Central Sensitization and Altered Central Pain Processing in Chronic Low Back Pain

Fact or Myth?

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Objective: The purpose of this narrative review is to analyze the available literature concerning central sensitization and altered central pain processing in patients with chronic low back pain (LBP).

Methods: Literature was screened using several electronic search databases. Additional literature was obtained by reference tracking and expert consultation. Studies evaluating central pain processing in conservatively treated patients with chronic LBP were included.

Results: Results of studies examining the responsiveness to various stimuli in patients with chronic LBP are conflicting. Some studies in patients with chronic LBP have demonstrated exaggerated pain responses after sensory stimulation of locations outside the painful region, while other studies report no differences between patients and healthy subjects. Studies examining the integrity of the endogenous pain inhibitory systems report unaltered activity of this descending inhibitory system. In contrast, studies analyzing brain structure and function in relation to (experimentally induced) pain provide preliminary evidence for altered central nociceptive processing in patients with chronic LBP. Finally, also psychosocial characteristics, such as inappropriate beliefs about pain, pain catastrophizing, and/or depression may contribute to the mechanisms of central sensitization.

Conclusions: It tempting to speculate that ongoing nociception is associated with cortical and subcortical reorganization and may play an important role in the process of the chronification of LBP. Future prospective research should explore to what extent these changes are reversible and if this reversibility is associated with improved functioning of patients.

Key Words: central nervous system, hyperexcitability, chronic pain, low back pain, hyperalgesia, neuroplasticity

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Low back pain (LBP) is one of the most common musculoskeletal disorders, affecting 70% to 85% of all adults at some point in their life.[1] The course of LBP is characterized by a recurring pattern of reports.[2] A systematic review revealed that 42% to 75% of patients still experience LBP after 12 months,[3] accounting for major expenses in health care and disability systems.[1] Chronic LBP therefore remains a public health burden for the industrialized world.

Despite the high incidence and prevalence of LBP,[4] little is known about the precise causes. Degenerative processes and/or impairments in body structures of the lumbar vertebral column and musculoskeletal structures related to movement are regularly seen on imaging results, but these impairments do not explain the symptoms in all patients with LBP, as they are also observed in healthy controls (HC).[5] The association between symptoms and imaging results has been consistently weak in patients with LBP.[6] As a precise pathoanatomic diagnosis cannot be given in approximately 85% of the patients with LBP,[4] LBP in these patients is therefore considered nonspecific LBP. The observation that only 25% of the variance of back pain intensity can be explained by the joint contribution of pathology and psychosocial factors,[7] confirms the need of further exploration of contributing and underlying mechanisms.

Pain in some other chronic conditions, such as fibromyalgia (FM), appears to result from abnormal central pain processing, rather than from damage and injury to anatomic body structures.[8] For example, prolonged or strong activity in the dorsal horn neurons may lead to increased neuronal responsiveness and central sensitization (CS).[9–11] This central hyperexcitability could account for mechanical hyperalgesia, allodynia, and/or referred pain which are frequently observed in chronic pain syndromes.[11–15]

As sensitization has been defined as an increased response to stimulation, this process may occur from nociceptors in peripheral tissues to brain areas responding to nociceptive inputs. Although the exact mechanisms causing CS remain to be established, several contributing mechanisms have been identified.[11,16,17] "Wind-up" *or temporal summation* refers to a spinal mechanism in which repetitive noxious stimulation results in a slow temporal summation that is experienced as increased pain.[18] While wind-up leads to facilitation of ascending pain mechanisms, *alterations of the descending inhibitory pathways*, arising from the periaqueductal gray matter and the rostral ventral medulla in the brainstem were also described.[19–21] The function attributed to these descending inhibitory pathways is to "focus" the excitation of the dorsal horn neurons, to

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generate an urgent, localized, and rapid nociceptive signal to biologically relevant stimuli, thereby suppressing surrounding extraneous neuronal activity.[22,23] Disruption of ≥ 1 elements of the inhibitory system can result in the equivalent of CS.[23]

Finally, besides descending inhibitory pathways, *facilitatory pathways* originating from the brainstem have been identified. Forebrain centers are capable of exerting powerful influences on various nuclei of the brainstem,[24] including the nuclei identified as the origin of the descending facilitatory pathway.[23] The activity in descending pathways is not constant but can be modulated, for example by the level of vigilance, attention, expectation, and stress.[25] It has been recognized that forebrain products such as cognitions, emotions, attention, motivation, and/or stress as personal factors may influence the clinical pain experience.[23] The term cognitive-emotional sensitization has been used to designate this facilitatory influence.[26] In HC, functional imaging studies revealed that psychosocial and cognitive factors such as pain catastrophizing and expectation were related to neural processing of nociceptive stimuli.[27,28]

Therefore, studies analyzing cerebral processing in relation to experimental induced pain in patients with chronic pain are of particular interest. Outstanding efforts have been made during the last decades to unravel brain processing of pain and decode underlying neuronal mechanisms using functional imaging studies.[29] Brain-imaging studies may offer both a functional and structural noninvasive approach to contribute to the understanding of chronic pain. The purpose of this narrative review is to analyze the available literature concerning CS and altered central pain processing in patients with chronic LBP.

First, we will discuss whether studies examining the responsiveness to various stimuli in patients with chronic LBP are available, and if so whether these studies provide evidence for hyperexcitability of the central nervous system. Second, experiments analyzing brain structure and function in relation to experimentally induced pain will be described. The new advances made in the development of imaging techniques may offer exciting perspectives in the study of pain. Imaging for example the brainstem and other structures involved in the descending control of pain and evaluating the function and biochemical profile of pain-processing regions may lead to more insight in the complex picture of chronic LBP. Finally, the importance of cognitive-emotional sensitization will be discussed.

Literature was screened by the first author. To identify relevant articles, the key word "low back pain" was combined with one of the following search terms: (central) sensitization, hyperresponsiveness, hyperalgesia, temporal summation, spatial summation, pain processing, pain inhibition, pain facilitation, cortical reorganization, diffuse noxious inhibitory controls (DNICs). In addition, reference lists of relevant articles were searched to make the search as complete as possible. All studies evaluating the concept of central pain processing in conservatively treated patients with chronic LBP were included.

EVIDENCE FOR SEGMENTAL AND EXTRASEGMENTAL HYPERRESPONSIVENESS IN PATIENTS WITH CHRONIC LBP?

