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Central sensitization and changes in conditioned pain modulation in people with chronic nonspecific low back pain: a case–control study

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Abstract

Quantitative sensory testing is widely used in human research to investigate the state of the peripheral and central nervous system contributions in pain processing. It is a valuable tool to help identify central sensitization and may be important in the treatment of low back pain. The aim of this study was to evaluate changes in local and segmental hypersensitivity and endogenous pain inhibition in people with chronic nonspecific low back pain. Thirty patients with chronic low back pain and thirty healthy subjects were studied. Pressure pain thresholds (PPTs) were measured from the lumbar region and over the tibialis anterior muscle (TA). A cold pressor test was used to assess the activation of conditioned pain modulation (CPM), and PPTs in the lumbar region were recorded 30 s after immersion of participant's foot in a bucket with cold water. People with chronic low back pain have significantly lower PPT than controls at both the lumbar region [89.5 kPa (mean difference) 95 % CI 40.9–131.1 kPa] and TA [59.45 kPa (mean difference) 95 % CI 13.49–105.42 kPa]. During CPM, people with chronic low back pain have significantly lower PPT than controls in lumbar region [118.6 kPa (mean difference) 95 % CI 77.9–159.2 kPa]. Women had significantly lower PPTs than men in both lumbar region [101.7 kPa (mean difference) 95 % CI 37.9–165.7 kPa] and over the TA [189.7 kPa (mean difference) 95 % CI 14.2–145.2 kPa]. There was no significant difference in PPTs in men between healthy controls and those with low back pain, suggesting the significant differences are mediated primarily by difference between women.

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Conflict of interest The authors have no conflict of interest to disclose.

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Keywords

Low back pain; Central nervous system sensitization; Hyperalgesia; Diffuse noxious inhibitory controls; Pain inhibition

Introduction

Low back pain (LBP) is an important public health problem (Airaksinen et al. 2006; Koldas Dogan et al. 2008; Delitto et al. 2012), is very prevalent (Airaksinen et al. 2006) and often persists for years or decades (Neziri et al. 2012). People with chronic low back pain have exaggerated pain responses to stimulation of peripheral tissues that are distant from the site of primary symptoms (Giesecke et al. 2004; Giesbrecht and Battie 2005; Latremoliere and Woolf 2009; Tamcan et al. 2010) and may demonstrate changes in the muscles, ligaments or joints; however, the severity of these structural dysfunctions weakly correlates with the clinical presentation and in most cases is not directly related to radiological findings (Chou et al. 2011). Substantial improvements in people with chronic low back pain are rare, causing most people to have to live with chronic pain (Tamcan et al. 2010).

Alterations in central nociceptive processes after peripheral lesions have been extensively documented in animal models and provide evidence for sensitization at different sites of the central nervous system (Giesecke et al. 2004). This is suggestive for a widespread augmentation of central nociceptive processes. From a management perspective, it is highly important to reduce pain intensity and to minimize the duration of pain (Carli et al. 2002; Fernandez-de-Las-Penas et al. 2007; Nijs et al. 2011). Furthermore, the selected set of pain assessments and the composite score of pain sensitivity could serve as a clinically applicable quantitative sensory pain assessment in the examination of LBP (O'Neill et al. 2014). Enhanced excitability in the central nervous system is an important phenomenon observed in people with chronic low back pain (O'Neill et al. 2007; Nijs et al. 2010; Imamura et al. 2013) and occurs in a variety of chronic pain conditions (Clauw et al. 1999; Huppe et al. 2004; Jensen et al. 2010; Pollard et al. 2012). One of the descending inhibitory mechanisms that modulates pain processing is diffuse noxious inhibitory controls (DNIC) (Yarnitsky et al. 2010; Nir and Yarnitsky 2015). In animals, activity of dorsal horn nociceptive neurons is attenuated in response to noxious stimuli applied to a remote area of the body. In humans, this is referred to as conditioned pain modulation (CPM) and results in an increase in pain threshold outside the site of noxious stimuli (Villanueva et al. 1996; Pielsticker et al. 2005; Arendt-Nielsen et al. 2008; Pud et al. 2009). Activation of CPM reduces neuronal activity of the spinal cord dorsal horn, decreasing pain and hyperalgesia in animals (Bouhassira et al. 1992) and humans (Bouhassira et al. 1992; Maixner et al. 1998; Meeus et al. 2008; Villanueva 2009; Pollard et al. 2012; Roussel et al. 2013). A recent systematic literature review compared the efficacy of CPM between chronic pain and healthy populations and concluded that CPM is impaired in populations with chronic pain (Lewis et al. 2012). The sex and age of participant were relevant moderators influencing effect size. CPM is reduced with age and is more impaired in females with chronic pain conditions compared to males with chronic pain conditions (Lewis et al. 2012). However, studies that have examined the responsiveness to various noxious stimuli in patients with chronic low back pain are

controversial with studies favoring (Clauw et al. 1999; Giesecke et al. 2004; Giesbrecht and Battie 2005; Laursen et al. 2005), rejecting (Peters et al. 1992; Diers et al. 2007; Meeus et al. 2010) or with mixed results (O'Neill et al. 2007) for enhanced excitability in people with chronic LBP.

