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REVIEW

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Electrophysiological response patterns of primary sensory cortices in migraine

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Abstract Migraine is an ictal disorder characterised by a particular vulnerability of patients to sensory overload, both during and outside of the attack. Central nervous system dysfunctions are supposed to play a pivotal role in migraine. Electroneurophysiological methods, which aim to investigate sensory processing, seem thus particularly appropriate to study the pathophysiology of migraine. We have thus reviewed evoked potential studies performed in migraine patients. Although results are in part contradictory, these studies nonetheless demonstrate an interictal dysfunction of sensory cortices, and possibly of subcortical structures, in migraine with and without aura. The predominant abnormality is a deficient habituation of evoked responses to repeated stimuli, probably due to cortical, and possibly widespread neural, "dysexcitability".

Keywords Migraine · Pathophysiology · Evoked potentials · Sensory cortices · Cortical excitability

Introduction

Migraine is a very common ictal neurological disorder; nonetheless its pathophysiology is still far from being completely understood. Both neuronal and vascular components are supposed to play a relevant role in migraine, but its clinical expression is also influenced by environmental factors. Migraine patients seem to be very vulnerable to any kind of sensory overload. Light exposure is not only able to worsen a migraine attack, but also to trigger it [1], and migraine patients commonly report a lower discomfort threshold to light exposure than healthy subjects [2]. Besides photophobia, an abnormal sensitivity to loud auditory stimuli seems to be a migraine marker, both during attacks and interictally [3, 4]. Osmophobia and taste abnormalities have been described as very specific of migraine attacks [5], and osmophobia is also considered as a reliable marker for migraine [6]. Thus, every modality of sensory stimulation may induce in migraine patients a higher discomfort than in non-migraine subjects.

Several neuronal structures are probably involved in migraine pathophysiology, such as the cerebral cortex, the brainstem (periaqueductal grey matter, aminergic nuclei), and both peripheral and central components of the trigeminovascular system. However, the global hypersensitivity of migraine patients to external sensorial stimulation leads many authors to investigate particularly the responsiveness of their primary sensory cortices. The methods of clinical neurophysiology seem particularly appropriate for this; the evoked responses, more than other methods such as transcranial magnetic stimulation (TMS), provide a peripheral-central approach, very similar to what happens in physiological conditions. During the last decade almost every

modality of stimulation has been used to study evoked responses in migraine. Various interictal and ictal abnormalities have been reported in migraine, although as yet there are no findings that can be used as a diagnostic tool [7]. We will review the available published data, discuss their findings and examine the possible neurobiological bases of the reported abnormalities.

Visual cortex response patterns in migraine

Visual evoked responses may be elicited by many stimulation modalities. In early studies it was preferred to use single flashes to evoke visual potentials (flash-evoked visual potentials). In almost all these pilot studies, the main evoked potential (EP) components showed higher amplitudes in migraineurs than in controls [8–10] except one [11]. Early visual evoked potential (VEP) components were reduced on the side opposite to the aura [12].

However, the visual stimulation modality used most often to investigate VEP in migraine has certainly been the reversal lighted checkerboard, normally used to obtain pattern reversal VEP (PR-VEP). The results of these studies in migraine were heterogeneous (Table 1). In most studies normal amplitudes were found [10, 13–22], but several investigators reported increased amplitudes between attacks [23–30] or in temporal proximity to an attack [31], whereas some other authors described decreased amplitudes [32, 33]. PR-VEP latencies were found to be increased in some studies [18, 23, 24, 31, 34–37] and decreased in others [25, 38].

VEP amplitude or latency asymmetries were found in subgroups of patients, occasionally with a relation to the side of the headache [28, 33, 38–41]. In migraine with aura patients, vector analysis of VEP showed alterations suggesting asymmetrical visual cortex activation [42].

In one study the PR-VEP amplitude seemed to decrease in correlation with the duration of migraine [30], but this finding was not confirmed [43].

