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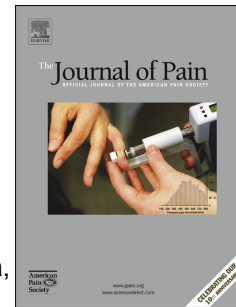
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1 **Psychophysical and electrophysiological evidence for**

2 **enhanced pain facilitation and unaltered pain**

3 **inhibition in acute low back pain patients**

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6
7 **RUNNING TITLE**

8 Pain facilitation and inhibition in acute low back pain
9

10 **DISCLOSURES**

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13 University of Bern.

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

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

21

1 **ABSTRACT**

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

15
16 This study was registered in the Clinical Trials Protocol Registration System (NCT00892411,
17 available at <https://clinicaltrials.gov/ct2/show/NCT00892411>).

19 **PERSPECTIVES**

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

23

1 KEY WORDS

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

4

ACCEPTED MANUSCRIPT

1. INTRODUCTION

Low back pain has a life prevalence of over 70%², with less than one third resolving annually¹⁴ and with over 60% of patient experiencing pain after 12 months³⁵. 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 healing⁵⁰.

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 system⁸⁶. 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 stimulus⁸⁸.

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

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

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

12

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

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

4 **2.1.1. Sample size considerations**

5 The original protocol required 40 acute low back pain that were randomly assigned in a 1:1 ratio to
6 either undergo assessment of electroencephalographic (EEG) activity as response to painful
7 stimulation or electrical stimulation with assessment of pain and reflex detection threshold. Thus,
8 20 acute low back pain patients and 20 healthy pain-free controls were assigned to this study.

9 **2.2. Descriptive variables**

10 Gender, age, height, weight, body-mass index (BMI) and duration of pain in weeks were recorded.
11 Additionally, pain intensity at the time of testing and maximum and minimum pain intensity in the
12 24 h prior to the experiment were assessed using the same NRS as described above. Volunteers
13 were also asked to complete the following questionnaires: Beck Depression Inventory (BDI)⁷,
14 State-Trait-Anxiety-Inventory (STAI)⁴⁴ and Catastrophizing Scale of the Coping Strategies
15 Questionnaire (CSQ)⁶⁹.

16 **2.3. Psychophysical and electrophysiological tests**

17 **2.3.1. Pressure stimulation**

18 Pressure pain tolerance (PPT) was measured with an electronic pressure algometer (Somedic AB,
19 Sweden), using a probe with a surface area of 1 cm². Pressure stimulation was performed at the
20 center of the pulp of the 2nd toe of the left foot. The pressure was increased from 0 kPa at a rate of
21 30 kPa/s to a maximum pressure of 1000 kPa. Pain tolerance was defined as the point at which the
22 subject felt pain as intolerable. Volunteers were instructed to press a button when this point was

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

3 **2.3.2. Electrical stimulation**

4 Electrical stimulation was performed through surface electrodes (Ag/AgCl, Ambu Neuroline, Ambu
5 A/S, Ballerup, Denmark) placed at the innervation area of the left median nerve, on the wrist, and
6 delivered by a computer-controlled constant current stimulator (NoxiTest IES 230, Aalborg
7 University, Denmark). Each stimulus consisted of a single, 2-ms square-wave pulse. The
8 stimulation intensity was established as a multiple of the subjective pain detection threshold (EPT),
9 the latter defined as the minimum current intensity reported as painful for a single stimulus. In order
10 to find the EPT, the current intensity was gradually increased from 1 mA in steps of 0.5 mA until a
11 painful sensation was elicited. The procedure was repeated three times, and the mean of the three
12 pain thresholds was multiplied by 1.5 to obtain the suprathreshold electrical stimulation (SES)
13 intensity that was used subsequently in the whole experiment. Repetitive SES consisted of trains of
14 5 stimuli, with an inter-stimulus interval of 200 ms (stimulation frequency: 5 Hz, total train
15 duration: 1 s). Each train was repeated 120 times at a random inter-train interval ranging from 4 to 6
16 s, resulting in stimulation blocks of approximately 10 min.

