Central Sensitization in Chronic Low Back Pain: A Narrative Review

Dibyendunarayan D Bid*, Neela C Soni, Priyanshu V Rathod***,**

*PhD Scholar, **Professor & Guide, ***Dean, Faculty of Medicine; School of Physiotherapy, RK University, Rajkot-360020.

*Senior Lecturer, Sarvajanik College of Physiotherapy, Rampura, Surat-395003

Abstract:

Objective: The aim of this narrative review is to examine the available literature related to central sensitization (CS) and altered central pain processing in chronic low back pain (CLBP) patients.

Methods: Literature was searched using many electronic databases. Additionally, reference list of most prominent articles were searched to increase the search accuracy, as much as possible. Studies which are evaluating the concept of CS in conservatively treated CLBP patients were included.

Results: Results of studies evaluating the responsiveness to various types of stimuli in CLBP patients are contradictory. Some studies in CLBP patients have showed increased pain responses after sensory stimulation of body parts outside the painful region, when some other studies report no differences between patients and healthy controls. Studies evaluating the integrity of the endogenous pain inhibitory systems describe unchanged activity of this descending inhibitory system. Conversely, studies examining brain structure and function in connection with experimentally induced pain provide initial proof for changed central pain processing in CLBP patients. Also inappropriate beliefs about pain, depression and/or pain catastrophizing, may lead to the development of CS.

Conclusions: Most of the literatures suggest that the CNS becomes centrally sensitized in a subgroup of patients with CLBP. However, the significance of this involvement is just starting to become clearer. This could be an active topic of future research. More studies are necessary for providing definite evidence for the clinical importance of CS.

Key Words: Central sensitization, central pain processing, chronic low back pain, hyperalgesia, cortical reorganization, widespread pain, temporal summation.

Author for correspondence: Dr. Dibyendunarayan D. Bid, Sarvajanik College of Physiotherapy, Rampura, Surat- 395003, e-mail: dnbid71@gmail.com

Introduction:

Low back pain (LBP) is a significant clinical, social, and financial problem frequently observed with prevalence ranging from 8% to 56% in USA and it is estimated that 28% people experience disabling LBP sometime during their lives, 14% experience episodes lasting at least two weeks, 8% of the entire working population will be disabled in any given year [(1)]. Volinn E [(2)] highlighted the fact that the 22 high-income countries, on which the research attention has largely been centered, represent less than 15% of the world's population. However, more recent reports from Tibet [(3)], Turkey[(4, 5)], and China[(6)] suggest that prevalence rates in non-European countries are not that dissimilar from Western countries with one year prevalence in adults in these research studies is between 36% and 64%.

Chronic low back pain (CLBP) is sometimes defined as back pain that lasts for more than 7–12 weeks and many others classify frequently repeated back pain as chronic pain since it intermittently affects an individual over a long period [(7)]. Very little is known about the precise causes despite the high prevalence and high incidence of LBP [(8)]. Degenerative changes seen in imaging studies in the structures of the lumbar vertebral column and as well in musculoskeletal structures do not explain the symptoms of LBP; as they are also seen in normal healthy subjects[(9, 10)] and consistently there is a weak association between symptoms of LBP and imaging results [(11)]. In approximately 85% of the patients with LBP a precise pathoanatomic diagnosis cannot be given, hence these patients are considered having nonspecific LBP [(8)]. It is observed that only 25% of the variance of back pain intensity can be explained by the combined contribution of pathology and psychosocial factors [(12)], hence it is imperative that further exploration of contributing factors and underlying mechanisms should be done.