Oelkers et al. [44] found increased N2 latency only with high spatial frequency of the stimulation pattern and suggested that this reflects dysfunction of the magnocellular pathway in migraine. High contrast and spatial fre-

Table 1 Pattern reversal visual evoked potentials

Authors	Diagnosis	Age groups	Components measured	Principal findings
Kennard et al., 1978 [23]	MA	Adults	N1, P1, N2	Increased amplitude and latency of P1 compared to controls
Benna et al., 1985 [39]	MO	Adults	N80, P100	Aspecific latency and amplitude asymmetries
Brinciotti et al., 1986 [10]	MO, MA	Children	P2	No differences compared to HV
Polich et al., 1986 [32]	MA	Adults	N75, P100, N145	Reduced P100 amplitude
Mariani et al., 1988 [13]	MO	Adults	P100	No differences compared to controls
Raudino, 1988 [31]	MO, MA	Adults	P100	Increased P100 latency and amplitude close to the attack
Diener et al., 1989 [34]	MO, MA	Adults	P100	Increased latency and amplitude
Lai et al., 1989 [14]	MO, MA	Adults	N1, P1	Latencies and amplitudes within normal limits
Drake et al., 1990 [15]	MO	Adults	N1, P1, N2	No differences compared to HV
Mariani et al., 1990 [24]	MA	Adults	N75, P100	Increased latencies of P100
Tsounis et al., 1993 [38]	MO, MA	Adults	P100	P100 latencies shorter on the symptomatic side (hemifield stimulation)
Tagliati et al., 1995 [33]	MO, MA	Adults	N70, P100	No difference compared to HV. Reduced amplitudes ipsilateral to visual aura
Schoenen et al., 1995 [16]	MO, MA	Adults	N1, P1, N2	No differences compared to HV
Rossi et al., 1996 [17]	MO, MA, ETTH	Children	P100	No differences in latencies compared to HV
Lahat et al., 1997 [26]	MO	Children	P1, N2	Increased amplitude
Shibata et al., 1997 [27]	MO, MA	Adults	N75, P100, N145	Increased P100amplitude in MA compared to HV
Sener et al., 1997 [18]	MO, MA	Adults	N70, P100	No differences compared to controls
Shibata et al., 1997 [28]	MO, MA	Adults	N75, P100	Increased P100 amplitude in MA, higher on the contralateral side of visual aura
Aloisi et al., 1997 [25]	MO, MA	Children	P100, N140	Shorter P100 latency and increased P100 amplitude (lowered by administration of magnesium)

Cont. →

Table 1 cont.

Authors	Diagnosis	Age groups	Components measured	Principal findings
Afra et al., 1998 [19]	MO, MA	Adults	N1, P1, N2	No differences in first block latencies and amplitude
Shibata et al., 1998 [40]	MA, ME (aura, no headache)	Adults	N/5, P100	Increased amplitude soon after attack. Amplitude asymmetry correlated to the disease duration
Oelkers et al., 1999 [44]	MO, MA	Adults	N1, P1, N2	Prolonged latency of N2 in MA during high spatial frequency stimulation
Wang et al., 1999 [20]	MO, ETTH, CTTH	Adults	N1, P1, N2	No differences in first block latency or amplitude
Lahat et al., 1999 [29]	MO	Children	N1, P1, N2	Increased amplitude of P1/N2
Afra et al., 2000 [48]	MA	Adults	N1, P1, N2	No increased VEP amplitude with red light (but increase in HV)
Afra et al., 2000 [73]	MO, MA	Adults	N1, P1, N2	No significant first block amplitude differences compared to HV
Yucesan et al., 2000 [43]	MO	Adults	N70, P100	No correlation between amplitudes of VEPs and duration of the disease
Khalil et al., 2000 [30]	MO+MA	Adults	P1	Increased amplitude of P1 (decreased in patients with long disease duration)
Sand and Vingen, 2000 [22]	MO, MA	Adults	N1, P1, N2	No differences in VEP amplitudes
Logi et al., 2001 [41]	MO, MA	Adults	N70, P100	Asymmetric topographic VEP distribution in migraineurs
Cautin-Churchman and Padron de Freytez, 2003 [42]	MA	Adults	P1, N2	Altered vector deviation after pattern-reversal and LED goggles stimulation according to the laterality of symptoms
Shibata et al., 2005 [45]	MO, MA	Adults	N75, P100, P135	Increased VEP amplitudes with high contrasts and high spatial frequency stimulation
Coppola et al., 2005 [56]	MO, MA	Adults	Early and late GFOs	Increased amplitude of early GFOs

