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Topographic analysis of laser evoked potentials in chronic tension-type headache: Correlations with clinical features

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Abstract

In the present study, we examined clinical and laser-evoked potentials (LEP) features in a group of chronic tension-type headache (CTTH) patients, in order to perform a topographic analysis of Laser evoked potentials (LEPs) and a correlation with clinical features. Eighteen patients suffering from CTTH [Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders 2nd ed. Cephalalgia 2004; 24 Suppl 1, 1–159.] participated in the study. Twelve age- and sex-matched controls were also examined. We performed a basal evaluation of clinical features, Total Tenderness Score (TTS) and a topographic analysis of LEPs obtained by the hand and the pericranial points stimulation in all patients vs healthy subjects. The later LEPs, especially the P2 component, were significantly increased in amplitude in the CTTH group, specially when the pericranial points were stimulated.

The P2 wave amplitude was correlated with TTS levels and anxiety scores.

The results of this study confirm that pericranial tenderness is a phenomenon initiating a self-sustaining circuit, involving central sensitization at the level of the cortical nociceptive areas devoted to attentional and emotional components of pain.

Keywords: Tension-type headache; Laser-evoked potentials; Pericranial tenderness

1. Introduction

Although tension-type headache (TTH) is the most common type of primary headache, its pathophysiology is poorly understood. The best documented abnormality in patients with TTH is increased pericranial myofascial tenderness (Vandenheede and Schoenen, 2002; Jensen, 2003). With manual palpation of head and neck muscles, increased pericranial tenderness was found in patients with both episodic and chronic TTH (CTTH). It was demonstrated that the pericranial tenderness was positively associated with both the intensity and the frequency of tension-type headache (Bendtsen, 2000; Jensen et al., 1993). It is generally accepted that myofascial tenderness probably plays a key role in the pathophysiology of tension-type headache. The search for peripheral mechanisms responsible for sensitization of myofascial nociceptors has however largely been unsuccessful, and muscle contraction appears to be a consequence of myofascial pain rather than a causal factor (Bendtsen, 2000). Recently, a pathophysiological model for tension-type headache was proposed. According to this hypothesis, the main problem is central sensitization at the level of the spinal dorsal horn/trigeminal nucleus, resulting from prolonged nociceptive inputs from pericranial myofascial tissues. This central sensitization is posited to cause supraspinal sensitization and central neuroplastic changes, possibly leading to increased pericranial muscle activity (Bendtsen, 2000). In a recent study we examined features of laser evoked potentials (LEPs) (Bromm and Treede, 1984, 1991), as well as cutaneous heat–pain thresholds to laser stimulation, in relation to the tenderness of pericranial muscles in chronic tension-type

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headache (CTTH), during a pain-free phase (de Tommaso et al., 2003). The amplitude of the N2–P2 complex elicited by stimulation of the pericranial zone was greater in CTTH patients than in controls; the amplitude increase was significantly associated with the Total Tenderness Score (TTS, Langermark and Olesen, 1987). Our findings suggested that pericranial tenderness may be a primary phenomenon that precedes headache, mediated by increased pain awareness at the cortical level. In that study, LEPs were examined by a derivation on the vertex to record the greatest waves. Multichannel recording of LEPs allows the performance of a topographic analysis, and the examination of all the LEP components (Valeriani et al., 2000), the earlier originating from the suprasylvian region (parietal operculum, SII), (Garcia-Larrea et al., 2003) mainly devoted to the discriminative component of pain, (Iannettia et al., 2005) and the later from the anterior cingulate cortex (ACC), (Garcia-Larrea et al., 2003) subtending the attentive and emotive features of pain (Peyron et al., 2000).

The aim of the present study was to extend previous analysis of LEPs in chronic tension-type headache, by performing multichannel topographic analysis in a new headache patients series during the pain-free phase in comparison to a group of normal subjects, and correlating the LEP findings with the Total Tenderness Score, the main clinical features, and the levels of anxiety and depression scored by the Zung (1965, 1976) scales.

