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Reduced habituation to experimental pain in migraine patients: a CO_2 laser evoked potential study

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Abstract

The habituation to sensory stimuli of different modalities is reduced in migraine patients. However, the habituation to pain has never been evaluated. Our aim was to assess the nociceptive pathway function and the habituation to experimental pain in patients with migraine. Scalp potentials were evoked by CO_2 laser stimulation (laser evoked potentials, LEPs) of the hand and facial skin in 24 patients with migraine without aura (MO), 19 patients with chronic tension-type headache (CTTH), and 28 control subjects (CS). The habituation was studied by measuring the changes of LEP amplitudes across three consecutive repetitions of 30 trials each (the repetitions lasted 5 min and were separated by 5-min intervals). The slope of the regression line between LEP amplitude and number of repetitions was taken as an index of habituation. The LEPs consisted of middle-latency, low-amplitude responses (N1, contralateral temporal region, and P1, frontal region) followed by a late, high-amplitude, negative–positive complex (N2/P2, vertex). The latency and amplitude of these responses were similar in both patients and controls. While CS and CTTH patients showed a significant habituation of the N2/P2 response, in MO patients this LEP component did not develop any habituation at all after face stimulation and showed a significantly lower habituation than in CS after hand stimulation. The habituation index of the vertex N2/P2 complex exceeded the normal limits in 13 out of the 24 MO patients and in none of the 19 CTTH patients ($P < 0.0001$; Fisher's exact test). Moreover, while the N1–P1 amplitude showed a significant habituation in CS after hand stimulation, it did not change across repetitions in MO patients. In conclusion, no functional impairment of the nociceptive pathways, including the trigeminal pathways, was found in either MO or CTTH patients. But patients with migraine had a reduced habituation, which probably reflects an abnormal excitability of the cortical areas involved in pain processing.
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1. Introduction

Although the pathophysiologic mechanisms underlying the migraine attack are far from being fully understood, it has been recently clarified that migraine is primarily a disease of the nervous tissue, which secondarily involves the vascular system (Olesen et al., 1981; Lauritzen, 1984; Blau, 1987; Silberstein, 1992; Hargreaves and Shepheard, 1999). The nervous dysfunction specific of migraine should be detectable in the headache-free period. Evoked potential (EP) techniques can assess non-invasively the excitability of the sensory cortices and its changes in pathological situations. The EP amplitude is a quantitative index of the neuronal population activated by certain sensory inputs; it tends to decrease during repetitive sensory stimulation, as the expression of a progressive reduction of the neuronal response. The physiologic phenomenon of a sensory cortex which progressively reduces its activity in being reached by repetitive stimuli is known as habituation. An evoked response may develop habituation to a lesser degree in case the brain areas that generate it are more excitable, or because the central systems that regulate habituation are less active, that is hypoexcitable (Bohotin et al., 2002). Several EP studies showed a reduced habituation in patients with migraine (Maertens de Noordhout et al., 1986; Schoenen et al., 1995; Evers et al., 1997; Schoenen, 1998; Afra et al.,

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1998a, 2000; Grosser et al., 2000; Ozkul and Uckardes, 2002).

However, in spite of the large number of EP studies in migraine, the function of the brain areas specifically devoted to nociception has never been explored. CO_2 laser evoked potentials (LEPs) have proved suitable to study the nociceptive pathway function in both clinical and neurophysiologic practice. CO_2 laser pulses are able to activate selectively the thin myelinated (Aδ) and unmyelinated (C) fibers without any concurrent activation of the larger, non-nociceptive afferents (Bromm and Treede, 1991).

By using the LEP technique, we aimed at assessing the nociceptive pathway function in patients with migraine, and comparing their habituation to experimental pain with that of patients with tension-type headache and control subjects (CS).

2. Materials and methods

2.1. Subjects

Seventy-one subjects, who gave their informed consent, took part in a multi-center study carried out in three different centers (Department of Neurology, Università Cattolica del Sacro Cuore, Roma; Department of Neurological Sciences, Università La Sapienza, Roma; and I Clinica Neurologica, Policlinico Universitario, Bari). Twenty-four patients had migraine without aura (MO) (mean age 33.7 ± 8.2, 10 men, 14 women), 19 patients had chronic tension-type headache (CTTH) (mean age 34.5 ± 10.6, 8 men, 11 women), and 28 were CS (mean age 32.5 ± 6.4, 11 men, 17 women). MO and CTTH patients were diagnosed according to the criteria of the International Headache Society (1988). The LEP recordings were performed no less than 72 h after the last headache attack. No MO nor CTTH patient took any drug during the 72 h before the LEP recording was performed.

