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Electro-encephalography during nociceptive stimulation in chronic pain patients: a systematic review.

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Key words: chronic pain; electro-encephalography, nociceptive stimulation

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Background: With its high temporal resolution, electroencephalography (EEG), a technique that records electrical activity of cortical neuronal cells, is a potentially suitable technique to investigate human somatosensory processing. By using EEG, the processing of (nociceptive) stimuli can be investigated, along with the functionality of the nociceptive pathway. Therefore, it can be applied in chronic pain patients to objectify whether changes have occurred in nociceptive processing. Typically, so-called event-related potentials (ERP) recordings are used, where EEG signals are recorded in response to specific stimuli and characterised by a latency and amplitude.

Objective: Summarize whether differences in somatosensory processing occur between chronic pain patients and healthy controls, measured with ERPs, and determine whether this response is related to the subjective pain intensity.

Design: Systematic review

Setting & Methods: Pubmed, Web of Science and Embase were consulted, and 18 case-control studies were finally included.

Subjects: The chronic pain patients suffered from tension-type headache, back pain, migraine, fibromyalgia, carpal tunnel syndrome, prostatitis, or complex regional pain syndrome.

Results: Chronic neuropathic pain patients showed increased latencies of the N2 and P2 components, along with a decreased amplitude of the N2-P2 complex, which was also obtained in FM patients with small fibre dysfunction. The latter also showed a decreased amplitude of the N2-P3 and N1-P1 complex. For the other chronic pain patients, the latencies and the amplitudes of the ERP components did not seem to differ from healthy controls. One paper indicated that the N2-P3 peak-to-peak amplitude correlates with the subjective experience of the stimulus.

Conclusions: Differences in ERPs with healthy controls can mostly be found in chronic pain populations that suffer from neuropathic pain or where fibre dysfunction is present. In chronic

pain populations with other etiological mechanisms, limited differences were found or agreed upon across studies.

Introduction

Chronic pain, which is defined by the International Association for the Study of Pain (IASP) as pain lasting for a period of time longer than 3 months, has recently been reported by the Global Burden of Disease reviews as one of the most prominent causes for disability worldwide (1,2). The prevalence of moderate to severe chronic pain has been indicated to be around 20% in Europe, which demonstrates the importance of this problem (3,4).

Although patients with chronic pain report a diversity of symptoms, they seem to share pain and disability, even if in different proportions (5). As chronic pain is often not related to a primary tissue damage or lesion of the somatosensory system (anymore), the definitions of pain which were first restricted to those of nociceptive or neuropathic pain, had to be expanded. This gave rise to the concept of nociplastic pain (6). Nociplastic pain has been defined by the IASP as "pain that arises from altered nociception despite the absence of clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain". This altered nociception is typically expressed in the form of hyperalgesia and allodynia in chronic pain syndromes (7). The presence of such common symptoms could be explained by the occurrence of a joint (neuro)physiological underlying process known as central sensitization (CS) (8–11).

The altered activation of nociceptors was already covered by the IASP definition of CS as an "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input" (12). The presence of hypersensitivity was highlighted in the

definition by Woolf, who defined CS as “an amplification of neural signalling within the central nervous system that elicits pain hypersensitivity” (8). In addition to the current definitions of CS, research has indicated the importance of alterations in cerebral responses related to chronic states of pain, in which an altered sensory processing in the brain has been pointed out as a possible feature of CS (13–16).

Research investigating the cerebral response to experimentally induced nociceptive stimulation has already been summarized for chronic low back pain and fibromyalgia (FM) patients, measured with functional magnetic resonance imaging (fMRI) (7,17–19). Besides changes in brain regions that were not related to pain, chronic low back pain patients showed an increased activity of pain-related regions (primary somatosensory cortex (20,21), secondary somatosensory cortex (20,21), posterior cingulate cortex (22) and insula (22,23)) in response to mechanical, thermal or electrical stimulation. In FM patients, similar findings were only partly obtained depending on the applied experimental nociceptive stimulation method (24). If experimental pressure stimulation was applied for example, similar findings to those in chronic low back pain patients were only obtained if the stimulus intensity was the same in patients and controls but not if it was based on the pain threshold (20–22). However, research based on MRI is less ideal to determine the reaction time of the brain (25).

Cerebral responses to nociceptive input can also be measured with electroencephalography (EEG), which stands out as a valuable tool since it is non-invasive, low cost and easy to use (26,27). In addition, it can provide reliable and relevant information during sensory stimulation by capturing the electrical activity of neuronal cell assemblies on a sub-millisecond time scale, and consequently represent the neuronal activity in real time (28,29). Therefore, it is an ideal method to investigate somatosensory processing during experimental nociceptive stimulation

paradigms. So-called event-related potentials (ERP) recordings, where EEG signals are recorded in response to specific stimuli and characterised by a latency and amplitude, are typically used for these evaluations as these are accepted as a gold standard in the assessment of the global integrity of the nociceptive system (30–34). The assessment of the global integrity of the nociceptive system is especially valuable in case of neuropathic pain mechanisms, whereas in nociplastic pain mechanisms, ERP analyses are rather used to elucidate on the functionality of the nociceptive pathways and central nervous system. In this case, the nociceptive ERP represents a physiological correlate of the global or integrated central nervous system processing which underlies the perception of pain (35–37).

A previous systematic review by dos Santos Pinheiro et al. (2016) found an increased alpha and theta power during spontaneous EEG in patients with neuropathic pain, and migraine, but neither in low back pain patients nor in FM patients (39). An even more recent paper found significantly increased connectivity at theta and gamma frequencies in frontal brain areas as well as global network reorganization at gamma frequencies in chronic pain patients, which confirms the presence of differences in resting-state brain activity between chronic pain patients and healthy controls (40). Changes in resting-state EEG have largely been documented and brought together, but the function of nociceptive pathways in chronic pain patients, which is widely being measured with ERPs, has not. Based on EEG measurements, different protocols have been developed to measure the ERPs. Laser-evoked potentials (LEP) are one example and are currently the most reliable tool to assess the function of the spinothalamic system in humans, but depending on the type of the induced nociceptive stimulus, other different EEG protocols and associated outcome measures have been drawn up (42–44). The latency and amplitude of the ERPs have moreover been shown to be associated with the intensity ratings of the experimentally induced nociceptive stimulation in healthy controls, whereas the presence of such associations is again unclear for chronic pain patients (45,46).

The evaluation of the cerebral response of chronic pain patients to (experimentally induced) nociceptive stimulation has already been clarified in different systematic reviews (7,17–19). The articles that were included in these reviews used MRI and focused mainly on the spatial aspect of the cerebral response. As MRI is less optimal to determine the temporal aspect of the cerebral response, research with EEG can add useful information to the current knowledge. Using the high temporal resolution of EEG, which is ideal to measure the instant response of the brain, the primary aim of this review is to investigate the somatosensory processing of chronic pain patients by comparing the ERP resulting from experimentally induced nociceptive stimulation between chronic pain patients and healthy controls. Secondly, this study aims at compiling the existing evidence considering the relationship between the subjective experience of the experimentally induced nociceptive stimulation, measured as the perceived pain intensity, and the ERP.

Methods

Protocol and registration

This systematic review was conducted following the preferred reporting items for systematic reviews and meta-analysis guidelines (PRISMA) (47). It was registered with the number CRD42019134924 (https://www.crd.york.ac.uk/PROSPERO).

Information sources and search

The databases Pubmed (www.ncbi.nlm.nih.gov/pubmed/), Web of science (www.webofknowledge.com), and Embase (https://www.embase.com/#search) were searched for relevant articles. The search strategy constructed for each database can be found in the supplementary material.

Eligibility criteria and study selection

To fulfil the primary goal of this review, a PICO approach was applied to formulate the following research question: what are the differences in cerebral response, measured with EEG (O), between chronic pain patients (P) and healthy controls (C) in response to experimentally induced nociceptive stimulation (I)? Based on this research question, different in- and exclusion criteria were formulated which can be found in table 1.

A first screening was performed independently by two researchers, D.L. and W.W., during which the compliance of the titles and abstracts of all articles to the inclusion criteria was checked. In case of conflicts, a consensus meeting was held and if necessary, the opinion of a third independent researcher, M.M., was consulted.

A second screening round was performed on the remaining articles, in which the same inclusion criteria were applied to the full texts. The decision process was constructed in a similar manner as for the first screening.

Risk of bias assessment

All articles included after the second screening were assessed based on the eight items of the Newcastle – Ottawa quality assessment scale, which is recommended for case-control studies and has been proposed by the Cochrane Collaboration (www.cochrane.org) (48,49). This scale evaluates selection (case definition, representativeness of cases, selection of controls, definition

of controls), comparability of cases and controls (sex and age), and exposure (ascertainment of exposure, method of ascertainment, non-response rate). If low risk of bias was considered for an item, one star was assigned. For each of the eight criteria a star could be obtained, with the exception of the criterion regarding comparability, where two stars could be awarded when studies controlled for age and sex, resulting in a maximum total score of nine stars, which indicated the highest methodological quality (48).