2. Methods

2.1. Subjects

Eighteen outpatients attending the Headache Centre of the Neurology Clinic of Bari University, who fulfilled the criteria of CTTH associated with a pericranial muscles tenderness, according to International Headache Society (code 2.3.1) (International Headache Society Headache Classification Committee, 2004), participated in the study. All patients had been attending the practice for at least 6 months, during which they had been requested to register all headache episodes in a diary. All patients underwent an interview, which was standardized in our Centre to describe all headache features, as well as a clinical neurological and psychiatric examination. Twelve gender- and age-matched controls were selected, each without any history of headache or other cranio-facial pain according to IHS criteria. The clinical features are summarized in Table 1. Subjects with general medical, neurological, psychiatric (according to American Psychiatric Association, 1994) diseases, and patients who were taking psychoactive drugs, prophylactic treatments for headache, or had displayed over-use of analgesic drugs in the last 2 months, were excluded. All patients who participated were instructed to come to the recording session free from pain and free of medication intake for at least the previous 12 h; longer intervals were not possible, since most of the patients experienced daily headache (Table 1).

All patients and controls gave their informed consent to the study, which was ethically approved by our Department (Neurological and Psychiatric Science Department of Bari University). The clinical examination and recording session were carried out between 12 and 55 h after the end of the last headache (mean 23±12.2 h), in the basal condition. The TTS was performed by manual palpation by one neurologist with experience in headache, who was experimentally blinded to the patients and the controls. The right frontalis, masseter, temporalis, pterygoid, sternocleidomastoid, and trapezius muscles, and the sternocleidomastoid and neck muscle insertions were examined using the TTS system. This method uses a combination of behavioural and verbal items, each of which is scored on a four-point Likert scale, defined as: 0 denial of tenderness, no visible reaction; 1 verbal report of discomfort or mild pain, no visible reaction; 2 verbal report of moderate pain, with or without visible reaction; 3 verbal report of marked pain and visible expression of discomfort, according to Langermark and Olesen (1987). The LEP recording was performed at least 1 h after the TTS examination.

Table 1
Clinical features of chronic tension-type headache patients and controls

Patients	Age	Sex	Age of illness (years)	Frequency of headache (days with headache/ month)	Total tenderness score	Self-evaluating anxiety scale (Zung)	Self-evaluating depression scale (Zung)
Patients							
M	39.1	10 F	4.8	22.8	5.2	36.2	34.4
SD	11.5	8 M	5	6.8	2.8	7.5	4.9
Controls							
M	33.6	6 F			0.2	27.5	25.5
SD	12.8	6 M			3.5	9.8	6.5

2.2. CO_2 laser stimulation and LEP recording

Each subject was seated in a comfortable chair positioned in a quiet room with an ambient temperature of 21–23 °C, in an awake and relaxed state, with eyes closed. Subjects and experimenters wore protective goggles during data acquisition. The pain stimulus was a laser pulse (wavelength 10.6 μm) generated by a CO_2 laser (Neurolas, Electronic Engineering, Florence, Italy; www.elengroup.com). The beam diameter was 2.5 mm and the duration of the stimulus pulse was 20 ms. EEG was recorded through 19 disk electrodes, according to the 10–20 International System (impedance below 5000 ohms), referring to the nasion with the ground at Fpz. Another electrode was placed above the right eye to record the electrooculogram (EOG). Signals were amplified, filtered (0.5–80 Hz), and stored on a biopotential analyser (Micromed System Plus; Micromed, Mogliano Veneto, Italy; www.micromed-it.com). Time analysis was for 1 s, at a sampling rate of 512 Hz. Trials contaminated by ocular or muscle artefacts were excluded from the analysis. An automatic artefact rejection system excluded from the average all runs containing transient signals exceeding 65 mV on any recording channel, including the EOG.

2.3. Stimulation

Cutaneous heat stimuli were delivered to the dorsum of the right hand , and to the skin above the right frontalis, masseter, temporalis, sternocleidomastoid, and trapezius muscles, and to the neck muscle insertions. The site of stimulation was visualized by a He–Ne laser beam. The location of the impact on the skin was adjusted slightly between two successive stimuli to avoid the sensitization of the nociceptors and nociceptor fatigue. A 7.5-W laser intensity was used in each case (Biehl et al., 1984). Subjects were requested to report the quality of sensation (pain rating: PR) after each stimulus presentation using a visual analogue scale (VAS) in which 0 indicated no pain in white, increasing in a gradual scale of reds to 100, which indicated the worst possible pain. Two series of 20 stimuli were delivered in each case with an interstimulus interval of 10 s. The order of the stimulation sites was varied randomly across patients and controls.