There is considerable variation in sensitivity to pain in the general population (Rolke et al. 2006), and the study of pain modulation characteristics may be an important factor in understanding the chronicity of pain. Given the increasing evidence supporting the clinical significance of central excitability in unexplained chronic pain, including chronic LBP, awareness is growing that central sensitization should be a treatment target (Nijs et al. 2011). Therefore, the aim of this study was to evaluate local and segmental pressure pain threshold and endogenous pain inhibition in people with chronic nonspecific low back pain in both men and women. The hypothesis of this study is that people with chronic low back pain have reduced PPT and deficiency in the CPM when compared to healthy subjects.

Materials and methods

Design of study

Thirty people with chronic nonspecific low back pain were recruited. Participants with low back pain were recruited from the physiotherapy clinic at the Universidade Cidade de São Paulo—UNICID/Brazil. To be included in the study, people must have experienced back pain for at least 3 months and have reported a minimal pain level of 3 on the 0–10 pain numerical rating scale (NRS) (Costa et al. 2008) in the last 7 days. Patients were excluded if they had taken pain medications on the day of the assessment or if they had serious spinal pathologies, such as fractures, tumors or inflammatory diseases, such as ankylosing spondylitis, nerve root compromise confirmed by clinical neurological tests (disk herniation and spondylolisthesis with neurological involvement, narrowing of spinal canal and other conditions) or severe cardiorespiratory diseases. Those who were pregnant, patients with cancer and those with a cardiac pacemaker were also excluded.

We classified patients as having chronic nonspecific low back pain using the diagnostic triage as recommended by the European Guidelines (Airaksinen et al. 2006) as well as by the American Physical Therapy Association Guidelines (Delitto et al. 2012) for the management of patients with low back pain.

Thirty asymptomatic healthy subjects were also recruited to form a control group. The controls were matched for sex and age in relation to the low back pain group. These participants must not have presented episodes of low back pain for more than 7 days in the last 12 months. Individuals aged 30–80 years and of both sexes were included in both groups.

The sample size was calculated based on a difference of 100 kPa between low back pain subjects and healthy controls during a CPM test, with a standard deviation of 87 kPa. The magnitude of pain inhibition during a CPM test was obtained from previous data on CPM and PPT in healthy controls by our research team (Correa et al. 2013; Liebano et al. 2013). At a significance level of 0.05 and power of 95 %, it was calculated that a minimum of 21

participants was required in each group (Minitab, v. 15, State College, PA). To allow for attrition, 30 participants were recruited for each group.

Evaluation

The study was approved by the UNICID Ethics and Research Committee. After the study participants' eligibility was evaluated, they were given information about the study and asked to sign the consent form to participate in the study. A demographic questionnaire was used to collect data related to sex, age, body mass index, pain intensity and duration of pain of the participants. An examiner was responsible for recording pain measures, and another examiner was responsible for application of the assessments.

Measurement instruments

Numerical rating scale for pain (NRS)—The NRS evaluates levels of pain intensity using an 11-point scale (range 0–10), with 0 being classified as "no pain" and 10 "pain as bad as could be." Pain evaluation was assessed verbally by having people report pain intensity for the last 7 days as a criterion for inclusion in the study. The instrument used has been translated and cross-culturally adapted for the Brazilian population (Costa et al. 2008).

Pressure pain threshold (PPT)—Pressure pain thresholds were measured over the lumbar region (paravertebral musculature) and the tibialis anterior muscle using a Type II digital pressure algometer (Somedic Inc., Hörby, Sweden). The algometer used a circular probe algometer (of 1 cm^2 area), and pressure was applied at a rate of 50 kPa/s. A total of two measurements (Arendt-Nielsen et al. 2010; Dailey et al. 2013) were collected from each area, separated by a 30-s interval and averaged.

The evaluating researcher conducted a preliminary study of intra-examiner reliability for PPT measurement of the evaluation points that were used in the study. Intra-examiner reliability for PPT measurements was estimated by calculating the intra-class correlation coefficients (type 3,2) for the tibialis anterior muscle (0.91; 95 % CI 0.31–0.95) and lumbar muscles (0.82; 95 % CI 0.65–0.97), which represent excellent reliability.

A measuring tape and a pen were used to mark the algometry evaluation points. The participant remained seated in a chair with upper limbs supported on a table, and then, two points were marked bilaterally, the first located 5 cm lateral to the L3 spinous process (Meeus et al. 2010; Correa et al. 2013) and the second 5 cm lateral to the L5 spinous process (Schenk et al. 2007; Correa et al. 2013). A point was also marked over the tibialis anterior muscle of the right leg 5 cm from the tibial tuberosity (Arendt-Nielsen et al. 2010; O'Neill et al. 2011; Dailey et al. 2013). Familiarization with the PPT was performed by applying the pressure twice for each patient on the dominant forearm extensor muscles to ensure that the test was understood. If there was any doubt, a third demonstration was performed.

During PPT measurement, the algometer was positioned perpendicular to the skin. The participants were asked to press and release a button when the sensation of pressure became a clear pain sensation. If the participant failed to report pain to a pressure of 1000 kPa, the test was stopped, and this value was recorded as the PPT (Liebano et al. 2011).

Activation of conditioned pain modulation (CPM)—A cold pressor test was used to induce pain and trigger the CPM response (Knudsen and Drummond 2009; Dailey et al. 2013). The conditioned stimulus was immersion of the leg in a bucket of ice water (2 min, 3 cm above lateral malleolus) on the side ipsilateral to the most painful lumbar region. If there was bilateral pain, the subject was instructed to report the more painful side (Neziri et al. 2012). If there was no consensus on the more painful side, the right leg was used. In volunteers without pain, the right leg was used. The lumbar PPT was recorded beginning 30 s after immersion of the leg (Neziri et al. 2012) with two PPT measures for each point. PPTs during CPM were compared to baseline PPTs. An interim analysis, using *t* test for independent samples, showed that women with LBP had lower PPT than men with LBP. Thus, a secondary analysis was performed to examine the relationship between sex and PPT.