Based on the risk of bias assessment, articles that did not match patients and controls for either age or sex (the comparability item), as well as articles that did not apply the same method of ascertainment for cases and controls were excluded from the review.

Based on the risk of bias assessment and the study design of the included articles, certain level of evidence was attributed to each article, which was determined according to the 2005 classification system of the Dutch Institute for Healthcare Improvement CBO (http://www.cbo.nl/). This level of evidence ranged from A1 (a systematic review of at least two independent studies of evidence level A2) to D (an opinion of experts). A level A2 was allocated for randomized double-blinded comparative clinical research of good quality and efficient size, whereas comparative research without the needed characteristics for A2 (including patient-control and cohort research) received a level B and non-comparative research was attributed a level C.

This risk of bias assessment was independently performed by the two researchers D.L. and W.W., and finalized after a consensus meeting. In case of uncertainty, the opinion of a third independent researcher, M.M. could be consulted.

Data extraction

The data extraction table was developed by consensus between D.L., M.M. and K.V. First author, year of publication, investigated pathology, description of control population, number

of participants, demographics of the participants (sex distribution, age, duration of disability, weight, length and BMI), type of cortical response measured, experimental nociceptive stimulation method, stimulus determination, brain activity registration set-up, outcomes and results were chosen and represented in the evidence table (Appendix), unless if (one of) these items were not reported in an article. Data extraction was independently performed by the authors D.L. and W.W. and afterwards compared to obtain a consensus.

Results

Study selection

The search strategies were inserted into all three databases on the 29th of May, 2019 and led to a total of 616 results in Pubmed, 552 in Web of Science and 1015 in Embase. After screening the title and abstract against the predetermined in- and exclusion criteria, 68 articles were included. By screening the full-texts of these included articles, 34 articles were identified that did not fulfil the inclusion criteria. Of these 34, 11 did not discuss a chronic pain population, 9 did not report EEG as an outcome, 7 did not include a control group, 4 were based on a study design that was not of interest for this review, 2 were written in a foreign language other than French, Dutch or English, and of 1 article no full-text could be obtained. Consequently, 34 articles were included in the risk of bias assessment, of which 16 did not fulfil the inclusion criteria concerning quality assessment. Finally, 18 articles were included in the systematic review.

The flowchart of the study selection can be found in figure 1.

Risk of bias

Identical results concerning risk of bias assessment were obtained by both raters for 266 of the 272 items (97.79%). Evaluation of the ambiguous items by the third independent researcher, M.M., resulted in a consensus on the remaining items. Resulting from this assessment, 16 articles were excluded from the review, all for the lack of matching the patients and controls either for age or sex. Consequently, 18 articles remained after risk of bias assessment (50–67). Possible risk of bias was mostly induced by inadequate case description and selection of controls. 14 articles (78%) did not describe whether they included an entire population, or a random sample of patients and 15 articles (83%) did not describe the source population for sampling the healthy controls or the source population was different than the one used for the patients. All articles were allocated a level of evidence B as none of them included a follow-up period. A more detailed representation of the quality assessment of the included articles can be found in table 2.

Study characteristics

Study design. All included studies had a case-control design.

Diagnosis. All patients included in the studies suffered from chronic pain due to tension-type headache (51,62,64,65,67), low back pain (52,54,57), migraine (58,61,63), FM (53,56,59,66), carpal tunnel syndrome (50), prostatitis (55), or complex regional pain syndrome (CRPS) (60).

Demographics. In total, 510 chronic pain patients and 384 healthy controls were described in the included studies. The sample size of the patient groups ranged from 10 (56) to 199 (66). Women (73.13% in the patient group and 71.36% in the control group) were more frequently assessed than men. Three studies included only females (53,56,58), whereas one study only included male participants (55). The mean age of the patient group was 40.75 years, which was

38.04 years for the healthy control group. The duration of disability was 12.74 years on average in the patient groups.

Experimental nociceptive stimulation. Brain activity was recorded in response to nociceptive stimuli, which were administered at the level of the pain threshold in most studies (51–53,56,58,60–62,67). Some of the studies applied stimuli at 7.5 Watt (63,65), at 70% of the pain tolerance (54), at 3 Watt above the pain threshold (66), or defined the intensity by multiplying the sensory or pain threshold by a factor of 1.2; 1.5 or 2 (50,55,59).

Method. Of the included articles, 11 discussed LEP of which one used an argon laser (50), one a Thulium-YAG laser (52) and nine a CO_2 laser (53,56,60–66); and seven examined somatosensory evoked potentials (SEP) based on electrical stimuli (51,54,55,57–59,67).

Outcome. Evaluating pain-evoked potentials with EEG can provide a quantitative evaluation of the cerebral response to nociceptive stimulation (50,68). Depending on the choice of number and placement of electrodes, certain components of the ERP will be measured. In case a multichannel EEG is chosen, all ERP components can be investigated, including the earlier ones, as well as the later components and the spatial distribution of the evoked response (69). These components are denoted by their polarity (P = positive; N = negative), their amplitude in microV and their latency in msec after stimulus onset (36). Subsequent to the recording,several analyses can be performed, such as determining the difference in voltage between maximum and minimum voltage of a wave, known as the peak-to-peak amplitude; or investigating the power of the pain-evoked brain potential (70). This power is said to reflect the intensity of the perceived pain (71,72). Lastly, dipolar source analyses can be performed to localize the source of a certain ERP component (51,63). The latency of ERP components was discussed in 13 studies (51–53,55–60,62,63,65,66), and the amplitude was reported in 15 articles (52–54,56–67). Dipolar source analysis was described in two studies (51,63), whereas spectral power was

discussed in one article (50). Associations between the EEG findings and subjective pain response were investigated in three studies (50,53,61).

EEG recording protocol. Different technical protocols were applied for the EEG recording concerning the number of electrodes, electrode placement and sampling rate. The number of recording electrodes ranged from 1 (50,53,55,57–59,61,62) to 128 (51), which were mostly placed according to the 10-20 international system, with the exception of one article which used the 10-5 montage (51). The sampling rate ranged between 100 (67) and 5000Hz (57).

Scalp location of the potentials. The N1 component was mainly measured at temporal electrodes (T3,T4, T5 or T6) (60,62–66) but was measured at Cz in two articles (58,59) and at C3-C4 in one article (56). The P2 component (52,56,61–66) was always measured at Cz, as well as the N2 component (52,56,60–66), whereas the N2b was measured at Fz in one article (63). The P1 component was measured at Cz (58)(59), as well as the N50 component (55), and the N9 component was measured at CP3 (57). One paper averaged across 9 scalp locations to determine the N150 and P260 components (54).

Synthesis of study findings

Fibromyalgia

Four studies included a patient population suffering from FM, of which three applied laser stimulation (53,56,66) and one applied electrical stimuli as experimental nociceptive stimulation method (59).

The latency of the P1 component was discussed in one article (59), as well as the P3 component (53), whereas the latency of the P2 component was discussed in two articles (56,66), as well as

that of the N1 component (59,66), and the amplitude of the N2 component was discussed in three articles (53,56,66).

Concerning the latency of the N2 (53,56,66), P1 (59), P2 (56,66) and P3 (53) component, no differences were found between FM patients and healthy controls. For the latency of the N1 component however, De Tommaso et al. (2014) reported no difference between FM patients and healthy controls when stimulating the hand, thorax or knee; whereas Uceyler et al. (2013) only found similar results for both populations for stimulation at the face or hand but found a prolonged latency in FM patients when stimulations were administered to the foot.

The amplitude of the N2-P3 complex was described in one article (53), as well as that of the N1-P1 complex, whereas the amplitudes of the N1, N2, P2 components and N2-P2 complex were described in two articles (56,66).

The amplitude of the N2 component was investigated by De Tommaso et al. (2014) and Lorenz et al. (1998), and was found to be similar across FM patients and healthy controls in both studies. The amplitude of the N1 and P2 component, as well as the N2-P2 complex were investigated by the same researchers but did not result in a consensus. Concerning the N1 and P2 component, no differences were found between both populations by De Tommaso et al. (2014), whereas higher amplitudes for both components were obtained in the FM population by Lorenz et al. (1998). Further contradiction was found in the N2-P2 amplitude which was shown to be reduced in FM patients when stimulations were administered to the hand or knee (66), whereas the study by Lorenz et al. (56) did not demonstrate any differences between FM patients and healthy controls for N2-P2 amplitude after stimulation of the hand. Similarly, no differences between both groups were found by De Tommaso et al. (2014) when stimulations were applied to the chest (66). Based on one article, the N2-P3 amplitude seemed to be larger in FM patients (53), whereas the N1-P1 amplitude was shown to be reduced in FM patients (59), when compared to healthy controls.

Associations between the subjective estimate of stimulus and cerebral response were only investigated in one article and showed a significant positive association between subjective estimate of stimulus intensity and peak-to-peak amplitude (N2-P3) in both patients and controls (53).

