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ORIGINAL ARTICLE

Motor corticospinal excitability abnormalities differ between distinct chronic low back pain syndromes

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Abstract
Objectives: It is not known whether cortical plastic changes reported in low-back pain (LBP) are present in all etiologies of LBP. Here we report on the assessment of patients with three LBP conditions: non-specific-LBP (ns-LBP), failed back surgery syndrome (FBSS), and sciatica (Sc).
Methods: Patients underwent a standardized assessment of clinical pain, conditioned pain modulation (CPM), and measures of motor evoked potential (MEPs)-based motor corticospinal excitability (CE) by transcranial magnetic stimulation, including short interval intracortical inhibition (SICI), and intracortical facilitation (ICF). Comparisons were also made with normative data from sex- and age-matched healthy volunteers.
Results: 60 patients (42 women, 55.1±9.1 years old) with LBP were included (20 in each group). Pain intensity was higher in patients with neuropathic pain [FBSS (6.8±1.3), and Sc (6.4±1.4)] than in those with ns-LBP (4.7±1.0, P<0.001). The same was shown for pain interference (5.9±2.0, 5.9±1.8, 3.2±1.9, P<0.001), disability (16.4±3.3, 16.3±4.3, 10.4±4.3, P<0.001), and catastrophism (31.1±12.3, 33.0±10.4, 17.4±10.7, P<0.001) scores for FBSS, Sc, and ns-LBP groups, respectively. Patients with neuropathic pain (FBSS, Sc) had lower CPM (-14.8±1.9, -14.1±16.7, respectively) compared to ns-LBP (-25.4±16.6; P<0.02). 80.0% of the FBSS group had defective ICF compared to the other two groups (52.5% for ns-LBP, P=0.025 and 52.5% for Sc,

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P=0.046). MEPs (140%-rest motor threshold) were low in 50.0% of patients in the FBSS group compared to 20.0% of ns-LBP (P=0.018) and 15.0% of Sc (P=0.001) groups. Higher MEPs were correlated with mood scores (r=0.489), and with lower neuropathic pain symptom scores(r=-0.415) in FBSS.

Conclusions: Different types of LBP were associated with different clinical, CPM and CE profiles, which were not uniquely related to the presence of neuropathic pain. These results highlight the need to further characterize patients with LBP in psychophysics and cortical neurophysiology studies.

Introduction

Low back pain (LBP) is defined as pain located between the 12th rib and gluteal sulcus [6,34]. Chronic LBP (pain present for the majority of days for more than 3 months) [75] is the leading cause of global productivity loss and the main cause of years lived with disability worldwide [36]. Multiple causes and risk factors are involved in the pathogenesis of LBP [39]. Non-specific low back pain (ns-LBP) is the most common type of LBP, and is characterized by the absence of a clear structural cause for the pain [47]. It is currently considered that the main mechanism of pain in the majority of patients with chronic ns-LBP is nociplastic pain [28]. Low back pain may also be caused by conditions that cause peripheral nerve injury associated with neuropathic pain, such as sciatica (Sc) [40,51] and patients with failed back surgery syndrome (FBSS) with radiculopathy [19,74]. These distinctions are important because patients with LBP associated with neuropathic pain have specific needs in terms of management and are more likely to respond to medication and to neuromodulatory approaches. In patients with ns-LBP, on the other hand, emphasis is put on rehabilitation and physiotherapy approaches rather than on medications [55], due to the higher probability of inefficacy and undesired outcomes [48] such as long term-opioid use.

The management of chronic low back pain is highly challenging, irrespective of its cause, and a large proportion of patients remain symptomatic despite treatment [48]. This is part due to still limited knowledge of the mechanisms leading to pain initiation and pain maintenance. In LBP, despite the regional location of the pain within the lumbar area, it has been extensively shown that patients experience CNS alterations related to pain, such as altered defective pain top-down modulatory pathways, connectivity between the nucleus accumbens and the medial prefrontal cortex, changes in thickness of cortical structures and changes in the cortical excitability of the central representation of back muscles such as the multifidus and paraspinalis muscles [57,84]. Some of these alterations have been shown to correlate with pain characteristics and some have been proposed as potential markers of pain recurrence [4,10,13,29,45,47,57,67,84].

However, most studies describing brain functional and connectivity changes in LBP to date have not distinguished between patients with ns-LBP, and those with neuropathic pain, limiting the generalizability of the findings [4,32]. So, it remains unknown if central functional, excitability and connectivity changes reported in LBP are present in all LBP subtypes, or if they represent a non-specific central epiphenomenon occurring in any type of LBP, and possibly occurring in other chronic pain syndromes as well. This information would provide a more in-depth understanding of the mechanisms of chronic LBP in general and the distinctions between the different etiologies of LBP, with potential future phenotyping and prognostic information. Here we report on the assessment of patients with LBP associated with three clinically common and relevant conditions: ns-LBP, FBSS, and sciatica. Patients were compared with a detailed and standardized clinical assessment, measurements of motor corticospinal excitability and state of the conditioned pain modulatory system.