Statistical analysis

Results are expressed as mean and standard deviations (SD). An average of the two PPT scores recorded at each site was used for analysis. Descriptive statistics were calculated for all variables, and the data were normally distributed (calculated by the Shapiro–Wilk test). Pain intensity and the PPT change data were therefore analyzed using a *t* test for independent samples. Associations among pain intensity, duration of pain, tibialis anterior PPT and PPT differences from baseline during CPM tests were assessed using Pearson's product–moment correlation coefficients. Statistical significance was set at $p < 0.05$. All analyses were performed using Statistical Package for Social Sciences (version 17.0; SPSS Inc., Chicago, IL) and Microsoft Excel 2007.

Results

Of a total of 36 people with chronic low back pain who were evaluated, 30 were included in the study from February to May 2013. The reasons for exclusion were: fibromyalgia (n = 1), previous back surgery (n = 1), lumbar pain due to nerve root compromise (n = 1), vertebrae fracture (n = 1) and pain intensity lower than 3 on the numerical pain scale (n = 2). The characteristics of study participants are described in Table 1.

Lumbar PPT and tibialis anterior PPT

People with nonspecific chronic low back pain had significantly lower pressure pain thresholds in the lumbar region (mean = 253 kPa, SD = 6.5) when compared to the control group (mean = 342.5 kPa, SD = 127.7) (between-group difference = 89.5 kPa, 95 % CI 40.9–131.1 kPa; $p = 0.001$). Similarly, PPT recorded over the tibialis anterior muscle (region segmental to the primary pain site) in people with chronic low back pain (mean = 262.4 kPa, SD = 93.1) was significantly lower when compared to the control group (mean = 321.8 kPa, SD = 84.5) (betweengroup difference = 59.4 kPa, 95 % CI 13.5–105.4 kPa; $p = 0.012$). The PPTs for lumbar and tibialis anterior for the two groups are summarized in Table 2.

When stratified by sex, women with nonspecific chronic low back showed lower PPTs over lumbar area (212.3 kPa, SD = 63.5) when compared to healthy women (327.4 kPa, SD = 88.02) (between-group difference = 115.2 kPa, 95 % CI 63.7–116.6 kPa; $P = 0.001$). In the tibialis anterior region, women with chronic low back again presented lower PPT (mean =

120.5 kPa, SD = 73.9) when compared to healthy women (mean = 315.3 kPa, SD = 88.6) (between-group difference = 194.8 kPa, 95 % CI 271.3–359.3 kPa; *P* = 0.004). In men, PPTs from the lumbar and tibialis anterior region were similar between those with chronic low back pain and healthy controls. When comparing PPTs from lumbar area in men (mean = 314.0 kPa, SD = 107.5) with women (mean = 212.3 kPa, SD = 63.5) in the low back pain group, women had lower PPTs (between-group difference = 101.7 kPa, 95 % CI 37.9–165.7 kPa; *P* = 0.003). Similar results were observed when comparing PPTs recorded over the tibialis anterior muscle in women (mean = 120.5 kPa, SD = 73.9) with men (mean = 310.2 kPa, SD = 101.3) in the low back pain group (between-group difference = 189.7 kPa, 95 % CI 14.2–145.2 kPa; *P* = 0.02; Table 3). No significant differences in PPTs were observed between men and women in the healthy control group. Thus, the differences observed in PPTs in those with chronic low back pain are due primarily to differences in women and not men.

Conditioned pain modulation (CPM)

People with nonspecific chronic low back pain showed a statistically significant decrease in lumbar PPT (mean = −47.17 kPa, SD = 73.3) during the cold pressor test when compared to the control group which showed an increase in PPT (mean = 71.4, SD = 83.8). There was a significant difference between the change in PPT between the healthy controls and those with chronic low back pain (between-group difference = 118.6 kPa, 95 % CI 77.9–159.2 kPa; $P < 0.001$; Table 2). When stratified by sex, both men and women in the low back pain group showed a decrease in PPT below baseline when compared to healthy control, which showed increases in PPT (Table 3). There were no differences between sexes in the difference score during CPM.

Correlation between pain intensity and duration and pain excitability and inhibition

There was no correlation between the intensity of pain over the last week and PPT over the tibialis anterior muscle (r = −0.08, *P* = 0.68) or between pain duration (r = −0.09, *P* = 0.65) and PPT over the tibialis anterior muscle in the group with chronic nonspecific low back pain. There was also no correlation between the intensity of pain during the last week and difference in PPT during CPM (r = 0.008, *P* = 0.97) or between the duration of pain and difference in PPT during CPM (r = 0.18, *P* = 0.34) in those with chronic low back pain.

Discussion

The current study showed a decrease in the PPT at the primary pain site in the lumbar spine and in the segmental pain area over the tibialis anterior when compared to healthy controls matched for sex and age, agreeing with prior studies (Clauw et al. 1999; Giesecke et al. 2004; Giesbrecht and Battie 2005; Laursen et al. 2005; Imamura et al. 2013). Our findings extend those of prior studies showing a significant difference between those with chronic low back pain and healthy controls only in women but not men (Popescu et al. 2010; Martel et al. 2013), suggesting that the differences in PPT between subjects with low back pain and healthy controls are primarily driven by changes in women who have enhanced widespread sensitivity.