To conclude, it is likely that the amplitude of the N2 component and the latency of event-related potentials does not differ between FM patients and healthy controls, with the exception of the N1 component, for which the outcome seems to depend on the stimulation site. There is however still conflicting evidence about differences in the amplitude of the N1 and P2 component, along with the amplitude of the N2-P2 complex. There are indications that the amplitude of both the N2-P3 and N1-P1 complex are altered in the FM populations and that a positive association can be found between the stimulus intensity and N2-P3 amplitude.

Chronic low back pain

Four studies, of which one based on LEP (52) and three on SEP induced by electrical stimuli (54,57,67), described a population with chronic low back pain (CLBP).

The latencies of the P2 and N2 components were investigated in one article (52), as well as those of the N9 components (57).

No differences in latency were found between CLBP patients and healthy controls, with the exception of the N9 latency, which seems to be longer in the patient population.

The amplitudes of the P3, N500 (67), N9 (57) were each only discussed in one article, whereas the amplitude of the N150 was investigated in two studies (54,67), as well as the amplitude of the P2 component (52,67).

No differences in amplitude between CLBP patients and healthy controls could be observed for any of the investigated ERP components. However, it must be said that the findings of the P3

and N500 were based on stimuli given at the intensity of the pain threshold, which was significantly lower in the CLBP group. Conflicting results were obtained for the amplitude of the N150 component (54,67). According to Flor et al. (2003), the N150 amplitude was not significantly different between CLBP patients and healthy controls (although both groups received significantly different stimulus intensities), whereas higher amplitudes were found in the CLBP group by Knost et al. (1999). The P2 amplitude was shown not to be different between the healthy and CLBP group in both articles (52,67).

Associations between the subjective estimate of stimulus and cerebral response were not investigated in any of the included studies.

To conclude, there are indications for the absence of differences in latency between CLBP patients and healthy controls, with the exception of the N9 latency, which seems to be longer in the CLBP group. There are also indications that the amplitudes of the ERP do not differ between CLBP patients and healthy controls, with conflicting evidence about the amplitude of the N150 component.

Migraine

Three studies described the cerebral response to nociceptive stimulation in a chronic migraine population and reported results of laser (61,63) and electrical stimulation (58).

The latencies of the N2a and P2 were investigated by two studies (61,63), and results for the latency of the N1 component were also found in two studies (58,63). The latency of the N2b component was only investigated by De Tommaso et al. (2005) (63).

Considering the latencies of the waveforms of the ERP in chronic migraine patients, the N2a (61,63), N2b (63), P2 (61,63) and N1 (58,63) (be it only at the contralateral side of the pain stimulus by Sohn et al.) were similar to those obtained from healthy controls. The study by

Sohn et al. (2016) did however find a decreased latency of the N1 waveform when registered at the side ipsilateral to the site of stimulation, which was not confirmed by other research (58). This same research found a decreased latency of the P1 component on both sides of the brain.

The amplitudes of the N1 and N2b were investigated in one study (63), as well as the N1-P1 amplitude (66), whereas the N2a and P2 amplitude were examined in two articles (61,63).

The amplitudes of the N1 (63), N2a (61,63), N2b (63) and P2 (61,63) waveform were found to be similar in healthy participants and chronic migraine patients. The N1-P1 amplitude was however increased in migraine patients, when measured at the contralateral side of the stimuli (58).

Associations between the subjective estimate of stimulus and cerebral response were only investigated in one study (61). A significant correlation was found between perceived intensity and the N2A-P2 amplitude in the healthy population, but could not be found in the migraine population.

In addition, *source localization,* which is an estimation of the locations of possible cortical generators that might explain the resulting signal recorded from the scalp electrodes, was performed by one study for the P2 dipole and showed a more anterior location of the dipole in the migraine population (63). Whereas the dipole was situated in the contralateral anterior cingulate cortex in healthy controls, it was shifted towards the ipsilateral rostral cingulate cortex in the migraine population.

To conclude, it is likely that the amplitudes of the ERP waveforms are similar between migraine patients and healthy controls. There are indications that the peak-to-peak amplitude (N1-P1) is however decreased in migraine patients. It is moreover likely that the latencies of the waveforms are not significantly different between both populations, with the exception of the ipsilateral N1 and P1 components. There are also indications for a relationship between the perceived intensity and peak-to peak amplitude, and for an anterior shift in the P2 dipole.

Tension-type headache

Five studies reported the response of the brain to experimentally induced nociceptive stimulation in chronic tension-type headache (51,62,64,65,67). Two of these studies applied electrical stimuli as nociceptive stimulation method (51,67), whereas the other three studies made use of a CO_2 laser (62,64,65).

The *latency* of the P3 component was investigated by one study (51), those of the N1 (51,65) and N2 (62,65) by two studies and the latency of the P2 component was investigated by three studies (51,62,65).

Latencies of the N1 (51,65), N2 (62,65), P2 (51,62,65) and P3 (51) waveform were shown to be similar across patients and healthy controls.

The amplitude of the N150 was investigated by one study (67), as well as the N260 (14), the P3 and N500 (67), whereas the amplitudes of the N1, N2 and P2 were investigated by the two same studies (63,65). The amplitude of the N2-P2 complex was also investigated by two studies (62,65).

Considering the amplitude of the cerebral response to pain, patients and controls exhibited a similar response for the N1 (63,65) and N150 (67) component. The amplitude of the P2 component was shown to be greater in the chronic tension-type headache population when stimuli were applied to pericranial sites (63,65) but following hand stimulation, this difference was only maintained by one of these studies (65), whereas the other (63) did not obtain a significant difference between both groups after hand stimulation. Similar results were found for the amplitude of the N2 component, where an increase of the amplitude was seen in chronic tension-type headache patients when stimulations were applied at the hand or pericranial sites, with the exception of stimulation at the Temporalis muscle (63,65). Research by Flor et al.

however found that stimulation at the hand elicited similar responses in N260 amplitude between patients and healthy controls. The peak-to-peak N2-P2 amplitude was shown to be greater in chronic tension-type headache patients for stimulation at all pericranial sites (62,65). Amplitudes of the P3 and N500 component were only investigated in one article and were shown to be similar between patients and healthy participants and larger in chronic tension-type headache patients respectively (67).

Associations between the subjective estimate of stimulus and cerebral response were not investigated in any of the included studies.

In addition, one study performed source localization and found a significant difference in the y coordinate of the P2 dipole (but did not state in which direction) between patients and healthy controls and obtained a larger magnitude of that dipole in the chronic tension-type headache population (51).

To conclude, it is likely that the latency of the cerebral response to nociceptive stimulation, along with the amplitude of the N1 component does not differ between patients and healthy controls. There are indications that similarly the amplitudes of the P3 and N500 components do not differ between both groups. However, the amplitudes of the P2 and N2 components do likely differ between both groups, with conflicting evidence about the response to hand stimulation. Similarly, the N2-P2 amplitude is likely to be higher in chronic tension-type headache patients following pericranial simulation. However, no significant differences in the N2-P2 amplitude were found after stimulation of the hand.

Neuropathic pain

Two studies discussed the cerebral response to experimentally induced nociceptive stimulation in neuropathic pain populations (50,60). The studies investigated carpal tunnel syndrome (50) and CRPS (60) based on LEP.

The latencies of the N2 and P2 components were discussed in one article (60).

The latency of both the N2 and P2 component was shown to be increased in patients suffering from CRPS, when compared to healthy controls (60). These results did not differ between CRPS patients suffering from the upper or lower limb.

The amplitude of the N2-P2 complex was investigated in one article (60).

The amplitude of the N2-P2 complex was reduced in the CRPS patients, when compared to healthy controls (60). Findings in the CRPS population were the same for patients suffering from the upper or lower limb.

Associations between the subjective estimate of stimulus and cerebral response were only investigated in one study (50). The correlation between the pain threshold and the EEG findings seemed to be absent.

In addition, the mean power of the event-related potentials was investigated in one article and was shown to be reduced at the third finger of the affected side in patients with carpal tunnel syndrome when compared to healthy controls (50).

To conclude, it is likely that a different cerebral response to induced nociceptive stimuli occurs in chronic neuropathic pain patients, compared to healthy controls. Moreover, there are indications that this alteration is characterized by a reduced amplitude and increased latency of the Aδ response and a reduced mean power of the ERP. There are also indications that there is no relationship between the pain threshold and the ERP characteristics.

Chronic prostatitis

Only one article discussed a population suffering from chronic prostatitis, which evaluated the cerebral response to electrical stimuli delivered through penile electrodes (55).

The latency of the N50 component was investigated and was shown to be decreased in the patient group, when compared to a healthy control group.

The amplitude of the ERP was not investigated.

Associations between the subjective estimate of stimulus and cerebral response were not examined.

To conclude, there are indications that the N50 latency is decreased in patients suffering from chronic prostatitis.

Discussion

The purpose of this study was to summarize the evidence for altered somatosensory processing by evaluating the cerebral response, measured with ERPs, to experimentally induced nociceptive stimulation in chronic pain patients and to check whether this cerebral response was related to the subjective experience of the induced stimulation.

