Abnormal pain processing in chronic tension-type headache: a high-density EEG brain mapping study

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Central sensitization caused by prolonged nociceptive input from muscles is considered to play an important role for chronification of tension-type headache. In the present study we used a new high-density EEG brain mapping technique to investigate spatiotemporal aspects of brain activity in response to muscle pain in 19 patients with chronic tension-type headache (CTTH) and 19 healthy, age- and sex-matched controls. Intramuscular electrical stimuli (single and train of five pulses delivered at 2 Hz) were applied to the trapezius muscle and somatosensory evoked potentials were recorded with 128-channel EEG both in- and outside a condition with induced tonic neck/shoulder muscle pain (glutamate injection into the trapezius muscle). Significant reduction in magnitude during and after induced tonic muscle pain was found in controls at the P200 dipole in response to both the first (baseline versus tonic muscle pain: \( P = 0.001 \); baseline versus post-tonic muscle pain: \( P = 0.002 \)) and fifth (baseline versus tonic muscle pain: \( P = 0.04 \); baseline versus post-tonic muscle pain: \( P = 0.04 \)) stimulus in the train. In contrast, there were no differences between the conditions in patients. No consistent difference was found in localization or peak latency of the dipoles. The reduction in magnitude during and after induced tonic muscle pain in controls but not in patients with CTTH may be explained by impaired inhibition of the nociceptive input in these patients. This may be the first evidence that the supraspinal response to muscle pain is abnormal in patients with CTTH.

Keywords: brain mapping; EEG; pain; somatosensory evoked potentials; tension-type headache

Abbreviations: CTTH = chronic tension-type headache; SEP = somatosensory evoked potential; TTH = tension-type headache


Introduction

The most prominent abnormal finding in patients with tension-type headache (TTH) is a high degree of tenderness in pericranial muscles (Langemark and Olesen, 1987; Jensen et al., 1993; Bendtsen et al., 1996). Previously, research into the mechanisms leading to TTH has therefore focused on a muscular origin. More recently, it has become clear that central factors, in particular central sensitization, play an important and probably decisive role in patients with chronic TTH (CTTH) (Bendtsen and Jensen, 2006; Mathew, 2006). Based on results from pain perception studies it has been hypothesized, that frequent nociceptive input from the muscles in cephalic region induces central sensitization or impaired supraspinal modulation in the central nervous system which leads to CTTH and generalized hyperalgesia (Mense, 1993; Woolf, 1996; Jensen, 1999; Bendtsen, 2000; Ashina, 2004). Yet, the supraspinal processing of muscle pain within the central nervous system and the cerebral structures related to pain processing in CTTH have never been examined, thus it is still unknown how the central influences impact the incoming nociceptive input to produce altered pain perception. In the present study we used high-density (128-ch) EEG brain mapping to investigate the spatiotemporal aspects of brain activity to intramuscular electrical stimulation in patients with CTTH and in healthy controls before, during and after experimentally induced tonic muscle pain.
Materials and methods
Nineteen patients with a diagnosis of CTTH (ICHD-2) were recruited. All patients completed a diagnostic headache diary during a 4 week run-in period to confirm the diagnosis. The inclusion criteria were a diagnosis of CTTH, age between 18 and 65 years and TTH on the day of examination. Nineteen healthy, age- and sex-matched volunteers served as controls. The controls were headache free on the day of examination and at least 12 h prior to the investigation. In both groups exclusion criteria were: use of prophylactic headache therapy, antiepileptics or anti-depressants, excessive use of simple analgesics, pregnancy, breastfeeding and serious diseases including depression. Subjects were not allowed to take analgesics or muscle relaxants 24 h prior to the examinations. A written consent from each subject was obtained prior to the study. The study was approved by the local ethical committee (KA 05085) and conducted in accordance with the Helsinki Declaration.

Experimental procedures
The examiner, who recorded and handled the EEG data, was blinded for the headache diagnosis. Each subject underwent three experimental conditions (Fig. 1).

