995; Bahra et al., 2001) which contains state-setting aminergic nuclei projecting to thalamus and cortex remains to be determined. Activation of these nuclei and of thalamo-cortical projections may contribute to an ictal normalization of the cortical preactivation level.

Supplementary studies of HFO are needed and of interest in migraine. Comparative recordings in other primary headaches such as tension-type headache would be useful to verify the specificity of our findings for migraine. Studying the effect of pharmacological agents, among which prophylactic antimigraine drugs and repetitive transcranial magnetic stimulations which are able to modify in opposite directions the excitability of the underlying cortex depending on stimulation frequency, can be used to modulate HFOs and shed light on the precise neuronal generators.

References


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