Methods

The study was approved by the Ethics Review Board (#62633116.8.0000.0068) and during recruitment information about the study was available online in the national research database, Plataforma Brasil (https://plataformabrasil.saude.gov.br/login.jsf). All participants provided written informed consent before inclusion in the study. This investigation complies with the STROBE Statement of cross-sectional studies [83] (Table S1).

Study design

Portuguese-speaking patients of both sexes (N=98), older than 18 years with a medical diagnosis of chronic low back pain (low back pain for 3 months or more) and without language or major hearing impairments were screened for participation. Screening for participation took place through telephone contact with patients referred for assessment at our Institution's pain center from primary care and pain centers in the referral area covered by the Hospital das Clínicas referral area in São Paulo. This was a convenience sample of consecutive patients attending our outpatient pain clinic. Data collection was performed between July 2019 and August 2021. Inclusion criteria were adults (18 -75 years), presence of symptoms of low back pain lasting three months or longer; with moderate to severe pain intensity: intensity above 3 in an 11-point verbal rating scale for pain intensity ranging from 0 (no pain) to 10 (maximal pain possible); availability to attend the hospital on the days of evaluations and exams. General exclusion criteria were known psychopathological disorders including bipolar affective disorder, neuropsychiatric disorders such as depression or anxiety under follow-up and/or treatment with a psychiatrist or presenting seizures oncological diseases; current acute or chronic

infections; pregnancy; Parkinson's disease; diabetes or diabetic neuropathy; fibromyalgia syndrome; presence of implanted pacemaker devices or spinal cord stimulation. Patients were allocated into three groups of 20 each according to the Quebec Task Force Classification of Spinal Disorders (QTFSD) [3,66] and the diagnostic criteria below.

Group 1 - Non-specific low back pain (ns-LBP): patients were classified as QTFSD 1, (low back pain without radiation), 2 (lumbar pain with radiation to the thigh, but not below the knee), or QTFSD 3 (lumbar pain with radiation to the limb below the knee) [7,66]. Patients in the ns-LBP group had no signs of radiculopathy or neuropathic pain, and their radiating pain was in all instances somatic referred pain from soft tissues. Importantly, these patients had no clear structural cause for their pain such as disc herniation, lumbar spinal stenosis or spondylolisthesis [7,23,27,59,66,77]. Group 2 and Group 3 were both formed by patients with chronic neuropathic pain according to the grading criteria for definite neuropathic pain [27]. Group 2 – Chronic low back pain associated with lumbosacral radiculopathy and neuropathic pain affecting the legs, called here sciatica (Sc) [40,51,64]: ie. patients who classified as QTFSD 4 (low back pain radiating to the lower limb with neurogenic signs). Group 3 – Chronic low back pain associated with failed back surgery syndrome (FBSS): patients with failed back surgery syndrome according to QTFSD 9 (Post-surgical pain 1 to 6 months after intervention) with signs of associated radiculopathy and neuropathic pain [19,81]. These patients had a clear aggravation of low back pain after surgery (laminectomy) compared to preoperative pain intensity, and additionally presented neuropathic pain of radicular etiology. In all cases, patients were assessed by two neurologists specialized in pain management and general laboratory tests and imaging (CT or MRI) was used to aid in the classification.

Clinical assessment

(1) The following scales and questionnaires were performed to characterize patients, pain, and related symptoms:
Sociodemographic Questionnaire: it consisted of questions about age, gender, educational level, current marital status, religion, current and previous use of tobacco, employment status, individual and family income, weight, and height;
(2) Short form of the McGill Pain Questionnaire (MPQ): multidimensional instrument that evaluates the three aspects of pain: sensory-discriminative, affective-motivational, and cognitive-evaluative [26,53];
(3) Visual Analog Scale (VAS), which is a pain scale for assessment of pain intensity ranging from zero (no pain) to 10 cm (maximal pain imaginable), or the 11-point verbal rating scale for pain ranging from 0 to 10 and having the same anchors as the VAS [34] for CPM measurements.
(4) Roland Morris Disability Questionnaire (RMDQ), which is a specific instrument for assessing the incapacity of patients with low back pain. It assesses the repercussions of low back pain at work and in daily activities [59];
(5) Pain Catastrophism Scale (PCS), which is a questionnaire that verifies pain intensity, emotional distress, pain-related disability, and painful behavior. It is subclassified into scores of three sub-items: rumination, magnification, and helplessness (feeling of lack of assistance) [69,72,82];
(6) Short form of the Brief Pain Inventory (BPI), which assesses pain intensity and pain's interference with daily activities [26];
(7) The Hospital Anxiety and Depression Scale (HADS): consists of 14 items, of which 7 assess anxiety symptoms (HAD-A) and 7 assess depression symptoms (HAD-D) [12,85];
(8) Douleur neuropathique 4 (DN4): is a specific questionnaire to identify patients with neuropathic pain. It consists of 10 items related to pain characteristics, seven of which are related to pain characteristics evaluated by their descriptive terms, and three physical examination scans to identify pain regions, reaction to touch or needle prick, or allodynia mechanics. DN4 is positive for neuropathic pain when affirmative responses are $\geq$4 [8];
(9) Neuropathic Pain Symptoms Inventory (NPSI), which is a specific inventory consisting of 12 questions. It was developed to assess pain during the 24 hours preceding the evaluation and was specifically designed to evaluate the different symptoms of neuropathic pain. Patients were classified in three subgroups: "pinpointed pain" (cluster 1), "evoked pain" (cluster 2), and "deep pain" (cluster 3) [9,16,20];
(10) Fear Avoidance Beliefs Questionnaire (FABQ), widely used to evaluate individuals with chronic low back pain. It consists of 16 self-portrait items, divided into two subscales: the one that assesses the fears and beliefs of individuals about work (FABQ-Labor) and the one that assesses their fears and beliefs about physical activities (FABQ-Phys) [1].