Abnormal pain processing in the central nervous system (CNS) rather than from actual damage and/or injury to anatomic structures of body may lead to increased neuronal response and central sensitization (CS) [13-15] and this may be responsible for mechanical hyperalgesia, allodynia, and/or referred pain which are frequently seen in chronic pain syndromes [15-19]. CS is described by the International Association for the Study of Pain (IASP) as: *"Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input"[20].* CS is also defined as "an augmentation of responsiveness of central neurons to input from unimodal and polymodal receptors"[21]. The outcome of the processes involved in CS is an increased responsiveness to a variety of peripheral stimuli including mechanical pressure, chemical substances, light, sound, heat, cold, and electrical stimuli. The increased sensitivity to various stimuli results in a large decreased load tolerance of the neuromusculoskeletal system. Although the precise mechanism of CS is not fully understood; several contributing mechanisms have been put forward: It may be an altered sensory processing in the brain [22], malfunctioning of descending anti-nociceptive mechanisms [23], increased activity of pain facilitatory pathways, temporal summation of second pain or wind-up [22, 24], and long-term potentiation of neuronal synapses in the anterior cingulate cortex [25]. Besides the above top-down mechanisms included in the pathophysiology of CS, it is important to understand that there are bottom-up mechanisms as well. For example, peripheral injury and other forms of stressors trigger the release of pro-inflammatory cytokines, with the consequent activation of spinal cord glia with cyclo-oxygenase-2 and prostaglandin E2 expression in the CNS [26-29].

"Wind up" denotes to a central spinal mechanism in which repetitive noxious stimulation results in a slow temporal summation that is experienced in humans as increased pain [30]. It leads to facilitation of ascending pain mechanisms and the literature also describes that there are alterations in the descending inhibitory pathways those arising from the periaqueductal gray matter and the rostral ventral medulla in the brainstem [31]. The work of these descending inhibitory pathways is to "focus" the excitation of the dorsal horn neurons, to generate an urgent, localized, and rapid nociceptive signal to biologically relevant stimuli, thereby suppressing surrounding extraneous neuronal activity [32, 33], and breakdown of one or more components of these inhibitory systems can result in CS [33]. It is recognized that there are facilitatory pathways originating from the brainstem; besides descending inhibitory pathways. Centres in the forebrain are capable of wielding powerful influences on various nuclei of the brainstem [34], including the nuclei recognized as the origin of the descending facilitatory pathway [33].

The activity in descending pathways can be modulated, as it is not constant; for example by the level of alertness, attention, anticipation, and stress [35]. It has been identified that forebrain functions such as cognitions, attention, emotions, motivation, and/or stress as personal factors may regulate the actual pain experience [33]. To name this facilitatory influence, the 'cognitive-emotional sensitization' term has been coined [36]. Functional imaging studies have showed in healthy subjects that pain catastrophizing and anticipations were related to neural processing of nociceptive stimuli; which are psychosocial and cognitive factors [37, 38]. During the last few decades great efforts have been made to untangle how brain processes pain and to decode involved neuronal mechanisms using functional imaging studies [39].

The intent of this narrative review is to search and analyse the available literature regarding CS and altered central pain processing in CLBP patients. The first author searched the literature and it was done by comprehensive computerized search on Science direct, National Library of Medicine (Pubmed), Biomed Central, Google Scholar, CINAHL, Pubmed central and Oxford Press. The key words "chronic low back pain" was used in combination with following terminologies: central sensitization, hyperalgesia, temporal summation, central pain processing, cortical reorganization, pain inhibition, pain facilitation, diffuse noxious inhibitory controls (DNICs) and widespread pain. Additionally, reference lists of most pertinent articles were searched to increase the search accuracy, as much

as possible. We have included all the available studies which are evaluating the concept of central sensitization (CS) in conservatively treated CLBP patients.

Does Segmental and Extrasegmental Sensitization exist in CLBP patients?

Hyperalgesia is showed by "a lowered pain threshold because of sensitization of nociceptive afferents or an increasing pain intensity as a function of graded nociceptive stimulation" in many chronic unexplained disorders, such as Fibromyalgia, Chronic regional pain syndrome (CRPS), Whiplash Associated Disorders (WADs) to detect CS [40]. In patients with LBP, lower thresholds may be found in areas innervated by spinal segments neighbouring to the spinal segments of the primary source of pain perception. These findings are termed as segmental CS [41]. If pain referral and many areas of hyperalgesia is found away from the site of symptomatic area of back pain than this is termed as widespread or extrasegmental CS[41]. Sixteen studies are found that deals with sensitivity of various types of stimuli in CLBP patients. Details of the study are shown in the Table-1.