2.4. LEPs analysis

LEP recordings were analysed by an investigator blind to the clinical conditions. Blocks of at least 15 trials free from artefacts were averaged offline. A grand average across the two series of stimuli was obtained for each patient. LEPs were identified based on their latency and distribution, and three responses, N1, N2 and P2, were labelled (according to the methods of Valeriani et al., 2000). Absolute latencies of scalp potentials were measured at the highest peak of each response component and the amplitude of each wave was measured from the baseline. The N1 component was measured on the temporal derivation (T3), the P2 and N2 components were analysed at the vertex (CZ), according to Valeriani et al. (2000). In each case an amplitude map was obtained at the latencies corresponding to the N1, N2 and P2 peaks, using Advanced Source Analysis (ASA 3.1) software from ANT Software (www.ant-software.nl/index.htm). The raw amplitude data computed by ASA on each channel, were submitted to statistic analysis, in order to obtain statistic probability maps (SPM) between patients and controls and in the patients' groups across the different conditions. In these maps, the values of ANOVA probability (p value$\times$1000) was computed for all electrodes, and the other point values were represented, according to a linear interpolation algorithm, applied by ASA software. In addition, in each case we evaluated the amplitude of N1 referring off-line the contralateral temporo-parietal derivations to Fz reference: the mean amplitude value across T5-Fz; T3-Fz; P3-Fz was the temporal N1. We also computed the amplitude of N2 (vertex N2) and P2 (vertex P2), computing in each case the mean value across the vertex and midline derivations (Cz-Fz-Pz, C3, C4, referred to the nasion).

3. Statistic analysis

The age, the SAS and SDS scales by Zung, Pain Rating and the Total Tenderness Score were compared between patients and controls using one-way ANOVA, with groups as factor. For each LEP wave, the Statistic Probability Maps were computed between patients and controls, using the ANOVA probabilities, which were projected into the spherical head model provided by ASA software. The SPMs were constructed when a probability <0.05 was found on at least three contiguous electrodes. The temporal N1 and the vertex P2 and N2 amplitudes were also considered to perform correlations between LEPs and the main clinical features, using the Pearson correlation test.

4. Results

4.1. Comparison between patients and controls

4.1.1. Clinical features

The pain ratings were not significantly different in patients and controls when the hand and the pericranial sites were stimulated (hand: $F=1.47$; $p=0.23$; frontal: $F=3.83$; $p=0.06$; temporalis $F=0.009$; $p=0.99$; masseter $F=0.74$ $p=0.49$; sternocleidomastoid $F=0.034$ $p=0.85$; neck muscles$=F=$ 1.15 $p=0.28$; trapezius: $F=0.52$ $p=0.47$).The mean TTS was significantly higher in patients than controls ($F=33.5$ $p<0.0001$) (Table 1). The SAS and the SDS scores were also significantly different between the two groups (SAS: $F=9.51$; $p<0.005$; SDS: $F=24.21$; $p<0.0001$) (Table 1). In patients, the SAS was significantly correlated with the Total Tenderness Score, while we did not find such a correlation for SDS (Table 2). In addition, both the SAS and the TTS were significantly correlated with age and duration of illness (Table 2). The TTS was not correlated with the frequency of headache (Table 2). In addition, we correlated the TTS with the interval since the last headache, measured in hours, and we failed to observe a statistically relevant result (Pearson correlation: 0.27 n.s).

4.1.2. LEPs

The latencies of N1, N2 and P2 LEP waves were similar in patients and controls, when all the sites of stimulation were considered. The temporal N1 amplitude was not significantly different between patients and controls for all the sites of stimulation; the amplitude of the vertex N2 was significantly different when all the stimulation points, except for the temporal site, were considered; the vertex P2 amplitude significantly differentiated patients from controls when all the pericranial points were stimulated (Table 3, Fig. 1). The vertex P2 correlated

Table 2
Results of Pearson correlation test between the main clinical features (TTS: total tenderness score; SAS: self evaluating scale by Zung; SDS: self evaluating depression scale by Zung; Freq: frequency-days with headache/month; dur: duration–duration of illness) in chronic tension-type headache patients: * $p<0.05$; ** $p<0.01$

	TTS	SAS	SDS	Freq.	Age	Dur.
TTS	1	0.557**	0.276	0.045	0.685 **	0.39
SAS	0.557**	1	0.642**	−0.241	0.421*	0.631**
SDS	0.3	0.642**	1	0.03	0.346	0.364
Freq	0	0.241	0.03	1	0.027	−0.481*
Age	0.685**	0.421*	0.346	0.027	1	0.044
Dur.	0.4	0.631**	0.364	−0.481*	0.044	1
N	18	18	18	18	18	18