17 **2.3.3. Cold pressor test and conditioned pain modulation**

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

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

5 **2.4. Electroencephalographic recordings**

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

13 **2.5. Experimental procedure**

14 The same investigator, AYN, performed all the experiments, assisted by ACN. During the testing
15 session the volunteers were lying in a bed, in a quiet room. Each subject underwent a training
16 session for all tests in order to familiarize with the stimulation procedures before starting the data
17 collection. Electrical stimulation was performed at the left wrist, whereas ice water stimulation was
18 performed on the right hand, as typically the conditioning has to be performed on a remote area³⁹.
19 PPT, EPT to single electrical stimulus and pain ratings to repetitive SES were initially assessed as
20 described in section 2.3, and then EEG data were recorded during repetitive SES for 10 min
21 (BASELINE condition). Afterwards, the cold pressor test was performed: immediately following
22 the initial 2 min (or the longest time that the volunteers were able to keep the whole hand
23 submerged), the PPT was assessed again. EEG data were then recorded again during repetitive SES

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

6 **2.6. Data analysis**

7 **2.6.1. Conditioned pain modulation**

8 The magnitude of the CPM effect, namely ΔCPM , was defined as the difference between PPT
9 measured immediately after, 3, 5 and 10 min after the CPT, and the PPT at baseline (i.e. before
10 CPT). Positive values of ΔCPM indicated successful pain inhibition and the volunteer is said to
11 respond to CPM testing⁶⁴.

12 **2.6.2. Event-related potentials**

13 EEG data was analyzed offline in MATLAB (Mathworks, Inc., USA). In particular, EEG data was
14 pre-processed using EEGLAB²⁰. For each subject and each condition, continuous EEG data were
15 band-pass filtered between 0.5 and 100 Hz, notch-filtered at 50-Hz and re-referenced to the average
16 of all channels. A time window of interest was defined by segmenting the data into epochs of 2000
17 ms that included 500 ms of pre-stimulus. The obtained epochs (120 in total) were visually inspected
18 to discard noisy channels and those epochs that contained gross artifacts due to e.g. movement and
19 muscle activity. In order to remove artifacts related to the electrical stimulation, eye movements and
20 blinks, the remaining epochs were evaluated using Infomax Independent Component Analysis
21 (ICA)⁴⁵. The ICA algorithm separated the scalp EEG signals into statistically independent
22 components of different brain and artifact sources, and the “clean” EEG signals were obtained by
23 eliminating the contributions of the artifactual components. These components were identified by

1 inspecting their time course, spectra and scalp topography³⁸. Subsequently, the rejected channels
2 were spatially interpolated with a spherical spline. Finally, epochs were averaged across trials and
3 baseline-corrected using the mean amplitude of the pre-stimulus period in order to obtain the ERPs.
4 A step-by-step guide for the pre-processing analysis applied using EEGLAB can be found at
5 https://sccn.ucsd.edu/wiki/EEGLAB_TUTORIAL_OUTLINE. As a result of the pre-processing
6 stage, one averaged waveform was obtained for each subject, channel and condition.

7 **2.6.3. Statistics**

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

15 ERP statistics were performed using Letswave (<http://nocions.github.io/letswave6/>). A point-by
16 point, mixed-model analysis of variance (ANOVA) was performed to evaluate the effects of the
17 factors condition (BASELINE vs. CPM) and group (CTRL vs. LBP) on the amplitude of the ERPs
18 in the time window of interest (2000 ms in total, from 500 ms before the stimulus to 1500 ms after
19 the stimulus). Since point-by-point analysis involves several statistical inferences made
20 simultaneously, a clustersize-based permutation testing approach was used to control the multiple
21 comparisons problem⁴⁹. This methodology defines clusters of significant differences in time (by
22 grouping the time points for which the p-value in the individual F-test is smaller than 0.05), while
23 controlling the false alarm rate. The size of each cluster was defined as the sum of the F-values
24 within the cluster. Then permutations are performed (250 in total), by shuffling the data between

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

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1 **3. RESULTS**

2 **3.1. Descriptive variables**

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

13 **3.2. Psychophysical and electrophysiological tests**

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

19 **3.3. Cold pressor test and conditioned pain modulation**

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

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

5 **3.4. Event-related potentials**

6 In general, subjects from both groups presented clear ERP components that are typically elicited
7 when applying electrical stimulation to the skin at suprathreshold levels⁸⁰. Early waves commonly
8 described as N20 and P30, presented evident lateralized scalp topography with negative and
9 positive excursions, respectively, contralateral to the stimulation site (Fig. 3, 20 ms and 30 ms).
10 These waves were followed by two negative deflections in central-parietal electrodes frequently
11 described as N70 and N120 (Fig. 3, 70 ms and 120 ms). The following wave was a positive peak in
12 central electrodes, symmetrically distributed, with a latency of ~225 ms (P200). The P200 was
13 coincident with the arrival of the second pulse of the stimulus train. After the fifth stimulus, the late
14 components of the ERP waveforms had a similar topography as the response to the first stimulus,
15 although the ERP amplitude was evidently decreased (Fig. 3, 870 ms, 920 ms and 1110 ms).
16 Grand-mean ERP waveforms are shown in Fig. 4, together with results of the point-by-point
17 ANOVA performed in each time point and channel. There was a significant main effect of
18 condition in the post-stimulus window, between ~45 – 400 ms and ~800 – 1200 ms. A significant
19 difference was also found prior to stimulus onset, between -140 – -20 ms. Scalp responses to
20 electrical stimulation were significantly smaller during the CPM condition for both groups.
21 Furthermore, there was a significant main effect of group in post-stimulus window (after the fifth
22 pulse in the stimulus train), between ~910 – 980 ms and ~1075 – 1135 ms, where LBP patients
23 showed larger ERP responses after the fifth stimulus compared to the CTRL group in both