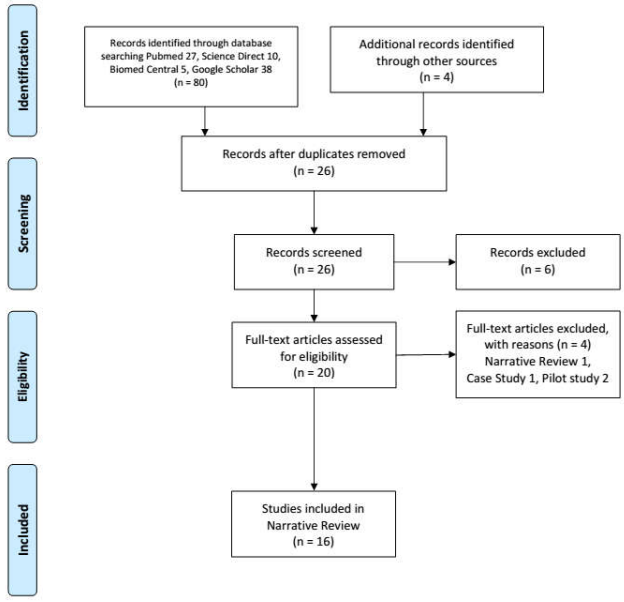

Figure-1: Flow Diagram of Literature Search

This table-1 describes the results of these studies in relation to the presence or absence of the central sensitization (CS+ or CS-) in CLBP patients.

Presence of Hyperalgesia in CLBP patients

There are four studies, which reported hyperalgesia to pressure to sites unrelated to the lumbo-pelvic area in CLBP patients, indicating generalized or widespread hyperalgesia at least in a subgroup of CLBP patients [44-47]. It was observed that there is a decreased pressure pain threshold (PPT) in a population of CLBP patients with and without radiation distal to the knee, both at sites related to lumbar area(paraspinal lumbar muscles) and unrelated to the lumbar area (extensor muscle of the wrist, finger, etc) [46]. Also contradictory results were reported in the literature suggesting that CLBP patients do not experience sensitization[49]. In a study conducted by O'Neill et al, pressure pain thresholds (PPTs) in tibialis anterior muscle were found significantly lower in CLBP patients, whereas PPTs of infraspinatus muscle were not different from healthy controls, suggesting segmental sensitization[48]. Lautenbacher et al [50] found no differences in pain threshold between patients with CLBP and HC when contact heat was used on the right hand using a Peltier thermode, but in another study by Derbyshire et al[51] reported that the patients experienced significant higher pain ratings on Visual Analog Scale (VAS) compared with healthy subjects, suggesting widespread hyperalgesia, but no allodynia (as there were no differences in VAS between patients and control group for the non-painful stimulation).After administering hypertonic saline injection, patients with herniated disk confirmed by MRI exhibited considerably higher pain intensity, duration, and larger areas of pain referral in both infraspinatus and tibialis anterior muscles in comparison with healthy controls, indicating widespread sensitization in these patients with CLBP [48].

In studies, where repeated pain stimulation is applied or continuous stimulation is applied; demonstrates the phenomena of enhanced temporal summation (wind-up) [52-55]. In various studies, to induce temporal summation mechanical, electrical, or thermal stimulation have been used (See Table: 1 Wind up).

The endogenous pain control system whose deficiency is supposed to contribute to chronic musculoskeletal pain is represented by

DNIC-like mechanisms [59, 60]. The DNIC-like mechanisms 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 [61]. It can be facilitated by serotonergic and opioidergic agents and inhibited by opioid antagonists and serotonin antagonists, respectively [62-64].