HV, healthy volunteers; *MO*, migraine without aura; *MA*, migraine with aura; *ME*, aura without headache; *ETTH*, episodic tension-type headache; *CTTH*, chronic tension-type headache

quency of the visual stimulation pattern seems also to induce increased amplitudes of VEP components [45].

These results were globally similar in migraine with and without aura [10, 14, 17, 18, 22, 25, 30, 31, 34], with the exception of abnormalities of the P100 amplitude, which were found on the side of the visual aura in migraineurs with aura [28, 33].

The discrepancies that emerged from these studies can in part be explained by methodological differences. Diagnostic groups tend to be less homogeneous in studies performed before the first Headache Classification of the International Headache Society (1988) [46] became available. More importantly, evoked cortical responses undergo profound modifications in the peri-ictal, ictal and immediate post-ictal periods, which was not always sufficiently controlled in all studies.

Taken together, classical studies of averaged PR-VEP do not provide any consistent clue for the CNS pathophysiology of migraine. By contrast, a considerable advance towards the comprehension of the patterns of cortical function in migraine patients was obtained when, instead of considering the PR-VEPs amplitudes *per se*, they were investigated with regards to their modifications following repeated stimulations.

Normally, when an innocuous/irrelevant stimulus is delivered repetitively a gradual decrease in the strength of the cortical responses is observed. This phenomenon is known as “habituation”. It plays an important role for adaptation because it protects against sensory overload and saves attentional and memory resources for meaningful novel stimuli. When applied to the electrophysiological data obtained in migraine patients, the analyses of the habituation of evoked potentials are more concordant. The first detailed studies of habituation performed on VEP showed that amplitudes of the N1-P1 and P1-N2 components decreased (i.e., habituated) during repetitive stimulation in healthy volunteers, while they remained unchanged or increased (i.e., potentiated) in migraineurs

between attacks [16, 19, 20]. By contrast, in migraine patients PR-VEP amplitude normalises just before and during the attack [47].

The interictal lack of habituation in migraine was not confirmed as such in two studies. In the first one [44], only a trend for an N1-P1 habituation deficit was found in migraine with aura when a low spatial frequency was used for stimulation, but technical differences (e.g., a higher contrast pattern) may explain the incongruence. In the second study [22], the majority of patients were recorded in the pre-ictal phase and while habituation was significant in healthy volunteers, it was not so in patients between attacks.

VEP potentiation was negatively correlated with amplitude in the first block of averaged responses [21], and red light, supposed to represent the most effective stimulus for the visual cortex, induced VEP potentiation in healthy subjects, but not in migraineurs [48]. These results may indicate that the visual cortex is less responsive in migraine. Interestingly, the reduced VEP habituation pattern is correlated, in migraine patients, with a reduced habituation to the nociceptive blink reflex, suggesting that both visual cortex and brainstem share similar neurobiological dysfunctions in migraine [49].

The degree of the VEP habituation deficit was very similar in related parent-child pairs of migraineurs, but not in unrelated pairs [50], which favours its familial, most probably genetic, character.

VEP studies are also partly contradictory in migrainous children. Some authors reported normal [10, 17], others increased amplitudes [25, 26, 29]; this was associated with decreased latencies in one study [25]. Deficient habituation to PR-VEP seems to be absent in childhood migraine [37].

Drug treatments may influence visual evoked responses in migraine patients. PR-VEP [34] and PR-VEP habituation [51] tended to return to values comparable to those of healthy subjects during prophylactic treatment with beta-blockers. The reduced PR-VEP habituation found in migraine patients normalises also during prolonged treatment with the specific serotonin reuptake blocker fluoxetine [52]. MEG signals evoked by visual stimulation are reduced in migraine patients during prophylactic treatment with sodium valproate [53].