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

3

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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 / pain⁸⁶. Alternative explanations to this observations

1 related to peripheral changes are less likely: in the case of pressure pain, peripheral receptor
2 sensitization could account for localized hyperalgesia at the site of pain (in this case, the low back),
3 but not for generalized widespread hyperalgesia tested at remote sites (in this case, the toes) ⁶⁰.
4 Enhanced pain facilitatory mechanisms are not the only possible explanation for these observations,
5 since it could be hypothesized that alterations in endogenous inhibitory systems may play a role in
6 pain hypersensitivity. Indeed, some of the aforementioned chronic pain conditions are also
7 associated to deficiencies in endogenous pain inhibition ^{56,58,61,77}. In this regard, the results of this
8 study do not provide psychophysical evidence of alterations in pain inhibitory mechanisms in acute
9 low back pain patients, as assessed by immersion times and by changes in pressure pain thresholds
10 during CPM. Both groups presented effective CPM immediately after CPT and up to 10 min later,
11 although the magnitude of the CPM effect decreased over time. Furthermore, no differences
12 between groups were found at any time point.

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

22 **4.2. Electrophysiological assessment**

23 The EEG analysis showed that both healthy volunteers and LBP patients presented reduced ERPs
24 during CPM. In this regard, the majority of previous CPM studies in healthy volunteers reported a
18

1 consistent amplitude reduction of the late ERP components^{5,9,27,28,40,53,62,67,83,85}. In contrast, chronic
2 pain patients generally did not display changes in the ERP amplitudes during CPM^{1,13,63,78},
3 although there are some examples in which cortical changes have been observed⁶⁵. It is worth
4 noting that expectations of analgesia/hyperalgesia can induce changes in CPM responses at spinal
5 and supraspinal level in healthy volunteers³⁰, although it was later shown that the modulatory
6 effects of expectations on spinal nociception are disrupted in fibromyalgia patients³¹. In relation to
7 acute pain patients, no previous studies have investigated the electrical brain activity during CPM.
8 The present electrophysiological evidence is in line with the psychophysical results, all suggesting
9 that acute low back pain patients might not have alterations in endogenous inhibition at this stage.
10 Regarding the brain responses to repetitive painful stimulation, the obtained ERP components
11 presented a visible reduction in the amplitude between the first and last stimulus of the train
12 consistent with results reported previously^{15,36}. This phenomenon is called repetition suppression,
13 and there are two proposed models to explain it: as a bottom-up process in which neuronal activity
14 is reduced due to fatigue of synaptic mechanisms or as a top-down process that reflect attenuation
15 of surprise responses to unexpected sensory input⁸¹. Under the bottom-up hypothesis, the
16 differences observed after the last stimulus between groups may partially reflect an augmented
17 afferent volley in the LBP group, possibly explained by an enhancement due to central
18 hyperexcitability. Whereas data from chronic back pain patients indicate a deficit in habituation to
19 repeated stimulus presentations²⁶, to our knowledge this is the first study to report significant
20 differences in neural correlates of pain facilitation between acute LBP patient and healthy
21 volunteers, specifically in ERP amplitudes after the last stimulus in a sensitized acute pain state.
22 The top-down alternative stems from considering evidence related to the functional significance of
23 the ERPs. Recent studies suggest that ERPs reflect the neural correlates underlying the detection
24 and reorientation of attention towards a potentially threatening stimulus, regardless of its sensory