Local and segmental hypersensitivity

The decrease in PPT at both the primary pain area and segmentally in those with low back pain shown in the current study, and in prior studies (O'Neill et al. 2007, 2011; Staud 2011; Neziri et al. 2012; Imamura et al. 2013; Mlekusch et al. 2013), suggests the existence of both primary and secondary hyperalgesia in people with chronic low back pain. It is generally accepted that sensitized central neurons amplify sensory input arising from the site of tissue damage and receptive fields of sensitized neurons expand to result in secondary hyperalgesia and pain (DeSantana et al. 2008). Despite the fact that several studies point toward altered central processing in people with chronic low back pain, the results are still controversial (Peters et al. 1992; Meeus et al. 2010; Imamura et al. 2013). Reduced pain threshold at the primary pain site and in locations removed from the primary pain site suggests generalized hyperalgesia (Clauw et al. 1999; Giesecke et al. 2004; Laursen et al. 2005). Segmentally, however, there are mixed results (Peters et al. 1989; Diers et al. 2007; O'Neill et al. 2007). The discrepancies between studies may be attributed to some methodological problems, such as small sample sizes, use of drugs and evaluation criteria for inclusion of people with low back pain.

Alternatively, the differences between studies could be related to sex differences since we show significant differences in PPTs between healthy controls and women with low back pain, but not men. It is well recognized that women have lower PPTs than men (Popescu et al. 2010); however, the finding that decreases in PPTs only occurred in women when compared to healthy controls is novel. Chronic pain is more common in women than men, including chronic low back pain (Berkley 1997; Greenspan et al. 2007; Boyan et al. 2013; Martel et al. 2013). Females have greater central excitability on a number of measures—temporal summation, secondary hyperalgesia, referred pain (Peters et al. 1992; Leffler et al. 2002; Sarlani et al. 2007; Shah et al. 2008; Knudsen and Drummond 2009; Meeus et al. 2010; Arendt-Nielsen et al. 2011) and decreased inhibition—CPM (Arendt-Nielsen et al. 2010; Popescu et al. 2010; Martel et al. 2013; Roussel et al. 2013). Indeed, in an animal model of muscle pain, female mice developed widespread hyperalgesia, while males developed localized hyperalgesia; female mice had longer-lasting hyperalgesia, and hyperalgesia was easier to induce in female mice (Gregory et al. 2013). The cause of the sex differences is not fully understood, but assumed to include physiological, psychological and environmental factors (Greenspan et al. 2007).

Conditioned pain modulation

In the present study, both men and women with chronic low back pain had significantly lower local PPT values than healthy subjects during CPM, suggesting a deficiency of the endogenous descending inhibitory system in both sexes. In a variety of chronic pain conditions, there is a loss of CPM (Lautenbacher and Rollman 1997; Laursen et al. 2005; Knudsen and Drummond 2009), agreeing with our findings in people with chronic low back pain. On the other hand, a prior study shows no difference in CPM in people with chronic low back pain compared to healthy subjects. However, the conditioned stimulus was a 12 °C water bath (Julien et al. 2005), as compared to 4 °C in the current study. Thus, differences could be related to the intensity of the conditioning stimulus, and in people with chronic low back pain, CPM may only be deficient at higher intensities (Julien et al. 2005).

Alternatively, we examined PPT values during CPM over the painful area (lumbar), while prior studies measured PPT values outside area of pain (leg and upper trapezius) (Knudsen and Drummond 2009; Martel et al. 2013). It is possible that CPM deficits occur in the primary or segmental sites of pain (Dailey et al. 2013), and sites that are extrasegmental are unaffected.

Our results are in agreement with previous studies that showed no differences between the sexes in CPM (France and Suchowiecki, 1999; Baad-Hansen et al. 2005; Pud et al. 2005). Nevertheless, other studies showed less efficient CPM in women than men (Staud et al. 2003; Ge et al. 2004; Arendt-Nielsen et al. 2008; Granot et al. 2008; Martel et al. 2013). Therefore, differences in CPM effect between sexes may depend on both the experimental methodology and the modes of measurement of the effect (Popescu et al. 2010).

Associations between pain measures

Deficiencies in endogenous pain modulation are thought to contribute to changes in pain sensation (O'Neill et al. 2007; Knudsen and Drummond 2009). Surprisingly, the current study saw no associations between clinical pain measures of pain intensity and duration, and quantitative sensory testing measures of PPT and CPM. Similar to the current study, Mlekusch and colleagues showed no association between measures of widespread central hypersensitivity (pressure pain tolerance threshold at the second toe and tolerance time during cold pressor test at the hand) or altered CPM at baseline with pain intensity at 12-to15-month follow-up in people with chronic low back pain and neck pain (Mlekusch et al. 2013). In a prospective study, Le Resche showed psychophysical test measures were not significant predictors of low back pain (4 months) (LeResche et al. 2013). The lack of association between clinical pain intensity and duration, and quantitative sensory testing measures suggests there may be other mechanisms that mediate pain intensity and pain duration in those with chronic low back pain that are not directly related to PPT and CPM measures.

Limitations

The present study has limitations, mainly related to the inclusion of a limited number of variables for examining the mechanisms underlying the stability of CPM. Future research in this area should examine the potential contribution of genetic, neurobiologic and other psychological factors as potential mechanisms underlying the stability of CPM. Future studies should also consider the influence of sex hormones or women's menstrual cycle when examining sex differences. In addition, the researchers responsible for tests applications and recording of pain measures were not blinded, which also represents a limitation of the study.