Since it was first described, the altered interictal habituation pattern in migraine patients has been considered by turns as expression of cortical hyper- or hypoexcitability. As repetitive TMS (rTMS) at different rates induces modifications of cortical excitability, in particular high-frequency rTMS over the occipital region activates the underlying cortex and low frequency rTMS has an inhibitory effect, the rTMS-induced effects on cortical excitability were used to investigate VEP habituation in migraine. The high-frequency rTMS was followed by a normalisation of VEP habituation in migraineurs, while the low-frequency rTMS induced a deficit of VEP habituation in normal controls [54]. After daily sessions of rTMS, it has been shown that these effects on habituation may last from hours to weeks both in controls and migraine patients [55]. These findings suggest that in migraine patients the reduced VEP habituation is associated to cortical hypoexcitability.

New methods of VEP analyses, such as the measure of visual evoked high-frequency oscillations in the gamma range (gamma frequency oscillations (GFOs), 20–60 Hz) may represent a further tool to investigate migraine pathophysiology. A recent pilot study, published in abstract form [56], showed that the late GFOs, which are supposed to represent post-synaptic evoked activity, present a significant habituation deficit in migraine patients. On the other hand, the early GFOs, which seem to be related to presynaptic mechanisms, have increased amplitudes in migraineurs with aura only, which may account for the visual discomfort more frequently reported by them.

Auditory cortex response patterns in migraine

Studies of short latency, i.e., brainstem auditory evoked responses (BAERs), provide contrasting results in migraine (Table 2). There were reported normal interictal latencies [22, 39, 57–59], increased latencies (especially for wave V) [60, 61], in particular during the attack [57, 58], and inter-aural asymmetries [60], especially in migraine with aura [62]. A negative correlation was also described between discomfort caused by low-intensity stimulations (55 dB) and wave IV-V amplitude [22]. During the migraine attack, the later BAERs components have increased latencies [57, 58].

Conversely, concordant results came from the few studies of cortical long-latency auditory evoked potentials, which did not show significant differences between migraineurs and controls with regard to N1, P2 and N2 component latency or amplitude [22, 61].

Few studies have explored habituation of cortical auditory evoked potentials. The first study reported potentiation of N1-P2 amplitude only at high stimulus intensities, contrasting with habituation in healthy volunteers [63]. This was not confirmed in another report [22], possibly because of methodological differences. In a later study [64], the intensity dependence of auditory N1-P2 and habituation for each stimulation intensity were measured simultaneously. In this study the finding of a greater potentiation for high- than for low-intensity stimulations

in migraineurs was confirmed, as opposed to habituation or absence of amplitude change for all stimulation intensities in controls.

"Gating of sensory input" is another central phenomenon, which plays a crucial role in the processing of incoming information. A typical expression of this phenomenon is the suppression of the cortical response to a test stimulus delivered after an identical conditioning stimulus. The middle-latency P50 component of the auditory evoked cortical potential is very sensitive to auditory sensory gating and thus a classical electrophysiological tool for its assessment. The study of sensory gating of the auditory P50 response [65] showed a marked reduction of gating in patients compared to healthy volunteers, which suggests that lack of habituation in migraine might result in part from a precortical dysfunction. A reduced sensory gating of the P50 wave in migraine patients was confirmed by another study [66] and considered as an expression of reduced short-term habituation.