2.2. Laser stimulation and LEP recording

The same laser apparatus and pulse characteristics (wavelength 10.6 μm, beam diameter 2 mm, duration 10 ms, CO_2 Neurolas, Electronic Engineering, Florence, Italy) were used in the three centers that took part in the study. All subjects received right and left stimulations over the hand dorsum and the face, but the site of the facial stimulations differed: while all MO patients and 17 CS (who were studied in center 1 and center 2) had the laser stimuli delivered to the perioral region, all CTTH patients and 13 CS (who were studied in center 3) had the laser stimuli delivered to the supraorbital region.

During LEP recording, the subjects lay on a couch in a warm and semi-dark room. The stimulation site was visualized by a He–Ne laser beam. After each stimulus the laser beam was slightly shifted to a nearby spot, to avoid nociceptor sensitization and skin damage. The sensory threshold (STh) was defined as the stimulus' intensity required to elicit a distinct sensation, and was determined by the method of limits in three series of increasing and decreasing stimulus intensities. In the LEP recording sessions, we used a fixed intensity set at 2.5 × STh to record LEPs (recording intensity, RI). For hand stimulation, the RI mean values ± standard deviation (SD) were 10.8 ± 2.44, 10.9 ± 2.8 and 10.7 ± 2.37 in CS, MO patients and CTTH patients, respectively. For face stimulation, the RI mean values (± SD) were 5.09 ± 1.02, 5.09 ± 0.98 and 5.13 ± 0.79 in CS, MO patients and CTTH patients, respectively. No difference in RI was found between groups (one-way ANOVA: $F = 0.06$, $P > 0.05$ and $F = 0.03$, $P > 0.05$ for hand and face stimulation, respectively). Our subjects were asked to define RI by using a 10-point visual analog scale (VAS) in which '0' corresponded to no sensation, '4' to pain threshold and '10' to intolerable pain. The mean VAS value corresponding to RI was 4.5 ± 0.4 in CS, 4.6 ± 0.3 in MO patients, and 4.4 ± 0.5 in CTTH patients. The interstimulus interval varied randomly between 8 and 12 s.

All subjects underwent a standard recording session with three scalp electrodes placed along the midline (Fz, Cz, and Pz positions of the 10–20 International System). In 19 MO patients and 14 CS also an additional multi-electrode recording with 19 scalp electrodes was performed. In both standard and multi-electrode recordings the reference electrode was placed at the nose and the ground on the forehead (Fpz), and eye movements and eye-blinks were monitored by electroculography (EOG). Signals were amplified, filtered (bandpass 0.3–70 Hz), and stored for off-line average and analysis. The analysis time was 1000 ms with a bin width of 2 ms. An automatic artifact rejection system excluded from the average all trials contaminated by transients exceeding ±65 μV at any recording channel, including EOG.

2.3. LEP analysis

LEPs were identified on the basis of their latency and polarity. We measured the amplitude from baseline of each single LEP component (N1, P1, N2, P2), and the peak-to-peak amplitude of the vertex N2/P2 complex. The N1–P1 amplitude was also measured off-line by referring the contralateral temporal electrode (T3 or T4) to the Fz lead (Kunde and Treede, 1993). For the analysis of LEP distribution, color maps were calculated by spline interpolation (Perrin et al., 1987).