Clinical implications

Recent evidence suggests that heightened baseline pain sensitivity and reduced basal CPM place individuals at greater risk of experiencing severe, acute, clinical pain (Clauw et al. 1999; Carli et al. 2002; Giesbrecht and Battie 2005; Diers et al. 2007; O'Neill et al. 2007, 2011; Meeus et al. 2010). More controversial is the hypothesis that such individual difference characteristics confer risk of, or protection against, chronic pain. Cross-sectional

studies indicate that people with chronic pain conditions differ from painfree controls in their responses to traditional psychophysical pain sensitivity tests with chronic pain patients showing greater pain sensitivity (Clauw et al. 1999; Giesecke et al. 2004; King et al. 2009) and less CPM (Lautenbacher and Rollman 1997; Banic et al. 2004; Herren-Gerber et al. 2004; Pielsticker et al. 2005; King et al. 2009; John 2011; Dailey et al. 2013).

The evaluation of these mechanisms may be important in the treatment of low back pain with the aim of decreasing enhanced excitability by increasing the pressure pain threshold and increasing central inhibition by activation of CPM. Moreover, conservative treatments (such as transcutaneous electric nerve stimulation (TENS), manual therapy or exercise) aim to desensitize the central nervous system and improve central inhibition (Nijs et al. 2011). Indeed, prior studies show that TENS in those with fibromyalgia or osteoarthritis can increase pressure pain thresholds outside the site of stimulation (Dailey et al. 2013; Vance et al. 2012) and restore CPM (Dailey et al. 2013). Prior work also shows that exercise can increase CPM (Naugle and Riley 2014) and decrease central excitability (Bement and Sluka 2005), and CPM predicts hypoalgesia produced by exercise (Lemley et al. 2015). Thus, understanding the underlying mechanisms of chronic pain may help to target therapies designed to normalize pain physiology.

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References

Airaksinen O, Brox JI, Cedraschi C, et al. European guidelines for the management of chronic nonspecific low back pain. Eur Spine J. 2006; 15(Suppl 2):S192–S300. Chapter 4. [PubMed: 16550448]

Arendt-Nielsen L, Sluka KA, Nie HL. Experimental muscle pain impairs descending inhibition. Pain. 2008; 140:465–471. [PubMed: 18977598]

Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, Graven-Nielsen T. Sensitization in patients with painful knee osteoarthritis. Pain. 2010; 149:573–581. [PubMed: 20418016]

Arendt-Nielsen L, Fernandez-de-Las-Penas C, Graven-Nielsen T. Basic aspects of musculoskeletal pain: from acute to chronic pain. J Man Manip Ther. 2011; 19:186–193. [PubMed: 23115471]

Baad-Hansen L, Poulsen HF, Jensen HM, Svensson P. Lack of sex differences in modulation of experimental intraoral pain by diffuse noxious inhibitory controls (DNIC). Pain. 2005; 116:359–365. [PubMed: 15979791]

Banic B, Petersen-Felix S, Andersen OK, Radanov BP, Villiger PM, Arendt-Nielsen L, Curatolo M. Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. Pain. 2004; 107:7–15. [PubMed: 14715383]

Bement MK, Sluka KA. Low-intensity exercise reverses chronic muscle pain in the rat in a naloxone-dependent manner. Arch Phys Med Rehabil. 2005; 86:1736–1740. [PubMed: 16181935]

Berkley KJ. Sex differences in pain. Behav Brain Sci. 1997; 20:371–380. discussion 435–513. [PubMed: 10097000]

Bouhassira D, Villanueva L, Bing Z, le Bars D. Involvement of the subnucleus reticularis dorsalis in diffuse noxious inhibitory controls in the rat. Brain Res. 1992; 595:353–357. [PubMed: 1467976]

Boyan BD, Tosi LL, Coutts RD, Enoka RM, et al. Addressing the gaps: sex differences in osteoarthritis of the knee. Biol Sex Differ. 2013; 4(1):4. [PubMed: 23374401]

Carli G, Suman AL, Biasi G, Marcolongo R. Reactivity to superficial and deep stimuli in patients with chronic musculoskeletal pain. Pain. 2002; 100:259–269. [PubMed: 12467997]

Chou R, Qaseem A, Owens DK, Shekelle P. Diagnostic imaging for low back pain: advice for high-value health care from the American College of Physicians. Ann Intern Med. 2011; 154:181–189. [PubMed: 21282698]

Clauw DJ, Williams D, Lauerman W, et al. Pain sensitivity as a correlate of clinical status in individuals with chronic low back pain. Spine (Phila Pa 1976). 1999; 24:2035–2041. [PubMed: 10528381]

Correa JB, Costa LO, de Oliveira NT, Sluka KA, Liebano RE. Effects of the carrier frequency of interferential current on pain modulation in patients with chronic nonspecific low back pain: a protocol of a randomised controlled trial. BMC Musculoskelet Disord. 2013; 14:195. [PubMed: 23802771]

Costa LO, Maher CG, Latimer J, Ferreira PH, Ferreira ML, Pozzi GC, Freitas LM. Clinimetric testing of three self-report outcome measures for low back pain patients in Brazil: Which one is the best? Spine (Phila Pa 1976). 2008; 33:2459–2463. [PubMed: 18923324]