Intensity dependence of auditory evoked potentials (IDAP) is supposed to be inversely related to central serotonin neurotransmission [67]. Thus the finding of an increased IDAP in migraine patients was particularly

Table 2 Auditory evoked potentials (AEPs)

Authors	Diagnosis	Age groups	Type of AEP recorded	Principal findings
Benna et al., 1985 [39]	MO	Adults	BAERs	No abnormalities or asymmetries compared to controls
Bussone et al., 1985 [60]	MO	Adults	BAERs	Increased and asymmetric I-V latencies in migraineurs
Yamada et al., 1986 [57]	MA (basilar migraine)	Adults	BAERs	IV and V wave latencies prolonged during headache
Podoshin et al., 1987 [58]	MO, MA	Adults	BAERs	No interictal differences compared to HV. Prolonged interpeak latencies during headache
Battistella et al., 1988 [59]	MO, MA	Children	BAERs	No difference compared to HV
Drake et al., 1989 [61]	MO	Adults	Long-latency AEPs	No differences in N100, P200 and N200 amplitudes and latencies with respect to HV
Schlake et al., 1990 [62]	MO, MA	Adults	BAERs	Asymmetric I, II, III and V latencies in migraineurs (especially in MA)
Drake et al., 1990 [15]	MO	Adults	BAERs	Prolonged I-V and III-V interpeak latencies in migraineurs compared to HV
Wang et al., 1996 [63]	MO, MA	Adults	Long-latency AEPs (IDAP)	Interictal increased IDAP in migraine patients
Proietti-Cecchini et al., 1997 [68]	M?	Adults	Long-latency AEPs (IDAP)	Increased IDAP after zolmitriptan 10 mg both in migraine patients and HV
Sandor et al., 1999 [50]	MO	Adults, children	Long-latency AEPs (IDAP)	Correlation of IDAP slopes in migraine pairs (parent-child)
Sand and Vingen, 2000 [22]	MA, MO	Adults	BAERs, long-latency AEPs (IDAP)	No difference compared to HV
Judit et al., 2000 [47]	MO, MA	Adults	Long-latency AEPs (IDAP)	Normalisation of IDAP just before and during an attack
Sandor et al., 2000 [51]	MO, MA	Adults	Long-latency AEPs (IDAP)	Reduction of IDAP in migraine patients during treatment with beta-blockers (but not riboflavin)
Afra et al., 2000 [21]	MO, MA	Adults	Long-latency AEPs (IDAP)	No correlation between IDAP slopes and VEP habituation
Siniatchkin et al., 2000 [70]	MO	Adults, children	Long-latency AEPs (IDAP)	Correlation of IDAP slopes in migraine pairs (parent-child)
Ambrosini et al., 2003 [64]	MO	Adults	Long-latency AEPs	Increased IDAP and deficit of AEP habituation in migraine

HV, healthy volunteers; *MO*, migraine without aura; *MA*, migraine with aura; *BAERs*, brainstem auditory evoked responses; *IDAP*, intensity dependence of auditory potentials

interesting [63], because this further example of abnormal information processing in interictal migraine has a well investigated biological background. Further evidence for IDAP as a surrogate marker for central serotonergic neurotransmission came from a study [68] showing that dexfenfluramine, a drug increasing serotonergic activity, decreases IDAP, while zolmitriptan, a 5-HT-$1_{B/D}$ receptor agonist, which is able to decrease brain serotonin via presynaptic inhibition of its release, increases IDAP. The increased IDAP normalises during the migraine attack [47]. IDAP abnormalities were correlated with personality profiles thought to be associated with lower serotonergic transmission in migraine, but not in post-traumatic headache [69].

Two independent studies [50, 70] found evidence for a familial influence on IDAP in migraineurs, pointing towards a genetic background, though a direct genetic link is still to be proven.

In spite of its well established neurochemical basis, IDAP is not useful for diagnostic purposes because of its limited repeatability both in pathophysiological [71] and in pharmacological studies [72]. This may be related to the fact that most of the IDAP increase in migraine could be due to the AEP habituation deficit at high-intensity stimulations [64]. Interestingly, degrees of amplitude-stimulus function slopes reflecting IDAP and PR-VEPs lack of habituation were not significantly correlated when investigated together in migraine patients [73].

Somatosensory cortex response patterns in migraine

Overall, no significant abnormalities of somatosensory evoked potentials (SEP) after median nerve or index finger stimulation were found in migraine when a classical analysis was performed [74–77] (Table 3). In a few studies on small numbers of subjects, some subtle differences with controls were reported: prolonged N13 latency interictally [74], reduced P22/N30 amplitude interictally [78], prolonged N19 latency and reduced amplitude during the aura [76].