2.4. Experimental procedure

Three consecutive repetitions were obtained for each stimulation site (right and left hand, and face). Since trigeminal LEPs are more reproducible between trials, and their average becomes stable after fewer trials than hand-evoked LEPs (Cruccu et al., 1999, 2001), the repetitions

Table 1
LEP latencies and amplitudes in repetition I

	RH			LH			RF			LF		
	Latency (ms)		Amplitude (μV)	Latency (ms)		Amplitude (μV)	Latency (ms)		Amplitude (μV)	Latency (ms)		Amplitude (μV)
N1–P1[a]												
HSs	155.5 ± 25		3.1 ± 1.7	151 ± 15		3.9 ± 2	112.8 ± 7.4		3.7 ± 2	114.5 ± 11.7		4.6 ± 2.4
MPs	150.1 ± 22.3		3.3 ± 1.7	149.6 ± 20.8		3.3 ± 1.7	110.4 ± 6.8		4.2 ± 2.3	111.3 ± 8.7		4.3 ± 1.7
N2/P2[b]												
	Latency (ms)		Amplitude (μV)	Latency (ms)		Amplitude (μV)	Latency (ms)		Amplitude (μV)	Latency (ms)		Amplitude (μV)
	N2a	P2		N2a	P2		N2a	P2		N2a	P2	
HSs	205.3 ± 36.6	337.7 ± 54.1	8.9 ± 3.4	205.7 ± 30.9	329.7 ± 43.4	12 ± 5.1	161.9 ± 18.4	265.7 ± 46.3	12.7 ± 6.8	170.9 ± 12.7	287.1 ± 52.8	11.4 ± 4.4
MPs	212.5 ± 34.7	326.1 ± 39.3	12.3 ± 8.8	217.5 ± 39.9	329.6 ± 37.7	11 ± 6	166 ± 14.7	261.6 ± 55.6	17 ± 11	162.1 ± 19.2	263.7 ± 40.3	16.4 ± 9.6
THPs	218.1 ± 26.5	343.8 ± 31.3	12.5 ± 7.7	222 ± 21.4	338.2 ± 24.7	10.6 ± 4.9	171.3 ± 19.2	275.7 ± 34.7	10.8 ± 6.8	171.1 ± 14.4	273.8 ± 29.3	11.5 ± 7.4

RH, right hand; LH, left hand; RF, right face; LF, left face; HSs, healthy subjects; MPs, migraine patients; THPs, tension headache patients.
[a] The latency values concern the negative potential (N1) recorded by the temporal electrode contralateral to stimulation in the monopolar montage, while the amplitudes are calculated in the bipolar temporo-frontal derivation.
[b] Values are issued from the C_3 trace.

of face stimuli consisted of 15 trials each, and the repetitions of hand stimuli 30 trials each. The stimulation sites were changed after 10-min intervals. The sequence of the stimulation sites was randomly varied across subjects.

2.5. Statistical analysis

LEP latencies and amplitudes obtained after the stimulation of both the right and the left side in each subject were compared by paired Student's *t*-test and by Wilcoxon's test, respectively. Latency and amplitude values recorded in the first repetition of each stimulation site were compared between patient groups by unpaired Student's *t*-test and by Mann–Whitney U-test, respectively. LEP latency habituation was investigated by one-way ANOVA, considering the repetition as a source of variability. Student's *t*-test with Bonferroni's correction for multiple comparison was used for the post hoc analysis. For the analysis of LEP amplitude habituation, the LEP amplitudes in the second and third repetition of a certain stimulation site were expressed as percentages of the amplitudes of the corresponding LEP components recorded in the first repetition, which were assumed as 100%. After this normalization, amplitudes were compared by one-way ANOVA by choosing the repetition as a source of variability. In the subjects who underwent the multi-channel LEP recording, also two-way ANOVA was performed by considering the repetition and the recording electrode as variables. Student's *t*-test was used for the post hoc analysis. Normalized LEP amplitudes obtained in the second and third repetition were compared between patients and CS by Student's *t*-test. In each subject, the normalized LEP amplitudes obtained in the second and third repetition from the right side were compared to those obtained from the left side by Student's *t*-test. In order to obtain an index of the habituation of the vertex N2/P2 amplitude, a linear regression analysis of the amplitudes in the three repetitions was performed for each site of stimulation, in each subject. The mean + 2 SD of the slope calculated in CS was assumed as the upper normal limit for LEP habituation. The difference in abnormality frequency between MO and CTTH patients was assessed by Fisher's exact test.