The examination of generalized, widespread hyperalgesia is a frequently used method to detect CS in several chronic unexplained disorders, such as complex regional pain syndrome, FM, and whiplash-associated disorders, as increased responsiveness to a variety of somatosensory stimuli represents a major characteristic of CS. Hyperalgesia is expressed as a lowered pain threshold because of sensitization of nociceptive afferents or an increased rate of growth of pain intensity as a function of graded nociceptive stimulation.[30] In patients with LBP, lower thresholds may be observed in areas innervated by spinal segments adjacent to the spinal segments of the primary source of nociception. These findings will be considered as segmental CS.[31] In case pain referral and numerous areas of hyperalgesia in sites outside and remote to the symptomatic site are observed, together with an extrasegmental general decrease in pain thresholds, the term widespread or extrasegmental CS will be used.[31] Seventeen studies analyzing sensitivity to various sensory stimuli in patients with chronic LBP were found. Details of the included studies are found in Table 1. In the last column, it is mentioned whether the results of these studies are favouring (CS +) or rejecting (CS −) the hypothesis of CS in chronic LBP.

Evidence for Segmental or Widespread Hyperalgesia?

Mechanical Pressure and/or Electrical Stimulation

Four studies reported hyperalgesia to pressure to sites unrelated to the lumbopelvic region in patients with chronic LBP, indicating generalized or widespread hyperalgesia at least in a subgroup of patients with chronic LBP.[8,34–36] In the study of Clauw et al[34] 38% (17/45) of the patients with chronic LBP had ≥ 11 tender points on a scale of 18, and approximately 20% (10/45) also had a history of widespread musculoskeletal pain, meeting the criteria for the diagnosis of FM.[47] Pain sensitivity (pressure pain thresholds at locations unrelated to the lumbar area, such as the forehead and the thumbnails) accounted for a significant proportion of variance in functional status (12%) and pain (12%), even after controlling for demographic, structural [magnetic resonance imaging (MRI) abnormalities], and psychosocial variables.[34] Decreased pressure pain thresholds were observed in a population of patients with chronic LBP with and without radiation distal to the knee, both at sites related (paraspinal lumbar muscles) and unrelated to the lumbar region (extensor muscle of the wrist, finger, etc.), after controlling for potential confounders such as medication use, sex, age, handedness, and disability insurance claim involvement[35] (Table 1, hyperalgesia to electrical and/or mechanical stimuli).

Contradicting results are also reported in the literature, suggesting that patients with chronic LBP do not experience sensitization (Table 1). No differences in pain perception threshold and pain tolerance threshold between patients with chronic LBP and HCs were found when the noxious stimulation occurred at the finger,[32] the arm,[38] or other remote sites.[39] One study even observed significant higher pain thresholds in patients with chronic LBP when compared with HCs.[33] Finally, also mixed results have been found. For example, in a study performed by O'Neill et al,[37] pressure pain thresholds in tibialis anterior muscle were significantly lower in patients with LBP, whereas pressure pain thresholds of infraspinatus muscle were not different, suggesting segmental sensitization. In this same study, however, patients reported significantly higher pain responses when suprathreshold stimulation was applied in both tibialis anterior and infraspinatus muscles (ie, pressure 1.2 and 1.4

TABLE 1. Overview of Studies Analyzing Sensory Stimuli in Patients With Chronic LBP

References	N (LBP—Healthy)	Definition LBP	Medication	Sensory Stimulus	Evaluation	Anatomic Location	Response in cLBP Versus Healthy
Hyperalgesia (mechanical and/or electrical stimuli)							
Peters et al[32]	20 male cLBP—20 male HC	Daily LBP > 6 mo No identified organic cause for the cLBP	Not specified	Mechanical pressure (modified Forgione Barber pressure stimulator)	Pain perception threshold Pain tolerance	Finger	No significant differences ($P > 0.05$) between LBP and controls (values are expressed in seconds) → CS −
Peters and Schmidt[33]	20 cLBP—23 HC	Daily continuous LBP > 1 y No malignancies	Use of analgesics is exclusion criterion	Electrical pain stimulus (constant current generator) Mechanical pressure (modified Forgione Barber pressure stimulator)	Pain perception threshold Pain tolerance	Ankle (electrical stimuli) Finger (mechanical pressure)	Higher pain perception threshold (electrical and pressure stimulus) Higher maximal pain tolerance threshold (only pressure stimulus) → CS −
Clauw et al[34]	45 cLBP	At least 3 mo No surgery No malignancy	No information regarding use of medication	Mechanical pressure (algometer)	Pressure pain threshold Pressure pain tolerance	18 tender points (lateral epicondyl, midtrapezius) 4 control points (thumbnail and forehead)	cLBP mean of 5, 2 tender points on 18 (greater than in normal population, but reference to literature) 10/45 widespread musculoskeletal pain = meeting diagnosis for FM → CS +
Giesecke et al[8]	11 cLBP—16 FM—11 HC	LBP > 12 wk Ideopathic LBP	No NSAIDs 3 d before testing		Pressure pain threshold	Thumbnail	Lower pressure pain thresholds in patients: 3.9 kg to produce pain in LBP, compared with 5.6 kg in HC ($P = 0.03$) → CS +
Giesbrecht and Battie[35]	30 female cLBP—30 female HC	LBP with/without leg pain below the knee > 6 mo No spine surgery	No medication on the day of testing	Mechanical pressure (electronic algometer)	Pressure pain perception threshold	Paraspinal C5, L3, L5 Wrist extensor, middle phalanx finger II Calf muscle	Significant lower mean PPDT values both at sites related to lumbar area ($P = 0.02$) as sites unrelatead to lumbar area ($P < 0.01$) compared with HC Significant lower mean global pain threshold: 5.6 lb/cm^2 in LBP compared with 6.9 in HC ($P = 0.02$) → CS +
Laursen et al[36]	10 female cLBP—41 female HC	LBP without root compression No malignancies.	Use of medication is exclusion criterion	Mechanical pressure (electronic algometer)	Pressure pain threshold	7 sites (abdomen, back, triceps, forefinger, dorsal forefinger, calf, scapula)	Lower median value at all sites in patients compared with HC ($P < 0.01$) → CS +

(*Continued*)

TABLE 1. (*continued*)