Electrical stimulation
The needle electrodes [Medtronic, Disposable Sensory Needle Electrode, 20 mm x 0.35 mm (28 G), active recording area 2.0 mm²] were placed (10 mm distance, 5 mm depth) in the trapezius muscle (2 cm laterally to the midpoint between the processus spinous of the seventh cervical vertebra and the lateral edge of the acromion). EMG activity was registered to confirm that the electrodes were placed in muscle tissue. A NoxiTest stimulator (NoxiTest Biomedical A/S, Aalborg, Denmark) was programmed to make 60 single stimuli (1 ms) and 60 train stimuli (five repeated single stimuli sampled with 2 Hz) in randomized order with inter stimulus interval between 4 and 6 s. Single stimuli were given with the electrical pain threshold for single pulses and train stimuli sampled with 2 Hz) in randomized order to make 60 single stimuli (1 ms) and 60 train stimuli (five (NoxiTest Biomedical A/S, Aalborg, Denmark) was programmed to make 60 single stimuli (1 ms) and 60 train stimuli (five repeated single stimuli sampled with 2 Hz) in randomized order with inter stimulus interval between 4 and 6 s. Single stimuli were given with the electrical pain threshold for single pulses and train stimuli were given with the electrical pain threshold for train pulses.

Induced tonic pain
Glutamate (0.2 ml of glutamate: l-monosodiumglutamate 1 M, 1 mmol–187 mg) was injected with 1 ml syringe and a 27 G x 3/4 in. cannula (Terumo Europe N.V., Belgium) into the trapezius muscle. The subjects were asked to rate the tonic muscle pain every 30 s. If the rating fell below pain threshold level another injection was given.

Quantitative sensory testing
Total tenderness score [total score of eight pairs of pericranial muscle and tendon insertion points, each scored on a 4-point scale (0–3), maximum possible score = 48] (Bendtsen et al., 1995) was recorded and the pressure pain thresholds were measured at the dorsum of the second finger (middle phalanx) and at the trapezius muscle using a pressure algometer (Somedic AB, Sweden, stimulation probe 0.5 cm², pressure loading rate of 22 kPa/s) (Jensen et al., 1986). Electrical pain thresholds for the single pulses and train pulses (fifth stimulus) were determined by method of limits (Vecchiet and Galletti, 1988).

EEG data acquisition
The EEG was recorded from 128 surface electrodes using a standard EEG-cap (Waveguard cap system, Cephalon A/S) employing the 10-5 montage system (Oostenveld and Praamstra, 2001). Impedance was kept below 5 kΩ. EEG signals were sampled at 2048 Hz. A 16-bit resolution in EEG quantification was used. The EEG was recorded by use of the EEProbe Software (A.N.T. A/S, Enschede, The Netherlands).

Analysis of EEG data
Epoching, artifact rejection and averaging were performed by use of custom made Matlab/Linux based EEG Inspect software (Kristian Hennings, Aalborg University). For single pulses epoch duration of somatosensory evoked potentials (SEP) ranged from 100 ms before to 600 ms after the stimulus onset. For each of the five train pulses epoch duration ranged from 100 ms before to 600 ms after the stimulus onset. Only the first and fifth pulse of the train stimulation were subjected to further analysis. The epochs were forward and reverse filtered with fourth order Butterworth band pass filter (0.5–100 Hz) in Matlab. All valid epochs were transformed to a common average reference offline. The averaged EEG data were further processed with the Matching Pursuit algorithm (Mallat and Zhang, 1993; Gratkowski et al., 2006) in order to eliminate the 50 Hz component and any other outer or inner disturbances.

From the compressed waveforms profile for each subject specific peak stages were extracted for the further analyses. For each of the extracted peak stages the localization and magnitude of the corresponding dipole was computed with the moving dipole model. The localization of each dipole is reported according to the subjects coordinate system (SCS) (provided by the manufacturer of the analysis software, ANT-Software A/S), which describes the dipole on the basis of three axes: x, y and z (Fig. 4). Based on the computed individual dipoles a mean x-, y- and z-coordinate, and magnitude was calculated for each group (CTTH and controls). Finally, the calculated dipoles were superimposed on MRI slices of the standard Montreal Neurological Institute (MNI) brain. Source analysis and topographic maps were created with the use of commercial available.

Fig. 1 Flow chart of the experiment. The experiment consisted of three SEP recordings: (i) baseline SEP recording (pre-tonic muscle pain), (ii) tonic muscle pain SEP recording (SEP recording during tonic pain induced by glutamate injection into the trapezius muscle) and (iii) post-tonic muscle pain SEP recording. The somatosensory potentials were evoked by intramuscular electrical stimuli (60 single stimuli and 60 train in randomized order) in the trapezius muscle. Prior to the experiment quantitative sensory testing was recorded.