Summary of results

The latencies of the N2 and P2 were found to be similar between chronic pain patients and healthy controls, with the exception of patients suffering from chronic neuropathic pain (51,52,56,60–63,65,66). About the latencies of the other components, no consensus was reached. These results should however be interpreted in the light of the different included pathologies. Whereas in CRPS patients the obtained differences point in the direction of a dysfunction of the thermonociceptive pathway (60), the differences found in CTS patients

should be interpreted as focal nerve lesions resulting in dysfunction of thin afferents (50). Similarly, one paper used the ERP analyses, in addition to other techniques, to discover dysfunctions of the small fibres, which showed that the pain in FM is closely related to neuropathic pain (59). These findings were supported by de Tommaso et al., who found reduced LEP amplitudes in a small sub-group of their FM patients that showed slight distal sensory deficits on neurological examination (66). Therefore, it is important to differentiate within FM between patients with or without small fibre dysfunction, as this could explain the contradicting findings that were obtained in this patient population.

In case of FM without small fibre dysfunction, differences between FM patients and healthy controls can be interpreted as the result of an increased central nervous system response to nociceptive input and/or an increased activity of cortical regions (53,56,59,66). The studies discussing CLBP, chronic migraine, chronic tension-type headache or chronic prostatitis interpreted the occurrence of differences between patients and controls as an abnormal central nervous system processing of nociceptive input due to a hypersensitivity created by an amplification of the pain signal at the central level or an impaired descending pain modulation (51,52,54,55,57,58,61–65,67).

Whether the amplitude of the separate components or the peak-to-peak amplitude of the N2-P2 complex differs between chronic pain patients and healthy controls is unsure due to the contradicting results (52,56,61–63,65–67). Firstly, given the fact that different pathologies were included, different results could be expected. Pathologies where fibre dysfunction is suspected seemed to show more consistent results and showed differences between patients with neuropathic pain or FM and healthy controls, such as a decrease in the amplitude of the N2-P2 complex, as well as of the N2-P3 and N1-P1 complex (50,59,60,66). Therefore, the contradicting results within the FM population could be due to the comparison of papers that did or did not screen the FM patients for neurological dysfunctions. Within the other included

populations, the amplitude of the P3 component and N500 component did not differ between tension-type headache patients or CLBP patients and healthy controls, and the N1 amplitude did not differ between migraine or tension-type headache patients and healthy controls. About the amplitude of the other components, no consensus was reached. These contradicting results could be explained by the strong influence of attention and emotion on these components (73–76). This is especially the case for the N1, N2 and P2 components. The N1 and N2 wave have been shown to be enhanced by special attention, which suggests that their sources are sensitive to "top-down" attentional mechanisms, whereas the P2 wave enhances with the probability of stimulus occurrence, which suggests that its sources are sensitive to "bottom-up" stimulus-driven mechanisms of arousal or attentional orientation (77,78). Findings of an increment in N2-P2 amplitude could therefore be the result of a pain-specific hypervigilance favoured by psychological factors (53,62,86). The importance and prevalence of anxiety and depression in a certain patient population or the inclusion of patients with psychiatric co-morbidities could therefore influence these results and explain some of the obtained contradictions. Moreover, these ERPs can only be entirely explained by a combination of multimodal and somatosensory-specific neural activities, whereas nociceptive-specific cortical activity cannot be explored with conventional analysis of scalp evoked potentials (87). However, the generation of these ERPs still relies on a functional nociceptive system, both peripheral as central. Therefore, evoked potentials can still reliably be used to obtain an (indirect) readout of the functionality of the afferent nociceptive system.

The absence of differences in amplitude or latency of the ERP components between chronic pain patients and healthy controls often co-occurred with an absence of differences in pain sensitivity between both groups (51,52,57,61–63,66). The combination of these findings could disprove central sensitization to be the predominant mechanism in the included patients of these studies. The possible influence of central sensitization was also repeatedly mentioned in the

articles that did find differences in cerebral response between the chronic pain patients and the healthy controls (51,53,55,58,64,65).

For different components, contradicting results were obtained. As mentioned, this can be the result of differences in etiologies or underlying mechanisms of the included pathologies, or due to differences in importance of central sensitization, stress and anxiety in different patient groups, but this can also be the result of differences in stimulation protocol. Firstly, whereas laser heat stimuli selectively excite nociceptive Aδ- and C-fibres, electrical stimulation concurrently activates non-nociceptive Ab-fibres, unless intra-epidermal electrical stimulation is used with a maximum stimulus intensity of twice the perceptual threshold (31,88). According to the gate control theory, activation of Aδ- and C-fibres would have a stimulatory effect on pain transmission, whereas activation of Ab-fibres would result in an inhibitory effect (55). However, recent findings have shown that the gate control theory is not correct in detail. The proposed inhibition of spinal nociceptive neurons by tactile afferents according to the gate control theory is namely exploited by highfrequency low-intensity protocols of transcutaneous electrical nerve stimulation or spinal cord stimulation, and synaptic efficacy can also be reduced by peripheral nociceptor input, which can lead to long-term depression (89,90). Secondly, a shorter inter-stimulus interval could cause greater sensitization at peripheral and/or central levels of the nervous system in chronic pain patients than in healthy controls (52). Thirdly, the applied stimulus intensity can influence whether alterations in ERP components can be found as this can influence the type of fibre recruitment on one hand, and as the presence of hypersensitivity can depend on the intensity of the applied stimulus on the other hand (52,67,88).

Evaluating ERP in response to nociceptive stimulation can provide a quantitative evaluation of pain perception and can add valuable information to the pain threshold determination, which merely refers to the quality of the perception by the patient (50,68). This technique is able to

detect alterations in cerebral responses, induced by chronic pain states, which are characterized by an amplification and prolongation of a pain signal at a central level (14). The nociceptive-evoked response is thought to reflect secondary processing of nociceptive input which is enhanced by immediate attention caused by the compelling sensation of pain (62,63). Depending on the choice of number and placement of electrodes, certain components of the ERP will be measured. The earlier components originate from the suprasylvian region, which are devoted to the discriminative component of pain, whereas the later components arise from the anterior cingulate cortex, which play a role in the attentive and emotive features of pain (69).

This review included a secondary aim to investigate the relationship between the subjective experience of the experimentally induced nociceptive stimulation, measured as the pain intensity, and the ERP. Strong relationships between the pain intensity and the cerebral response have repeatedly been reported in previous studies with healthy participants (71,91–93). Such associations were only discussed in two of the included studies (50,53,61), but only one study found an association between both in chronic pain patients. This concerned a positive association between the peak-to-peak amplitude of the N2-P3 complex and the stimulus intensity in the FM group (53). Recent findings in healthy controls have however indicated that laser-evoked EEG responses are not determined by the perception of pain per se, but that they are mainly determined by the saliency of the eliciting nociceptive stimulus (94,95). Moreover, gamma band oscillations have been shown to predict the subjective pain intensity (96–98). To the best of our knowledge, neither the relationship between the saliency of a stimulus and the ERP, nor between the gamma band oscillation and the subjective pain intensity have been investigated yet in chronic pain populations.

The mean power of the ERP was shown to be reduced in patients with carpal tunnel syndrome when compared to healthy controls (50). Measuring the power of the evoked potential has been

found to be an adequate technique to quantify the perception of burning pain, which can be elicited with laser stimulation (72).

A shift in the location of the P2 dipole was reported in two articles (51,63). Whereas the direction of the shift was not reported in the chronic tension-type headache patients, the y-coordinate was located more anterior in chronic migraine patients. Consequently, the P2 source in healthy participants was located in the anterior cingulate cortex, which is involved in orientating reactions and target detection to direct a subject's attention toward a possible noxious stimulus so that a motor reaction can be prepared (99). In chronic migraine patients, the P2 source was located in the rostral anterior cingulate cortex, which is associated with the affective reaction that coincides with pain unpleasantness (63,100). This could be explained by the higher levels of stress and anxiety during nociceptive stimulation in the chronic migraine population that activate the rostral anterior cingulate cortex and that facilitate the trigeminal nociceptive inputs (63,101).

Limitations & strengths

Due to the large variety in populations and outcome measures, a meta-analysis was not performed. As early components of noxious-related ERPs are thought to reflect the sensory-discriminative aspect of pain and the later components represent the emotional or affective-motivational aspect, it was decided not to pool the overall differences in latency and amplitude of the early and late ERP between the described chronic pain populations and healthy controls (69,102,103).

The quality of the systematic review was ensured by the collaboration between two independent researchers who appealed for a third independent opinion in case of doubt. In addition, exclusion based on quality assessment ensured inclusion of only high quality research.

However, articles only had to match the patient and healthy control group on either age or sex, whereas ideally only articles would have been retained that matched for both factors. As applying this strict rule would produce insufficient results, only one criterion had to be fulfilled for inclusion.

As pain is by definition a subjective experience and can therefore only be measured by self-report, brain imaging measures a concept related to but not necessarily equal to pain, namely nociception (41). This nociception has been defined as an objective measure for the "neural process of encoding noxious stimuli which can have autonomic (e. g. elevated blood pressure) or behavioral (motor withdrawal reflex or more complex nocifensive behavior) consequences without necessarily implying pain sensation" (International Association for the Study of Pain [IASP]: https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698#Nociception). However, imaging of pain can be useful if expression of pain sensation is impaired, or to improve insights in certain pathologic conditions and consequently improve current therapy options for patients suffering from such (chronic) pain.