References	N (LBP—Healthy)	Definition LBP	Medication	Sensory Stimulus	Evaluation	Anatomic Location	Response in cLBP Versus Healthy
O'Neill et al[37]	12 cLBP and 12 HC	MRI-confirmed hernia and clinical image of radiculopathy (radiating under the knee and positive neurological exam) LBP > 6 mo	No pain medication on the day of testing	Mechanical pressure (algometer) Hypertone saline injection in 2 muscles	Pressure pain threshold Supratreshold stimulation Experimentally induced muscle pain	Muscle infraspinatus Muscle tibialis anterior (ipsilateral to leg pain)	Lower PPT in tibialis anterior Higher VAS to supratreshold PP stimuli Increased VAS, duration and RP following injection in both infraspinatus and tibialis→CS +
Diers et al[38]	14 cLBP—11 HC	Nonradicular chronic musculoskeletal pain > 12 mo	Use of centrally acting analgesics is exclusion criterion		Pain threshold Pain tolerance	Arm Back	No differences in pain threshold or pain tolerance between LBP and HC→CS−
Meeus et al[39]	21 cLBP—31 HC	Nonspecific LBP > 3 mo	No medication use before study	Mechanical pressure (algometer)	Pressure pain threshold	Calf, deltoid, hand, back	No differences between LBP and HC→CS−
Hyperalgesia (thermal stimuli)							
Lautenbacher et al[40]	19 cLBP and 19 HC	Lumbosacral disc disease		Thermal stimuli (Peltier thermode)	Pain threshold	Hand	No differences in pain threshold between LBP and HC ($P > 0.05$)→CS−
Derbyshire et al[5]	16cLBP and 16 HC	Inclusion of patients with degenerative spine changes or disk herniations, but exclusions of neurological deficits	Use of medication is exclusion criterion	Thermal stimuli (thermal threshold stimulator)	VAS ratings for non painful, mild painful and moderately painful	Back of the right hand	Patients experienced higher VAS ratings at higher temperatures when compared with HC ($P < 0.01$)→CS +
Wind-up							
Peters et al[32]	20 male cLBP—20 male HC	Daily LBP > 6 mo No identified organic cause for the cLBP	Not specified	Mechanical pressure (mod Forgione Barber pressure stimulator)	Pain perception threshold after repeated stimulation	Finger	PPT increase in healthy, showing habituation PPT decreased in LBP, showing sensitization ($P = 0.05$)→CS +
Arntz et al[41]	22 cLBP—21 HC	LBP > 6 mo No identified organic cause for the cLBP	Analgesics free on the day of testing	Electrical pain stimulus (constant current generator)	VAS score after repeated stimulation (shock level based on subjective pain level at pretest)	Finger	Both groups showed habituation in their subjective pain levels (same shock intensity, but lower pain rating) ($P = 0.56$).→CS−
Kleinbohl et al[42]	15cLBP—23 HC	LBP > 6 mo, without identifiable orthopedic or neurological origin	Use of medication is exclusion criterion	Tonic and phasic heat stimuli	Pain thresholds for phasic and tonic pain Index of sensitization	Thenar eminence of dominant hand	Patients with LBP demonstrated stronger and earlier sensitization ($P < 0.01$)→CS +
Flor et al[43]	30 cLBP—30 HC	Continuous LBP > 6 mo Cause of LBP is muscular, degenerative or nonspecific	Use of centrally acting analgesics is exclusion criterion	Electrical pain stimulus	Pain threshold Pain tolerance threshold Repeated stimulation at different intensities	Arm and back muscles	Elevated pain thresholds throughout extinction phase, compared with decrease in thresholds in HC in this phase→CS +

(*Continued*)

TABLE 1. (*continued*)

References	N (LBP—Healthy)	Definition LBP	Medication	Sensory Stimulus	Evaluation	Anatomic Location	Response in cLBP Versus Healthy
Diers et al[38]	14cLBP—11 HC	Nonradicular chronic musculoskeletal pain > 12 mo	Use of centrally acting analgesics is exclusion criterion	Electrical intracutaneous and intramuscular stimulus	NRS for repeated stimulation Short interstimulus interval to induce temporal sensitization	Arm (extensor digitorum) and back (left erector spinae at L3)	Sensitization occurs in all conditions in LBP ($P < 0.05$) but not in HC ($p > 0.10$)→CS +
DNIC							
Julien et al[44]	30 cLBP—30 HC	Localized pain in lumbar area > 6 mo, no root compression or sensory disturbances		Immersion in noxious cold water (12°C)	VAS rating during ascending or descending session (spatial summation procedure)		Descending session result in lower VAS and unpleasantness No spatial summation effect was found for the increasing area. In contrast a significant spatial summation effect was found for the decreasing session→CS−
Endogenous inhibition during exercise							
Hoffman et al[45]	8 cLBP—10 HC	LBP for at least 1 y of non-neurological origin, but from degenerative or muscular origin	Use of narcotic analgesia is exclusion criterion	Mechanical pressure (pressure pain stimulator)	Pressure pain thhreshold	Middle phalanx index finger	Pressure pain thresholds increase and pain ratings decrease following exercise, but no differences are observed between LBP and HC→CS−
Meeus et al[39]	21 cLBP—31 HC	Nonspecific LBP > 3 mo	No medication use before study	Mechanical pressure (algometer)	Pressure pain threshold	Calf, deltoid, hand, back	No differences between LBP and HC→CS−
Flexion reflex							
Peters et al[46]	12cLBP, 12 oral surgery, 12 HC	Daily back pain for 1 y with/without radiation to leg Cause of LBP is unknown	No use of medication on day of testing	Electrical pain stimulus	Nociceptive flexion reflex threshold		No significant differences between LBP patients and healthy controls→CS−

cLBP indicates chronic low back pain; CS−, not indicative for central sensitization; CS +, indicative for central sensitization; DNIC, diffuse noxious inhibitory control; FM, fibromyalgia; NSAIS, Non Steroidal Anti-Inflammatory Drugs; HC, healthy controls; PPT, pressure pain threshold; PPDT, pressure pain detection threshold; VAS, Visual Analog Scale.

times of their individual pain threshold in both muscles), which is indicative for widespread sensitization.[37] It has to be mentioned that these patients had an MRI-confirmed–herniated disk, including radicular symptoms distal to the knee. These results may therefore not be generalized to patients with nonspecific LBP without radicular symptoms.

Thermal Pain

No differences in pain threshold were found between patients with chronic LBP and HC when contact heat was applied on the right hand using a Peltier thermode,[40] but the patients experienced significant higher pain ratings [Visual Analog Scale (VAS)] compared with healthy subjects[5] (Table 1, hyperalgesia to thermal stimuli), suggesting widespread hyperalgesia, but no allodynia (there were no differences in VAS between patients and control patients for the nonpainful stimulation).

Experimentally Induced Muscle Pain by Injection of Hypertonic Saline

After hypertonic saline injection, patients with MRI confirmed-herniated disk displayed significantly higher pain intensity, duration, and larger areas of pain referral in both infraspinatus and tibialis anterior muscles when compared with HCs, suggesting widespread sensitization in these patients with chronic LBP.[37]

In summary, the results of studies analyzing hyperalgesia in patients with chronic LBP are equivocal. Some studies in patients with chronic LBP have demonstrated exaggerated pain responses after sensory stimulation of

locations outside the painful region (generalized or widespread sensitization), whereas other studies report segmental sensitization (areas segmentally related to the lumbar spine, such as the lower extremities). Finally, some studies did not find differences at all between patients with chronic LBP and HCs suggesting absence of sensitization.

Evidence for Enhanced Temporal Summation?

Evidence for enhanced temporal summation or wind-up comes from studies where pain stimulation is repeated[32,38,41,43] or where continuous stimulation is applied.[42] Mechanical, electrical, or thermal stimulation have been used to induce temporal summation (Table 1, wind-up).