The initiation of endogenous pain inhibitory systems by the spatial summation test was assessed [56] using immersion of different surfaces of the arm in circulating noxious cold (12ºC) water. Both patients with CLBP and healthy controls perceived their pain in different manner during the ascending and descending sessions. The descending session resulted in smaller pain intensity and unpleasantness, which the authors ascribed to a full recruitment of inhibitory systems at the beginning of the descending session in contrast to a gradual recruitment during the ascending session. During the ascending session pain perception remained static, regardless the stimulated area, whereas a correlation was observed between pain and stimulated area during the descending session. Hence the observations from this study do not support a deficit of this endogenous pain inhibitory system in CLBP.

In normal conditions, pain thresholds increase during physical activity because of the release of endogenous opioids, growth factors [65], and other strong inhibitory mechanisms (descending inhibition) engineered by the CNS [66]. However, in patients with CLBP, pain ratings from an experimentally induced pressure pain stimulus increased in response to submaximal aerobic exercise [57], as they are in healthy controls [67], indicating normal pain processing in response to exercise. Meeus M et al studied pain response in relation to exercise in patients with chronic fatigue syndrome and chronic widespread pain, in patients with CLBP, and in pain-free sedentary controls. The absence of endogenous inhibition during exercise was only seen in patients with chronic fatigue and chronic widespread pain, but not in the group of CLBP patients [49].

Most of the above-mentioned studies are based on the patients' pain assessment, which are actually subjective measurements. Measuring the minimal intensity of transcutaneous electrical stimulation essential to elicit a spinal reflex may provide a better objective measurement of spinal hyperexcitability and CS [68]. The minimal intensity of the stimulus that is sufficient to evoke a reflex at a well-defined latency, known as the reflex threshold, usually represents the minimal stimulus intensity required to elicit a perception of pain [69]. Peters ML et al elicited a nociceptive flexion reflex after noxious stimulation in CLBP patients [58]. There were no differences observed in nociceptive flexion reflex (RIII) threshold between CLBP patients and healthy controls after noxious electrical stimulation of the ankle [58]. Hence, there is no evidence to suggest that spinal reflexes are varied in CLBP patients.

Altered Brain Function in CLBP

Flor et al first showed that cortical hyperactivity and reorganization in CLBP patients [70]. Diers et al [55] used EEG to evaluate brain responses in relation to pain in patients with CLBP. No significant differences were observed in pain threshold, but patients exhibited extrasegmental sensitization when repeated stimulation was applied to evoke temporal summation, but no significant sensitization was seen among healthy controls [55]. Evidence for augmented central pain processing has been found in studies using fMRI [45]. In a positron emission tomography study [51] conducted on CLBP patients and HCs with thermal pain stimulation; the regional cerebral blood flow correlated partially well with subjective pain experience in many brain areas, such as the cerebellum, thalamus, midbrain, etc. in both the groups. Hence these data provide some initial evidence for altered central pain processing in CLBP patients [51].

Cognitive Emotional Sensitization

Following characteristics namely, Catastrophizing [71], depressive feelings [72], and fear avoidance [73-75] have been reported to occur in CLBP patients. Inappropriate beliefs have been linked with the development of overstated pain perception [76, 77] or other negative effects. All these psychological factors are cited as yellow flags as

they are associated with a poor prognosis, may heighten facilitatory pathways in the CNS, leads to sensitization of dorsal horn spinal cord neurons. Initial research findings suggest that cognitive and emotional factors can contribute and/or may sustain the mechanisms of CS in CLBP patients.

Discussion

The purpose of this article was to review and evaluate the existing scientific literature regarding the role of CS in CLBP of different aetiologies. Different assessment methodologies were utilized for evaluating the phenomenon of CS, intending to understand the different changes in pain sensitivity observed in this population. Nine out of the 16 articles that were considered in this narrative review seem to support an emerging key role for CS in CLBP. This was confirmed through by means of different parameters like pain perception threshold, pain tolerance, pain ratings etc. All these findings are considered clinical manifestations of CS [(78)]. Furthermore, similar findings have been previously seen in some other chronic pain conditions such as whiplash injury [(79)] or fibromyalgia [(45)], suggesting these conditions are caused by the same altered central pain processing mechanism.

