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Psychophysical and electrophysiological evidence for enhanced pain facilitation and unaltered pain inhibition in acute low back pain patients

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RUNNING TITLE

Pain facilitation and inhibition in acute low back pain

DISCLOSURES

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Author contributions: PHV and FGA equally contributed to this study. AYN, ACN, LAN and MC designed the experiment. AYN performed the experiments, assisted by ACN. FGA and JABM performed the data analysis and statistics. PHV, FGA and JABM wrote the manuscript, assisted by OKA, LAN and MC. All authors discussed the results, commented on the manuscript and approved its final version. No author has any conflict of interests related to the content of this paper.

Preliminary findings from this study were presented in abstract form at the 15th World Congress on Pain (October 6 – 11, 2014 – Buenos Aires, Argentina)

ABSTRACT

The aim of this case-control study was to examine differences in neural correlates of pain facilitatory and inhibitory mechanisms between acute low back pain patients and healthy individuals. Pressure pain tolerance (PPT), electrical pain detection thresholds (EDT), pain ratings to repetitive suprathreshold electrical stimulation (SES) and conditioned pain modulation (CPM) were assessed in 18 patients with acute low back pain (LBP) and 18 healthy controls (CTRL). Furthermore, event-related potentials (ERPs) in response to repetitive SES were obtained from high-density electroencephalography. Results showed that the LBP group presented lower PPT and higher pain ratings to SES compared to the CTRL group. Both groups displayed effective CPM, with no differences in CPM magnitude between groups. Both groups presented similar reductions in ERP amplitudes during CPM, but ERP responses to repetitive SES were significantly larger in the LBP group. In conclusion, acute low back pain patients presented enhanced pain facilitatory mechanisms, whereas no significant changes in pain inhibitory mechanisms were observed. These results provide new insight into the central mechanisms underlying acute low back pain.

This study was registered in the Clinical Trials Protocol Registration System (NCT00892411, available at https://clinicaltrials.gov/ct2/show/NCT00892411).

PERSPECTIVES

This article present evidence that acute low back pain patients show enhanced pain facilitation and unaltered pain inhibition compared to pain-free volunteers. These results provide new insight into the central mechanisms underlying acute low back pain.

KEY WORDS

acute low back pain (LBP), conditioned pain modulation (CPM), endogenous inhibition, event-related potentials (ERPs).

1. INTRODUCTION

Low back pain has a life prevalence of over 70% [2], with less than one third resolving annually [14] and with over 60% of patient experiencing pain after 12 months [35]. The anatomical causes of acute low back pain are largely unclear. In recent years, attention has concentrated on the potential role of dysfunction of central nociceptive pathways in the pathophysiology of different pain conditions. Afferent signals encoding nociceptive information are dynamically modulated by spinal and supraspinal inhibitory/excitatory mechanisms before being integrated in the brain, resulting in the subjective feeling of pain [25,34,59]. These central mechanisms play pivotal functions: inhibition of nociceptive inputs reduces the risk that pain compromises escape in potentially dangerous circumstances, whereas facilitation is involved in protective and recuperative behaviors to limit further tissue damage and promote healing [50].

Central sensitization and endogenous inhibition are two central modulatory mechanisms that are frequently studied in the context of up/down regulation of nociceptive activity and pain. Central sensitization is defined as an increased excitability and synaptic efficacy of nociceptive neurons in the central nervous system [86]. In humans, it can be experimentally induced by diverse noxious conditioning stimuli and can be assessed by electrophysiological or imaging techniques. On the other hand, conditioned pain modulation (CPM) is a frequently used paradigm to test endogenous inhibitory pain mechanisms triggered when the response to a painful stimulus is inhibited by the concurrent presence of another painful stimulus[88].

In humans, alterations of these mechanisms have been linked to the development of chronic pain [3,48,73,87]. Central sensitization has been reported in a number of chronic pain states, including migraine, fibromyalgia, whiplash injury, endometriosis, low back and neck pain and osteoarthritis, among others [6,8,29,32,57,72,74]. Moreover, deficiencies in CPM have been observed in these and other chronic pain conditions [56,58,61,77]. Only a few studies have investigated concurrent alterations of

these mechanisms in different chronic pain conditions [4,73,75], and little is known in acute low back pain. Research is required to better understand the role of central pain modulation in the pathophysiology of acute low back pain, as this could give insights into the mechanisms underlying acute low back pain, its recurrence, and transition to a chronic pain state.

The aim of the present study was to examine differences in pain facilitatory and inhibitory mechanisms between acute low back pain patients and healthy individuals. For that purpose, psychophysical and electrophysiological responses were obtained from both groups before and during CPM induced by the cold pressor test (CPT). Psychophysical tests included pain threshold to electrical and mechanical stimulation, whereas the electrophysiological assessment consisted in the quantification of event-related potentials (ERPs) in response to repetitive painful electrical stimulation.

2. MATERIALS AND METHODS

This case-control study comparing patients with acute low back pain with pain-free controls was approved by the ethics committee of the Canton Bern, Switzerland (No. 103/08) and registered in the Clinical Trials Protocol Registration System (NCT00892411, available at https://clinicaltrials.gov/ct2/show/NCT00892411), as part of a large prospective cohort study on low back pain. Data collection for the part pertaining to the preset study was performed between January 1, 2009 and October 31, 2011 at the Department of Anesthesiology and Pain Therapy, University Hospital, Inselspital Bern, Switzerland. All participants gave written informed consent.