During 8 consecutive trials of identical pain stimulation (mechanical pressure applied to the finger), a clear tendency toward a decrease of the pain threshold from the first to the eighth trial was observed in patients with chronic LBP, suggesting extrasegmental sensitization.[32] Interestingly, no differences in pain intensity ratings (VAS) were noted between patients with LBP and pain-free in this experiment.

In the study of Diers et al,[38] 800 painful electrical stimuli were applied at arm and back. Using needle electrodes, both intracuteaneous and intramuscular electrical stimulation was applied. A short interstimulus interval was used to provoke temporal summation effects. Perceived intensity of stimulation was compared before and after 800 painful stimulation trials, to determine the occurrence of sensitization. Patients with chronic LBP reported significantly higher pain ratings and sensitization coefficients at the end of the stimulation, for all conditions (back and arm stimulation, and intracutaneous as intramuscular) suggesting widespread sensitization, compared with the lack of significant sensitization among the HCs.[38] In contrast, Arntz and colleagues reported an identical reaction to repeated stimuli in patients with chronic LBP and HCs. The intensity of the shock levels applied to the finger was determined using subjective pain ratings (> 50 on a 0 to 100 mm VAS).[41] Despite the fact that a lower amperage was necessary to attend the 50-mm criterion in patients, subjective pain ratings decreased at the end of the experiment in both HCs and patients with chronic LBP, which is not indicative for sensitization. Furthermore, autonomic responsiveness to pain was not enhanced in patients. These authors therefore concluded that patients with chronic LBP are not characterized by impairment in habituation to painful stimuli.[41]

The evaluation of pain thresholds can be considered as a kind of static index of pain sensitivity, as it only evaluates the final effect of neuroplastic changes.[42] To study more dynamic changes in pain sensation, a tonic heat paradigm was used to assess early sensitization (15 to 100 s) to experimental pain. Change in pain sensation during prolonged continuous stimulation was evaluated using a dual sensitization method, combining subjective ratings and behavioral responses. Stimulations of identical intensity were applied to the hand, without providing information regarding the intensity to the patient. Patients were asked to rate the intensity of the temperature, and to change this according to the reference temperature in the beginning of the session (although it was still the same temperature). By calculating the difference between the 2 temperatures (and VAS scores for each temperature), the authors determined an index for the degree of sensitization.[42] The degree of sensitization was linearly related to stimulus temperature (ie, increasingly higher pain intensity ratings in response to painful tonic heat stimuli). Patients with chronic LBP sensitized earlier and stronger than HCs. Enhanced sensitization was independent of altered pain thresholds. Finally, discriminant analysis showed good sensitivity (77%) and specificity (74%) of individual sensitization measures to distinguish patients from HCs, especially in combination with pain thresholds (specificity of 96%).

In summary, CS processes in patients with LBP seem to have an effect on spinal "wind-up" as assessed by temporal summation experiments. However, the observed widespread effect may depend on the assessment method.

Evidence for Altered Descending Inhibition and Spatial Summation of Pain?

DNIC-like mechanisms represent an endogenous pain control system whose deficiency is assumed to contribute to chronic musculoskeletal pain.[48,49] The DNIC system originates from the serotonergic dorsoreticular subnucleus in the caudal medulla, is activated by nociceptive afferents and in turn modulates the impending noxious input by the inhibition of wide dynamic range neurons in the dorsal horn.[50] It can be facilitated by serotonergic and opioidergic agents and inhibited by opioid antagonists and serotonin antagonists, respectively.[51–53] For assessment of DNIC-like effects in humans the paradigm of heterotopic noxious conditioning stimulation has been used.[54] In this paradigm, the effects of a conditioning, mainly tonic and intense pain stimulus on the sensation elicited by a second, mainly phasic and less intense pain stimulus, which is classified as test stimulus, are assessed.

High-intensity stimulation of nociceptive fibers thus leads to an endogenous antinociceptive response, causing a generalized inhibition of the wide dynamic range neurons in the dorsal horn. As a result, pain relief may occur even at sites not initially involved in nociception. This model can be employed as an experimental approach to test the integrity of 1 descending inhibitory system. In various chronic pain forms (eg, chronic osteoarthritis, FM, tension-type headache, or chronic fatigue syndrome) a deficiency occurred probably leading to an increased noxious input, whereas in others (eg, Parkinson disease) further descending inhibitory mechanism are thought to be involved.[48,49,55–57]

In addition to the evaluation of the inhibition of the phasic stimulus by the tonic stimulus, DNIC activity can also be assessed by a spatial summation test. Spatial summation depends on the number of central neurons recruited and thus the stimulated area.[58] As the stimulated area increases, inhibitory interactions take place between nociceptive afferent inputs within this area. In HCs, no correlation between the stimulated surface area and the pain perception is observed when the surface is gradually increased, as the inhibitory efferents counterbalance the nociceptive afferents.[59] However, when the surface is gradually decreased, inhibitory systems are fully recruited from the beginning, whereas nociceptive afferent signaling gradually decreases, resulting in an overcompensation of the pain inhibition as the surface further decreases. Consequently, a correlation is observed between perceived pain and the stimulated area, and pain perception is lower than during the increasing session.

The activation of endogenous pain inhibitory systems by the same spatial summation test was evaluated in 30 patients with FM, 30 patients with chronic LBP, and 30 HCs.[44] VAS ratings of pain were used during immersion of

different surfaces of the arm in circulating noxious cold (12°C) water. Both patients with chronic LBP and HCs perceived their pain differently during the ascending and descending sessions. The descending session resulted in lower pain intensity and unpleasantness, which the authors attributed to a full recruitment of inhibitory systems at the beginning of the descending session in opposition to a gradual recruitment during the ascending session. During the ascending session pain perception remained stable, regardless the stimulated area, whereas a correlation was observed between pain and stimulated area during the descending session. These data therefore do not support a deficit of this endogenous pain inhibitory system in chronic LBP.

In summary, while a deficit of endogenous pain inhibitory systems has been suggested to contribute to several chronic pain conditions, the only study examining the DNIC system in patients with chronic LBP suggests an unaltered activity of this descending inhibitory system. However, as DNIC-like mechanisms represent only 1 descending inhibitory control system, we cannot conclude on the contribution of further descending modulatory mechanism.

Evidence for Endogenous Inhibition During Exercise?