Table 3
Mean values (*M*) and standard deviations (SD) of the temporal N1 and vertex N2 and P2 amplitudes (μV) in CTTH patients ($n=18$) and control ($n=12$)

		Frontal		Temporal		Masseter		Sterno		Trapezius		Neck		Hand	
		M	SD	*M*	SD	*M*	SD	*M*	SD	*M*	SD	*M*	SD	*M*	SD
N1 temp(μV)	CTTH	−1.33	6.9	−1.69	5.22	−0.73	6.72	−1.31	6.63	−3.27	5.32	−2.2	4.3	−1.6	2.3
	Controls	−1.12	2.9	−2.09	5.58	−1.82	4.94	−1.04	5.29	−1.36	4.57	−1.2	3.4	−1.2	3.4
N2 vert(uV)	CTTH**	−19.8	19.03	−14.7	13.91**	−15.03	10.02**	−16.68	13.18*	−9.77	7.56*	−10.1	4.5*	−10.1	12.3
	Controls	−3.9	5.71	−7.5	9.28	−4.77	5.21	−4.18	5.91	−3.55	5.08	−4.5	5	−5.7	8.9
P2 vert (uV)	CTTH*	11.6	7.72**	14.11	8.9**	13.34	8.43**	13.57	9.26*	11.49	5.8*	10.9	6.7	−7.5	7.6
	Controls	5.6	4.97	5.25	7.48	5.17	4.23	6.15	3.97	6.6	4.01	6.9	4.5	−5.1	4.7

Results of ANOVA are shown: * $p<0.05$, ** $p<0.01$.

significantly with both the total and local TTS for the most of the pericranial points (Table 4). Indeed, the vertex N2 did not correlate with the TTS and local tenderness in any of the stimulated points. The vertex P2 and N2 did not correlate with the frequency of headache when all the points of stimulation were considered, but the P2 was correlated with the SAS at the frontal site (0.53 $p=0.021$), the trapezius (0.515 $p=0.029$), the masseter points (0.725 $p=0.018$), and the temporal point (0.53 $p=0.011$).

When the SPMs across the two groups were considered, we found that in chronic tension-type headache patients both N2 and P2 amplitude were significantly increased for most of the pericranial points, specially on the areas around the vertex (Fig. 2): at the temporal level, the N2 increase was evident only around the vertex (Fig. 2). For the neck and the trapezius points, the significance of both N2 and P2 amplitude was not largely diffused over the scalp (Fig. 3). The stimulation of the hand evoked an increase of N2 over almost the entire scalp, but the P2 amplitude increase was limited in a strict zone close the vertex and the frontal areas (Fig. 3).

5. Discussion

In the present chronic tension-type headache series, we confirmed the results previously observed (de Tommaso et al.,