Habituation of SEP has only been measured in one study up to now. Ozkul and Uckardes [79] found poten-

Table 3 Somatosensory evoked potentials (SEP)

Authors	Diagnosis	Age groups	Stimulation site	Components measured	Principal findings
Montagna et al., 1985 [74]	M?, TTH	Adults	Median nerve (wrist)	N13, ?	Prolonged latency of N13 in migraineurs with respect to TTH patients.
Firenze et al., 1988 [75]	MO, TTH, CH	Adults	Median nerve (wrist)	N1, P2	No differences compared to HV
Chayasirisobhon, 1995 [76]	MA	Adults	Median nerve (wrist)	N13, N19, P25	Prolonged N19 latencies and reduced amplitude of N19-P25 during the aura. Normal values during headache.
Marlowe, 1995 [77]	M?, TTH	Adults	Index finger	P1, N1, P2	No differences in P1-N1 and N1-P2 amplitudes, reduced intensity-dependence of P1-N1 amplitudes
De Tommaso et al., 1997 [78]	MO, MA	Adults	Median nerve (wrist)	N13, N20, P22, P25, P27, N30	Reduced amplitude of P22/N30 complex in migraineurs (asymmetric in migraine with aura)
Sakuma et al., 2004 [83]	MO, MA	Adults	Median nerve (wrist)	SEPs, high-frequency oscillations (HFOs) – N9, N13, N20, P25	Reduced HFOs amplitudes in migraineurs
Valeriani et al., 2005 [80]	MO	Children	Median nerve (wrist)	N13, N20, P24, N30	Higher SEPs recovery cycle in migraineurs
Coppola et al., 2005 [84]	MO, MA	Adults	Median nerve (wrist)	Early and late SEPs, high-frequency oscillations (HFOs) – N13, N20, P25, N33	Reduced amplitude of early HFOs in migraineurs

HV, healthy volunteers; *MO*, migraine without aura; *MA*, migraine with aura; *TTH*, tension-type headache; *CH*, cluster headache

tiation of median nerve SEP N20 component in migraineurs, contrasting with habituation in healthy controls.

However, the more interesting news about the response pattern of sensory cortices in migraine came mainly from some recent SEP studies, when more sophisticated techniques of recording and analysis were used. The finding of a shorter SEP recovery cycle in migraine children than in controls suggested a somatosensory system disinhibition [80], possibly due to abnormalities of inhibitory interneuron function, as suggested by psychophysiological and TMS studies [81, 82]. Investigations into the high-frequency oscillations (HFOs) embedded in SEP, which are supposed to reflect spike activity in thalamo-cortical cholinergic fibres (early HFOs) and in cortical inhibitory GABAergic interneurons (late HFOs) were performed in two independent studies. One study [83] considered HFOs without regarding their latency; they were found to be reduced in migraine patients with respect to healthy subjects, and this finding was suggested to be due to a diminished inhibitory mechanism. The other one [84] showed a reduced amplitude and area-under-the-rectified-curve of early HFOs in migraine patients, whereas late HFOs were similar in migraineurs and controls, suggesting a reduced thalamo-cortical activation but normal intracortical inhibition in migraine.

The migraine response pattern of somatosensory cortex has also been investigated with magneto-encephalography [85]. In this study the equivalent current dipole of the first MEP cortical component, the N20m, was increased in migraine patients and positively related to their mean attack frequency, which led the Authors to suggest that the population of neurons in the primary somatosensory cortex underlying the N20m are hyperexcitable and that this hyperexcitability is linked to the frequency of migraine attacks. Curiously, in this study there was no difference of habituation patterns in migraine patients and controls, because both groups showed no habituation to repeated stimuli, in contrast with all previous evoked potential studies in healthy subjects.