3. Results

3.1. Latency, amplitude, and scalp topography of LEP components

In all subjects, standard recordings from midline electrodes showed a late, high-amplitude, negative–positive complex (N2/P2) (Table 1). The patients and CS who underwent the topographic study by multi-channel recording array (Figs. 1 and 2), besides the N2/P2 complex showed a negative N1 potential in the temporal region contralateral to stimulation and, at approximately the same latency, a positive P1 potential in the frontal region. These potentials

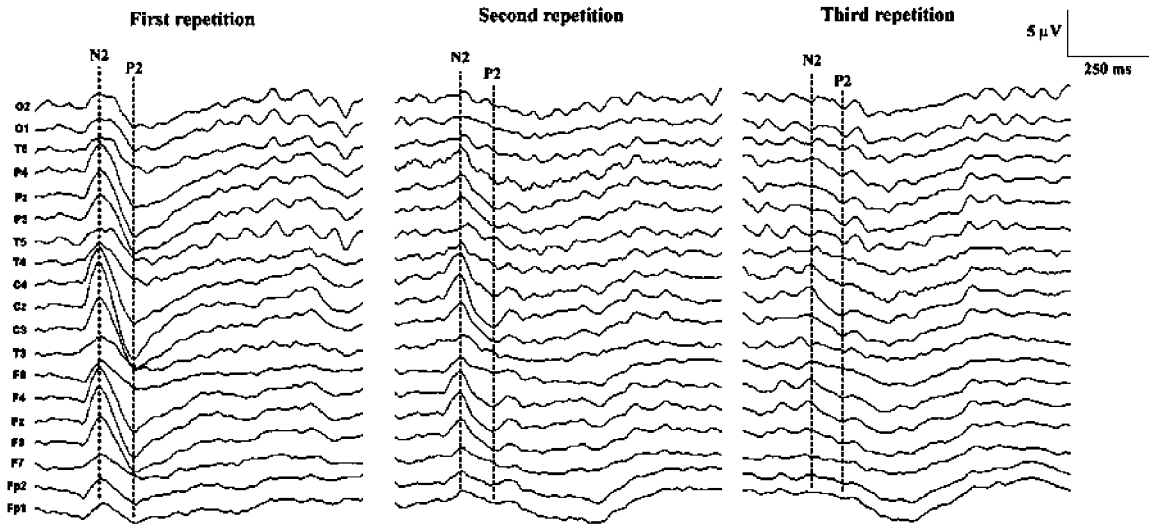

Fig. 1. LEPs recorded from 19 scalp electrodes in a representative control subject after right hand stimulation. Note the marked suppression of the N2 and P2 potentials in the second and third repetition.

are shorter in latency and lower in amplitude than the N2 and P2 responses. The topographical maps showed a typical dipolar field distribution at the N1–P1 latency, with the negative pole in the temporal region and the positive counterpart in the frontal cortex; the late N2 and P2 components were widespread and reached their maximum amplitude at the vertex.

Neither latency nor amplitude value of any LEP component significantly differed between MO patients, CTTH patients, and CS.

3.2. Habituation of the middle-latency LEP components in CS and MO patients

The latency and scalp topography of the N1–P1 components did not change across the three repetitions either in CS or in patients.

In contrast, the N1–P1 amplitude was significantly reduced across repetitions after hand stimulation in CS, but not in MO patients (Table 2). After face stimulation, the N1–P1 amplitude did not change across repetitions in either CS or MO patients (Table 2).

3.3. Habituation of the late LEP components in all subject groups

Once again, the latency and scalp topography of the N2/P2 components did not change across the three repetitions in either CS or patients.

After hand stimulation, the N2/P2 amplitude reduction across repetitions was statistically significant in all groups (Table 2). The statistical comparison between the groups showed that while CS and CTTH patients did not differ