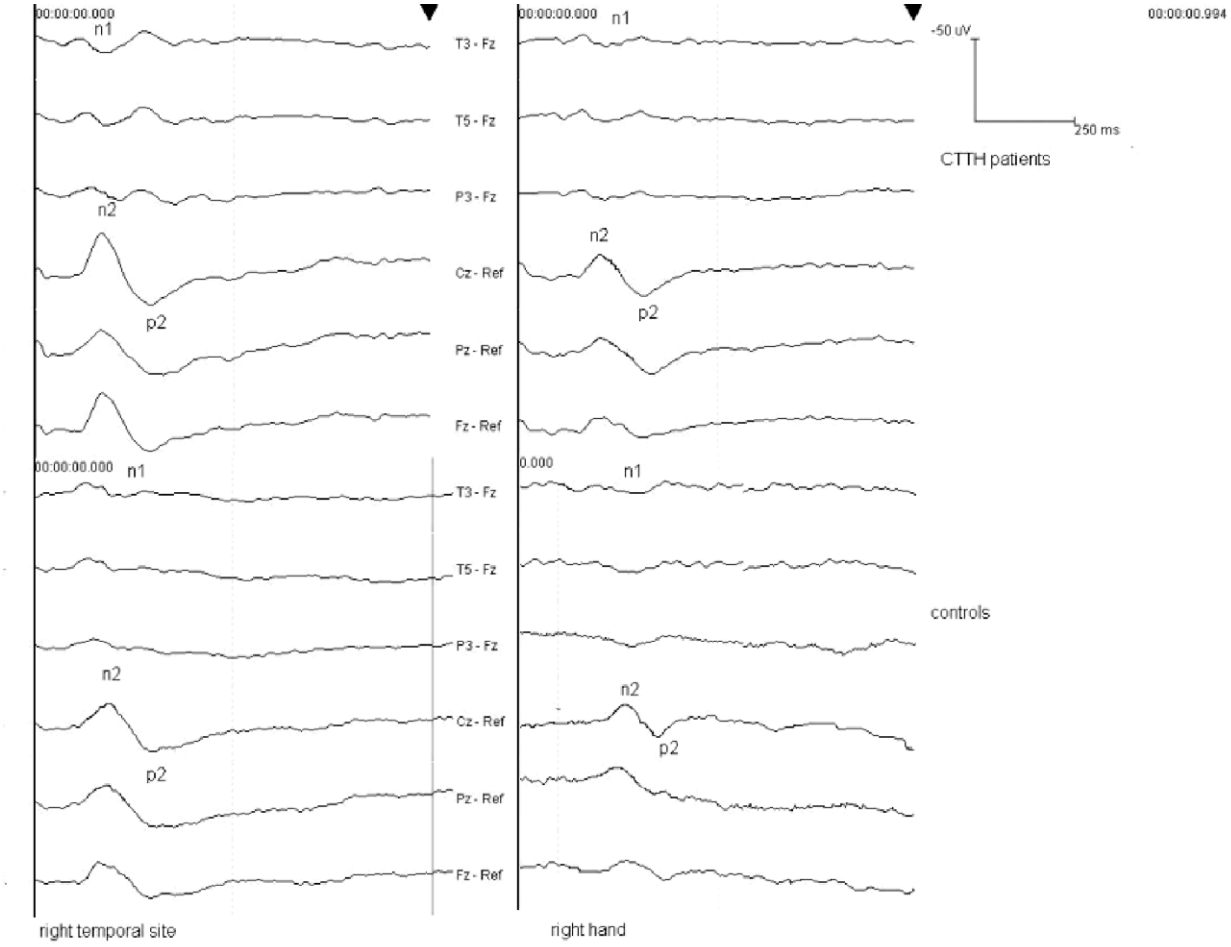

Fig. 1. Grand average of LEPs across 18 chronic tension-type headache patients and 12 controls, for the right hand and the right temporal point stimulation.

Table 4
Pearson correlation coefficient computed between LEPs waves amplitudes and TTS scores for the different stimulation points

	Front. Local TTS	Front. Total TTS	Stern. Local TTS	Stern. Total TTS	Trap. Local TTS	Trap. Total TTS	Mass. Local TTS	Mass. Total TTS	Temp. Local TTS	Temp. Total TTS	Neck Local TTS	Neck Total TTS
P2	0.57*	0.54*	0.52*	0.65**	0.63**	0.53*	0.54*	0.51*	0.41	0.42*	0.42	0.40
N2	0.35	0.12	0.36	0.22	0.25	0.35	0.18	0.24	0.23	0.26	0.21	0.19
N1	0.01	0.09	0.11	0.19	0.05	−0.12	−0.03	−0.15	0.17	−0.16	−0.04	−0.14

P2: vertex P2; N2: vertex N2; N1 temporal N1. Front.: frontalis. Stern. : sternocleidomasteoid. Trap: trapezius. Mass.: masseter. Temp: temporalis. Neck: posterior neck muscles. TTS: total tenderness score. * $p<0.05$; ** $p<0.01$.

2003), i.e., increased TTS during a pain-free phase: though most of our patients experienced daily headache and the interval since the last headache was very short, they did not show an increased sensitivity to laser stimulus, which may be referred to central sensitization phenomena (Bendtsen, 2000): in addition the TTS was not correlated with the interval since the last headache. According to previous results, (de Tommaso et al., 2003) the increased pericranial tenderness may be a primary phenomenon in CTTH, which is present without signs of sensitization persisting since the preceding headache. Looking at the correlations across the main clinical conditions, the Total Tenderness Score was not correlated with headache frequency and duration, rather it showed a significant correlation with anxiety Zung scales. The TTS may be a predisposing factor, as previously suggested (de Tommaso et al., 2003), linked with anxiety levels. Our patients were not affected by psychiatric disturbances, as coded by DSMIV, but the application of self evaluating scales by Zung revealed sub-clinical symptoms of anxiety and depression, according to previous studies about psychiatric comorbidity in tension-type headache (Puca et al., 1999). The anxiety seemed to get worst during the course of the disease, as suggested by the significant correlation with age and illness duration, and in our series appeared an important factor in CTTH disease.