2.1. Participants

The study involved consecutive acute low back pain patients (LBP group) and healthy pain-free controls (CTRL group). LBP patients received 200 Swiss Francs, whereas volunteers from the CTRL group received 100 Swiss Francs for their participation. Patients were referred from primary care physicians. Inclusion criteria were acute low back pain of less than 6 weeks, age 18 to 80 years, pain of 4 or more on a numerical rating scale (NRS) ranging from 0-10 (whereby 0=no pain and 10=worst pain). Healthy controls were recruited by advertisement and among staff from the Department of Anesthesiology and Pain Medicine, Bern University Hospital. Participants were not informed about the specific study hypothesis. Healthy volunteers were selected to match patients in the acute low back-pain population for gender and age (±3 years). Exclusion criteria for both groups were: inability to understand the tests, lacking knowledge of German language, history of chronic low back pain or other chronic pain conditions, radicular pain (as defined by leg pain associated with an MRI finding of a herniated disk or foraminal stenosis with contact to a nerve root), neurological conditions potentially affecting sensory function (i.e., polyneuropathy, diabetes mellitus, or alcohol abuse), pregnancy (ruled out by pregnancy test), breast-feeding, intake of oral

contraceptives or hormones, intake of strong opioids and antidepressants during the previous 2 weeks, and intake of other analgesics or drugs known to modulate pain up to 48 hours before testing. Additional exclusion criteria for healthy controls were any pain at the time of testing.

2.1.1. Sample size considerations

The original protocol required 40 acute low back pain that were randomly assigned in a 1:1 ratio to either undergo assessment of electroencephalographic (EEG) activity as response to painful stimulation or electrical stimulation with assessment of pain and reflex detection threshold. Thus, 20 acute low back pain patients and 20 healthy pain-free controls were assigned to this study.

2.2. Descriptive variables

Gender, age, height, weight, body-mass index (BMI) and duration of pain in weeks were recorded. Additionally, pain intensity at the time of testing and maximum and minimum pain intensity in the 24 h prior to the experiment were assessed using the same NRS as described above. Volunteers were also asked to complete the following questionnaires: Beck Depression Inventory (BDI) [7], State-Trait-Anxiety-Inventory (STAI) [44] and Catastrophizing Scale of the Coping Strategies Questionnaire (CSQ) [69].

2.3. Psychophysical and electrophysiological tests

2.3.1. Pressure stimulation

Pressure pain tolerance (PPT) was measured with an electronic pressure algometer (Somedic AB, Sweden), using a probe with a surface area of 1 cm^2. Pressure stimulation was performed at the center of the pulp of the 2nd toe of the left foot. The pressure was increased from 0 kPa at a rate of 30 kPa/s to a maximum pressure of 1000 kPa. Pain tolerance was defined as the point at which the subject felt pain as intolerable. Volunteers were instructed to press a button when this point was

reached. The algometer displayed the pressure intensity at which the button was pressed. If the subject did not press the button at a pressure of 1000 kPa, this value was considered as threshold.

2.3.2. Electrical stimulation

Electrical stimulation was performed through surface electrodes (Ag/AgCl, Ambu Neuroline, Ambu A/S, Ballerup, Denmark) placed at the innervation area of the left median nerve, on the wrist, and delivered by a computer-controlled constant current stimulator (NoxiTest IES 230, Aalborg University, Denmark). Each stimulus consisted of a single, 2-ms square-wave pulse. The stimulation intensity was established as a multiple of the subjective pain detection threshold (EPT), the latter defined as the minimum current intensity reported as painful for a single stimulus. In order to find the EPT, the current intensity was gradually increased from 1 mA in steps of 0.5 mA until a painful sensation was elicited. The procedure was repeated three times, and the mean of the three pain thresholds was multiplied by 1.5 to obtain the suprathreshold electrical stimulation (SES) intensity that was used subsequently in the whole experiment. Repetitive SES consisted of trains of 5 stimuli, with an inter-stimulus interval of 200 ms (stimulation frequency: 5 Hz, total train duration: 1 s). Each train was repeated 120 times at a random inter-train interval ranging from 4 to 6 s, resulting in stimulation blocks of approximately 10 min.

2.3.3. Cold pressor test and conditioned pain modulation

For the cold pressor test (CPT), the participants immersed the right hand in a container with ice-saturated water (0.7 ± 0.1 °C, regularly mixed and constantly monitored with a digital thermometer) to the wrist level, for a maximum of 2 min. The container had an inner compartment and an outer compartment separated by a mesh screen. The mesh screen prevented direct contact between the ice (placed in the outer compartment) and the hand of the subject (placed in the inner compartment). Volunteers were instructed to withdraw the hand when they felt the pain as intolerable and the time of hand immersion was recorded. If the hand was not withdrawn at 2 min, this time was recorded

for data analysis as a measure of pain tolerance. The CPT also served as conditioning stimulus for the measurement of conditioned pain modulation (CPM). Following the CPT, volunteers were requested to immerse only the fingers of the right hand in the ice-saturated water, and maintain them immersed for the duration of the electrical stimulation block (approximately 10 min).