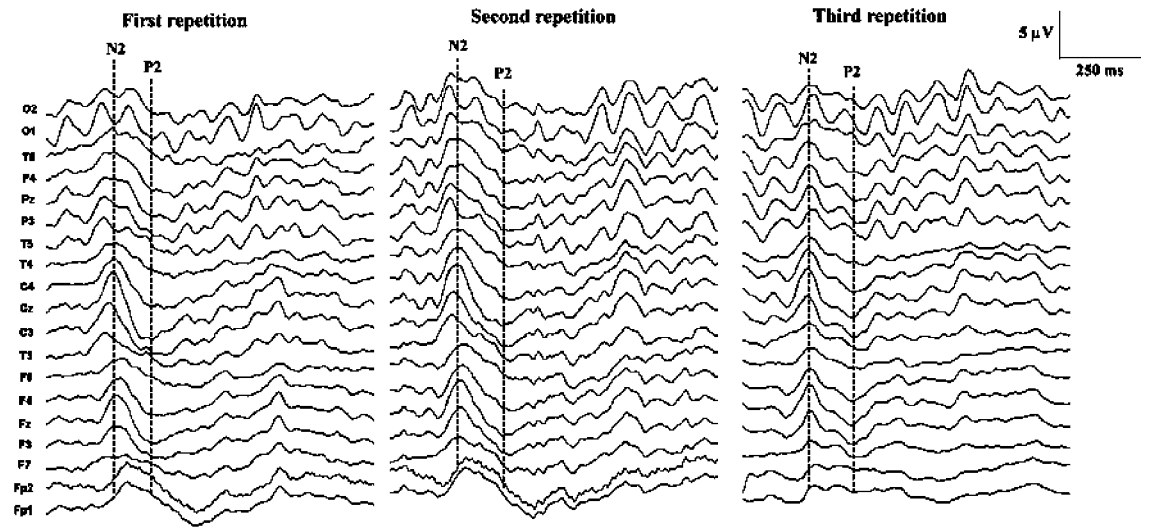

Fig. 2. LEPs recorded from 19 scalp electrodes in a representative migraine patient after right hand stimulation. The amplitude of the N2 and P2 potentials is only slightly reduced in the second and third repetition.

Table 2
Statistical analysis

	Latency modifications across repetitions					
	CS		MO		CTTH	
	Face	Hand	Face	Hand	Face	Hand
N1–P1						
F	0.92	1.84	0.05	0.04		
P	0.4	0.17	0.95	0.96		
N2						
F	1.4	1.55	0.6	0.04	0.06	0.22
P	0.25	0.22	0.54	0.96	0.94	0.8
P2						
F	0.2	0.07	0.03	0.1	0.19	0.09
P	0.82	0.93	0.97	0.37	0.83	0.92
Amplitude modifications across repetitions						
N1–P1						
F	0.66	5.2	1.37	0.34		
P	0.52	0.008[a]	0.26	0.71		
N2/P2						
F	7.74	36.5	2.17	4.31	7.09	7.08
P	0.0008[a]	<0.00001[a]	0.12	0.02[a]	0.001[a]	0.001[a]

[a] Significant values.

(Fig. 3), the habituation in MO patients (Fig. 2) was less than in CS (Figs. 1 and 3) or CTTH patients ($P < 0.05$).

After face stimulation, the N2/P2 amplitude in CS was significantly reduced across repetitions after both perioral and supraorbital stimulations (Table 2). In CTTH patients, who received the supraorbital stimulation, the habituation was also significant (Table 2) and similar to that of normal subjects (Fig. 3). Only in MO patients, who received the perioral stimulation, habituation was not observed (Table 2).

3.4. Comparison of the habituation index in MO and CTTH patients

Among the various LEP data, the peak-to-peak amplitude of the vertex N2/P2 complex after hand stimulation showed the maximum degree of habituation. This habituation index had a normal distribution in CS and the range was relatively narrow. Thirteen out of 24 MO patients exceeded the normal limits after the stimulation of at least one site, whereas all 19 CTTH patients fell within the normal limits after stimulation of all sites (Fig. 4). The difference in abnormality frequency between MO and CTTH patients was highly significant ($P < 0.0001$; Fisher's exact test).

3.5. Side differences

We found no differences between the right and left sides of stimulation in any LEP data, including habituation, in any subject group (Table 1). Furthermore we did not find significant differences between the side predominantly affected and the contralateral side in patients with lateralized migraine.

4. Discussion

Our study yielded two main results: firstly, patients with MO did not show any functional abnormality of the nociceptive pathways, including the trigeminal pathways, and, secondly, compared to CS and patients with tension-type headache they had a reduced habituation to repetitive noxious stimuli.