The main advantage of EEG over other neuroimaging techniques, is its high temporal resolution (28,29). Moreover, it employs a low cost and portable device for which patients do not have to lie down to acquire data and are not restricted by metallic implants in the body or claustrophobia (39). It must however be said that EEG data has been shown to provide low accuracy concerning structural identification in general, and of deep brain structures in specific (26,39).

For chronic neuropathic pain and chronic prostatitis, respectively only two and one article were included, which is insufficient to infer well-grounded decisions. The same can be said for the relationship between the pain intensity and the ERP, which was only discussed in two of the included articles. Therefore, the secondary research question of this systematic review could not be sufficiently answered.

No recent papers were included (later than 2016) and 6 of the included studies were carried out by the same research group, which could be considered as a limitation of this systematic review. Another limitation could be the decision not to exclude articles based on the number of electrodes that were used during the EEG recordings, resulting in the inclusion of some articles that only used one electrode, neither did we exclude or distinct on basis of the applied method to compute the ERPs.

Recommendations for future research

Firstly, as both age (104–108) and sex (109–112) could influence the pain perception and the cerebral response, future research should match their patient and control groups for both factors. Secondly, no articles describing contact-heat-evoked potentials were retained, therefore future high quality research using contact-heat stimuli should be performed to check whether similar conclusions can be found when such stimuli are applied. Thirdly, more research is needed that relates the EEG outcomes to the subjective experience of the nociceptive stimulus, be it under the form of the relationship between the saliency of the stimulus and the ERP, or between the pain intensity and the gamma band oscillations. Fourthly, due to the possible influence of anxiety, stress and attention, future research should evaluate these aspects and their influence on the results. Lastly, additional research is needed in chronic neuropathic pain patients and patients suffering from chronic prostatitis in specific, and in the chronic pain conditions that were not described in this review in general. Moreover, a thorough neurological examination should be performed in patient populations where fibre dysfunction or neuropathic mechanisms can be suspected to ensure a correct interpretation of the obtained findings.

Conclusion

Chronic neuropathic pain patients showed increased latencies of the N2 and P2 components, along with a decreased amplitude of the N2-P2 complex, which was also obtained in FM patients with small fibre dysfunction. The latter also showed a decreased amplitude of the N2-P3 and N1-P1 complex. In chronic tension-type headache, prostatitis, low back pain or migraine patients, the latency of the N2, P2, or P3 component did not seem to differ between patients and controls whereas no consensus could be reached on the latency of the other included components. Similarly, in these chronic pain populations a consensus was only reached for the amplitudes of the P3, N500, N9 and N260 components, that did not differ from those of healthy controls.

The latency of the N9 component was increased in CLBP patients and the latency of the N50 component was decreased in patients suffering from chronic prostatitis. The dipole localization of the P2 component did however seem to differ between chronic pain patients and healthy controls and there were some indications that the N2-P3 peak-to-peak amplitude correlates with the subjective experience of the nociceptive stimulus. Based on these findings, differences in ERPs with healthy controls can mostly be found in chronic pain populations that suffer from neuropathic pain or where fibre dysfunction is present. In chronic pain populations with other etiological mechanisms, limited differences were found or agreed upon across studies. However, limited evidence was available and future research is needed to consolidate the results.

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1 Appendix

2 Table of evidence

Author **Publication year**	**Pathology** **Diagnostic criteria** **Healthy controls**	**Number of participants (N); Sex (% women); Age: mean(SD) or (SEM)*; Duration of disability; Weight; Height; BMI: mean (SD)**	**Response type**	**Stimulation device and location** **Stimuli characteristics**	**Brain activity registration: localization of electrodes** **Measured components**	**Results**
L. Arendt-Nielsen, et al. 1991	Carpal tunnel syndrome (CTS) Electrophysiologically verified Age- and sex matched healthy controls	**N:** CTS: 13; HC: 13 **Sex:** CTS: 69.23%; HC: 69.23% **Age:** CTS: male: 35(4), female: 40(13); HC: male: 35(8), female: 40(13)	LEP	Device Argon laser: 200 ms, beam diameter: 3 mm (0.07 cm²) Location Both hands: volar part of middle phalanges on finger 3 and 5 Stimuli *Type*: Laser *Characteristics*: **Intensity:** 1.2 times the pain threshold at finger 5	**Electrode locations** Platinum needle electrode inserted over the vertex of the scalp with reference to the linked earlobes **Components** 1) Mean power 2) Difference in power between finger 5 and 3 3) Correlations	**1)** CTS: Stimulation of most affected finger: reduced ($p<0.05$); stimulation of finger 5: no significant difference **2)** Significantly different ($p<0.01$) **3)** No correlation between mean power and pain threshold

					Number: 2 subsequent recordings of 25		
L. Buchgreitz et al. 2008	Chronic tension-type headache (CTTH) Diagnostic headache diary (4weeks) Age- and sex matched healthy controls	**N:** CTTH: 19; HC: 16 **Sex**: CTTH: 47,36%; HC: 50% **Age**: CTTH: men: 35(11), women: 38(13); HC: men: 31(3), women: 38(12) **Ilness duration (years):** CTTH: 10.4 (range 1–25)	SEP	Device		**Electrode locations**	**1)** No significant difference (single pulse: P= 0.4; train pulse: P= 0.3) **2)** N1, P2, P3 latency: no significant difference **3)** Significant difference in the y coordinate of the P2 dipole
				Needle electrodes (20 mm x 0.35 mm, active recording area: 2.0mm², 10 mm distance)		128 electrodes , position: 10-5 montage system	
				Location		**ERP computation**	
				M. Trapezius (5 mm depth)		Grand average	
				Stimuli		**Components**	
				Type	*Characteristics*	1) Pain threshold 2) N1 P2, P3 (Latency) 3) Source localization	
				Electrical	**Intensity**: electrical pain threshold **Number**: 60 single stimuli (1ms) + 60 train stimuli (5 stimuli at 2Hz) **Inter-stimulus interval:** 4-6sec		
G. Caty et al. 2013	Chronic complex regional pain syndrome (CRPS) Budapest criteria	**N:** upper limb: CRPS: 7; HC: 7 lower limb: CRPS: 18; HC: 18 **Sex**: upper limb: CRPS: 100%; HC: 100% lower	LEP	Device		**Electrode locations**	**1)** Patients: substantially prolonged (> 300 milliseconds increase) **2) Latency**: N2: no significant differences; P2: CRPS: significant increase T = 2.669, P= 0.018); N1: no significant differences
				CO2 laser (beam diameter: 10 mm, duration: 50 milliseconds).		19 electrodes, positions: International 10–20 system, reference: linked earlobes.	
				Location		**ERP computation**	
				Patients: asymptomatic limb, healthy controls: left hand		*Method*: Grand average *Electrodes*: N1: Temporal electrode contralateral (Tc) to the stimulated hand, referenced to Fz.	

	Age- and sex matched healthy controls	<u>limb</u>: CRPS: 61,11%; HC: 66,67% **Age**: CRPS: 40,2(11,1) <u>HC: upper limb:</u> 39,6(11,3) <u>HC: lower limb</u>: 42,5(9,1) **Illness duration (years):** CRPS: 5,1(4,7)				N2: Cz, referenced to linked earlobes A1A2	**Amplitude**: N2-P2: Patients: significant decrease; N1: no significant differences.
				Stimuli		**Components**	
				Type	*Characteristics*	1) Detection rate 2) N1,N2,P2 (Amplitude, latency and N2-P2 amplitude)	
				Laser	**Intensity**: clear pricking and burning sensation **Number**: 30 (blocks of 10 separated by 1 minute) **Inter-stimulus interval:** 8 - 15 sec		
M. de Tommaso et al. 2003_*A*	Chronic migraine (CM) Criteria according to Olesen (2001) Age- and sex matched healthy controls	**N:** CM: 25; HC: 15 **Sex**: CM: 84%; HC: 66,67% **Age**: CM: range 20-41; HC: range: 22-46 **Ilness duration (years):** CM: 27(9,9)	LEP	Device		**Electrode locations**	**1)** No significant difference **2)** Latency and amplitude: no significant difference Peak-to-peak amplitude: CM: reduced increment (hand: F=12,11,P<0,0001; supra-orbital: F=10,57,P<0,0001). **3)** HC: <u>significant correlation:</u> perceived intensity & peak-to-peak amplitude; CM: no significant correlation.
				CO2-laser (wavelength: 10.6mm, beam diameter: 2.5 mm, duration: 45ms)		Vertex (Cz), reference: linked earlobes (A1 A2)	
				Location		**ERP computation**	
				Dorsum right hand + right supra-orbital zone		*Method*: Not available *Electrodes*: N2, P2: Cz	
				Stimuli		**Components**	
				Type	*Characteristics*	1) Pain threshold 2) N2a, P2 (amplitude, N2a–P2 peak-to-peak amplitude) 3) correlations	
				Laser	**Intensity:** Perceptive and pain threshold **Number**: 20 (single pulse) at each intensity		