2.4. Electroencephalographic recordings

Continuous high-density EEG data were acquired with a 128-channel system (asalab®, ANT Neuro B.V., The Netherlands), using an EEG cap (Waveguard®, ANT Neuro B.V., The Netherlands) with an electrode placement scheme in accordance with the International 10-5 system. All the electrodes were referred to the left mastoid (M1) ipsilateral to the site of stimulation, and the ground electrode was incorporated in the cap between AFz and Fz on the nasion-inion line. The electrodes impedance was kept below 5 kΩ and recordings were made using asa® 4.7.3 software (ANT Neuro B.V., The Netherlands) at a sampling rate of 2048 Hz.

2.5. Experimental procedure

The same investigator, AYN, performed all the experiments, assisted by ACN. During the testing session the volunteers were lying in a bed, in a quiet room. Each subject underwent a training session for all tests in order to familiarize with the stimulation procedures before starting the data collection. Electrical stimulation was performed at the left wrist, whereas ice water stimulation was performed on the right hand, as typically the conditioning has to be performed on a remote area [39]. PPT, EPT to single electrical stimulus and pain ratings to repetitive SES were initially assessed as described in section 2.3, and then EEG data were recorded during repetitive SES for 10 min (BASELINE condition). Afterwards, the cold pressor test was performed: immediately following the initial 2 min (or the longest time that the volunteers were able to keep the whole hand submerged), the PPT was assessed again. EEG data were then recorded again during repetitive SES

for 10 min, while only the fingers of the right hand remained immersed in ice water (CPM condition). The fingers were immersed again in ice water in order to sustain the CPM effect for a longer interval and to allow for the considerable longer duration required for ERP recording. During the CPM condition, PPT was reassessed at 3, 5 and 10 min. A summary of the experimental procedure is shown in Fig. 1.

2.6. Data analysis

2.6.1. Conditioned pain modulation

The magnitude of the CPM effect, namely ΔCPM, was defined as the difference between PPT measured immediately after, 3, 5 and 10 min after the CPT, and the PPT at baseline (i.e. before CPT). Positive values of ΔCPM indicated successful pain inhibition and the volunteer is said to respond to CPM testing [64].

2.6.2. Event-related potentials

EEG data was analyzed offline in MATLAB (Mathworks, Inc., USA). In particular, EEG data was pre-processed using EEGLAB [20]. For each subject and each condition, continuous EEG data were band-pass filtered between 0.5 and 100 Hz, notch-filtered at 50-Hz and re-referenced to the average of all channels. A time window of interest was defined by segmenting the data into epochs of 2000 ms that included 500 ms of pre-stimulus. The obtained epochs (120 in total) were visually inspected to discard noisy channels and those epochs that contained gross artifacts due to e.g. movement and muscle activity. In order to remove artifacts related to the electrical stimulation, eye movements and blinks, the remaining epochs were evaluated using Infomax Independent Component Analysis (ICA) [45]. The ICA algorithm separated the scalp EEG signals into statistically independent components of different brain and artifact sources, and the “clean” EEG signals were obtained by eliminating the contributions of the artifactual components. These components were identified by

inspecting their time course, spectra and scalp topography [38]. Subsequently, the rejected channels were spatially interpolated with a spherical spline. Finally, epochs were averaged across trials and baseline-corrected using the mean amplitude of the pre-stimulus period in order to obtain the ERPs. A step-by-step guide for the pre-processing analysis applied using EEGLAB can be found at https://sccn.ucsd.edu/wiki/EEGLAB_TUTORIAL_OUTLINE. As a result of the pre-processing stage, one averaged waveform was obtained for each subject, channel and condition.

2.6.3. Statistics

Descriptive variables are reported as mean ± standard deviation or as median (interquartile range), depending on whether the underlying data satisfied the normality assumption or not (Shapiro-Wilk test). Differences in descriptive variables between groups were analyzed using an unpaired *t* test or a Mann-Whitney rank sum test, depending on whether the underlying data satisfied the normality (Shapiro-Wilk test) and equal variance (Levene's test) assumptions or not, respectively. Differences in ΔCPM between groups were assessed by an analysis of covariance (ANCOVA) using time as a covariate.

ERP statistics were performed using Letswave (http://nocions.github.io/letswave6/). A point-by point, mixed-model analysis of variance (ANOVA) was performed to evaluate the effects of the factors condition (BASELINE vs. CPM) and group (CTRL vs. LBP) on the amplitude of the ERPs in the time window of interest (2000 ms in total, from500 ms before the stimulus to 1500 ms after the stimulus). Since point-by-point analysis involves several statistical inferences made simultaneously, a clustersize-based permutation testing approach was used to control the multiple comparisons problem [49]. This methodology defines clusters of significant differences in time (by grouping the time points for which the p-value in the individual F-test is smaller than 0.05), while controlling the false alarm rate. The size of each cluster was defined as the sum of the F-values within the cluster. Then permutations are performed (250 in total), by shuffling the data between

conditions. Each permutation will result in a new set of clusters that are used to build the permutation distribution. Finally, the significant clusters from the original data are identified as those whose size is over a threshold was defined as the 95^{th} percentile of the z-distribution from the largest cluster obtained during the permutation testing.