The results of the LEP amplitudes partly confirmed previous findings (de Tommaso et al., 2003): the LEPs were enhanced in chronic tension-type headache patients with respect to controls when all the pericranial points were stimulated, and this phenomenon was independent from the sensitivity to laser stimulus, which was observed in another chronic pain syndrome, fibromyalgia (Gibson et al., 1994). In fibromyalgia, an increase in LEP amplitude has been documented (Lorenz et al., 1996). This abnormal amplitude increase was associated with reduced heat pain thresholds and greater suprathreshold laser intensity ratings. These findings may indicate a primary hyperalgesia to heat due to peripheral sensitization, but alternative mechanisms include central sensitization, deficient descending inhibition, or enhanced attentional modulation (Treede et al., 2003). In our CTTH series, the rating of laser intensity was the same as in normal subjects, confirming that the enhanced LEPs pattern may be linked with a disturbed central pain modulation. In contrast to the previous study, we also found a significant increase of LEP amplitudes at the level of the hand, as a general phenomenon, not limited to the pericranial area. The novelty of the present study was the topographic analysis of LEPs, which showed a peculiar increase of the later N2 and specially P2 waves, measured at the vertex regions. The N1 wave appeared not significantly increased in our series. This amplitude increase of LEPs was not linked to an increased sensitivity to laser stimuli, though the correlation between the pain rating and LEP waves is well known (Treede et al., 2003). In a recent study, the origin of the main LEP waves was confirmed in the opercular, insular, and cingulate cortex (Iannettia et al., 2005): the authors found a significant correlation between pain rating and N1 and N2 amplitude, while the P2 wave amplitude was independent from the rating of the heat stimuli. According to the findings in normal subjects (Bentley et al., 2003) and migraine patients (de Tommaso et al., 2004), the N2–P2 complex, specially the later P2, originate in the anterior cingulate (ACC), a cortical region mainly devoted to the elaboration of the attentive and emotive components of pain (Peyron et al., 2000). Lenz and his co-workers have reported P2-like peaks from subdural electrodes implanted over the parasylvian area (generated in the underlying parietal operculum/insula) (Lenz et al., 1998; Ohara et al., 2004); furthermore, Legrain et al. (2003) and Dowman (2001, 2004) present evidence that the P2 peak is similar to the P3a event-related potential. Taking in account all these reports, the response properties of the P2 peak strongly suggest that the P2 generators are involved at least in part in attention towards pain. Despite the fact that both the N2 and P2 waves were found to be increased in chronic tension-type headache patients, only the latter was correlated with the TTS when most of the pericranial points were stimulated, confirming that pericranial tenderness is a primary phenomenon, linked with significant attentive and emotive involvement in pain elaboration. Like the TTS, the P2 amplitude was correlated with anxiety levels when most of the pericranial points were stimulated, and both phenomena may be induced by high levels of cortical arousal to the painful stimuli from the pericranial points. The SPM maps confirmed that the later LEP waves increased over almost the entire scalp, especially on the vertex, compared to normal subjects. This suggests substantial activation of the mesial cortical regions which elaborate the painful laser stimuli. In CTTH patients, the spreading of LEP amplitude increase was quite limited when the hand was stimulated, for a prevalent increase of the nociceptive cortex activation by stimulation of the pericranial points.

Taken together, the results of this study may confirm that pericranial tenderness seems to be a primary phenomenon in chronic tension-type headache, present in the headache — free phase and linked with anxiety. It was correlated with strong activation of the cortical nociceptive areas subtending the emotive reaction to painful pericranial stimuli. When the muscle tenderness increases, for a worsening of the emotive behaviour,