In normal circumstances, pain thresholds increase during physical activity because of the release of endogenous opioids, growth factors,[60] and other strong inhibitory mechanisms (descending inhibition) orchestrated by the central nervous system.[16] Two pilot studies were performed to evaluate pain processing in response to exercise in patients with chronic pain. Patients with chronic fatigue syndrome (which often also experience chronic pain) have a dysfunction of endogenous nociceptive inhibition during exercise, as these patients demonstrated a decrease in pain threshold after exercise.[61] However, in patients with chronic LBP, pain ratings from an experimentally induced pressure pain stimulus increased in response to submaximal aerobic exercise,[45] as they are in HCs,[62] suggesting normal pain processing in response to exercise. These findings were confirmed recently in a larger study.[39] We analyzed pain response in relation to exercise in patients with chronic fatigue syndrome and widespread pain, in patients with chronic LBP, and in pain-free sedentary controls. The lack of endogenous inhibition during exercise was only present in patients with chronic fatigue and chronic widespread pain, but not in the group of patients with chronic LBP.[39]

In summary, the results of the 2 available studies performed in patients with chronic LBP suggest that endogenous inhibition of pain during exercise seems to be normal in this population.

Evidence for Altered Spinal Reflexes?

Most of the results of the above-mentioned studies are based on the patients' pain reports, which can be considered as subjective measurements. Quantifying the minimal intensity of transcutaneous electrical stimulation necessary to evoke a spinal reflex may provide a more objective measurement of spinal hyperexcitability and CS.[63] The minimal intensity of the stimulus that is sufficient to elicit a reflex at a well-defined latency, known as the reflex threshold, usually corresponds to the minimal stimulus intensity necessary to elicit a perception of pain.[64] A lower reflex threshold has already been demonstrated in patients with chronic pain after whiplash and patients with FM,[14] providing electrophysiological evidence for hypersensitivity of the spinal cord in these patients.

Only 1 study elicited a nociceptive flexion reflex after noxious stimulation in patients with chronic LBP.[46] No differences in nociceptive flexion reflex (RIII) threshold were observed between patients with chronic LBP and HCs after noxious electrical stimulation of the ankle.[46] It has nevertheless to be mentioned that the use of the RIII reflex in the clinical evaluation of patients with neuropathic pain is limited.[63] In this study, patients with from LBP and radicular symptoms in the legs were included. Fifteen percent of the patients (7/45) had even had ≥ 1 nerve blockade, which could explain the observed results.[46]

In summary, no evidence exists to suggest that spinal reflexes are altered in patients with chronic LBP. Further research is, however, warranted to analyze these mechanisms in patients with nociceptive chronic LBP.

EVIDENCE FOR ALTERED BRAIN FUNCTION IN PATIENTS WITH CHRONIC LBP?

Brain Activity in Relation to Painful Stimulation

Magnetoencephalography

Flor and colleagues first demonstrated cortical hyperactivity and reorganization in patients with chronic LBP. Standard, nonpainful, and painful electric stimulations were applied to the left back and index finger. The power of the early evoked magnetic field elicited by painful stimulation of the back (but not of the finger) in patients with chronic LBP was elevated when compared with the HCs. Moreover, a linear increase with chronicity ($r = 0.74$) was observed, indicating increased cortical responsivity with increasing chronicity.[65] The location of maximal activity in primary somatosensory cortex elicited by painful stimulation of the back (ie, the cortical representation) was shifted more medially in patients with very chronic LBP, suggesting that site-specific (segmental) cortical reorganization may occur in patients with chronic pain.

Electroencephalography (EEG)

In the study of Diers et al,[38] EEG was used to evaluate brain responses in relation to pain in patients with chronic LBP. No significant differences in pain threshold were observed, but patients demonstrated extrasegmental sensitization when repeated stimulation was applied to elicit temporal summation, compared with the lack of significant sensitization among HCs. A larger EEG component was recorded 80 ms after stimulation in the patients with LBP, across stimulus conditions (intracutaneus vs. intramuscular) and stimulus locations (arm vs. back). The authors suggest that this corresponds to the sensory-discriminative aspect of pain, as N80 is thought to originate from the primary somatosensory cortex. Interestingly, this enhanced cortical reactivity of N80 was positively correlated with the sensitization measure and thus extend previous results of segmental sensitization in patients with LBP observed by Flor et al[65] to widespread sensitization. Finally, a significantly lower P260 amplitude was found, suggesting less activation of the cingulated cortex.[38] This reduced activity after experimentally induced (phasic) pain can be explained by an inhibition because of the chronic, tonic pain, experienced by the patients with chronic LBP. The affective-motivational response (activation of the

cingulated cortex) that is observed in the HCs is masked by the chronic pain experience.[38]

Transcranial Magnetic Stimulation (TMS)

Cortical excitability can be assessed by using TMS to provide information on inhibitory and excitatory cortical circuits.[66] Studies in chronic neuropathic pain and in FM provided evidence for reduced activity of inhibitory neuronal circuits that was reversed by high-frequency rTMS of the motor cortex, suggesting that reduced inhibitory activity of the motor cortex is a reversible feature of central sensitization in these diseases.[67,68] So far, no studies in patients with chronic LBP are available. Altered cortical excitability would suggest possible therapeutic effects of rTMS. Of further interest is the modulation of experimentally induced pain by repetitive TMS in healthy volunteers and in patients with chronic pain.[69] It was shown that similarities between HCs and patients with chronic LBP, but differences to patients with neuropathic pain, exist. Neuropathic pain patients exhibit an increased susceptibility to thermal pain following high-frequency rTMS of the motor cortex within the site of pain, whereas patients with LBP and HCs experienced decreased thermal perception.[70–72] However, as these changes refer to the site of pain in neuropathic pain patients but not in patients with chronic LBP, one can only conclude that in LBP no generalized changes in the modulation of perception thresholds by rTMS occurs. Thus, the painful area should be further assessed and compared with neuropathic patients.

Functional Magnetic Resonance Imaging (fMRI)

Further evidence for augmented central pain processing has been provided in studies using fMRI.[8] Applying equal amounts of pressure to the thumbnail elicited significantly more neuronal activation in pain-related areas such as the primary and secondary contralateral somatosensory cortices, inferior parietal lobule, cerebellum, and ipsilateral somatosensory cortex in patients with LBP compared with HCs. These brain regions have all been implicated in pain processing. In contrast, only the contralateral somatosensory cortex was activated in HCs. As the pain stimulus was applied to the finger, one can conclude widespread changes. In another study,[73] the pressure necessary to evoke a VAS score of 3 and 5 was applied in the lumbar region. Patients with LBP demonstrated enhanced activity at right insula, posterior cingulated cortices, and supplementary motor area. In addition, tenderness of the back and a higher aversive reaction were observed in patients.[73] As stimulation was applied only in the primary region of nociception (lumbar spine), no information can be drawn regarding the widespread character in this last experiment. Also, Lloyd et al[74] used fMRI during tactile stimulation of the lower back. They divided patients with chronic LBP in 2 groups based on the number of positive Waddell signs (ie, signs suggestive for a nonorganic or psychological component of LBP, indicative of somatization),[75] and hypothesized that patients with low Waddell signs (good adjustment to LBP) would activate cortical affective-cognitive functions differently in response to sensory stimulation (ie, intense nonpleasant tactile stimulation of the back). Significantly, more activation was seen in patients with low Waddell signs in regions previously associated with normal affective-cognitive processing of sensory input, such as the posterior cingulate and parietal cortices. The magnitude of this activation negatively correlated with catastrophizing scores. Successful adjustment to chronic LBP is apparently associated with a patient's capacity to effectively activate a sensory modulation system. Patients, who are not able to activate this system, may predispose to altered affective and behavioral responses, with poor adjustment to pain.