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

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

11 **4.3. Strengths and limitations**

12 Psychophysical and electrophysiological evidence were integrated in the present study to study pain
13 facilitatory and inhibitory mechanisms in acute low back pain patients in the same experimental
14 protocol. In this regard, it has to be noted- that the psychophysical assessment as well as the
15 electrophysiological measurements quantified in this study provide only indirect evidence of the
16 underlying mechanisms, and these mechanisms are not necessarily specific for pain. With regards to
17 CPM, current experimental protocols do not allow to distinguish between specific inhibitory
18 mechanisms at spinal or supraspinal level and the contribution of attention and expectation on the
19 resulting brain responses^{30,31,41,54,71}. Furthermore, it is not possible to determine whether this
20 inhibition is specific for nociception or not^{70,79}. The same can be observed for facilitatory
21 mechanisms and their correlation to brain activity^{10,11,24}. Even though ERP responses present
22 components correlated to somatosensory input, they are largely influenced by the context (e.g.
23 saliency, novelty, relevance)^{47,55,68,82,84}, which makes it difficult to draw conclusions regarding the
24 specific spinal and supraspinal contribution to the observed changes. Furthermore, no sizable
20

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

5 Finally, it was not possible to find a direct explanation for the activity in the pre-stimulus interval,
6 since all the surveyed studies in relation to anticipatory or non-cued effects in the pre-stimulus
7 interval display frontal negativity and not positivity, as observed in our results¹². Analysis of the
8 corresponding scalp maps revealed that this activity was synchronized to the stimulus and present in
9 both groups, that it was localized fronto-centrally and modulated by CPM, so it is possible to
10 hypothesize that it was generated by an unknown sensory cue within the experimental setup.
11 Nevertheless, this artifact does not influence the main outcomes of the study.

12 **4.4. Conclusion**

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

20

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- 9

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 (Δ CPM) 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 low 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.

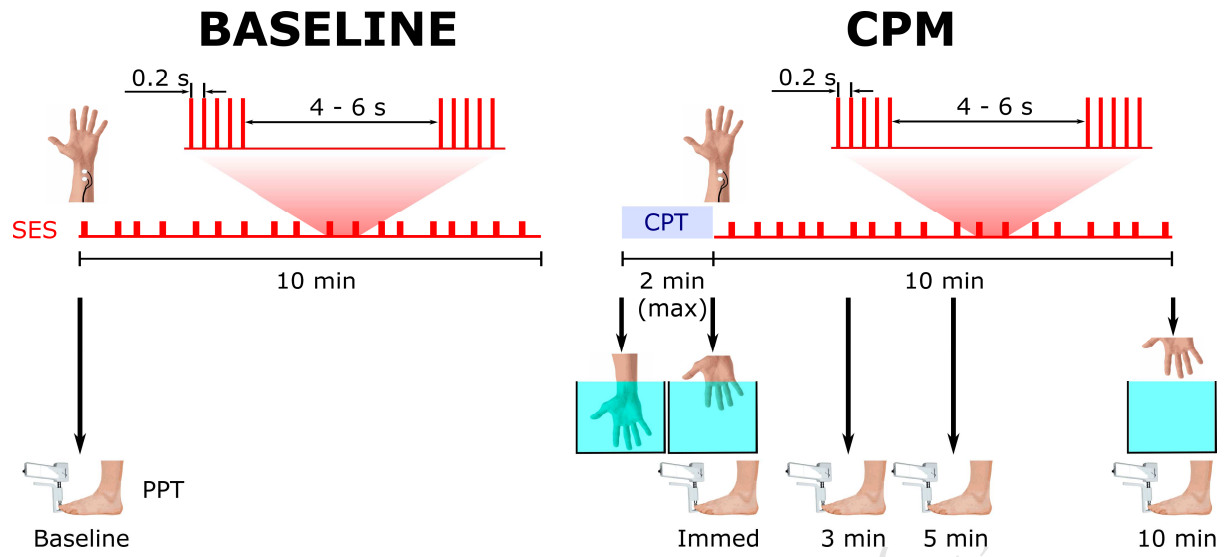
	Healthy controls (CTRL, n = 18)	Acute low back pain patients (LBP, n = 18)	Test statistic
Age (years)	36.3 (13.1)	38.5 (14)	$U = 156.000, p = 0.862$
BMI (kg/m ²)	25.6 ± 4.1	24.9 ± 3.9	$t_{34} = 0.528, p = 0.601$
BDI(score 0-63)	2.0 (3.0)	4.0 (3.8)	$U = 82.500, p = 0.012$
STAI-state (score 20-80)	34.0 (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