					Inter-stimulus interval: 20-40sec.		CM: <u>significant negative correlation:</u> percentage increment of N2a–P2 amplitude & duration of illness (Hand: -0.6491,P<0,05; face:-0.6832,P<0,05.)
M. de Tommaso et al. 2003_*B*	Chronic tension-type headache International Headache Society diagnosis Age- and sex matched healthy controls	**N:** Patients: 12; HC: 11 **Sex**: Patients: 66,67%; HC: 72,72% **Age**: Patients: 36,3(10,6); HC: 36,55(11) **Illness duration (years):** Patients: 7(4,8)	LEP	Device		**Electrode locations**	**1)** No significant difference **2) Latency:** N2a and P2: no significant difference **Amplitude**: Peak-to-peak N2a–P2: TTH: significantly increased (peri-cranial; hand: not significant)
				CO2 laser (wavelength: 10.6 mm, beam size: 2.5 mm, 5 mm², duration: 45 ms)		Vertex (Cz), reference: linked earlobes (A1 A2)	
				Location		**ERP computation**	
				Dorsum of right hand + skin above right frontal muscle, M. Masseter, M. Temporalis, M. Pterygoideus , M. Sternocleidomastoideus and M. Trapezius.		*Method*: Grand average *Electrodes*: T4: contralateral N1, T3: ipsilateral N1	
				Stimuli		**Components**	
				Type	*Characteristics*	1) Pain threshold 2) N2, P2, N1 (latency and amplitude)	
				Laser	**Intensity**: Perceptive and pain threshold **Number**: 25 at each intensity **Inter-stimulus interval:** 20-40sec.		
M. de Tommaso, et al. 2005_*A*	Tension-type headache (CTTH)	**N:** CTTH: 18; HC: 12	LEP	Device		**Electrode locations**	**1)** N1: No significant difference
				CO2 laser		23 scalp electrodes: 10–20 System	

	International Headache Society criteria Age- and sex matched healthy controls			Location Dorsum of the hand and the cutaneous zones corresponding to pericranial muscles Stimuli *Type*: Laser; *Characteristics*: Not described	**ERP computation** *Method*: Not available *Electrodes*: N1: temporal electrodes; N2a, P2: Cz **Components:** 1) Amplitude: N1, N2A, P2	N2A; P2: significantly different: increased in CTTH
M. de Tommaso et al. 2005_*B*	Chronic migraine (CM) Criteria of Headache Classification Committee Age- and sex matched healthy controls	**N:** Patients: 16; HC: 12 **Sex**: Patients: 75%; HC: 75% **Age**: Patients: 34,37(9,29); HC: 34(6,9)	LEP	Device CO2 laser (wavelength: 10.6 mm, beam diameter: 2.5 mm, duration: 20 ms) Location Right supraorbital zone Stimuli *Type*: Laser; *Characteristics*: **Intensity**: 7.5W **Number**: 2 series of 20 **Inter-stimulus interval:** 10 sec	**Electrode locations** 23 electrodes, position: 10–20 international system, reference: nasion, ground: Fpz **ERP computation** Method: Grand average Electrodes: N1: T5,T6 ; N2a, P2: Cz ; N2b: Fz **Components** 1) Stimulus sensation (VAS) 2) T5, T6: N1 component; Cz: P2 and N2a; Fz: N2b component (Latency and amplitude) 3) Source localization	**1)** Subjective sensation: no significant difference (F=0.75;P=0.47) **2)** Latency and amplitude: no significant difference **3)** Chronic migraine: More anterior location of P2 dipole
M. de Tommaso et al. 2006	Chronic tension-type	**N**: CTTH: 18; HC: 12	LEP	Device CO2 laser (wavelength 10.6 µm, beam diameter: 2.5 mm, duration: 20 ms)	**Electrode locations** 19 electrodes, position: 10–20 international system, reference: nasion, ground: Fpz	**1)** No significant difference (hand: F=1.47; p=0.23; frontal: F=3.83; p=0.06; temporalis:

	headache (CTTH) International Headache Society criteria Age- and sex matched healthy controls	**Sex**: CTTH: 55,55%; HC: 50% **Age**: CTTH: 39,1(11,5); HC: 33,6(12,8) **Illness duration (years):** 4.8(5)		Location Dorsum right hand + skin above right frontalis, M. Masseter, M. Temporalis, M. Sternocleidomastoid, and M. Trapezius + neck muscle insertions. Stimuli *Type*: Laser *Characteristics*: **Intensity:** 7.5-W **Number:** 2 series of 20 **Inter-stimulus interval:** 10 sec	**ERP computation** *Method*: Grand average *Electrodes*: N1: T3; N2,P2: Cz **Components** 1) Pain rating 2) N1,N2 and P2 (Latency and amplitude)	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) **2) Latency**: no significant difference **Amplitude**: N1: no significant difference; N2: significantly different (except for temporal site); P2: significantly different
M. de Tommaso, et al. 2014	Fibromyalgia (FM) Wolfe et al. criteria Age- and sex matched healthy controls	**N:** FM: 199; HC: 109 **Sex**: FM: 85,93%; HC: 81,65% **Age**: FM: 40,55 (10,5); HC: 40,32 (9,99)	LEP	Device CO2 laser (wavelength 10.6 lumen, diameter 2.5 mm, duration stimulus pulse 30 ms) Location Dorsum of right hand Additional: patients: tender points at right knee + between clavicle and first rib Stimuli *Type*: Laser *Characteristics*: **Intensity**: 3W above pain threshold	**Electrode locations** 6 scalp electrodes: Fz, Cz, and Pz: positions: 10–20 International System, reference: nasion, ground: Fpz T3 and T4 derivation, reference: Fz **ERP computation** *Method*: Grand average *Electrodes*: N1: T3; N2,P2: Cz **Components** 1) Pain threshold 2) Subjective pain sensation	**1)** No significant difference **2)** No significant difference **3) Latency:** N1, N2, P2: no significant difference **Amplitude:** N1: no significant difference; N2–P2 complex: FM: significantly reduced (hand and knee) vs non-significant for chest **4)** N2-P2 habituation index: FM: significantly increased

					Number: 3 series of 10 (inter-series interval: 1min) **Inter-stimulus interval:** 10s	3) T3-Fz: N1 component; Vertex (Cz): N2 and P2 components (Amplitude and latency) 4) Habituation	
H. Flor et al. 2003	Chronic back pain (CLBP): IASP classification Chronic tension headache (THA): criteria of International Headache Society Age- and sex matched healthy controls	**N:** CLBP: 16; THA:16; HC:16 **Sex**: CLBP: 62,5%; THA: 50%; HC: 62,5% **Age**: CLBP: 42,2(12,9); THA: 42,5(12,5); HC: 38,6(10,2) **Pain duration (months):** CLBP: 105,3(79); THA: 149,3(113)	SEP	Device Electrical stimulator (rectangular impulses, duration: 0.01 ms). Location Gold electrode (diameter: 0.95 mm, length: 1 mm): epidermal opening in third digit: non-dominant hand. Reference and ground electrodes: joint of finger and hand Stimuli *Type*: Electrical *Characteristics*: **Intensity**: at perception, pain, and 10% below pain tolerance threshold **Number**: 10 (frequency: 1 Hz)		**Electrode locations** Fz, Cz, Pz **ERP computation** *Method*: Grand average *Electrodes*: Not available **Components** 1) Pain threshold & pain tolerance 2) N150, P260, P3, N500 (amplitude)	**1)** CLBP: significantly smaller pain thresholds and pain tolerance than controls and THA (P<0,05). THA: significantly higher pain tolerance than HC (P<0,05) **2)** N150, P260, P3: no significant differences. N500: larger amplitudes in THA (THA vs HC: P<0,01).
M. Franz, et al. 2014	Non-specific chronic low back	**N:** CLBP: 16; HC: 16	LEP	Device A thulium : yttrium-aluminium-garnet laser device (pulse duration: 1.0 ms;		**Electrode locations** 63 Ag–AgCl electrodes attached to the scalp: extended	**1)** No significant difference [F=0.02;p>0.89; η2=0.001]