General neurological assessment

All patients underwent a standardized neurological assessment consisting of examining tactile, thermal, and painful sensitivity in the corresponding dermatomes (L1, L2, L3, L4, L5, and S1), the patellar and ankle reflexes, and muscle strength [5,46,63,81].

Assessment of motor strength

The muscle groups assessed were: (1) hip flexors, (2) knee extension, (3) ankle dorsiflexion, (4) ankle plantar flexion, and (5) hallux extensor. The muscle strength test was performed and scored according to the six-point Likert Medical Research Council scale, ranging from 0-5 [73]: 0: No muscle activation; 1: Trace muscle activation, such as a twitch, without achieving full range of motion; 2: Muscle activation with gravity eliminated, achieving full range of motion; 3: Muscle activation against gravity, full range of motion; 4: Muscle activation against some resistance, full range of motion; 5: Muscle activation against examiner's full resistance, full range of motion. Score range for the 5 muscle groups evaluated: 0-25.

Assessment of myotatic reflexes

The score consisted of the sum of two reflexes in the lower limbs: patellar, and ankle reflexes [78] for each side of the body, using a Babinski percussion hammer (©2014 GF Health Products, Inc., Atlanta, GA, USA). Myotatic reflex score 0: No response / reflex abolished; 1: Reduced reflex; 2: Normal reflex; 3: Increased reflex; 4: Hyperreflexia with clonus provocation [32]. Clonus was characterized by repeated rhythmic contractions in the agonist muscle group, and is always considered an abnormal finding [56]. Data were presented in a grouped way and the scores were classified according to the sum of the reflex values (patellar and ankle). A sum of 4 on each side was classified as normal, below 4 as reduced and above 4 as hyperreflexia [5].

Sensory assessment

Tactile, painful (pinprick stimuli), and thermal (cold sensitivity) sensations were assessed in 6 areas of the lower limbs, corresponding to the dermatomes of L1, L2, L3, L4, L5, and S1. For each modality of sensation tested, a score was given of 0-3 in each area, where 0 was no sensation, 1 was diminished sensation, 2 was normal sensation and 3 was increased sensation. This gave a total score range for all dermatomes tested of 0-18, for each modality of sensation [21,81].

a. Tactile sensation was examined using a von Frey monofilament.
b. Mechanical nociceptive perception was tested using a safety pin.
c. Nonpainful cold sensitivity (thermal sensitivity) was tested using a metal tuning fork at room temperature. The test was performed in the TMS laboratory, located at the Institute of Psychiatry of the Medical School of São Paulo, with a controlled room temperature of 23°C [5,11,81].

Standardized myofascial assessment

All patients were evaluated for pressure pain detection threshold, pain intensity (on a visual analogue scale -VAS) to suprathreshold stimulation and the presence active trigger points bilaterally in the quadratus lumborum, psoas, piriformis, gluteus medius, gluteus minimus, vastus lateralis, and medial gastrocnemius muscles. Pressure pain threshold measurements were performed with a handheld pressure algometer - FDX® algometer (Wagner instrument, Greenwich, USA). The algometer consists of a rubber circular disc with 1cm^2 of surface fixed at the end of a cylinder coupled to a dynamometer with values expressed in kg/cm^2. Pressure was applied gradually at 1kg/cm2/sec. During pressure pain detection threshold assessment patients were instructed to indicate the presence of the slightest perception of pain (pressure pain threshold). The VAS was used to quantify pain (ranging from zero: no pain) to 10 cm (maximal pain imaginable). Suprathreshold pain measurements (i.e., pressure pain hyperalgesia) was performed by the delivery of a pressure 30% above each muscle pressure pain detection threshold for 3 seconds and measuring the evoked pain intensity with a VAS. Trigger points were considered active when reproducing referred pain at the time of the test and when the patient reported a similarity of at least 50% of his current pain complaint with pain caused by pressure at the point [70,81].