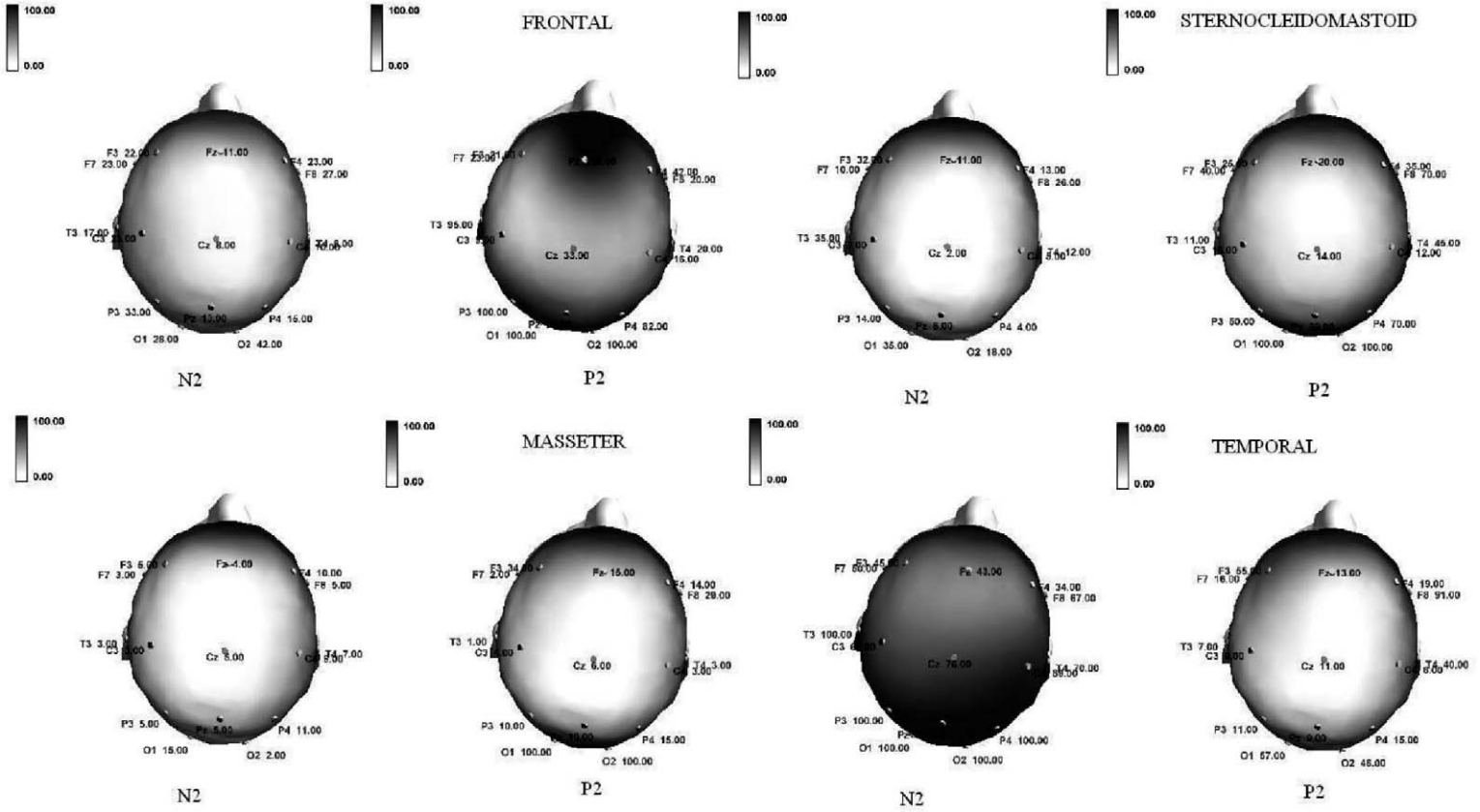

Fig. 2. Statistic probability maps (SPM) for N2 and P2 amplitude computed on 19 scalp derivations between patients ($n=18$) and controls ($n=12$), for the stimulation of the frontal, sternocleidomastoid, masseter and temporal points. Results of ANOVA are shown in a grey scale: the value of p is represented (p value × 1000), in which white is the maximum probability ($p<0.0000$) and black the minimum probability ($p=0.1$). In this figure the values of F7,F3,Fz,F4,F8, T3,C3,Cz,C4,T4,P3,PZ,P4,O1 and O2 electrodes were shown.