Statistical analysis
The primary end-point was difference in dipole components (peak latency, magnitude, localization) between baseline and tonic muscle pain in patients and controls to single and repeated phasic stimuli. The secondary end-point was difference in dipole components (peak latency, magnitude, localization) during tonic muscle pain between patients and controls to single and repeated phasic stimuli. Further, differences in quantitative sensory parameters between patients and controls were analysed.

SEP and dipole components were analysed with two-way RM ANOVA. The two factors were: ‘condition’ (baseline/tonic muscle pain/post-tonic muscle pain) and ‘group’ (CTTH/Control). Accordingly, ‘condition’ × ‘group’ interaction, ‘condition’ effect (difference between the three conditions when the participants were not separated into the two groups) and ‘group’ effect (difference between the two groups when all conditions were analysed together) were analysed. The results are expressed in mean values ± SE. Five percent was taken as level of significance for the overall effect and post hoc Tukey HSD test in comparison of means. In the analyses of quantitative sensory testing independent samples t-test and Mann–Whitney U-test were used as appropriate. Statistical analyses were done using SPSS®, version 12.0 software (SPSS Inc., Chicago, IL, USA) and SigmaStat 2.03 program (for EEG analyses).

Results
All participants completed the experiment, but three healthy controls were excluded because of large artefacts in the EEG data. Clinical data on the patients and controls are presented in Table 1. The patients had been suffering from CTTH for a minimum of 1 year. Mean duration was 10.4 years (range 1–25 years). The controls had only very few days with TTH per year (0–4 days per year) and none of them had migraine.

Quantitative sensory testing (Table I)
Patients had a higher tenderness score than healthy controls (17.7 versus 4.4, F = 5.0, P < 0.001). Pressure pain threshold was lower in patients than in controls in the finger (258 kPa versus 364 kPa, F = 0.1, P = 0.03) and tended to be lower also in the trapezius muscle (326 kPa versus 436 kPa, F = 0.04, P = 0.08). There was no difference in electrical pain threshold for single pulses (3.1 mA versus 3.8 mA, P = 0.4) or in electrical pain threshold for train pulses (1.2 mA versus 2.1 mA, P = 0.3) between patients and controls. The electrical pain threshold for train pulses was lower than the electrical pain threshold for single pulses both in patients (1.2 mA versus 3.1 mA, P < 0.001) and in controls (2.1 mA versus 3.8 mA, P < 0.001). The difference between the electrical pain threshold for train pulses and the electrical pain threshold for single pulses was the same in patients as in controls (P = 0.3).

Compressed SEP waveform profiles and extraction of peak stages
In the compressed waveforms profile of the grand average three specific peak stages were observed consistently as common features independently of experimental condition (baseline/tonic muscle pain/post-tonic muscle pain), group (CTTH/controls) and stimulation mode (single/train). Thus, they were selected for the further analyses. The first major peak was a negative peak occurring around 100 ms after stimulus onset (N100). The second and third major peaks were positive peaks occurring around 200 ms (P200) and 300 ms (P300) after stimulus onset. In Fig. 2 the peaks are labelled on the compressed waveforms profile of the grand average for patients at baseline following single pulse stimulation. There was no significant difference in peak latencies between patients and controls or between the

![Fig. 2 Compressed waveform single pulse (patients at baseline).](image-url)
baseline, tonic muscle pain and post-tonic muscle pain conditions.

**Magnitude of the dipoles**

In controls, a reduction in magnitude between the conditions was found at the P200 dipole in response to both the first (ANOVA: $F = 3.3, P = 0.04$) and the fifth train stimuli (ANOVA: $F = 3.3, P = 0.04$) (Fig. 3). Compared with baseline recordings the magnitude was lower during the tonic muscle pain condition (first: $P = 0.001$; fifth: $P = 0.04$) and the post-tonic muscle pain condition (first: $P = 0.002$; fifth: $P = 0.04$). This was in contrast to patients, where none of the post hoc analyses showed significant differences in magnitude between the three conditions. In addition, a significant reduction in magnitude was found as a ‘condition’ effect in several of the dipoles. From baseline to the tonic muscle pain condition the ‘condition’ effect was significant at all peaks (N100, P200 and P300) for single stimuli and at P200 for the first train stimulus. From baseline to the post-tonic muscle pain condition the ‘condition’ effect was significant at all peaks (N100, P200 and P300) for both single stimuli and the first train stimulus and at N100 for the fifth train stimulus. At baseline, patients had a lower magnitude than controls at P200 for the first train stimuli (ANOVA: $F = 3.3, P = 0.04$, post hoc: CTTH versus controls = 0.01). In the tonic muscle pain and the post-tonic muscle pain conditions there was no difference in magnitude of the dipoles between patients and controls.