Dailey DL, Rakel BA, Vance CG, et al. Transcutaneous electrical nerve stimulation reduces pain, fatigue and hyperalgesia while restoring central inhibition in primary fibromyalgia. Pain. 2013; 154:2554–2562. [PubMed: 23900134]

Delitto A, George SZ, Van Dillen LR, et al. Low back pain. J Orthop Sports Phys Ther. 2012; 42:A1–A57. [PubMed: 22466247]

DeSantana JM, Walsh DM, Vance C, et al. Effectiveness of transcutaneous electrical nerve stimulation for treatment of hyperalgesia and pain. Curr Rheumatol Rep. 2008; 10:492–499. [PubMed: 19007541]

Diers M, Koeppe C, Diesch E, et al. Central processing of acute muscle pain in chronic low back pain patients: an EEG mapping study. J Clin Neurophysiol. 2007; 24:76–83. [PubMed: 17277582]

Fernandez-de-Las-Penas C, Ge HY, Arendt-Nielsen L, Cuadrado ML, Pareja JA. The local and referred pain from myofascial trigger points in the temporalis muscle contributes to pain profile in chronic tension-type headache. Clin J Pain. 2007; 23:786–792. [PubMed: 18075406]

France CR, Suchowiecki S. A comparison of diffuse noxious inhibitory controls in men and women. Pain. 1999; 81:77–84. [PubMed: 10353495]

Ge HY, Madeleine P, Arendt-Nielsen L. Sex differences in temporal characteristics of descending inhibitory control: an evaluation using repeated bilateral experimental induction of muscle pain. Pain. 2004; 110:72–78. [PubMed: 15275754]

Giesbrecht RJ, Battie MC. A comparison of pressure pain detection thresholds in people with chronic low back pain and volunteers without pain. Phys Ther. 2005; 85:1085–1092. [PubMed: 16180957]

Giesecke T, Gracely RH, Grant MA, Nachemson A, Petzke F, Williams DA, Clauw DJ. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheum. 2004; 50:613–623. [PubMed: 14872506]

Granot M, Weissman-Fogel I, Crispel Y, Pud D, Granovsky Y, Sprecher E, Yarnitsky D. Determinants of endogenous analgesia magnitude in a diffuse noxious inhibitory control (DNIC) paradigm: Do conditioning stimulus painfulness, gender and personality variables matter? Pain. 2008; 136:142–149. [PubMed: 17720319]

Greenspan JD, Craft RM, LeResche L, et al. Studying sex and gender differences in pain and analgesia: a consensus report. Pain. 2007; 132(Suppl 1):S26–S45. [PubMed: 17964077]

Gregory NS, Gibson-Corley K, Frey-Law L, Sluka KA. Fatigue-enhanced hyperalgesia in response to muscle insult: induction and development occur in a sex-dependent manner. Pain. 2013; 154:2668–2676. [PubMed: 23906552]

Herren-Gerber R, Weiss S, Arendt-Nielsen L, Petersen-Felix S, Di Stefano G, Radanov BP, Curatolo M. Modulation of central hypersensitivity by nociceptive input in chronic pain after whiplash injury. Pain Med. 2004; 5:366–376. [PubMed: 15563322]

Huppe A, Brockow T, Raspe H. Chronic widespread pain and tender points in low back pain: a population-based study. Z Rheumatol. 2004; 63:76–83. [PubMed: 14991280]

Imamura M, Chen J, Matsubayashi SR, Targino RA, Alfieri FM, Bueno DK, Hsing WT. Changes in pressure pain threshold in patients with chronic nonspecific low back pain. Spine (Phila Pa 1976). 2013; 38:2098–2107. [PubMed: 24026153]

Jensen OK, Nielsen CV, Stengaard-Pedersen K. Low back pain may be caused by disturbed pain regulation: a cross-sectional study in low back pain patients using tender point examination. Eur J Pain. 2010; 14:514–522. [PubMed: 19811937]

John MT. Whiplash is likely to be associated with temporomandibular disorder symptoms, but the magnitude of this association is not known. J Evid Based Dent Pract. 2011; 11:127–128. [PubMed: 21855808]

Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain. 2005; 114:295–302. [PubMed: 15733656]

King CD, Wong F, Currie T, Mauderli AP, Fillingim RB, Riley JL 3rd. Deficiency in endogenous modulation of prolonged heat pain in patients with irritable bowel syndrome and temporomandibular disorder. Pain. 2009; 143:172–178. [PubMed: 19278784]

Knudsen L, Drummond PD. Cold-induced limb pain decreases sensitivity to pressure-pain sensations in the ipsilateral forehead. Eur J Pain. 2009; 13:1023–1029. [PubMed: 19171493]

Koldas Dogan S, Sonel Tur B, Kurtais Y, Atay MB. Comparison of three different approaches in the treatment of chronic low back pain. Clin Rheumatol. 2008; 27:873–881. [PubMed: 18188660]

Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain. 2009; 10:895–926. [PubMed: 19712899]

Laursen BS, Bajaj P, Olesen AS, Delmar C, Arendt-Nielsen L. Health related quality of life and quantitative pain measurement in females with chronic non-malignant pain. Eur J Pain. 2005; 9:267–275. [PubMed: 15862476]

Lautenbacher S, Rollman GB. Possible deficiencies of pain modulation in fibromyalgia. Clin J Pain. 1997; 13:189–196. [PubMed: 9303250]

Leffler AS, Hansson P, Kosek E. Somatosensory perception in a remote pain-free area and function of diffuse noxious inhibitory controls (DNIC) in patients suffering from long-term trapezius myalgia. Eur J Pain. 2002; 6:149–159. [PubMed: 11900475]