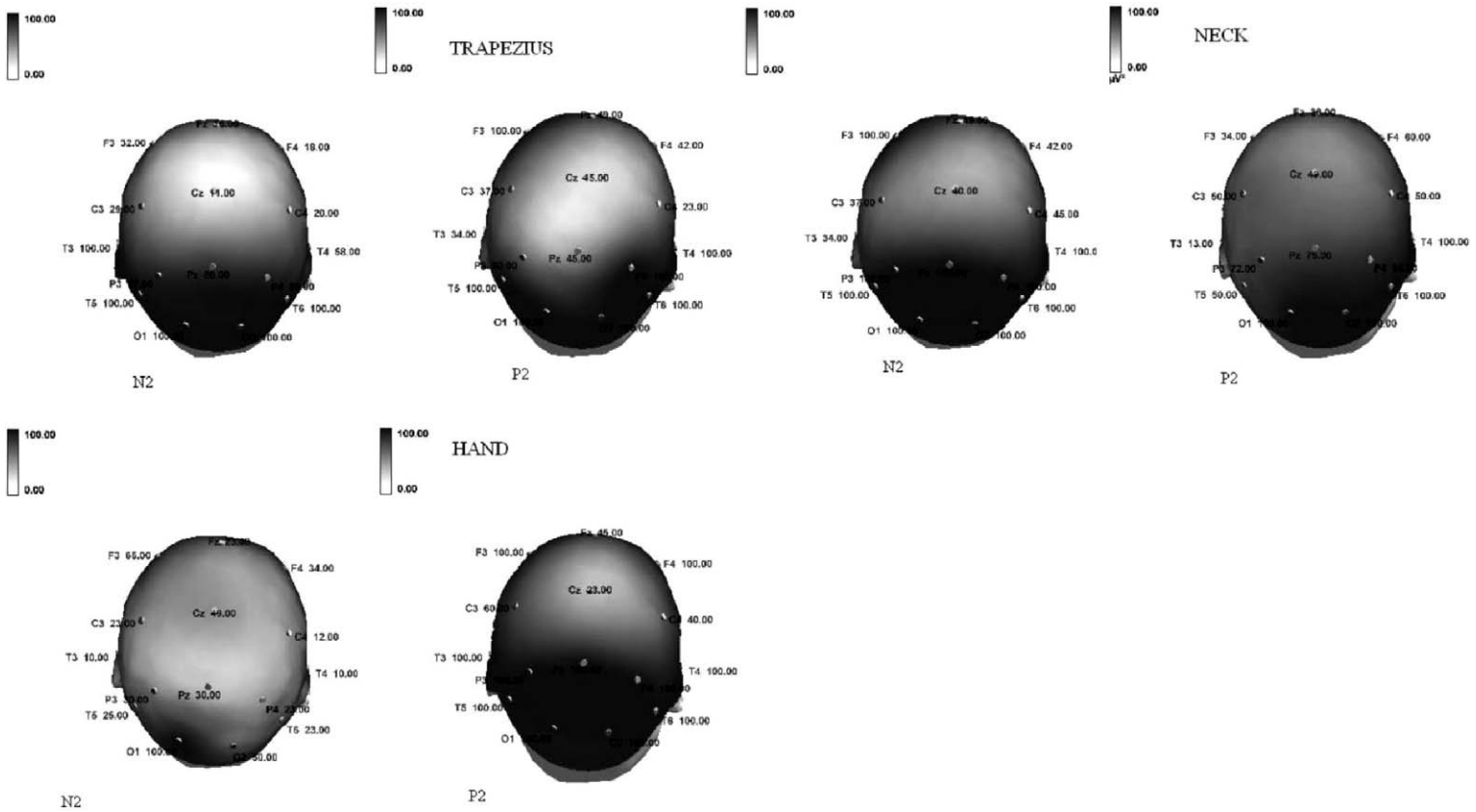

Fig. 3. Statistic probability maps (SPM) computed on 19 scalp derivations for N2 and P2 amplitude between patients ($n=18$) and controls ($n=12$), for the stimulation of the trapezius, neck and hand points. Results of ANOVA are shown in a grey scale: the values of p is represented (p value × 1000), in which white is the maximum probability ($p<0.0000$) and black the minimum probability ($p=0.1$). In this figure the values of F3,Fz, F4, C3,Cz,C4,T5,P3,PZ,P4,T6, O1 and O2 electrodes were shown.

headache may occur: according to Bendsten's hypothesis, prolonged nociceptive input from pericranial myofascial tissues causes central sensitization at the level of the spinal dorsal horn/ trigeminal nucleus, with supraspinal sensitization and activation of cortical nociceptive areas, which may further increase the pericranial muscle activity and the painful afferent stimuli, with a self-sustaining circuit leading to chronic headache.

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