**Localization of the dipoles**

The dipole localization in patients at P200 for the fifth train stimulus was different (ANOVA: $F = 3.3, P = 0.03$, post hoc: $y$-coordinate, $P = 0.03$) from the localization in controls (patients: $y = 0.67$ mm; controls: $y = -19.79$ mm); but only at baseline recordings (Fig. 4). During induced tonic muscle pain, no differences in the localizations of the dipoles between patients and controls were found ($P > 0.05$). Likewise, no difference in dipole localization ($x$, $y$, $z$) at N100, P200 or P300 between baseline and induced tonic muscle pain were found either in patients or in controls ($P > 0.05$). The only difference that was found between baseline and the tonic muscle pain condition was a ‘condition’ effect at P300 for the first train stimulus in the localization of the $z$-coordinate (ANOVA: $F = 4.40, P = 0.02$, post hoc: baseline versus tonic muscle pain $= 0.01$).

**Discussion**

The major finding in the present study was the significant reduction in magnitude of the P200 dipole in response to both the first and fifth train stimuli during and after induced tonic muscle pain in controls. In contrast, none of the post hoc analyses showed significant differences in magnitude between the three conditions in patients. In addition, a significant reduction in magnitude was found as a ‘condition’ effect in several of the dipoles. This overall reduction in magnitude during and after induced muscle pain was pronounced in controls but not in
patients (Fig. 3). Thus, the significant 'condition' effects are most likely explained by the differences between the conditions in controls. At baseline, the magnitude of the P200 dipole in response to the first train stimuli was lower in patients than in controls.

Pain sensitivity
Consistent findings of increased pericranial tenderness in both episodic TTH and CTTH (Langemark and Olesen, 1987; Jensen et al., 1993; Bendtsen et al., 1996) but decreased pain thresholds only in CTTH patients (Langemark et al., 1989; Schoenen et al., 1991; Langemark et al., 1993; Bendtsen et al., 1996; Jensen et al., 1998) and not in patients with episodic TTH (Bovim, 1992; Gobel et al., 1992; Jensen et al., 1993; Jensen, 1996), support the hypothesis on central sensitization in TTH. In agreement, we found that patients had a higher tenderness score and a lower pressure pain threshold in the finger compared with healthy controls. No difference in pressure pain threshold in the trapezius muscle or in electrical pain threshold was found, which is in line with other studies that have included a relatively small number of subjects. This is explained by the relatively high inter-individual variability of pain threshold recordings as previously discussed in detail (Farella et al., 2000; Ashina et al., 2005).

Pain processing
Compared with the vast published research on cerebral responses to acute nociceptive pain in healthy subjects, relatively little knowledge exists about the processing of somatosensory stimuli in patients suffering from TTH where brain imaging is in its infancy. To our knowledge only one former imaging study in TTH has been performed. Using MRI and voxel-based morphometry Schmidt-Wilcke et al. (2005) demonstrated a significant grey matter decrease in patients with CTTH compared with healthy controls. The decrease was restricted to structures known to be involved in pain processing and positively correlated with the duration of headache. These findings by Schmidt-Wilcke et al. suggest that the brains of CTTH patients are different on a structural level from the brains of healthy controls. Similar results have been found in patients with chronic back pain (Apkarian et al., 2004).

Using slightly different source localization techniques than the present study, high-density EEG has recently been used to study supraspinal processing of pain in two other chronic pain conditions. In patients with chronic low back pain Diers et al. (2007) found that the response to intramuscular electrical stimulation was generally higher at N80 and lower at P260, compared with healthy controls, while no difference was found at N150 (Diers et al., 2007). The authors suggested, that the higher activation at N80 might be explained by central sensitization and the reduced activation at P260 by a deficient pain-inhibiting effect. In their study SEPs were recorded from 57 electrodes and the response was calculated as a ‘root mean square’, which is not directly comparable with our magnitude. In patients with chronic pancreatitis Dimcevski et al. (2007) recorded EEG using 64 electrodes and found that painful electrical stimulation of the esophagus, stomach and duodenum led to changes in cortical projections of the nociceptive system (Dimcevski et al., 2007). Again, it is difficult to link these findings to our results because different methodology was used.