3. RESULTS

3.1. Descriptive variables

During EEG assessment, recorded files from two patients and two healthy controls were corrupted and data were irrecoverable, so the final analysis was performed on 18 subjects per group. An overview of the volunteers' characteristics and statistical tests results can be seen in Table 1. Eight patients were regularly using diclofenac (median 150mg/day, IQR 75 mg/day), six were regularly using ibuprofen (median 1600 mg/day, IQR 0 mg/day), and one was using mefenacid (1500 mg/day). Only one patient used a weak opioid, tramadol slow release 100 mg bid, combined to ibuprofen 1600 mg/day. No significant differences were found in age and BMI between groups. Regarding the psychological assessment, the LBP group presented higher BDI and STAI-trait scores compared to healthy volunteers, but no significant differences in STAI-state or catastrophizing scores.

3.2. Psychophysical and electrophysiological tests

Statistical test results for the psychophysical and electrophysiological tests are presented in Table 2. In summary, the LBP group presented significantly lower baseline PPT compared to the CTRL group. None of the volunteers from any of the groups reported a PPT higher than 1000 kPa. Additionally, even though there were no significant differences in EPT, the LBP group reported significantly higher subjective pain ratings to repetitive SES.

3.3. Cold pressor test and conditioned pain modulation

For the CPT, no significant difference was detected in immersion times between groups, with 5 volunteers from the CTRL group (27.8 %) and 4 volunteers from the LBP group (22.2 %) reaching the maximum immersion time for the hand of 2 min. . CPT successfully induced CPM, as assessed

by a decrease in PPT after CPT compared to baseline (Fig. 2). The magnitude of ΔCPM was significantly related to the elapsed time ($F_{1,141}$ = 17.90, p < 0.001). After controlling for the effect of the elapsed time, there was no significant difference in the magnitude of ΔCPM between groups ($F_{1,141}$ = 0.578, p = 0.448).

3.4. Event-related potentials

In general, subjects from both groups presented clear ERP components that are typically elicited when applying electrical stimulation to the skin at suprathreshold levels [80]. Early waves commonly described as N20 and P30, presented evident lateralized scalp topography with negative and positive excursions, respectively, contralateral to the stimulation site (Fig. 3, 20 ms and 30 ms). These waves were followed by two negative deflections in central-parietal electrodes frequently described as N70 and N120 (Fig. 3, 70 ms and 120 ms). The following wave was a positive peak in central electrodes, symmetrically distributed, with a latency of ~225 ms (P200). The P200 was coincident with the arrival of the second pulse of the stimulus train. After the fifth stimulus, the late components of the ERP waveforms had a similar topography as the response to the first stimulus, although the ERP amplitude was evidently decreased (Fig. 3, 870 ms, 920 ms and 1110 ms).

Grand-mean ERP waveforms are shown in Fig. 4, together with results of the point-by-point ANOVA performed in each time point and channel. There was a significant main effect of condition in the post-stimulus window, between ~45 – 400 ms and ~800 – 1200 ms. A significant difference was also found prior to stimulus onset, between -140 – -20 ms. Scalp responses to electrical stimulation were significantly smaller during the CPM condition for both groups. Furthermore, there was a significant main effect of group in post-stimulus window (after the fifth pulse in the stimulus train), between ~910 – 980 ms and ~1075 – 1135 ms, where LBP patients showed larger ERP responses after the fifth stimulus compared to the CTRL group in both

conditions. The significant differences of both factors were mainly located in the right central region, contralateral to the site of electrical stimulation. No interaction effects were observed.

4. DISCUSSION

In this study, differences in pain modulatory mechanisms between acute low back pain patients and healthy individuals were studied using psychophysical and electrophysiological tests. Patients presented lower PPT and higher pain intensity ratings to repetitive SES compared to the control group, although no differences were detected in EPT to single electrical stimulus. Furthermore, both groups displayed effective CPM, reflected in positive differences in PPT immediately after and up to 10 min after CPT compared to baseline. No differences in immersion time or in the magnitude of the CPM effect assessed by PPT were found between groups at any time point. Additionally, electroencephalographic evidence showed that both groups presented similar reductions in ERP amplitudes in response to electrical stimulation during CPM, although responses to repetitive SES were significantly larger in the acute low back pain patient group.

4.1. Psychophysical assessment

Psychophysical assessment indicated that acute low back pain patients presented lower PPT and higher pain ratings to repetitive SES compared to healthy individuals. These results can be interpreted as a state of pain hypersensitivity in acute pain patients [8,51] . Pain hypersensitivity is commonly observed in several chronic pain conditions, such as fibromyalgia, whiplash and osteoarthritis, among others [6,8,18,29,32,57,72,74]. With regards to the mechanisms behind these changes, evidence from animal experiments suggests that one of the contributors of pain hypersensitivity is an abnormal, widespread and long lasting increase in spinal excitability, either due to an increase of the number of responsive neurons or an expansion of the neuronal receptive fields [16,21,43]. These changes are normally attributed to central mechanisms since electrical stimulation completely bypasses skin receptors, and currently there are no theories that account for an increase in peripheral nerve sensitivity remote to the site of injury / pain [86]. Alternative explanations to this observations

related to peripheral changes are less likely: in the case of pressure pain, peripheral receptor sensitization could account for localized hyperalgesia at the site of pain (in this case, the low back), but not for generalized widespread hyperalgesia tested at remote sites (in this case, the toes) [60].