Conditioned pain modulation (CPM)

Conditioned pain modulation was performed as previously described [2] with a test stimulus of heat pain applied to the right thigh of participants and conditioning stimulus of immersion of the left hand in cold water (cold pressor test). Stimulation intensities were delivered to maximal 50°C and 0°C in a relatively steep ramp (1°C per second) to avoid causing a tissue lesion [63]. Test stimulus: heat pain threshold was detected using a contact thermode (30 × 30 mm Medoc, Israel); temperature increase 1°C/second, methods of limits, three trials were performed consecutively, separated by at least 30 seconds with no further delays, and results were averaged. A minimal temporal interval between measurements was intended to avoid skin habituation at the stimulation site. The test stimulus was set 2°C above heat pain thresholds and delivered for 5 seconds, after which period participants were asked to report pain intensity in a VAS (0-10cm). The conditioning stimulus consisted of immersion of the left-hand flat in a basin with water and ice at constant temperature (4°C). Patients were asked to indicate the moment when pain intensity reached 5-6 / 10 pain intensity in a verbal rating scale of pain intensity (0: No pain; 10: Maximal pain imaginable). The test stimulus was delivered initially (unconditioned) and immediately after the conditioning stimulus (conditioned test stimulus). CPM was calculated as the absolute difference between conditioned and unconditioned pain intensity ratings. We also provided a CPM change (in %) by dividing the result of this difference by the unconditioned test stimulus. CPM change results were compared between the three groups, and to data from 60 healthy individuals matched for age and sex from our labs reference data [2].

Motor corticospinal excitability measures (CE)

CE assessments were performed as previously reported [30]. Patients underwent a single assessment on a single day, scheduled to take place preferentially in the morning. Patients sat in a comfortable reclining armchair and were asked to remain as relaxed as possible. A MagPROX100 machine (Magventure Tonika Elektronic, Farum, Denmark) was used to make CE measurements with a circular-shaped coil (C-100 Magventure Tonika Elektronic, Farum). Motor corticospinal excitability testing included the determination of rest motor threshold (RMT) [65]; motor evoked potentials (MEPs); short-interval intracortical inhibition (SICI) at interstimulus intervals (ISI) of 2ms and 4ms; and intracortical facilitation (ICF) at ISI 10ms and 15ms (paired-pulse protocol) [22,42,43]. CE measurements were tested in both hemispheres. MEP was recorded over the cortical representation of the hand area contralateral to the stimulated motor cortex. It used an EMG amplifier module (Tonika Elecktronic, Denmark) and surface electrodes (Skovlunde, Denmark), amplified (50−500 mV/division), filtered (20−2,000 Hz). The MEPs were recorded from first dorsal interosseous muscle. We considered RMT as a MEP of at least 50 μV in amplitude in 5 out of 10 trials; The stimulus intensity was set at 120% and 140% of RMT, as described in previous studies

[17,54,65]. Facilitation and inhibition intracortical responses were studied using the paired-pulse paradigm. The trial consisted of 80% of the output of the RMT value for a conditioning stimulus and 120% of the output of the RMT value for the test stimulus. After the hotspot and RMT were determined, paired-pulse responses were recorded as the average of five trials by each ISI [17,54]. Results from SICI measured at ISI of 2 and 4 msec were averaged for further comparisons. Results from ICF measured at ISI of 10 and 15msec were averaged for further analyses. Every individual's data was classified as normal, low, or high according to published normative data from healthy volunteers from our center (Table S2) [17] and matched for age and sex, so that the proportion of patients with results higher, lower or within CI95% values of healthy individuals were compared.

Statistical analyses

Data were expressed as mean ± standard deviation (minimum-maximum). Descriptive statistics were used to characterize the clinical sample. Qualitative variables were described as frequency and percentages. Fisher's Exact Test was used for categorical data. The Kruskal-Wallis test was used to compare differences between the groups and was followed by the Mann-Whitney U tests. In cases of multiple sequential comparisons, the Bonferroni correction was employed. The Wilcoxon signed-rank test was used to compare related samples (side-to-side differences). We additionally compared individual results to normative data of cortical excitability from healthy subjects and classified patients' results as low, normal, or high [17] for each parameter. Spearman's test was used in the correlations of CE, CPM, and clinical variables. CE parameters found to be different between groups were explored for correlations with clinical data. Only moderate or high correlation coefficients (rho>0.4 were reported) [15,68]. Sample size was estimated based on alpha=0.05, power of 80%, and a relatively large effect size of f^2=0.35 [15,61] based on previous related findings on CE changes in other pain syndromes [25,38,54,65]. When data were related to both sides of the body (e.g., myofascial pain assessment, neurological and muscle strength assessment, and CE), pooled data was presented if no side-to-side difference (P>0.2) existed. All statistical calculations were performed using the software Statistical Package for Social Sciences (SPSS, version 22.0.0.0; SPSS Inc., Chicago, IL, USA).

Results

General sociodemographic data

Sixty patients with low back pain (42 women, 55.1 ± 9.1 years old) (Table S3) and 20 healthy controls (17 women, 56.1±6.2 years old) were included in this study.

Clinical characteristics

Pain intensity was higher in patients with neuropathic pain [FBSS (6.8±1.3), and Sc (6.4±1.4)] than in those with ns-LBP (4.7±1.0, P<0.001). The same was shown for pain interference (5.9±2.0, 5.9±1.8, 3.2±1.9, P<0.001), disability (16.4±3.3, 16.3±4.3, 10.4±4.3, P<0.001), and catastrophism (31.1±12.3, 33.0±10.4, 17.4±10.7, P<0.001) scores for FBSS, Sc, and ns-LBP groups, respectively (Table 1).