Lemley KJ, Hunter SK, Bement MK. Conditioned pain modulation predicts exercise-induced hypoalgesia in healthy adults. Med Sci Sports Exerc. 2015; 47:176–184. [PubMed: 24870571]

LeResche L, Turner JA, Saunders K, Shortreed SM, Von Korff M. Psychophysical tests as predictors of back pain chronicity in primary care. J Pain. 2013; 14:1663–1670. [PubMed: 24290446]

Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. J Pain. 2012; 13:936–944. [PubMed: 22981090]

Liebano RE, Rakel B, Vance CG, Walsh DM, Sluka KA. An investigation of the development of analgesic tolerance to TENS in humans. Pain. 2011; 152:335–342. [PubMed: 21144659]

Liebano RE, Vance CG, Rakel BA, et al. Transcutaneous electrical nerve stimulation and conditioned pain modulation influence the perception of pain in humans. Eur J Pain. 2013; 17:1539–1546. [PubMed: 23650092]

Maixner W, Fillingim R, Sigurdsson A, Kincaid S, Silva S. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain: evidence for altered temporal summation of pain. Pain. 1998; 76:71–81. [PubMed: 9696460]

Martel MO, Wasan AD, Edwards RR. Sex differences in the stability of conditioned pain modulation (CPM) among patients with chronic pain. Pain Med. 2013; 14:1757–1768. [PubMed: 23924369]

Meeus M, Nijs J, Van de Wauwer N, Toeback L, Truijen S. Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: an experimental study. Pain. 2008; 139:439–448. [PubMed: 18617327]

Meeus M, Roussel NA, Truijen S, Nijs J. Reduced pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low back pain: an experimental study. J Rehabil Med. 2010; 42:884–890. [PubMed: 20878051]

Mlekusch S, Schliessbach J, Camara RJ, Arendt-Nielsen L, Juni P, Curatolo M. Do central hypersensitivity and altered pain modulation predict the course of chronic low back and neck pain? Clin J Pain. 2013; 29:673–680. [PubMed: 23370065]

Naugle KM, Riley JL. Self-reported physical activity predicts pain inhibitory and facilitatory function. Med Sci Sports Exerc. 2014; 46:622–629. [PubMed: 23899890]

Neziri AY, Dickenmann M, Scaramozzino P, Andersen OK, Arendt-Nielsen L, Dickenson AH, Curatolo M. Effect of intravenous tropisetron on modulation of pain and central hypersensitivity in chronic low back pain patients. Pain. 2012; 153:311–318. [PubMed: 22100357]

Nijs J, Van Houdenhove B, Oostendorp RA. Recognition of central sensitization in patients with musculoskeletal pain: application of pain neurophysiology in manual therapy practice. Man Ther. 2010; 15:135–141. [PubMed: 20036180]

Nijs J, Meeus M, Van Oosterwijck J, Roussel N, De Kooning M, Ickmans K, Matic M. Treatment of central sensitization in patients with 'unexplained' chronic pain: What options do we have? Expert Opin Pharmacother. 2011; 12:1087–1098. [PubMed: 21254866]

Nir RR, Yarnitsky D. Conditioned pain modulation. Curr Opin Support Palliat Care. 2015 Feb 19. [Epub ahead of print].

O'Neill S, Manniche C, Graven-Nielsen T, Arendt-Nielsen L. Generalized deep-tissue hyperalgesia in patients with chronic low-back pain. Eur J Pain. 2007; 11:415–420. [PubMed: 16815054]

O'Neill S, Kjaer P, Graven-Nielsen T, Manniche C, Arendt-Nielsen L. Low pressure pain thresholds are associated with, but does not predispose for, low back pain. Eur Spine J. 2011; 20:2120–2125. [PubMed: 21512842]

O'Neill S, Manniche C, Graven-Nielsen T, Arendt-Nielsen L. Association between a composite score of pain sensitivity and clinical parameters in low-back pain. Clin J Pain. 2014; 30:831–838. [PubMed: 24121529]

Peters ML, Schmidt AJ, Van den Hout MA. Chronic low back pain and the reaction to repeated acute pain stimulation. Pain. 1989; 39:69–76. [PubMed: 2530488]

Peters ML, Schmidt AJ, Van den Hout MA, Koopmans R, Sluijter ME. Chronic back pain, acute postoperative pain and the activation of diffuse noxious inhibitory controls (DNIC). Pain. 1992; 50:177–187. [PubMed: 1408314]

Pielsticker A, Haag G, Zaudig M, Lautenbacher S. Impairment of pain inhibition in chronic tension-type headache. Pain. 2005; 118:215–223. [PubMed: 16202520]

Pollard LC, Ibrahim F, Choy EH, Scott DL. Pain thresholds in rheumatoid arthritis: the effect of tender point counts and disease duration. J Rheumatol. 2012; 39:28–31. [PubMed: 22089464]

Popescu A, LeResche L, Truelove EL, Drangsholt MT. Gender differences in pain modulation by diffuse noxious inhibitory controls: a systematic review. Pain. 2010; 150:309–318. [PubMed: 20557999]

Pud D, Sprecher E, Yarnitsky D. Homotopic and heterotopic effects of endogenous analgesia in healthy volunteers. Neurosci Lett. 2005; 380:209–213. [PubMed: 15862887]