Enhanced pain facilitatory mechanisms are not the only possible explanation for these observations, since it could be hypothesized that alterations in endogenous inhibitory systems may play a role in pain hypersensitivity. Indeed, some of the aforementioned chronic pain conditions are also associated to deficiencies in endogenous pain inhibition [56,58,61,77]. In this regard, the results of this study do not provide psychophysical evidence of alterations in pain inhibitory mechanisms in acute low back pain patients, as assessed by immersion times and by changes in pressure pain thresholds during CPM. Both groups presented effective CPM immediately after CPT and up to 10 min later, although the magnitude of the CPM effect decreased over time. Furthermore, no differences between groups were found at any time point.

Only very few studies have investigated CPM in the acute pain stage, mostly in relation to prediction of postoperative pain [42,89]. Specifically regarding low back pain, a recently published study from our group also investigated the time course of CPM in patients with acute and chronic low back pain [51]. The reported results indicated that both groups of patients presented effective CPM immediately after CPT, with only small differences in the time course of CPM between patients and healthy individuals. Taking into consideration studies involving chronic low back pain as well [37,52], the existing psychophysical evidence seems to indicate that inhibitory mechanisms related to CPM are largely unaltered in patients with acute low back pain. However, until now there were no studies providing electrophysiological data that would support this hypothesis.

4.2. Electrophysiological assessment

The EEG analysis showed that both healthy volunteers and LBP patients presented reduced ERPs during CPM. In this regard, the majority of previous CPM studies in healthy volunteers reported a

consistent amplitude reduction of the late ERP components [5,9,27,28,40,53,62,67,83,85]. In contrast, chronic pain patients generally did not display changes in the ERP amplitudes during CPM [1,13,63,78], although there are some examples in which cortical changes have been observed [65]. It is worth noting that expectations of analgesia/hyperalgesia can induce changes in CPM responses at spinal and supraspinal level in healthy volunteers [30] , although it was later shown that the modulatory effects of expectations on spinal nociception are disrupted in fibromyalgia patients [31]. In relation to acute pain patients, no previous studies have investigated the electrical brain activity during CPM. The present electrophysiological evidence is in line with the psychophysical results, all suggesting that acute low back pain patients might not have alterations in endogenous inhibition at this stage.

Regarding the brain responses to repetitive painful stimulation, the obtained ERP components presented a visible reduction in the amplitude between the first and last stimulus of the train consistent with results reported previously [15,36]. This phenomenon is called repetition suppression, and there are two proposed models to explain it: as a bottom-up process in which neuronal activity is reduced due to fatigue of synaptic mechanisms or as a top-down process that reflect attenuation of surprise responses to unexpected sensory input [81]. Under the bottom-up hypothesis, the differences observed after the last stimulus between groups may partially reflect an augmented afferent volley in the LBP group, possibly explained by an enhancement due to central hyperexcitability. Whereas data from chronic back pain patients indicate a deficit in habituation to repeated stimulus presentations [26], to our knowledge this is the first study to report significant differences in neural correlates of pain facilitation between acute LBP patient and healthy volunteers, specifically in ERP amplitudes after the last stimulus in a sensitized acute pain state.

The top-down alternative stems from considering evidence related to the functional significance of the ERPs. Recent studies suggest that ERPs reflect the neural correlates underlying the detection and reorientation of attention towards a potentially threatening stimulus, regardless of its sensory

modality [46,47,55,68,82,84]. Attentional bias towards pain-related information has been previously described in chronic pain patients and explained as a probable state of hyper-vigilance [17,19,33]. It might therefore be possible that the LBP patients presented a top-down attentional modulation towards the stimulated hand, which could partially explain the larger brain responses in the LBP group compared to healthy subjects.

Finally, it is worth mentioning that differences were found between the psychological profiles of patients and healthy volunteers, specifically related to depression and trait anxiety. In this regard, it has been shown that higher levels of anxiety and catastrophizing are usually associated with enhanced subjective pain outcomes [22,23] but not with measures of spinal excitability, e.g. the nociceptive withdrawal reflex [8,18,57,66,76].

4.3. Strengths and limitations

Psychophysical and electrophysiological evidence were integrated in the present study to study pain facilitatory and inhibitory mechanisms in acute low back pain patients in the same experimental protocol. In this regard, it has to be noted- that the psychophysical assessment as well as the electrophysiological measurements quantified in this study provide only indirect evidence of the underlying mechanisms, and these mechanisms are not necessarily specific for pain. With regards to CPM, current experimental protocols do not allow to distinguish between specific inhibitory mechanisms at spinal or supraspinal level and the contribution of attention and expectation on the resulting brain responses [30,31,41,54,71]. Furthermore, it is not possible to determine whether this inhibition is specific for nociception or not [70,79]. The same can be observed for facilitatory mechanisms and their correlation to brain activity [10,11,24]. Even though ERP responses present components correlated to somatosensory input, they are largely influenced by the context (e.g. saliency, novelty, relevance) [47,55,68,82,84], which makes it difficult to draw conclusions regarding the specific spinal and supraspinal contribution to the observed changes. Furthermore, no sizable

changes were detected in measures of pain inhibition, but this cannot be taken as direct evidence that no real difference exists; indeed, such differences might be detected using a larger sample or alternative assessment methods, and so further research into this issue is necessary to confirm these prospects.