	pain (CLBP) Classified as 'non-specific low back pain' Age- and sex matched healthy controls	**Sex**: CLBP: 50%; HC: 50% **Age**: CLBP: 43; HC: 41,9 **Pain duration** (months): CLBP: 114		wavelength: 1.96 m; beam diameter: 6 mm)		international 10–20, reference: FCz	**2)** No significant difference [F=0.01;p>0.91; η2<0.001] **3) Latency**: N2: no significant difference [F<0.01;p>0.98; η2<0.001]; P2: no significant difference [F=2.73;p>0.10; η2=0.084] **Amplitude**: N2: no significant difference [F=0.57;p>0.45; η2=0.019]; P2: no significant difference [F=0.01;p>0.94; η2<0.001]
				Location		**ERP computation**	
				Skin of the painful body site (paraspinal lumbar) and a pain-free control area (ipsilateral abdomen).		*Method*: Wavelet *Electrodes*: N1, N2a, P2: Cz	
				Stimuli		**Components**	
				Type	*Characteristics*	1) Pain threshold 2) Pain intensity in response to laser stimuli 3) N2 (180 ms) and P2 (290 ms) components (Latency and amplitude)	
				Laser	**Intensity**: pain threshold **Number**: 2 blocks of 30 **Inter-stimulus interval**: 20-25sec		
S.J. Gibson, et al. 1994	Fibromyalgia (FM) Criteria for primary fibromyalgia by Wolfe et al. 1990 Age- and sex matched	**N**: FM: 11; HC: 11 **Sex**: FM: 100%; HC: 100% **Age**: FM: 28,3(2,6)*; HC: 26,6(2,1)* **Pain duration** (months): FM: 74,4(15,4)*	NER	Device		**Electrode locations**	**1) Latency**: no significant difference **Amplitude**: FM: increased (F = 18.04, P < 0.0001) **2)** Increased peak-to-peak amplitude: FM: greater magnitude of increase **3)** FM: significant intensity reduction (F=5.617,P<0.022).
				CO2 laser (wavelength: 10.6 pm, diameter: 5 mm, duration: 33 ms)		Vertex (Cz), reference: linked ears (Al A2), ground: forehead: Fpz	
				Location		**ERP computation**	
				Dorsal surface of right or left hand		*Method*: Grand average *Electrodes*: Cz	
				Stimuli		**Components**	
				Type	*Characteristics*	1) Peak latency + peak-to-peak amplitude at pain threshold level 2) Peak-to-peak amplitude at 1.5 times threshold 3) Pain threshold	
				Laser	**Intensity**: pain or 1.5 x pain threshold **Number**: 36 **Inter-stimulus interval:** 20-40sec		

	healthy controls					4) Subjective estimate of intensity 5) Correlations	**4)** No significant difference (F=0.91, P=0.347) **5)** VAS pain rating: highly correlated with amplitude of NER, and subjective rating of stimulus magnitude.
B. Knost et al. 1999	Chronic low back pain (CLBP) Age- and sex matched healthy controls	**N:** CLBP: 13; HC: 14 **Sex:** CLBP: 61.54%; HC: 64.29% **Age:** CLBP: 44.08 (7.73); HC: 37.44 (11.8) **Illness duration (years):** 33.31 (7.05)	SEP	Device		**Electrode locations**	**1)** N150: CLBP: higher amplitudes (in a low muscle tension condition: t=-2.42, p<0.05) P260: no significant difference
				Tönnies electric stimulus generator		9 scalp locations: Fz, F3, F4, Cz, C4, C3, Pz, P3, P4: 10-20 system and referenced to linked earlobes	
				Location		**ERP computation**	
				2 gold electrodes: upper layer of skin at left M. Flexor Communis Digitorum and left M. Erector Spinae		*Method*: Grand average *Electrodes*: Averaged across 9 scalp locations	
				Stimuli		**Components**	
				Type	*Characteristics*	1) N150 and P260 (amplitude)	
				Electrical	**Intensity**: 70% pain tolerance **Number**: 35 **Inter-stimulus interval:** 4-8sec		
			SEP	Device and location		**Electrode locations**	

<table>
<tr><td rowspan="5">S. Korkmaz et al. 2015</td><td rowspan="5">Chronic prostatitis (CP)

Diagnosed by the urology out-patient clinic

Healthy controls</td><td rowspan="5">N: CP: 17; HC:17
Sex: CP: 0%; HC: 0%
Age: CP: 38(8,5); HC: 34,6(8)
Weight: CP: 77,6(4,2); HC: 77,6(4,2)
Height: CP: 170,5(2,7); HC: 170,8(3,2)</td><td rowspan="5"></td><td colspan="2">Penile ring electrodes (cathode 1 cm proximal to anode)</td><td>Recording electrodes: Cz’ (2 cm posterior to Cz), reference: Fz’ (midway positions between Fz and Fpz), position: 10–20 International System</td><td rowspan="5">1) No significant differences (P>0.05)
2) Patients: significantly shorter (P<0.0001).</td></tr>
<tr><td colspan="2">Stimuli</td><td>ERP computation</td></tr>
<tr><td>Type</td><td>Characteristics</td><td>Method: Grand average
Electrodes: N50: Cz</td></tr>
<tr><td>Electrical</td><td>Intensity: 2 x sensory threshold
Number: 3 series of 300
Duration: 0.1ms
Frequency: 4.1Hz</td><td>Components
1) Sensory threshold
2) N50 (Latency)</td></tr>
<tr><td colspan="2"></td><td></td></tr>
<tr><td rowspan="8">J. Lorenz et al. 1998</td><td rowspan="8">Fibromyalgia (FM)

Diagnostic criteria of Fibromyalgia syndrome

Age-matched, pain-free controls</td><td rowspan="8">N: FM: 10; HC: 10
Sex: FM: 100%; HC: 100%
Age: FM: 45,9(12,5)</td><td rowspan="8">LEP</td><td colspan="2">Device</td><td>Electrode locations</td><td rowspan="8">1) FM: lower pain threshold
2) FM: significantly higher N1 and P2 amplitudes</td></tr>
<tr><td colspan="2">CO2-laser stimulator (wavelength 10.6 mm, beam diameter 5 mm, duration 20 ms)</td><td>5 scalp positions: Fz, Cz, Pz, C3, C4 reference: linked ear-lobes</td></tr>
<tr><td colspan="2">Location</td><td>ERP computation</td></tr>
<tr><td colspan="2">Dorsum of the left hand</td><td>Method: Grand average
Electrodes: N1: C3-C4; N2,P2: Cz</td></tr>
<tr><td colspan="2">Stimuli</td><td>Components</td></tr>
<tr><td>Type</td><td>Characteristics</td><td rowspan="2">1) Pain threshold
2) Middle- (N1) and long-latency (N2, P2) components (Amplitude)</td></tr>
<tr><td>Laser</td><td>Intensity: Detection and pain threshold
Number: 60</td></tr>
<tr><td colspan="2"></td><td></td></tr>
</table>

					Inter-stimulus interval: 10-15sec		
C. Puta et al. 2016	Chronic low back pain (CLBP) Classified as ‘‘non-specific low back pain’’ Age- and sex matched healthy controls	**N:** CLBP: 11; HC: 10 **Sex:** CLBP: 63,64%; HC: 60% **Age:** CLBP: 39,2(15,2); HC: 37,2(15,8) **Pain duration:** CLBP: 168(175) **Weight**: CLBP: 67,7(12,5); HC: 72,4 (11,2) **Height**: CLBP: 171(8); HC: 172(8)	SEP	Device		**Electrode locations**	**1) Latency**: CLBP: significantly longer (T=2.411; P=0.028). **Amplitude**: no significant differences (T=0.19,P=0.855)
				“Technomed Europe”, bipolar pad electrode, inter-electrode distance: 2cm		Erb’s point (2–3 cm above clavicle) + active electrode: ipsilateral to stimulation (EPi) + reference: contralateral Erb’s point(EPc) Contralateral scalp electrode (centroparietal,CP3) + reference: frontal scalp electrode (Fz).	
				Location		**ERP computation**	
				Median nerve of right arm		*Method*: Grand average *Electrodes*: N9: CP3	
				Stimuli		**Components**	
				Type	*Characteristics*	1) Erb’s point: N9 (Latency & amplitude)	
				Electrical	**Intensity**: Small reproducible muscle switch: sum of intensities for motor and sensory threshold **Number**: 300 trains of biphasic constant current square wave pulses **Duration**: 0.2 ms per pulse		

					Frequency: 2.5Hz		
J. Sohn et al. 2016	Chronic migraine (CM) International classification of headache disorders. Age- and sex matched healthy controls	**N**: CM: 30; HC: 40 **Sex**: CM: 100%; HC: 100% **Age**: CM: 43,07 (11,09); HC: 43,73 (11,75) **Illness duration (years):** CM: 14,13 (10,00)	SEP	Device		**Electrode locations**	**1)** No significant differences **2) Latency**: CM: decreased (left N1, left and right P1) ($p < 0.05$) **Amplitude**: CM: larger right amplitude (PPA) ($p < 0.05$)
				2 planar concentric surface stimulating electrodes		Cz, reference: earlobes (A1–A2), position: international 10–20 system	
				Location		**ERP computation**	
				Both sides lower forehead : 10 mm above supraorbital foramen		*Method*: Grand average *Electrodes*: N1, P1: Cz	
				Stimuli		**Components**	
				Type	*Characteristics*	1) Pain threshold 2) N1 and P1 (Latency and peak-to-peak amplitudes)	
				Electrical	**Intensity**: 1.5 × pain perception threshold **Number**: 11 trains of 3 pulses (Inter-pulse interval: 5 ms) **Inter-stimulus interval:** 18-22sec **Duration**: 0.5 ms per pulse		
N. Üçeyler et al. 2013	Fibromyalgia (FM)	**N:** FM: 25; HC: 25	Pain-related	Device		**Electrode locations**	**1)** Latency: P1 + N1 (Face and hand): no significant difference; N1 feet: FM: prolonged
				Concentric planar electrodes		Subcutaneous needle above Cz, referred to linked earlobes according to 10-20 system	