4.1. LEPs in migraineurs

To assess the nociceptive pathway function, we examined latency and amplitude of all the LEP components recorded in the first repetition. The N1, P1, N2, and P2 components, as well as the scalp topography, were similar in patients and CS. The LEP components recorded after skin stimulation at noxious intensity have proved to be generated by inputs transmitted by Aδ fibers (Bromm and Lorenz, 1998). Abnormalities of LEP latency or amplitudes were demonstrated in diseases involving the peripheral Aδ afferents or the central spinothalamic pathway, and showed a strict correlation with the loss of pain sensation (Kakigi et al., 2000). Since migraineurs neither have hypoalgesia in the pain-free period nor during attacks, we may expect not to find dampened LEPs. Nevertheless, patients with trigeminal neuralgia (i.e. another painful condition also mediated by the trigeminal system), who – like migraineurs – do not have a clinically apparent hypoalgesia, indeed have severe delays or even an absence of trigeminal LEPs (Cruccu et al., 2001). In our LEP study, we did not find any significant facilitation of the trigeminal nociceptive pathways: this has been reported by several studies using reflex responses in patients with migraine (De Tommaso et al., 2000; Kaube et al., 2002; Sandrini et al., 2002). Probably the aforesaid findings reflect a hyperactivity of the brainstem's interneuronal nets that mediate the reflex responses.

4.2. LEP habituation after repetitive noxious stimuli

The only significant abnormality we found in MO patients was a reduction or a lack of habituation. In CS, the vertex LEP components (N2/P2) underwent an intense amplitude reduction in the second repetition, and particularly in the third one. According to traditional views, pain is a multidimensional sensation which includes sensory-discriminative and emotional-motivational aspects (Melzack and Casey, 1968; Melzack and Katz, 1994). Studies on LEP generators showed that the N2 and P2 responses are mostly generated by neurons in the cingulate cortex (Tarkka and Treede, 1993; Bromm and Chen, 1995; Valeriani et al.,