Finally, it was not possible to find a direct explanation for the activity in the pre-stimulus interval, since all the surveyed studies in relation to anticipatory or non-cued effects in the pre-stimulus interval display frontal negativity and not positivity, as observed in our results [12] . Analysis of the corresponding scalp maps revealed that this activity was synchronized to the stimulus and present in both groups, that it was localized fronto-centrally and modulated by CPM, so it is possible to hypothesize that it was generated by an unknown sensory cue within the experimental setup. Nevertheless, this artifact does not influence the main outcomes of the study.

4.4. Conclusion

This is the first study to investigate changes in correlates of pain modulatory mechanisms in acute low back pain patients. Results showed that acute low back pain patients presented enhanced pain facilitatory mechanisms, whereas no significant changes in pain inhibitory mechanisms were observed. Future studies should be aimed at isolating and identifying specific mechanisms of inhibition and facilitation, determining at which time point in the transition from acute to chronic pain the inhibitory mechanisms begin to fail, and clarifying the mechanisms behind these alterations.

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FIGURE CAPTIONS

Fig. 1. Experimental procedure. During BASELINE, pressure pain tolerance (PPT) was first assessed, and then suprathreshold electrical stimulation (SES) was applied to the left median nerve for 10 min. Afterwards, conditioned pain modulation (CPM) was induced by immersing the right hand up to the wrist into ice water (cold pressor test, CPT) for a maximum of 2 min, after which only the fingers remained immersed. PPT was assessed immediately after (Immed), and SES was applied again for 10 min. During this time, PPT was assessed at 3, 5 and 10 min.

Fig. 2. Magnitude of the conditioned pain modulation effect (ΔCPM) as a function of time. CTRL: control group; LBP: acute low back pain patients group; Immed: immediately after the cold pressor test (CPT).

Fig. 3. Grand average scalp topographies of event-related potentials (ERPs) in response to repetitive suprathreshold electrical stimulation (SES) at selected time points. Each row depicts the topographical distributions for the control group (CTRL) and acute low back pain patients group (LBP) in the baseline condition (BASELINE) and during conditioned pain modulation (CPM).

Fig. 4. Event-related potential (ERP) analysis. A) Grand average waveforms of ERPs in response to repetitive suprathreshold electrical stimulation (SES) at electrode C2 for the control group (CTRL) and acute lowFig back pain patients group (LBP) in the baseline condition (BASELINE) and during conditioned pain modulation (CPM). Shaded areas indicate the standard deviation. Left panels show the condition effect (BASELINE vs. CPM) on the magnitude of the ERPs; right panels show the group effect (CTRL vs. CPM). Grey zones define the significant clusters ($p < 0.05$). B) Scalp topographies of the magnitude of the clustered p-values describing the condition effect (right) and group effect (right) on the ERPs.

Table 1. Descriptive and psychological variables.

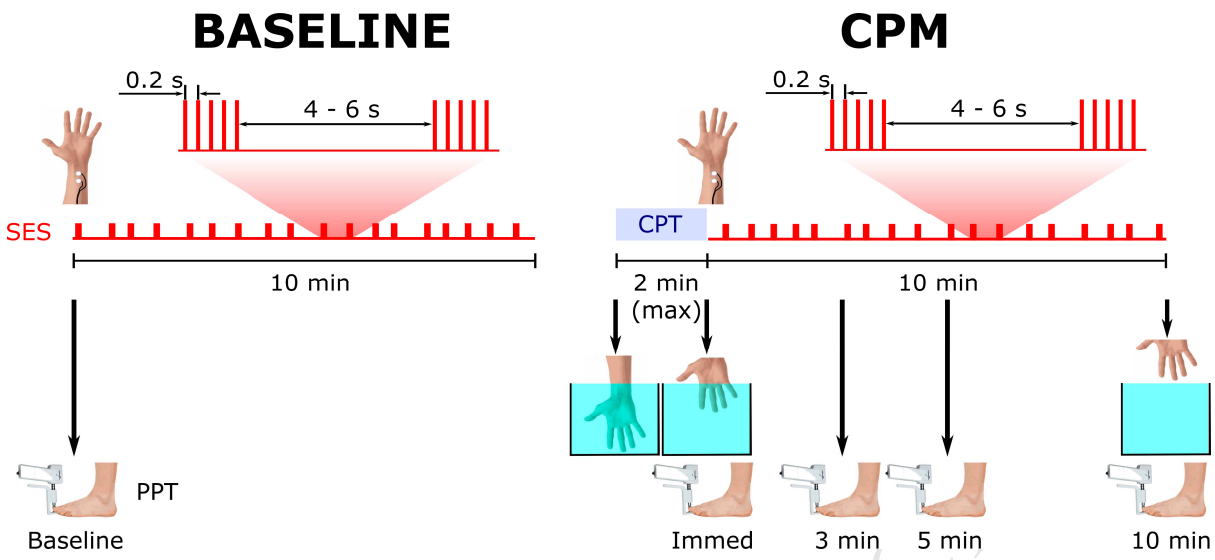
	Healthy controls (CTRL, n = 18)	Acute low back pain patients (LBP, n = 18)	Test statistic
Age (years)	36.3 (13.1)	38.5 (14)	$U = 156.000$, $p = 0.862$
BMI (kg/m^2)	25.6 ± 4.1	24.9 ± 3.9	$t_{34} = 0.528$, $p = 0.601$
BDI(score 0-63)	2.0 (3.0)	4.0 (3.8)	$U = 82.500$, $p = 0.012$
STAI-state (score 20-80)	34.0 (7.5)	33.5 (7.0)	$U = 152.500$, $p = 0.776$
STAI-trait (score 20-80)	29.5 (8.8)	37.0 (8.8)	$U = 81.000$, $p = 0.011$
CSQ catastrophizing (mean score 0-6)	1.2 (1.5)	1.5 (1.8)	$U = 130.000$, $p = 0.318$
Duration of pain (weeks)	NA	1.5 (1.8)	NA
Maximum pain intensity over the last 24 h (NRS 0-10)	NA	7.0 (2.0)	NA
Minimum pain intensity over the last 24 h (NRS 0-10)	NA	2.0 (2.0)	NA
Average pain intensity over the last 24 h (NRS 0-10)	NA	5.0 (2.8)	NA