	1990 American college of rheumatology criteria	**Sex:** FM: 92%; HC: 88% **Age (median):** FM: 59; HC: 56 **Illness duration (median in years):** 21	evoke potentials	Location		**ERP computation**	N1-P1 Peak-to-peak amplitude: reduced in FM
				Bilateral at face (above eyebrow), hands (medial phalanx, second and third digit), and feet (dorsum)		*Method*: Grand average *Electrodes*: N1, P1: Cz	
				Stimuli		**Components**	
				Type	*Characteristics*	1) N1, P1: latency and peak-to-peak amplitude	
				Electrical	**Intensity**: 2 x pain threshold **Number**: 20 triple pulses **Inter-stimulus interval**: 15-17s **Duration**: 0.5ms per pulse		

Abbreviations: BMI, body mass index; CLBP, chronic low back pain; cm, centimetre; CM, chronic migraine; CRPS, complex regional pain syndrome; CTS, carpas tunnel syndrome; CTTH, chronic tension-type headache; FM, fibromyalgia; HC, healthy controls; LEP, laser-evoked potentials; mm, millimetre; ms, milliseconds; N, negative; SEP, somatosensory evoked potentials; mm, milimeter; N, number; NER, nociceptive-evoked response; M., muscle; P, positive; SD, standar deviation; SEM, standard error of the mean; W, Watt

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Supplementary material

Supplementary material: Search strategies

Database	Search strategy
Pubmed	(("Chronic Pain"[Mesh] OR chronic pain OR persistent pain OR persisting pain OR long lasting pain) AND ("Pain Measurement"[Mesh] OR pain measurement OR pain assessment OR electrical stimulation OR nociceptive reflex OR nociceptive flexor reflex OR nociceptive flexion reflex OR cold water pressor OR cold pressor test OR pain detection OR pressure pain threshold OR pain pressure threshold OR pressure algometer OR algometer OR algometry OR quantitative sensory testing OR QST OR conditioned pain modulation OR diffuse noxious inhibitory control OR counterirritation OR CPM OR ischemic pain OR laser stimulation OR thermal stimulation OR experimental muscle injury pain OR experimental muscle pain OR pain sensitivity OR "Pain Threshold"[Mesh] OR pain threshold OR "Sensory Thresholds"[Mesh] OR Sensory Threshold OR pain response OR pain tolerance OR temporal summation OR wind-up OR wind up OR spatial summation OR pain assessment OR experimental pain OR allodynia OR hyperalgesia) AND ("Electroencephalography"[Mesh] OR "Electroencephalography Phase Synchronization"[Mesh] OR Electroencephalography OR EEG OR Electroencephalography Phase Synchronization OR Electroencephalogram OR laser-evoked potentials OR "Laser-Evoked Potentials"[Mesh] OR Somatosensory evoked potential OR "Evoked Potentials, Somatosensory"[Mesh] OR contact heat evoked potential))
Web of science	((TS= chronic pain OR TS= persistent pain OR TS= persisting pain OR TS= long lasting pain) AND (TS= Pain Measurement OR TS= pain measurement OR TS= pain assessment OR TS= electrical stimulation OR TS= nociceptive reflex OR TS= nociceptive flexor reflex OR TS= nociceptive flexion reflex OR TS= cold water pressor OR TS= cold pressor test OR TS= pain detection OR TS= pressure pain threshold OR TS= pain pressure threshold OR TS= pressure algometer OR TS= algometer OR TS= algometry OR TS=

	quantitative sensory testing OR TS= QST OR TS= conditioned pain modulation OR TS= diffuse noxious inhibitory control OR TS= counterirritation OR TS= CPM OR TS= ischemic pain OR TS= laser stimulation OR TS= thermal stimulation OR TS= experimental muscle injury pain OR TS= experimental muscle pain OR TS= pain sensitivity OR TS= Pain Threshold OR TS= pain threshold OR TS= Sensory Thresholds OR TS= Sensory Threshold OR TS= pain response OR TS= pain tolerance OR TS= temporal summation OR TS= wind-up OR TS= wind up OR TS= spatial summation OR TS= pain assessment OR TS= experimental pain OR TS= allodynia OR TS= hyperalgesia) AND (TS= Electroencephalography phase synchronization OR TS= Electroencephalography OR TS= EEG OR TS= Electroencephalogram OR TS= laser-evoked potentials OR TS= Somatosensory evoked potential OR TS= contact heat evoked potential))
Embase	('chronic pain' OR 'persistent pain' OR 'persisting pain' OR 'long lasting pain') AND ('pain measurement' OR 'electrical stimulation' OR 'nociceptive reflex' OR 'nociceptive flexor reflex' OR 'nociceptive flexion reflex' OR 'cold water pressor' OR 'cold pressor test' OR 'pain detection' OR 'pressure pain threshold' OR 'pain pressure threshold' OR 'pressure algometer' OR algometer OR algometry OR 'quantitative sensory testing' OR qst OR 'conditioned pain modulation' OR 'diffuse noxious inhibitory control' OR counterirritation OR cpm OR 'ischemic pain' OR 'laser stimulation' OR 'thermal stimulation' OR 'experimental muscle injury pain' OR 'experimental muscle pain' OR 'pain sensitivity' OR 'pain threshold' OR 'sensory thresholds' OR 'sensory threshold' OR 'pain response' OR 'pain tolerance' OR 'temporal summation' OR 'wind up' OR 'spatial summation' OR 'pain assessment' OR 'experimental pain' OR allodynia OR hyperalgesia) AND ('electroencephalography phase synchronization' OR electroencephalography OR eeg OR electroencephalogram OR 'laser-evoked potentials' OR 'somatosensory evoked potential' OR 'contact heat evoked potential')

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Table 1: In- and exclusion criteria

	Inclusion	Exclusion
Population	Adults (18-65 years old) Suffering from chronic pain (>3 months)	Children or elderly Healthy controls Suffering from acute pain
Intervention	Experimental nociceptive stimulation	Spontaneous pain Resting-state measurements Absence of nociceptive stimulation
Controls	Healthy adults	Children or elderly People suffering from any pain condition
Outcome	EEG (including LEP and contact-heat evoked potentials)	Magneto-encephalography fMRI Positron emission tomography Single-photon emission computed tomography No brain imaging
Study design	Comparative studies	(Systematic) review/meta-analysis Preliminary data/pilot study/case reports Other study designs
Language	Dutch, English, French	Other languages
Quality	Matching of patient and healthy participant group on age or sex Utilization of same method of ascertainment for cases and controls	Not matching patients and controls for either age or sex Different method of ascertainment for cases and controls

Table 2: Risk of bias assessment

Author Year of publication	Case definition[1]	Case description[2]	Selection controls[3]	Definition controls[4]	Comparability[5]	Exposure ascertainment[6]	Same method[7]	Non-response rate[8]	Level of evidence
Arendt-Nielsen 1991	+	-	-	-	++	+	+	+	B
Buchgreitz 2008	+	-	-	+	++	+	+	-	B
Caty 2013	+	-	-	+	++	+	+	+	B
De Tommaso 2003_A	+	-	-	+	++	+	+	+	B
De Tommaso 2003_B	+	-	-	+	++	+	+	+	B
De Tommaso 2005_A	+	-	-	+	++	+	+	+	B
De Tommaso 2005_B	+	+	-	+	++	+	+	-	B
De Tommaso 2006	+	-	-	+	++	+	+	+	B
De Tommaso 2014	+	+	+	+	++	+	+	+	B
Flor 2004	+	-	-	-	++	-	+	+	B
Franz 2014	+	-	-	-	++	-	+	+	B
Gibson	+	+	-	+	++	+	+	+	B

1994									
Knost 1999	-	+	+	-	++	-	+	+	B
Korkmaz 2015	+	-	-	+	+ (¥)	+	+	-	B
Lorenz 1998	+	-	-	-	++	+	+	+	B
Puta 2016	+	-	-	+	++	-	+	+	B
Sohn 2016	+	-	+	+	++	+	+	+	B
Üçeyler 2013	+	+	+	-	++	+	+	+	B

Newcastle-Ottawa Quality Assessment Scale: + = score fulfilled; - = score not fulfilled

1 = Is the case definition adequate? (independent validation: >1 person/record/time/process to extract information, or reference to primary record source such as x-rays or structured injury data); 2 = Representativeness of cases (All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined team/competition/sport, or a random sample of those cases); 3 = Selection of controls (Controls selected from the same source population as the cases); 4 = Definition of controls (Explicitly stated that controls have no history of this outcome); 5 = Comparability (Controlled for the most important confounders [age and sex ¥]); 6 = Ascertainment of exposure (Structured injury data, e.g. record completed by medical staff, or structured interview where blinded to case/control status); 7 = Same method of ascertainment for cases and controls; 8 = Non-response rate: (Same for both groups)*