Pud D, Granovsky Y, Yarnitsky D. The methodology of experimentally induced diffuse noxious inhibitory control (DNIC)-like effect in humans. Pain. 2009; 144:16–19. [PubMed: 19359095]

Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain. 2006; 123:231–243. [PubMed: 16697110]

Roussel NA, Nijs J, Meeus M, Mylius V, Fayt C, Oostendorp R. Central sensitization and altered central pain processing in chronic low back pain: Fact or myth? Clin J Pain. 2013; 29:625–638. [PubMed: 23739534]

Sarlani E, Garrett PH, Grace EG, Greenspan JD. Temporal summation of pain characterizes women but not men with temporomandibular disorders. J Orofac Pain. 2007; 21:309–317. [PubMed: 18018992]

Schenk P, Laeubli T, Klipstein A. Validity of pressure pain thresholds in female workers with and without recurrent low back pain. Eur Spine J. 2007; 16:267–275. [PubMed: 16680447]

Shah JP, Danoff JV, Desai MJ, Parikh S, Nakamura LY, Phillips TM, Gerber LH. Biochemicals associated with pain and inflammation are elevated in sites near to and remote from active myofascial trigger points. Arch Phys Med Rehabil. 2008; 89:16–23. [PubMed: 18164325]

Staud R. Evidence for shared pain mechanisms in osteoarthritis, low back pain, and fibromyalgia. Curr Rheumatol Rep. 2011; 13:513–520. [PubMed: 21833699]

Staud R, Robinson ME, Vierck CJ Jr, Price DD. Diffuse noxious inhibitory controls (DNIC) attenuate temporal summation of second pain in normal males but not in normal females or fibromyalgia patients. Pain. 2003; 101:167–174. [PubMed: 12507711]

Tamcan O, Mannion AF, Eisenring C, Horisberger B, Elfering A, Muller U. The course of chronic and recurrent low back pain in the general population. Pain. 2010; 150:451–457. [PubMed: 20591572]

Vance CG, Rakel BA, Blodgett NP, DeSantana JM, Amendola A, Zimmerman MB, Walsh DM, Sluka KA. Effects of transcutaneous electrical nerve stimulation on pain, pain sensitivity, and function in people with knee osteoarthritis: a randomized controlled trial. Phys Ther. 2012; 92(7):898–910. [PubMed: 22466027]

Villanueva L. Diffuse Noxious Inhibitory Control (DNIC) as a tool for exploring dysfunction of endogenous pain modulatory systems. Pain. 2009; 143:161–162. [PubMed: 19339115]

Villanueva L, Bouhassira D, Le Bars D. The medullary subnucleus reticularis dorsalis (SRD) as a key link in both the transmission and modulation of pain signals. Pain. 1996; 67:231–240. [PubMed: 8951916]

Yarnitsky D, Arendt-Nielsen L, Bouhassira D, et al. Recommendations on terminology and practice of psychophysical DNIC testing. Eur J Pain. 2010; 14:339. [PubMed: 20227310]

Table 1

Demographic characteristics of the study participants

Variable	Healthy (*n* = 30)	Chronic low back pain (*n* = 30)
Gender		
Malg	12 (40)	12 (40)
Female	18 (60)	18 (60)
Age (years)	47 (7.7)	51 (8.7)
Body Mass Index—BMI (kg/m^2)	26.1 (3.6)	28.1 (4.1)
Pain intensity in the last week (0–10)	–	7.8 (1.6)
Duration of pain (months)	–	90.6 (72.4)

Categorical variables are expressed as a number and percentage. Continuous variables are expressed as a mean and standard deviation

Table 2

Values obtained in the CPM and PPT evaluations for both groups

Outcomes	Mean (SD)		Between-group differences (95 % CI)	*P* value
	Healthy (*n* = 30)	Low back pain (*n* = 30)		
Lumbar PPT (kPa)	342.5 (127.7)	253.0 (96.5)	89.5 (40.9–131.1)	0.001*
Tibialis anterior PPT(kPa)	321.8 (84.5)	262.4 (93.1)	59.4 (13.5–105.4)	0.012*
CPM (difference from baseline)	71.4 (83.8)	−47.17 (73.3)	118.6 (77.9–159.2)	<0.001*

CPM in kPa is expressed as the difference in pressure pain threshold during–before cold pressor test

CPM conditioned pain modulation, *PPT* pressure pain threshold, *CI 95 %* confidence interval, *SD* standard deviation

*A statistically significant difference compared to the control group

Table 3

Values obtained in the CPM and PPT evaluations for both sex

Outcomes	Low back pain mean (SD)		Healthy mean (SD)		Healthy group versus low back pain group *P* value		Female versus male *P* value	
	Male	Female	Male	Female	Male	Female	Low back pain	Healthy
Lumbar PPT (kPa)	314.0 (107.5)	212.3 (63.5)	363.9 (95.2)	327.4 (88.02)	0.2	0.001*	0.003+	0.3
Tibialis anterior PPT (kPa)	310.2 (101.3)	120.5 (73.9)	331.6 (80.3)	315.3 (88.6)	0.6	0.004*	0.02+	0.6
CPM (difference scores, kPa)	−72.2 (80.9)	−30.5 (64.8)	60.2 (91.4)	23.4 (229.6)	0.001*	0.001*	0.1	0.6

CPM in kPa is expressed as the difference in pressure pain threshold during–before cold pressor test

CPM conditioned pain modulation, *PPT* pressure pain threshold

* A statistically significant difference between healthy versus low back pain group

+ A statistically significant difference between female and male in same group