Olfactory cortex response patterns in migraine

At present only two studies are available investigating olfactory cortex responses in migraine patients. The first one [86] demonstrated smaller olfactory ERP amplitudes in migraineurs. The second study, published only in abstract form [87], suggested that the above-described deficit of habituation, which seems to characterise cortical response patterns of migraine patients, is present also in olfactory evoked potentials.

Discussion

The majority of evoked potential studies in migraine have shown two main abnormalities: increased amplitudes of grand averagings in the main EP components and lack of habituation in successive blocks of EP averagings. At first sight, increased amplitudes of cortical evoked responses would favour the hypothesis that migraine is characterised by cortical hyperexcitability between attacks [88]. However, from a strictly semantic point of view, we can refer to hyperexcitability when a normal stimulus produces an abnormally increased response. However, this is not what emerges from evoked potential studies in migraine patients, when evoked responses are averaged over a great number of stimulations. By contrast, in the first blocks of low numbers of averaged trials recorded in the beginning of the recording sessions, the amplitudes are generally lower, not higher, in migraineurs than in healthy volunteers. It is thus likely that the increased EP amplitudes found in some studies are not due to cortical hyperexcitability as such, but to the lack of habituation of the responses during sustained stimulation [16].

Thus, lack of habituation was indeed the most consistent abnormality found in migraineurs, described for every modality of stimulation (visual, auditory, somatosensory and olfactory) and responsible both for the increased amplitudes of EP components and the increased intensity dependence of evoked potentials (Table 4).

Although habituation of cortical evoked responses is a complex neurobiological phenomenon, it might crucially depend on the preactivation excitability level of the sensory cortices. According to the "ceiling theory" [89], a low preactivation level would allow a wide range of suprathreshold activation before reaching the "ceiling" and initiating a "reducing" response, i.e., habituation. When applied to EP findings in migraineurs this model would explain both the low first block amplitude for most EP components and lack of habituation on trial repetition. The preactivation level of cortical excitability depends on the so-called "state-setting, chemically addressed connections" that originate in the brainstem and involve serotonin and noradrenaline as transmitters [67, 90]. Low interictal activity of these systems, especially of the raphe-cortical serotonergic pathway, could indeed be responsible in migraineurs for the observed electrophysiological abnormalities [91].

If this hypothesis were correct, manipulations of the cortical preactivation level would produce modifications in the habituation pattern in migraine patients and healthy volunteers. In fact, high-frequency rTMS over the occipital region, known to activate the underlying cortex, was followed by a normalisation of VEP habituation in migraineurs, while low-frequency rTMS, which has an

inhibitory effect, induced a deficit of VEP habituation in normal controls [54]. This finding would suggest that a lower preactivation level effectively characterises the migrainous brain, although a "dysexcitability" of intracortical inhibitory interneurons cannot be excluded. As a matter of fact, low-frequency rTMS was shown to have a paradoxical effect on the migraine cortex [92], which may suggest that the effect of TMS depends on the excitability level of the underlying cortex.

The ictal normalisation of EP amplitudes and habituation suggests that the cortical preactivation levels increase in temporal proximity to the migraine attack, which could be part of a homeostatic process according to the biobehavioural theory of migraine [93].

The concordance of EP habituation findings in migraine contrasts with the results on visual cortex excitability assessed with magnetophosphenes. The phosphene threshold (PT) in migraine patients was found to be lower than in healthy volunteers in some studies, but similar or higher in others (reviewed in [94]). Some discrepancies could be due to methodological differences that may be device- and patient-dependent.