Our finding of a reduction in magnitude of the dipoles from baseline to the tonic muscle pain and post-tonic muscle pain condition in controls but not in patients is the first report of abnormal supraspinal response to muscle pain in patients with CTTH. Moreover, it is the first
evidence that the brain processing in patients with CTTH are different on a functional level from healthy controls. To infer mechanisms that explain this finding we need to proceed with caution. In previous pain perception studies it has been argued that the hypersensitivity found in CTTH could be caused by: (i) sensitization of second order neurons at the level of the spinal dorsal horn/trigeminal nucleus, (ii) sensitization of supraspinal neurons and/or (iii) impaired supraspinal modulation (e.g. impaired descending inhibition). The expansion of hypersensitivity from muscle tissue to other tissues such as the skin (referred hyperalgesia) and the qualitatively altered stimulus-response function for pressure versus pain found in these patients could be explained by sensitization of second order neurons at the level of the spinal dorsal horn/ trigeminal nucleus (Bendtsen and Jensen, 2006; Mathew, 2006). The widespread nature of the hypersensitivity (e.g. decreased pain thresholds both at cephalic and extra- cephalic locations) however, suggests that increased excitability or deficient descending inhibition in the central nervous system at a supraspinal level plays a crucial role in CTTH (Bendtsen and Jensen, 2006; Mathew, 2006). On this background, our finding of a reduction in magnitude of the dipoles between the conditions in controls but not in patients may be explained by deficient descending inhibition of the nociceptive input in patients. Deficient descending inhibition is also expected to play an important role in other chronic pain conditions and our finding is probably not specific to CTTH. The present study does, however, not indicate which of the different dimensions of pain, i.e. sensory discriminatory, affective motivational and cognitive evaluative, that are affected in patients with CTTH. This could be investigated in future studies.

**Temporal summation**

The lower electrical pain threshold for train pulses than for single pulses both in patients and in controls is most likely explained by temporal summation. Facilitated temporal summation has been demonstrated in several musculoskeletal pain conditions (e.g. whiplash lesion, fibromyalgia and low back pain) (Arendt-Nielsen et al., 2007) and may also be essential in CTTH. In the present study we did, however, not find any differences in temporal summation between patients with CTTH and controls. This is in agreement with previous findings by Ashina et al. (2006). Moreover, the reduction in magnitude at the P200 dipole during and after induced tonic muscle pain was found to be of comparable degree in response to the first and fifth train stimuli in controls.

**Methodological considerations**

A major strength of the study is that the examiner who recorded and handled the EEG data was blinded for the headache diagnosis. Moreover, the technique we used has a very high temporal resolution and a high number of recording electrodes. This made it possible to study short-term functional changes in the brain and perform the source localization analysis. The SEPs recorded at the scalp surface are directly related to the underlying intracerebral activities. This relationship is mediated by the physical properties of the head tissues, which therefore have to be modelled appropriately (‘forward problem’). In the present study a ‘realistic head shape model’ (boundary element method) was used as a head volume conductor model. This model describes the electrical properties of the head as a number of homogenous and isotropic compartments (e.g. skull, brain, skin). The computation of the intracranial sources (source reconstruction) from the measured EEG is called the solution of the ‘inverse problem’. In the present study a ‘moving dipole model’ was used to perform the source localization. The inverse problem lacks a unique solution thus this approach, like all of the other models, depends on certain model assumptions which are discussed in details elsewhere (Lopes da Silva et al., 1991; Michel et al., 2004).

In the present study we did not find any consistent changes in localization of the dipoles. This suggests that there is no difference between patients and healthy controls in cortical projections of the nociceptive system. However, there was a great inter-individual variability in the localization of the individual dipoles and therefore considerable variance in the calculated means. The inter-individual variability in the localization of the dipoles could most likely have been reduced by superimposing the dipoles on individual brain images and by using Polhemus (Polhemus FASTRACK®, www.polhemus.com) to mark the positions of the recording electrodes (and individual MRI). Finally, in the present study intramuscular stimulation was used, because this type of stimulation is more clinically relevant in TTH than stimulation of the skin. Similar topographies and waveforms are found for sensory inputs from the skin and muscle and they are processed in nearly the same cerebral areas, but differences do exist. Muscle SEPs do not contain early SEP components, but has the first post-stimulus peak after 80–90 ms (Niddam et al., 2001, 2005).

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