Neurological and muscle strength assessment

Myotatic reflexes and muscle strength were statistically different between groups. Scores were higher in the ns-LBP group (24.5±1.8 and 4.0±0.0) compared to the Sc (22.3±2.5 and 2.9±1.0,) and FBSS (13.0±8.9 and 2.2±0.9) groups, respectively, P<0.02 (Table S4).

Myofascial pain assessment

Pain intensity was significantly different between groups. Overall, the ns-LBP group had lower pain intensity to suprathreshold experimental pain (i.e., lower deep pressure hyperalgesia) and fewer active trigger points when compared to the neuropathic pain groups (Sc and FBSS). Pressure pain thresholds in the three groups were mostly below 4kg/cm^2 (Table S5).

CPM change

Neuropathic pain groups (FBSS and Sc) had CPM change significantly lower (-14.1±16.7 and -14.8±13.9, respectively) compared to the ns-LBP group (-25.4±16.6), P<0.02. CPM values were similar between ns-LBP group and matched healthy controls (P=0.481) (Table S6). CPM change did not correlate with pain intensity in any group.

Measures of motor corticospinal excitability

Motor corticospinal excitability parameters from the right and left hemispheres were similar for all groups, and were pooled for further analyses [54] (Table S7). As expected, motor corticospinal excitability parameters were not different when comparing means (Table S8). After the individual classification of each parameter for each patient according to matched normative data, important abnormalities were observed. More than 60% of all participants showed abnormalities in CE parameters. Significant group differences were found: 80.0% of patients in the FBSS group had reduced ICF compared to the other two groups (52.5% in ns-LBP, P=0.025 and 52.5% in Sc, P=0.046). MEP at 120% were low in 22.5% of patients in the FBSS group compared to 5.0% of ns-LBP (P=0.046) and 12.5% of Sc (P=0.040) groups, and MEP at 140% were low in 50.0% of patients in the FBSS group compared to 20.0% of ns-LBP (P=0.018) and 15.0% of Sc (P=0.001) groups (Table 2).

The Sc and ns-LBP groups showed no correlations between clinical variables (e.g., pain intensity and interference, mood, CPM, and quality of life) with cortical excitability findings. However, in the FBSS group, which had the most marked MEP amplitude and ICF reductions, significant correlations were found. MEPs at 120%RMT were correlated with depression scores (r=0.489) and to catastrophizing thoughts (r=0.406), while MEPs at 140%RMT were correlated with lower scores in sensory dimensions of pain (r=-0.416), ability to appreciate life in the BPI interference score (r=0.478), and symptoms of neuropathic pain in the NPSI (r=-0.415), and also with depressive mood (r=0.513) and catastrophizing thoughts (r=0.427).

Table 1 Clinical assessment of patients.