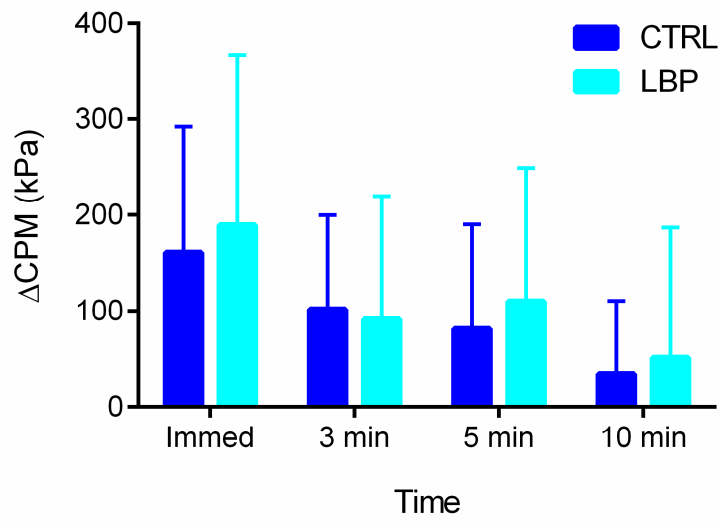
Values are presented as mean ± standard deviation or median (inter-quartile range). BMI: body mass index; BDI: Beck depression inventory; STAI: state-trait anxiety inventory; CSQ: coping strategies questionnaire; NA: not applicable.

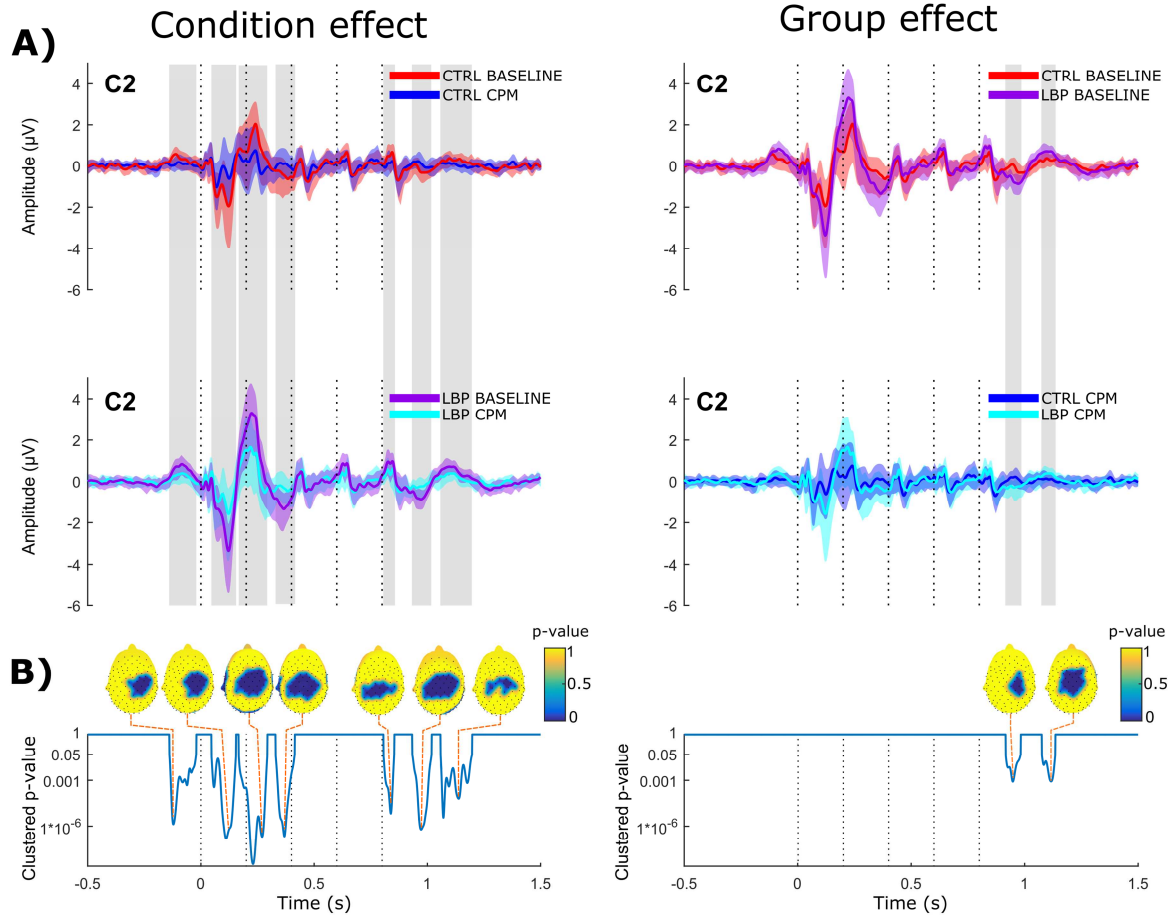
Table 2. Psychophysical and electrophysiological tests.

	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.