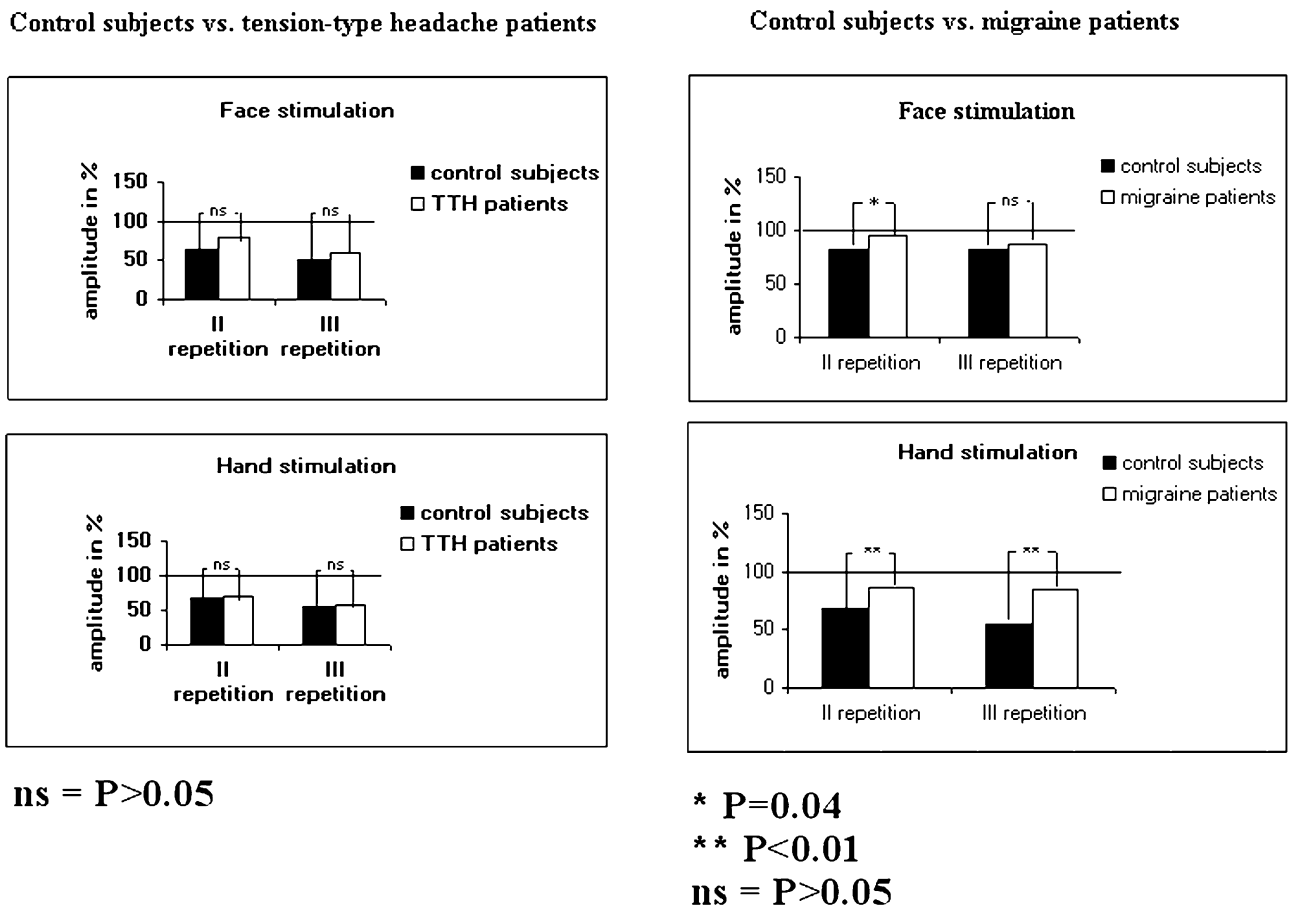

Fig. 3. Mean N2/P2 amplitude in the second and third repetition in CS and tension-type headache patients (left), and in CS and migraine patients (right), after face and hand stimulation. The N2/P2 amplitudes are expressed as percentages of the corresponding amplitudes recorded in the first repetition, assumed as 100%. While the amplitude values are very similar in CS and tension-type headache patients, they are higher in migraine patients than in CS.

1996, 2000; Lenz et al., 1998), which is a part of the limbic system, and is important for the emotional component of sensation (Derbyshire et al., 1997; Casey, 1999; Peyron et al., 1999; Buchel et al., 2002). Instead, the middle-latency N1–P1 wave, which is probably generated in the secondary somatosensory area (SII) (Valeriani et al., 1996, 2000; Frot et al., 1999), may represent the neurophysiologic correlate of the sensory-discriminative aspect of pain. While a reduction of amplitude of the vertex N2/P2 complex after repetitive noxious stimulations has been previously demonstrated (Bjerring and Arendt-Nielsen, 1988; Weiss et al., 1997), the behavior of the N1–P1 amplitude after repetitive stimuli has never been investigated. In our CS, the N1–P1 amplitude was reduced in the second and third repetition after hand stimulation, although this decrement was not as intense as that of the vertex N2/P2 components. A significant N1–P1 habituation was not observed after face stimulation, probably due to the lower number of stimuli used for trigeminal LEP (15), compared to hand LEP (30) recording.

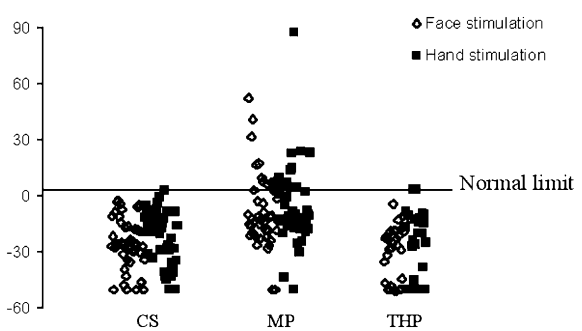

Fig. 4. Scatterplot of the habituation index in CS, migraine patients (MP), and patients with tension-type headache (THP). Each subject is represented by two symbols, referring to the index obtained for hand and face stimulation. The horizontal line indicates the normal limit (mean + 2 SD), which is overtaken in 13 MP after stimulation of at least one site. In contrast, all tension-type headache patients remain within the normal limits.