Finally, acute thermal pain was experimentally induced to the lower back in 24 patients with chronic LBP and 11 HC.[76] When spontaneous pain (ie, in the absence of external stimuli) was contrasted to experimental noxious thermal stimulation, the medial prefrontal cortex was activated during spontaneous high pain, and this activity correlated with spontaneous pain intensity in patients. In contrast, insular activity was seen during experimentally induced pain in both groups, and correlated with pain intensity for thermal stimulation and with the duration of the sponteanous LBP. Furthermore, a strong negative correlation was observed between the activity in dorsolateral prefrontal cortex (DLPFC) and medial prefrontal cortex in the patients with LBP during the spontaneous high pain. These findings suggest that subjective spontaneous pain of patients with chronic LBP involves specific spatiotemporal neuronal mechanisms (activation of emotional region such as the medial prefrontal cortex), distinct from those observed for acute experimental pain (activation of sensory regions, eg, the insula).[76]

Positron Emission Tomography

Positron emission tomography data were collected during thermal pain stimulation applied to the hand in patients with chronic LBP and healthy patients.[5] The regional cerebral blood flow correlated with subjective pain experience in several brain areas, such as the cerebellum, midbrain, thalamus, etc. in both the groups. Despite the fact that some differences in brain activity were observed between patients with chronic LBP and HCs, the authors of this experiment considered these differences to be not sufficient to suggest abnormal nociceptive processes in patients with chronic LBP.[5] It has to be mentioned that patients were significantly older than the HCs in this experiment.

In summary, these data provide preliminary evidence for altered central nociceptive processing in patients with chronic LBP.

Structural Evaluation of the Brain in Patients With Chronic LBP

Two studies evaluating brain morphology reported a loss of gray matter volume in patients with chronic LBP compared with HCs. A decrease of 5% to 11% in neocortical gray matter volume was observed in a mixed population of patients with both neuropathic and non-neuropathic LBP and this decrease correlated with pain duration.[77] Gray matter density was reduced in DLPFC bilateral and right thalamus. Gray matter density reduction was strongly related to pain characteristics in a pattern distinct for neuropathic and non-neuropathic LBP.[77] Furthermore, a significant decrease of gray matter in brainstem and somatosensory cortex was reported.[78] A strong negative correlation was revealed between pain unpleasantness or pain intensity and gray matter volume in these areas.[78] In contrast to Apkarian et al,[77] Schmidt-Wilcke et al[78] found a significant increase in gray matter bilaterally in the basal ganglia and the left thalamus. It is not clear why these research groups found contradictory results concerning the thalamus (decreased vs. increased). Small patient groups,

and inclusion of different types of LBP (only nonspecific without radicular symptoms in the study of Schmidt-Wilcke et al,[78] vs. mixed population of nonspecific and neuropathic pain in the study of Apkarian et al[77]) may have accounted for these differences.

In summary, it is tempting to speculate that ongoing nociception is associated with cortical and subcortical reorganization on a structural level and may play an important role in the process of the chronification of LBP, but further prospective research is warranted. Indeed the conclusions of these studies are based on cross-sectional observations, and a cause and effect relationship may not be drawn based on these data. Longitudinal studies should be undertaken to support this hypothesis.

Chemical Brain-imaging Studies

Grachev and colleagues used in vivo single-voxel proton magnetic resonance spectroscopy in 3 studies to explore the biochemical profile of several brain regions in LBP patients and HCs. In their first study, reduction of *N*-acetyl aspartate and glucose was demonstrated in the DLPFC of patients with LBP, whereas no chemical concentration differences were found in cingulate, sensorimotor, and other brain regions.[79]

They further analyzed the role of anxiety, and observed that the concentration of *N*-acetyl aspartate in the orbitofrontal cortex could distinguish between anxiety levels (high vs. low) and between patient groups (patients with LBP vs. pain-free controls). A relationship between perception and brain chemistry was demonstrated. The chemical-perceptual network best related to pain in patients with chronic LBP was comprised of the DLPFC and orbitofrontal cortex; the chemical-anxiety network was best related to all 4 regions (DLPFC, orbitofrontal cortex, cingulated, and thalamus) in patients with LBP; and the cingulate was best related to the affective component of pain.[80]

This group finally evaluated the role of depression in relation to brain chemistry. Again, reduction of *N*-acetyl aspartate levels was demonstrated in the right DLPFC of patients with chronic LBP and depression, as compared with the HCs. A correlation of -0.99 was found between depression levels in patients with chronic LBP and *N*-acetyl aspartate levels in the DLPFC. The reduction of *N*-acetyl aspartate levels in the DLPFC therefore appears to be more associated with depression than with pain.[81]

Finally, alterations in biochemistry in 3 brain regions (prefrontal cortex, anterior cingulated cortex, and thalamus) were associated with pain processing. Using a pattern recognition method, it was possible to discriminate between patients with LBP and HCs with high accuracy.[82]

In summary, these findings provide evidence for alterations in the biochemical profile of the brain in patients with chronic LBP.

EVIDENCE FOR COGNITIVE EMOTIONAL SENSITIZATION?

The role of various psychological factors in the maintenance and development of chronic symptoms has repeatedly been reported in the literature. Catastrophizing,[83] depressive feelings,[84] and fear avoidance[85–87] have been reported to occur in patients with chronic LBP. Inappropriate beliefs have been associated with the development of exaggerated pain perception[88,89] or other negative consequences. All these psychological factors, often referred to as yellow flags as they are associated with a poor prognosis, may enhance facilitatory pathways in the central nervous system, resulting in sensitization of dorsal horn spinal cord neurons. It has for example been demonstrated in a prospective follow-up study that patients with a good clinical outcome experienced less serious consequences, reported fewer emotional responses such as fear or anger, perceived less symptoms that they attributed to their back problem, and had stronger perceptions about the controllability of their difficulties.[90] It is out of the scope to fully review the literature regarding the influence of psychosocial factors in patients with chronic LBP. Instead, only the studies investigating these psychological factors in relationship to experimentally induced pain will be discussed.