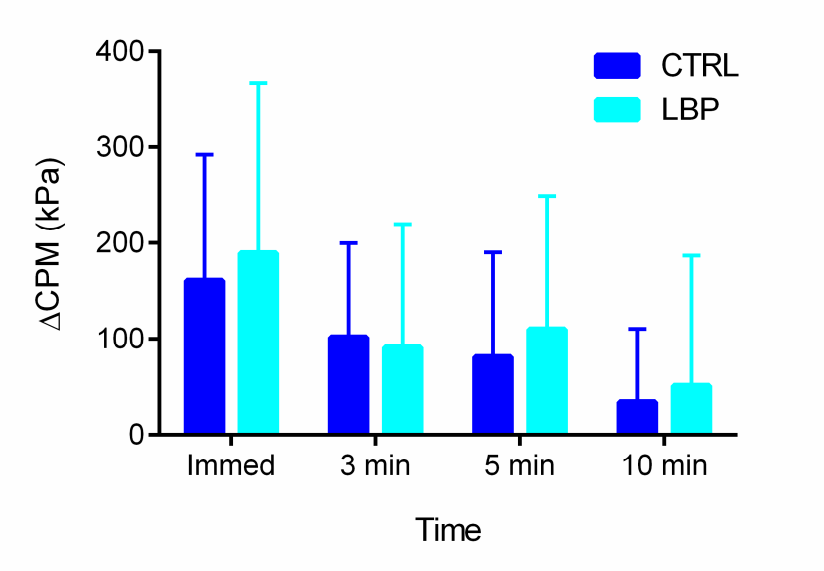
Values are presented as mean ± standard deviation or median (inter-quartile range). BMI: body mass index; BDI: Beck depression inventory; STAI: state-trait anxiety inventory; CSQ: coping strategies questionnaire; NA: not applicable.

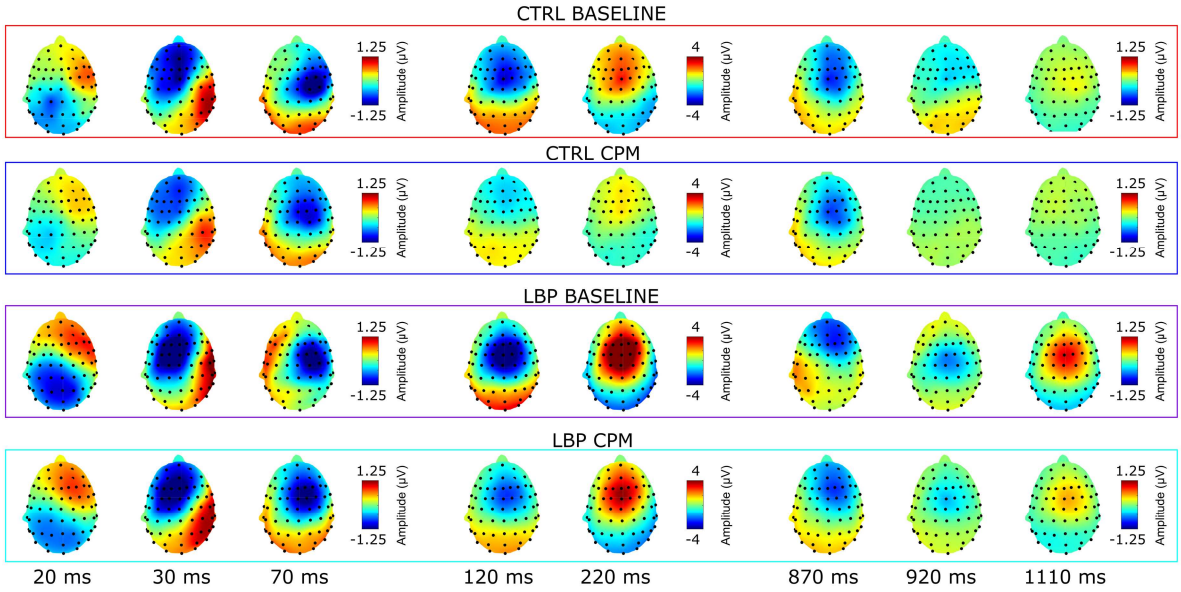
Table 2. Psychophysical and electrophysiological tests.