In patients with migraine, the habituation of the N2/P2 components was significant after stimulating the hand, but not after face stimulation. Moreover, when the N2 and P2 amplitudes recorded in the second and third repetition were compared with those of CS, significantly higher values were found in MO patients after both face and hand stimulation. These results suggest that the cortical areas devoted to pain

processing have an abnormal excitability in MO patients during the interictal phase, and that this dysfunction, yet predominant in the face representation, involves also the cortical projections of other parts of the body, such as the hand.

Also the middle-latency N1–P1 components showed less habituation in the MO patient group than in the CS. The N1–P1 potential is considered a pre-perceptive component, being scarcely affected by attention manipulations or by the intensity of perceived pain (Garcia-Larrea et al., 1997). Therefore, the lack of N1–P1 habituation in MO patients, rather than reflecting affective-motivational changes, probably represents a specific marker of an abnormal excitability of the sensory cortex in migraine.

In CTTH patients, the habituation of the late components was very similar to that of CS, and in MO patients the habituation was significantly less than in CTTH patients. Therefore, the reduced habituation in MO patients cannot be interpreted as an unspecific effect of pain, but it is probably linked to the pathophysiological mechanisms underlying the migraine disease.

In our experimental paradigm, habituation was studied across three repetitions separated by a 5-min interval. One could argue that the rest period between successive repetitions entails 'dishabituation'. However, if this were so, CS and CTTH patients should have not shown a significant LEP habituation.

Our results suggest that the cerebral areas involved in both the sensory-discriminative and affective-motivational processing of pain show an abnormal excitability in migraineurs and that this abnormality may constitute the background from which the migraine attack develops.

4.3. Cerebral cortex excitability in migraine

The abnormal cortical excitability in migraineurs proves that migraine involves primarily the neurones, while the painful stimulation of the trigemino-vascular system represents only the terminal step of a cascade of events that started from the brain. The evidence of higher amplitude EPs in patients with migraine than in CS has been attributed to a lack of habituation or to a potentiation (see Schoenen, 1998 for a review); moreover, this phenomenon was thought to be caused by an increased cortical excitability. Also the lower threshold for phosphene induction by transcranial magnetic stimulation of the occipital cortex in migraineurs than in CS agrees with this hypothesis (Aurora et al., 1998). It is worth to mention that Aurora et al.'s findings were not confirmed (Afra et al., 1998b). Bohotin et al. (2002) recently demonstrated the recovery of a normal habituation pattern of the P100 visual evoked potential (VEP) in patients with migraine after high frequency (10 Hz) repetitive transcranial magnetic stimulation (rTMS) of the occipital cortex. On the contrary, CS submitted to low frequency (1 Hz) rTMS of the occipital cortex showed no P100 amplitude habituation. Given that the rTMS at 10 and 1 Hz increases and reduces the cortical excitability, respectively, the authors argued that migraineurs exhibit a normal habituation when their cortical excitability is raised up to the level of CS and that, on the contrary, CS lose the VEP habituation if their occipital cortex is inhibited. According to these results, patients with migraine show a hypoexcitability of the visual cortex during the interictal phase and the lack of habituation is explained by the 'ceiling effect model' (Knott and Irwin, 1973; Schoenen, 1996). In this model, the habituation depends on the pre-activation level of the visual cerebral cortex, which is very low in migraine and prevents any further excitability reduction.

4.4. Conclusions

What is new in this study is that the function of nociceptive pathways and the habituation to experimental pain had never been investigated in patients with migraine. The amplitude, latency and scalp topography of all LEP components were similar in MO patients and CS, thus showing that migraineurs have a normal nociception. Instead, MO patients showed a lower habituation to repetitive noxious stimuli in comparison with CS and CTTH patients. This phenomenon, which involves both the pre-perceptive LEP components (N1–P1) and the vertex responses (N2/P2), probably represents the consequence of an abnormal excitability of the sensory areas that process the nociceptive input. Habituation slopes were significantly smaller in MO patients, compared to CS and CTTH patients (one-way ANOVA: $F = 28.5$, $P < 0.01$ and $F = 11.7$, $P < 0.01$ for hand and face stimulation, respectively). Moreover, if the mean CS slope + 2 SD was assumed as the upper normal limit for LEP habituation, abnormal habituation slopes were observed in more than 50% of MO patients and in none of CTTH patients. This finding suggests that habituation to pain in migraineurs largely differs from the one in CS or in patients with non-migraine headache.

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