Thus, considering decreased thresholds for magnetophosphenes in migraine as evidence for increased excitability of the visual cortex may be premature. The fact that opposite results were obtained in different laboratories with similar methods suggests that phosphenes are too subjective and variable to be used to measure

Table 4 Habituation in evoked potentials

Authors	Diagnosis	Age groups	Type of recordings	Components measured	Principal findings
Schoenen et al., 1995 [16]	MO, MA	Adults	PR-VEP	N1, P1, N2	Potentiation of N1-P1 and P1-N2 amplitudes in migraineurs; habituation in HV
Afra et al., 1998 [19]	MO, MA	Adults	PR-VEP	N1, P1, N2	N1-P1 amplitudes: lack of habituation in MA, potentiation in MO. P1-N2 amplitudes: slight potentiation in both groups
Wang et al., 1999 [20]	MO, ETTH, CTTH	Adults	PR-VEP	N1, P1, N2	Reduced habituation of N1-P1 and P1-N2 amplitudes in migraine, but not in chronic or episodic tension-type headache
Oelkers et al., 1999 [44]	MO, MA	Adults	PR-VEP	N1, P1, N2	No difference between groups (non-significant N1-P1 and P1-N2 amplitude potentiation in MA limited to the lower spatial frequency)
Sandor et al., 1999 [50]	MO	Adults, children	PR-VEP	N1, P1	Similar lack of habituation patterns in related migrainous pairs
Afra et al., 2000 [48]	MA	Adults	PR-VEP	N1, P1	With red-tinted glasses potentiation of N1-P1 in HV. No effect in MA
Afra et al., 2000 [73]	MO, MA	Adults	PR-VEP	N1,P1	Negative correlation between 1st block amplitude and habituation
Sand and Vingen, 2000 [22]	MO, MA	Adults	PR-VEP	N1, P1, N2	Significant habituation to small checks in HV, but not in migraineurs (except in patients recorded just before an attack)
Ambrosini et al., 2001 [65]	MO	Adults	AEP	P50	Reduced P50 gating in migraine patients
Bohotin et al., 2002 [54]	MO, MA	Adults	PR-VEP and rTMS	N1, P1, N2	Normalisation of VEP habituation in migraineurs after high-frequency rTMS. Deficit of VEP habituation in healthy subjects after low-frequency rTMS
Ozkul and Bozlar, 2002 [52]	MO, MA	Adults	PR-VEP	N1, P1	Normalisation of VEP habituation in migraineurs during treatment with fluoxetine
Ozkul and Uckardes, (2002) [79]	MO, MA	Adults	Median nerve SEP (wrist)	N9, N13, N20	Deficit of habituation of N20 in migraineurs

Cont. →

Table 4 cont.

Authors	Diagnosis	Age groups	Type of recordings	Components measured	Principal findings
Ambrosini et al., 2003 [64]	MO	Adults	Long-latency AEPs	N1, P2 – IDAP	Increased IDAP and deficit of AEP habituation in migraine
Siniatchkin et al., 2003 [66]	MO	Adults	AEP	P50	Reduced P50 gating in migraine patients
Di Clemente et al., 2005 [49]	MO	Adults	PR-VEP and nociceptive Blink Reflex	N1, P1	Positive correlation between VEP habituation and habituation of the nociceptive blink reflex in migraine patients
Coppola et al., 2005 [56]	MO, MA	Adults	PR-VEP	Early and late GFOs	Deficit of habituation of late GFOs
Oelkers-Ax et al., 2005 [37]	MO, MA, TTH	Children	PR-VEP	N80, P100, N180	Normal VEP habituation in migraine children
Fumal et al., 2006 [55]	MO, MA	Adults	PR-VEP and rTMS	N1, P1	Long-lasting normalisation of VEP habituation in migraineurs after daily high-frequency rTMS and long-lasting deficit of VEP habituation in controls after daily low-frequency rTMS

HV, healthy volunteers; *MO*, migraine without aura; *MA*, migraine with aura; *TTH*, tension-type headache; *ETTH*, episodic tension-type headache; *CTTH*, chronic tension-type headache

excitability of the visual cortex. This was confirmed in a recent study by Antal et al. [95], who measured PT in different sessions over a long time period and found that controls showed PT stability over time, whereas there were great variations of PT values in migraine patients. This study suggests that more objective and reliable methods to assess cortical excitability are preferable. On the other hand, it could account for the contrasting results obtained with magnetophosphenes in migraine patients, and suggest that the main characteristic of the migrainous brain is functional instability, i.e., dysexcitability rather than hyper- or hypoexcitability.

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