Questionnaires	ns-LBP (N=20)	Sc (N=20)	FBSS (N=20)	P Inter groups	P ns-BP vs. Sc	P ns-LBP vs. FBSS	P Sc vs. FBSS
BPI Pain Intensity (NRS)							
Worst pain in last 24 hours	6.2±1.5 (4.0−9.0)	7.7±1.7 (4.0−10.0)	8.1±1.3 (4.0−9.0)	0.001**	0.003**	0.001**	0.934
Least pain in last 24 hours	2.7±1.2 (1.0−6.0)	4.7±2.2 (2.0−9.0)	5.3±1.6 (1.0−6.0)	0.001**	0.002**	0.001**	0.338
Pain on average	4.9±1.5 (2.0−8.0)	6.5±1.4 (4.0−9.0)	6.8±1.5 (2.0−8.0)	0.001**	0.002**	0.001**	0.761
Pain right now	5.2±1.1 (4.0−8.0)	6.4±1.5 (4.0−10.0)	7.0±1.6 (4.0−8.0)	0.002**	0.018*	0.001**	0.230
Improvement of pain in the last 24h due to treatment and medicine	55.5±28(0.0-100.0)	49.0±18.9(20.0−90.0)	40.0±23.5 (10.0−80.0)	0.095	0.253	0.055	0.143
BPI Pain Interference (NRS)							
General activity	4.9±2.1 (0.0−8.0)	7.0±1.7 (3.0−10.0)	7.3±2.1 (2.0−10.0)	0.001**	0.001**	0.001**	0.483
Mood	2.7±2.5 (0.0−8.0)	5.8±2.4 (1.0−10.0)	5.1±3.2 (0.0−10.0)	0.004**	0.001**	0.023*	0.568
Walking ability	3.5±2.9 (0.0−8.0)	5.8±2.8 (0.0−10.0)	7.0±2.4 (2.0−10.0)	0.002**	0.020*	0.001**	0.194
Normal work (including housework)	4.1±2.5 (0.0−8.0)	6.8±2.5 (0.0−10.0)	6.8±2.6 (0.0−10.0)	0.001**	0.001**	0.003**	0.967
Relations with other people	2.4±2.9 (0.0−8.0)	4.5±2.6 (0.0−10.0)	3.5±2.9 (0.0−10.0)	0.028*	0.008**	0.254	0.124
Sleep	3.8±2.5 (0.0−8.0)	6.7±2.2 (2.0−10.0)	6.5±2.9 (0.0−10.0)	0.003**	0.001**	0.007**	0.967
Enjoyment of life	1.3±1.6 (0.0−5.0)	4.5±2.9 (0.0−10.0)	5.2±3.3 (0.0−10.0)	0.001**	0.001**	0.001**	0.506
BPI Pain intensity index	4.7±1.0 (3.5−7.2)	6.4±1.4 (3.5−9.2)	6.8±1.3 (4.5−9.2)	0.001**	0.001**	0.001**	0.569
BPI Pain interference daily activity score	3.2±1.9 (0.0−6.4)	5.9±1.8 (3.0−9.4)	5.9±2.0 (2.0−9.0)	0.001**	0.001**	0.001**	0.903
DN4 Total score	0.9± 0.8 (0.0− 2.0)	6.7±1.4 (4.0−10.0)	6.8 ±1.3 (5.0−9.0)	0.001**	0.001**	0.001**	0.803
DN4 Positive	0.0 (0.0%)	20.0 (100%)	20.0 (100%)				
RMDQ Total score	10.4±4.3 (3.0−17.0)	16.3±4.3 (6.0−22.0)	16.4±3.3 (11.0−21.0)	0.001**	0.001**	0.001**	0.683
MPQ Total score	7.5±1.8 (4.0−12.0)	11.5±2.5 (7.0−15.0)	10.8±2.1 (7.0−15.0)	0.001**	0.001**	0.001**	0.375
MPQ Sensory	3.8±1.3 (1.0−7.0)	6.6±1.4 (3.0−8.0)	6.2±1.3 (3.0−8.0)	0.001**	0.001**	0.001**	0.329
MPQ Affective	2.6±0.8 (1.0−4.0)	3.5±1.3 (0.0−5.0)	3.3±1.1 (1.0−5.0)	0.044*	0.016*	0.073	0.503
MPQ Evaluative	1.0±0.2 (1.0−2.0)	1.4±0.5 (1.0−2.0)	1.4±0.5 (1.0−2.0)	0.012*	0.004*	0.009**	0.752
NPSI Total score	1.0±0.9 (0.1−3.6)	5.2±1.8 (1.7−8.5)	4.5±2.0 (1.4−8.1)	0.001**	0.001**	0.001**	0.323
NPSI Pinpointed pain (cluster 1)	2.0 (10.0%)	0.0	7.0 (35.0%)	0.007**			
NPSI Evoked pain (cluster 2)	1.0 (5.0%)	4.0 (20.0%)	2.0(10.0%)	0.481			
NPSI Deep pain (cluster 3)	17.0(85.0%)	16.0(80.0%)	11.0 (55.0%)	0.123			
PCS Total score	17.4±10.7 (6.0−43.0)	33.0±10.4 (9.0−50.0)	31.1±12.3 (10.0−46.0)	0.001**	0.001**	0.001**	0.695
PCS Rumination	8.8±3.9 (3.0−16.0)	13.1±2.2 (8.0−16.0)	11.8±3.8 (6.0−16.0)	0.002**	0.001**	0.018**	0.436
PCS Magnification	2.8±3.2 (0.0−10.0)	6.9±3.4 (0.0−12.0)	6.3±3.6 (0.0−11.0)	0.003**	0.001**	0.007**	0.703
PCS Helplessness	5.7±5.0 (0.0−18.0)	12.9±5.9 (1.0−23.0)	12.9±6.3 (3.0−23.0)	0.001**	0.001**	0.001**	0.978
HADS Total score	12.1±6.9 (1.0−25.0)	18.9±6.1 (8.0−28.0)	18.4±8.8 (6.0−38.0)	0.011**	0.001**	0.023*	0.860
HADS Anxiety	7.1±3.9 (1.0−14.0)	10.0±3.5 (4.0−16.0)	10.2±4.5 (2.0−19.0)	0.060	0.049*	0.038*	0.643
HADS Depression	4.9±3.8 (0.0−12.0)	8.9±3.5 (3.0−15.0)	8.1±4.9 (2.0−19.0)	0.009**	0.003*	0.035*	0.385
FABQ Physical activity (Score)	19.4±6.0 (2.0−29.0)	19.9±7.8 (5.0−30.0)	25.1±5.9 (11.0−30.0)	0.007**	0.659	0.002**	0.017*
FABQ Labor (Score)	19.5±11.5 (0.0−38.0)	30.7±10.4 (4.0−48.0)	34.5±6.3 (22.0−47.0)	0.001**	0.004**	0.001**	0.255
VAS Visual analogue scale	52.0±11.9 (40.0−80.0)	62.2±16.7 (40.0−100.0)	69.5±17.3 (40.0-100.0)	0.005**	0.047*	0.001**	0.187
Pain duration (months)	85.8±43.7 (12.0−180.0)	151.8±79.3 (24.0−288.0)	161.1±80.4 (30.0−372.0)	0.003**	0.052*	0.001**	0.786