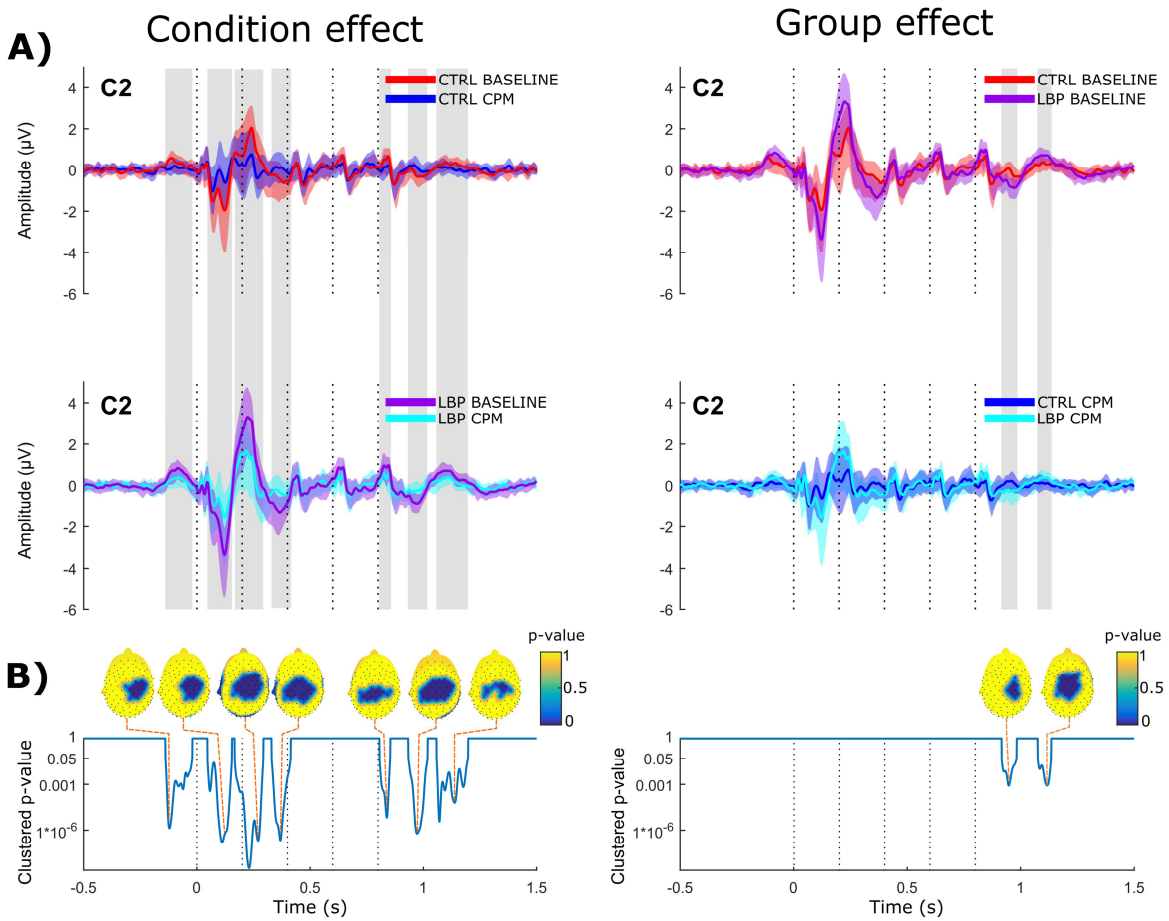
	Healthy controls (CTRL, n = 18)	Acute low back pain patients (LBP, n = 18)	Test statistic
PPT baseline (kPa)	561.8 ± 177.7	418.3 ± 166.4	t_{34} = 2.501, p = 0.017
EPT (mA)	10.1 ± 4.4	10.9 ± 3.8	t_{34} = -0.660, p = 0.514
Pain ratings to repetitive SES (NRS 0-10)	6.6 ± 1.0	7.2 ± 0.9	t_{34} = -2.065, p = 0.046
CPT immersion time (s)	68.5 (74.5)	43.5 (50.8)	U = 121.0, p = 0.196

Values are presented as mean ± standard deviation or median (inter-quartile range). PPT: pressure pain tolerance; EPT: electrical pain threshold; SES: suprathreshold electrical stimulation; NRS: numerical rating scale; CPT: cold pressor test.









Highlights

- Pain inhibition and facilitation are assessed in acute low back patients.
- Mechanisms were assessed using psychophysical and electrophysiological tests.
- Patients presented enhanced pain facilitation but no difference in pain inhibition.