The importance of *depression* and *fear avoidance* was analyzed in response to experimentally induced pain and temporal summation in an uncontrolled cross-sectional study performed in patients with chronic LBP.[91] The evaluation of thermal pain sensitivity did not contribute significantly to pain intensity after controlling for depression. Both fear-avoidance beliefs and temporal summation of evoked thermal pain influenced pain-related disability. Also, significant differences were observed between patients with LBP, when the Waddel signs are taken into account.[74] In patients with low Waddell signs, regions associated with normal affective-cognitive processing of sensory input were activated, and the magnitude of this activation negatively correlated with catastrophizing scores, whereas contrasting findings were observed in patients with high Waddell signs.[74]

Finally, the role of *operant conditioning* was examined in 30 patients with chronic LBP and 30 matched HCs.[43] Pain threshold and pain tolerance were determined for back and arm muscles, and repeated stimuli of different intensities were provided together with positive or negative feedback. Half of each group was reinforced for increased pain reports (ie, positive feedback when the actual pain rating of the patients was higher than the average baseline rating), half for decreased pain reports (ie, positive feedback when the actual pain rating of the patient was lower than the average baseline rating) during simultaneous EEG recording. The authors concluded that pain reports in both patients and HCs can be brought under operant control, but that differences exist between patients and pain-free subjects. Whereas fast extinction of pain ratings was observed in HCs, pain ratings of patients with chronic LBP maintained elevated during the extinction phase. This corresponded with a slower extinction of the cortical (N150) pain response. These data suggest that patients with LBP may be more influenced by operant conditioning factors than HCs and that this contributes to chronicity of LBP.[43]

In summary, preliminary findings suggest that cognitive and emotional factors could contribute and/or sustain the mechanisms of CS in patients with chronic LBP.

DISCUSSION AND NEW PERSPECTIVES

Many studies trying to unravel chronic pain suggest that these patients should be approached from a more "central" point of view. Changes in descending and ascending central modulatory mechanisms for the perception of pain, which have been called "neuronal plasticity"[22] may be responsible for deregulated antinociception or central sensitization. CS may involve both functional changes and structural changes.[92,93]

Despite the fact that several studies point in the direction of CS and suggest that altered central pain mechanisms are present in patients with chronic LBP, the results are equivocal. Whereas reduced pain thresholds suggestive of widespread or extrasegmental hyperalgesia[8,34–36] are observed in some studies, other studies only observe a segmental hyperalgesia,[37] and finally some authors report no hyperalgesia at all.[32,33,38] Similar results are found when temporal summation is experimentally induced in patients with chronic LBP.[32,38,41–43] Differences in experimental protocols may account for the observed discrepancies, such as stimulation procedure (20 vs. 800 trials or continuous stimulation to elicit temporal summation) or definition of outcome parameters. For example, when subjective pain intensity is used as single measure to evaluate the reaction on repeated stimulation, different results have been reported. No sensitization is observed in the study performed by Arntz et al,[41] whereas both segmental and extrasegmental sensitization is demonstrated by Diers et al.[38] When pain thresholds or sensitization indexes are calculated,[32,42] widespread or extrasegmental sensitization has been demonstrated in patients with chronic LBP. Not all studies analyzing hyperalgesia evaluated whether patients used centrally acting pain medication, which may also influence the study' results. Moreover, some authors further mention a high variability in pain ratings of patients with chronic LBP, which reflect the inhomogeneity of this patient group.[38] Finally, inclusion and exclusion criteria for participation in studies are not always well defined.

We have chosen to include all studies dealing with conservatively treated chronic LBP patients. European guidelines regarding the management of patients with chronic LBP advice a diagnostic triage, thereby differentiating patients with nonspecific, specific, and radicular LBP.[4] The differentiation between these groups is not always easy. Patients with disk herniation are mostly considered as specific or radicular when spinal nerves are involved, whereas degenerative disk diseases are considered nonspecific. Also, the definition of radicular pain is not always clear. Several studies of the present manuscript included both patients with and without symptoms distal to the knee. Pain below the knee has nevertheless been found as useful diagnostic item from the clinical history to infer the presence of neuropathic pain in patients with suspected sciatica.[94] Recently, an alternative classification for patients with LBP has been proposed, differentiating between patients with nociceptive LBP, peripheral neuropathic LBP, and central sensitization. The detailed description of these subgroups[95–97] will allow better classification of patients in the future.

Measurement of pain thresholds alone does not provide direct evidence for central pain processing. The evaluation of spinal reflexes may be considered as a more objective and direct indication for central hyperexcitability and rules out the subjective nature of pain reports. Results from the only study performed in patients with chronic LBP do not report an enhanced hyperexcitability.[46] It has, however, been suggested that the clinical use of evaluation of spinal reflexes in patients with neuropathic pain may be questioned. As patients with LBP experienced radicular symptoms in that study, which may be a sign that their pain is from neuropathic origin, further research is warranted.

In contrast to what was previously thought, functional organization of the adult brain is not fixed, but plastic changes of the primary cortical areas may occur as a consequence of injury, stimulation, and training.[98] Ongoing painful stimulation might therefore result in cortical alterations.[65,99] Evidence that alterations in the brain structure, brain function, and brain chemistry may occur in patients with chronic nonspecific LBP is growing.[8,65,77,78,81,100] Functional brain-imaging techniques are particularly useful to visualize the brain structures involved in pain processing during elicited pain and unravel brain circuitry.

Of particular interest is the observed gray matter decrease in right DLPFC and in brainstem in patients with chronic LBP.[77,78] Brainstem gray matter decrease, an area associated with inhibitory pain control, may lead to a loss of effective antinociception. This reasoning is supported by the strong negative correlation between gray matter decrease in brainstem and somatosensory cortex, and both pain intensity and pain unpleasantness in patients with chronic LBP.[78] The DLPFC seems to be involved in attention to pain[101] and in top-down control of pain, by contributing to descending inhibitory control of pain.[24] Furthermore, activity in DLPFC in HCs has been negatively correlated with catastrophic thinking about pain[27] and with pain intensity and unpleasantness.[24] In patients with chronic LBP, reduction of *N*-acetyl aspartate levels in the DLPFC were related to depression levels,[81] and reduction in gray matter density was strongly related to pain characteristics.[77] Finally, a strong negative correlation was demonstrated between medial prefrontal cortex activity and DLPFC activity during spontaneous pain in patients with chronic LBP.[76] These findings confirm previous observations, that activity in medial prefrontal cortex and DLPFC are inversely related.[102,103] In studies with healthy people, emotionally neutral reasoning resulted in enhanced activity in DLPFC and suppression of activity in the medial prefrontal cortex. Emotionally salient reasoning resulted in enhanced activation in medial prefrontal cortex and suppression of activation DLPFC.[104] These observations lead to the hypothesis that the emotional brain may play an important role in patients with LBP, as they may have difficulties in the disengagement from pain[76] and that cognitive emotional sensitization can therefore certainly contribute to the chronicity of the symptoms.