Notes: Results are presented as mean ± s.d (min-max); Qualitative variables were described by frequency and percentages N (%); Fisher's exact test was used for categoric data; Kruskal Wallis's test was used to investigate the values of P intergroup with Bonferroni correction; *P<0.05; **P<0.0125; U-Mann Whitney was performed two-by-two; BPI: Brief Pain Inventory; NRS: Numeric rating scale; DN4: Douleur Neuropathique 4; RMDQ: Roland Morris Disability Questionnaire; MPQ: McGill Pain Questionnaire (Short Form); NPSI: Neuropathic Pain Symptom Inventory; PCS: Pain Catastrophizing Scale; HADS: Hospital Anxiety and Depression Scale; FABQ: Fear-Avoidance Beliefs Questionnaire; VAS: Visual analogue scale 0-100 mm; ns-LBP: Non-specific low back pain; Sc: Sciatic; FBSS: Failed back surgery syndrome; vs: versus.

Discussion

We have found that patients with LBP of different etiologies have different motor corticospinal and pain modulatory status state, and these changes are not only related to the presence of neuropathic pain. Patients with LBP associated with neuropathic pain, such as FBSS and Sc, had more pain and pain-related symptoms, and lower conditioned pain modulation change. Additionally, although changes in motor corticospinal excitability were largely present in all patient groups, they were more marked in patients with FBSS with a lower amplitude of motor evoked potentials, indicating abnormal neuronal membrane excitability, and defective intracortical facilitation, which depends on interneuronal intracortical glutamate signaling [18]. In the FBSS group only, excitability changes did not correlate with pain intensity but did correlate with a series of symptoms such as depressive mood, catastrophizing, and neuropathic pain descriptors.

In the present study, pressure pain suprathreshold was reduced in all groups. However, patients with neuropathic pain (FBSS and Sc) had increased pain intensity compared to ns-LBP. Indeed, studies indicate that pain intensity does not appear to be homogeneous [31,62] across all etiologies of LBP. When these patients were examined using quantitative sensory testing (QST) to assess for possible changes in pain modulatory pathways, they showed different pain sensitivity profiles [35,56,62], and increased pain sensitivity compared to healthy controls. We also found reduced CPM changes in neuropathic pain groups (Sc and FBSS) compared to ns-LBP and healthy control data, while the CPM changes in the ns-LBP group were similar to those of healthy individuals. These findings suggest that different diseases leading to f LBP may present different magnitudes of the endogenous pain diffuse inhibitory control. This further supports that a proper patient characterization is mandatory when reporting CPM values in chronic pain patients with LBP [60]. A recent meta-analysis reported that patients with LBP had impaired CPM compared to healthy controls or reference data, and the magnitude of these differences for CPM seemed to be influenced by chronicity and the severity of the pain [51]. However, in a significant proportion of patients reported in the literature, it is not possible to determine if ns-LBP patients were distinguished from LBP due to other etiologies such as neuropathic pain.

CNS alterations related to LBP have been shown in numerous previous studies [57]. One of the methods to evaluate the CNS is through motor corticospinal excitability (CE) measurements assessed by transcranial magnetic stimulation (TMS). Here we found that motor evoked potential (MEP) was lower in patients with FBSS compared to not only ns-LBP, but also to sciatica, another LBP syndrome with neuropathic pain. MEP decreases have been shown in acute experimental pain studies in healthy volunteers [24,44,79,80] and in patients with chronic pain of mixed etiologies [41]. In LBP, studies of MEP changes are still not conclusive. Some studies observed that patients with chronic pain have no differences in MEP compared to controls [49,50,71], while others have suggested that not only are they relevant, but can also constitute a biomarker of pain recurrency, and potentially the development of chronic pain, after acute pain attacks [37]. Our data provided a more fine-grained glimpse into CE changes in different etiologies of patients with LBP and suggest that these conflicting results may be affected by the different of etiologies of LBP included in some previous studies. Indeed, our original data suggest that group-based comparisons may not be adapted for inferential analyses related to CE, as we found significant differences when patients had CE results individually categorized based on age and sex-matched normative data. Many patients had some of the CE parameters altered compared to healthy data, and there was a high heterogeneity within each patient group in terms of each CE change profiles [14,49,50,76]. Additionally, in several studies CE was assessed at muscles related to the pain region such as erector spinae, which is another source of variability, as the presence of pain in the muscles where CE measurements are being recorded may affect baseline muscle tonus and thus influence results. In fact, such an approach demands the use special coils for stimulation, or the use of very high stimulation intensities, not to mention that assessing motor contractions by neurophysiology at the site of pain is subject to several types of bias related to pre-stimulus muscle activation, local changes in excitability due to pain and tolerability [37]. We have opted for an approach used previously and assessed CE measurements in muscles not affected by the primary disease or pain. It has been shown that areas such as the hand motor representation in the primary motor cortex can show CE alterations that correlate with pain located in other body parts in fibromyalgia and even in neuropathic pain [30,38,43,54]. Here, FBSS patients had a larger proportion of low MEPs compared to patients with ns-LBP and sciatica. Intracortical facilitation, which corresponds to excitatory interneuronal glutamatergic activity within the motor cortex was also found to be reduced in 80% of patients with FBSS. ICF has also been reported to be reduced in fibromyalgia, and is unlikely to be specific to neuropathic pain, since it was also abnormal in patients with ns-LBP [38,54]. Patients with FBSS had defective intracortical facilitation in 80% of cases, suggesting a lack of excitatory control mediated by glutamatergic neurotransmission in this group compared to ns-LBP and sciatica. Even when comparing two groups of LBP associated with neuropathic pain with similar pain intensity and interference, the group with FBSS was more affected than that with sciatica.