Central Sensitization and Altered Pain Processing: A Common Mechanism in Several Chronic Pain Conditions?

Several authors suggest that a similar underlying mechanism, that is CS and/or altered central pain processing may be responsible for symptoms in patients with chronic pain.[11,37] There is increasing evidence that long-term changes occur after noxious input and that plasticity of the nervous system alters the body's response to further peripheral stimuli.[105] After an initiating noxious input, neurobiological and biopsychosocial influences may alter tissue sensitivity, leading to enhanced pain transmission. Once this process has been established, only low-level peripheral input may be required to maintain a painful state.[22] It has been suggested that both functional and structural changes in the modulatory mechanisms of nociception may occur in the process of chronification of pain.[78] Decrease in gray matter volume or intensity has for example also been observed in other chronic pain conditions, such as for example patients with complex regional pain syndrome type I,[106] patients with chronic tension-type headache,[107] patients with FM,[108] and patients with phantom pain after amputation.[109] Longitudinal studies may offer exciting

perspectives, as it has been demonstrated that treating patients with LBP can restore normal brain function, and that the degree of brain recovery depended on the extent of the patient's improvement after treatment.[110]

Could Central Changes Leading to a Sensorimotor Conflict be Interpreted as Cause of LBP?

Analyzing alterations in brain function in relation to chronic pain may offer new perspectives. Harris hypothesized >10 years ago that cortical reorganization may lead to the generation of ongoing, movement-related pain, originating from the brain.[111] Moving involves generation of a motor intention and motor commands, monitored by feedback to the sensorimotor cortex from basal ganglia, cerebellum, and spinal cord. The outcome of this intention is monitored by muscle and joint proprioception, and vision.[111] In the presence of pain or after a painful experience, strategies used by the central nervous system to control trunk muscles may be altered. Although numerous studies demonstrated that motor control can be altered after a painful experience in patients with chronic nonspecific LBP, less consensus exists about the exact cause(s) for these "maladapative" changes, which may remain altered even after resolution of the symptoms. Human motor control is based on complex interactions between several cortical, subcortical and somatosensory levels.[112] The observed structural changes in basal ganglia[78] may for example be related to motor control changes in patients with LBP.

Harris[111] suggested that altered cortical representation of somatic input may falsely signal an incongruence between motor intention and movement. Central nervous systems generating motor activity are closely coupled to sensory feedback systems, which are monitored to detect any deviation from the predicted response.[113] Presenting incongruent information—a mismatch between intention, proprioception, and visual feedback or sensorimotor conflict—to HCs not only leaded to an increased neuronal activity in right DLPFC,[114] but also induced pain and sensory disturbances in HCs[115,116] and increased baseline symptoms in those with chronic pain.[117] It has hence been proposed that a prolonged sensorimotor conflict may provoke long-term symptoms in HCs and that pain generated by this conflict may be considered as a warning signal to alert the individual to abnormalities within information processing.[100,116]

It is plausible that a sensorimotor conflict may exist in patients with chronic LBP and may be related to the chronic symptoms. First, patients with chronic nonspecific LBP experience proprioception deficits,[118] tactile acuity deficits,[119] and exhibit altered motor control of the spine.[120,121] Moreover, deficits in postural control have been associated with reorganization of trunk muscle representation at the motor cortex in individuals with recurrent LBP.[122] Patients with LBP also present a disruption of body schema of the trunk.[123,124] Results from a pilot study demonstrated that patients were unable to delineate the outline of their trunk and mentioned that they could "not find it." Abnormal proprioceptive representation of the back in the primary somatosensory cortex and an altered body schema may be a possible source of sensorimotor incongruence in patients with chronic LBP.[100]

Second, lack of visual input of moving segments can enhance sensorimotor incongruence,[100,111] as vision dominates other senses.[125] As it is not possible to "see" the lumbar spine during task performances, abnormal cortical proprioceptive representation cannot be corrected by visual feedback.[100] Finally, inducing a sensorimotor conflict leads to increased activity in right DLPFC in HC.[114] As already mentioned, both structural and functional alterations of DLPFC have been observed in patients with chronic nonspecific LBP.[77,78,81] In support of these findings, Wand and O'Connell hypothesized that alterations in proprioceptive representation, subsequent sensorimotor incongruence, and preexisting depressed mood lead to overactivation and neurodegenerative change in DLPFC. They furthermore speculated that in patients with LBP, sensorimotor incongruence may directly produce pain and sustain altered motor control strategies and contribute to fear and catastrophic thoughts.

Further Research Perspectives?

A relation between pain catastrophizing and brain activity in regions involved in motor response and motor planning has been demonstrated in HC.[27] Mounting evidence exists for altered motor response in patients with LBP, but only few studies examined brain activity in these regions. Despite an increasing amount of research in this area, an in-depth understanding of the bidirectional pain-motor interaction is still far from being achieved[126,127] but it may have important messages for rehabilitation.[21] For example, it may be interesting to analyze the inhibitory influence of pain on motor response, and evaluate the clinical importance.

In summary, despite yet speculative, there are different mechanisms that may provide an explanation for the CS and cortical reorganization observed in patients with chronic LBP. It is arguable that after an initial painful incident, a cascade of events (hyperalgesia, allodynia and referred pain due to wind-up, deficient descending and/or ascending central modulatory mechanisms, cognitive emotional sensitization, and a sensorimotor conflict) occurs in a subgroup of patients with LBP, leading to central reorganization that maintains pain in absence of ongoing peripheral nociception. The fact that the results between some studies differ, may be ascribed to some methodological concerns. First, the power of most studies is either not calculated, or studies are underpowered. Study samples are small, and may account for differences between studies. Second, many studies demonstrate an association between several variables, but are cross-sectional in nature. A longitudinal rather than a cross-sectional design will be needed to answer the question of causality. Third, medication use is not registered in all studies. Some studies describe medication use as an exclusion criterion, whereas other studies do not mention whether patients stopped their medication before the experiment. Fourth, inclusion criteria of patients with chronic LBP strongly differ between studies. Some studies mention that their patients suffer from nonspecific LBP, but include some postoperative patients, patients with radicular symptoms, etc. Other studies use a mix of both neuropathic and non-neuropathic pain patients. This inhomogeneity may influence study results and may explain the subgroups observed in patients with LBP.

Further work is necessary firstly to identify the proportion of patients with chronic LBP experiencing generalized or widespread sensitization and altered central pain processing, and secondly to determine the clinical consequences of CS in patients with chronic LBP. Evaluation

of CS and altered central pain processing should therefore be included as outcome parameters or as diagnostic criteria to include or exclude patients. Guidelines for the recognition of CS in patients with musculoskeletal pain, including patients with chronic LBP, are available.[31,95] Once established in individual cases of chronic LBP, several treatment options for targeting CS are accessible to clinicians (reviewed by Nijs et al[128]).

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