Although CPM changes did not correlate with pain intensity and other symptoms, we found that the FBSS group showed correlations between CE and depressive symptoms, catastrophizing and neuropathic pain descriptors. These findings do not implicate causality, and it remains to be determined if these changes can be modulated towards normal values with effective treatment, as has been reported in fibromyalgia and patients with neuropathic pain under therapeutic repetitive TMS and thus be used to either monitor treatment response or to help select patients for treatment [43,54].

Our study has a relatively small sample size. Although sample size choice was predetermined based on effect size calculations and was similar to some of the previous studies assessing CE changes in patients with chronic pain, the chance of type II errors is not excluded. Also, even though both LBP groups with neuropathic pain had similar pain intensity and general pain impact in functioning, and that no CE changes or CPM results correlated with pain intensity, the

Table 2 Motor corticospinal excitability assessment classified according to normative data.

CE		ns-LBP	Sc	FBSS	P	P ns-BP vs. Sc	P ns-LBP vs. FBSS	P Sc vs. FBSS
RMT	Low	8 (20.0%)	10 (25.0%)	8 (20.0%)	0.948	0.817	0.864	0.904
	Normal	6 (15.0%)	7 (17.5%)	8 (20.0%)				
	High	26 (65.0%)	23 (57.5%)	24 (60.0%)				
MEP 120%	Low	2 (5.0%)	5 (12.5%)	9 (22.5%)	0.034*	0.239	0.046*	0.040*
	Normal	10 (25.0%)	5 (12.5%)	12 (30.0%)				
	High	28 (70.0%)	30 (75.0%)	19 (47.5%)				
MEP 140%	Low	8 (20.0%)	6 (15.0%)	20 (50.0%)	0.002*	0.496	0.018*	0.001*
	Normal	5 (12.0%)	9 (22.5%)	2 (5.0%)				
	High	27 (67.5%)	25 (62.5%)	18 (45.0%)				
SICI	Low	5 (12.5%)	10 (25.0%)	6 (15.0%)	0.673	0.334	0.910	0.626
	Normal	13 (32,5%)	10 (25.0%)	11 (27.5%)				
	High	22 (55.0%)	20 (50.0%)	23 (57.5%)				
ICF	Low	21 (52.5%)	21 (52.5%)	32 (80.0%)	0.048*	0.765	0.025*	0.046*
	Normal	16 (40.0%)	14 (35.0%)	6 (15.0%)				
	High	3 (7.5%)	5 (12.5%)	2 (5.0%)				

Notes: Qualitative variables were described by frequency and percentages N (%); Fisher's exact test was used for categoric data values of P intergroups with Bonferroni correction; *P<0.05; CE: Corticospinal excitability; RMT: Rest motor threshold; MEP: Motor evoked potentials; SICI: Short inhibitory cortical inhibition; ICF: Intracortical facilitation; ns-LBP: Non-specific low back pain; Sc: Sciatic; FBSS: Failed back surgery syndrome; vs: versus.

ns-LBP group was significantly less impacted by pain in terms of intensity and interference with general activities. We have actively chosen not to stratify or select patients to the ns-LBP group based on pain intensity, because as has been reported previously, patients with neuropathic pain are intrinsically more impacted by pain and higher pain than patients with ns-LBP where no neurological lesion exists. In general, patients with chronic sciatica and FBSS have longer standing diseases and are more refractory to usual treatments than ns-LBP [74]. Another limitation of the present study is that it assessed patients with moderate and severe pain. This was chosen because these are usually the patients more challenging to manage, and therefore more commonly included in clinical trials. This was also a pragmatic choice intended to decrease variability in pain intensity in an exploratory study. This means that it remains to be determined to what extent results would be influenced by the inclusion of all ranges of pain intensities in the three groups.

In conclusion, chronic low back pain is a heterogeneous condition, and may include pain of different mechanisms. Patients with neuropathic pain and LBP have more impacted pain modulatory systems compared to ns-LBP, and even within neuropathic pain groups, changes in cortical excitability may exist, with FBSS groups having more patients with lower MEP amplitudes and lower ICF, which correlated with clinical pain characteristics. These changes were different from sciatica and patients with ns-LBP and further support the idea that mechanism and neurophysiological studies in LBP must specify the type of patients under scrutiny in order to improve external validity and clinical usefulness of these efforts.

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Declaration of Competing Interest

There are no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.neucli.2023.102853.

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