CS demonstrates itself at different degrees over a continuum from no CS at all to severe CS. Although prevalent in chronic pain, generalized central hypersensitivity is not present in every patient [(80)]. For instance, in some populations (e.g., fibromyalgia), CS may be the characteristic feature of the disorder. In others, such as in CLBP, not all patients have CS, but only a subgroup of them, has it.

There are many studies which suggest that chronic pain should be seen from a "Central" view point. Changes in ascending and descending central modulatory mechanisms for the perception of pain, which is termed as "neuronal plasticity" [(32)] may be responsible for CS. CS may involve both functional changes and structural changes in the CNS [(81, 82)].

Though there are many studies that indicate presence of altered central pain mechanisms in CLBP patients but results are ambiguous. Some studies observed reduced pain thresholds suggestive of extrasegmental hyperalgesia [(44-47)], some other studies only observed a segmental hyperalgesia [(48)], and while some authors did not find hyperalgesia at all [(42, 55, 83)]. Same results were found when temporal summation was experimentally induced in CLBP patients [(55, 83)].

Now it is understood that functional organization of the adult brain is not fixed, but plastic changes of the primary cortical areas may happen as a result of injury, stimulation, and training [(84)]. Continued painful stimulation may result into cortical changes [(70, 85)]. There is growing evidence that changes in the brain structure, brain function, and brain chemistry may happen in CLBP patients [(45, 70, 86, 87)]. Functional brain-imaging techniques are especially useful to visualize the brain structures engaged in pain processing during evoked pain and to understand the mysteries of brain circuitry.

So far there is no gold standard available for diagnosis of CS [(15)]. Different clinical and laboratory methods are used for detecting potential involvement of CS in musculoskeletal pain conditions (i.e., QST and brain imaging techniques), without having any comparatively superior or reliable method. All of them evaluated the same basic concept of CS, but in its different expressions related to the different aspects of sensitization [(88)]. For example, widespread hyperalgesia, which is an expression of CS, can be evaluated quantitatively in a standardized way by using pressure algometry. Most studies of this review assessed the presence of CS in laboratory conditions and used costly and complex equipment; which are not available for most of the clinicians. Further investigation regarding the assessment of CS in CLBP is required in order to provide new assessment methodologies for CS, which is simple and less costly for the clinicians. With this view-point, the recently proposed 'Central Sensitization Inventory' should be investigated in CLBP patients [(89)].

Conclusion

Most of the literatures reviewed here suggest that the CNS becomes centrally sensitized in a subgroup of patients with CLBP. However, the significance of this involvement is just starting to become clearer. This could be an active topic of future research. More studies are necessary for providing definite evidence for the clinical importance of CS.

Acknowledgement:
We thankfully acknowledge the valuable inputs and constructive suggestions provided by Dr. A. Thangamani Ramalingam [PT], Lecturer; The Sarvajanik College of Physiotherapy, Surat.

References:

1. Manchikanti L. Epidemiology of low back pain. Pain physician. 2000;3(2):167-92.
2. Volinn E. The epidemiology of low back pain in the rest of the world. A review of surveys in low- and middle-income countries. Spine. 1997;22(15):1747-54.
3. Hoy D, Toole MJ, Morgan D, Morgan C. Low back pain in rural Tibet. The Lancet.361(9353):225-6.
4. Cakmak A, Yucel B, Ozyalcn SN, Bayraktar B, Ural HI, Duruoz MT, et al. The frequency and associated factors of low back pain among a younger population in Turkey. Spine. 2004;29(14):1567-72.
5. Gilgil E, Kacar C, Butun B, Tuncer T, Urhan S, Yildirim C, et al. Prevalence of low back pain in a developing urban setting. Spine. 2005;30(9):1093-8.
6. Barrero LH, Hsu YH, Terwedow H, Perry MJ, Dennerlein JT, Brain JD, et al. Prevalence and physical determinants of low back pain in a rural Chinese population. Spine. 2006;31(23):2728-34.
7. Andersson GBJ. Epidemiological features of chronic low-back pain. The Lancet.354(9178):581-5.
8. Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, et al. Chapter 4 European guidelines for the management of chronic nonspecific low back pain. European Spine Journal. 2006;15(Suppl 2):s192-s300.
9. Kovacs FM, Arana E. Degenerative disease of the lumbar spine. Radiologia. 2016.
10. Steffens D, Hancock MJ, Pereira LS, Kent PM, Latimer J, Maher CG. Do MRI findings identify patients with low back pain or sciatica who respond better to particular interventions? A systematic review. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society. 2015.
11. van Tulder M, Becker A, Bekkering T, Breen A, del Real MT, Hutchinson A, et al. Chapter 3. European guidelines for the management of acute nonspecific low back pain in primary care. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society. 2006;15 Suppl 2:S169-91.
12. Peters ML, Vlaeyen JW, Weber WE. The joint contribution of physical pathology, pain-related fear and catastrophizing to chronic back pain disability. Pain. 2005;113(1-2):45-50.
13. Baranauskas G, Nistri A. Sensitization of pain pathways in the spinal cord: cellular mechanisms. Progress in neurobiology. 1998;54(3):349-65.
14. Staud R. Evidence of involvement of central neural mechanisms in generating fibromyalgia pain. Current rheumatology reports. 2002;4(4):299-305.
15. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2-15.
16. Sorensen J, Graven-Nielsen T, Henriksson KG, Bengtsson M, Arendt-Nielsen L. Hyperexcitability in fibromyalgia. The Journal of rheumatology. 1998;25(1):152-5.
17. 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. European journal of pain. 2002;6(2):149-59.
18. Banic B, Petersen-Felix S, Andersen OK, Radanov BP, Villiger PM, Arendt-Nielsen L, et al. Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. Pain. 2004;107(1-2):7-15.
19. Meeus M, Nijs J, Huybrechts S, Truijen S. Evidence for generalized hyperalgesia in chronic fatigue syndrome: a case control study. Clinical rheumatology. 2010;29(4):393-8.
20. Loeser JD, Treede RD. The Kyoto protocol of IASP Basic Pain Terminology. Pain. 2008;137(3):473-7.
21. Meyer RA, Campbell JN, Raja SN. Peripheral neural mechanisms of nociception. 3 ed. Wall PD, Melzack R, editors. Edinburgh: Churchill Livingstone; 1995.
22. Staud R, Craggs JG, Robinson ME, Perlstein WM, Price DD. Brain activity related to temporal summation of C-fiber evoked pain. Pain. 2007;129(1-2):130-42.
23. 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(2):439-48.
24. Meeus M, Nijs J. Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. Clinical rheumatology. 2007;26(4):465-73.
25. Zhuo M. A synaptic model for pain: long-term potentiation in the anterior cingulate cortex. Molecules and cells. 2007;23(3):259-71.
26. Maier SF, Watkins LR. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. Psychological review. 1998;105(1):83-107.
27. Watkins LR, Maier SF. Implications of immune-to-brain communication for sickness and pain. Proceedings of the National Academy of Sciences. 1999;96(14):7710-3.
28. Bazan NG. COX-2 as a multifunctional neuronal modulator. Nat Med. 2001;7(4):414-5.
29. Samad TA, Moore KA, Sapirstein A, Billet S, Allchorne A, Poole S, et al. Interleukin-1beta-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature. 2001;410(6827):471-5.
30. Gracely RH, Grant MA, Giesecke T. Evoked pain measures in fibromyalgia. Best practice & research Clinical rheumatology. 2003;17(4):593-609.
31. Nijs J, Van Houdenhove B. From acute musculoskeletal pain to chronic widespread pain and fibromyalgia: application of pain neurophysiology in manual therapy practice. Manual therapy. 2009;14(1):3-12.
32. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science (New York, NY). 2000;288(5472):1765-9.

33. Zusman M. Forebrain-mediated sensitization of central pain pathways: 'non-specific' pain and a new image for MT. Manual therapy. 2002;7(2):80-8.
34. Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. Brain : a journal of neurology. 2003;126(Pt 5):1079-91.
35. Rygh LJ, Tjolsen A, Hole K, Svendsen F. Cellular memory in spinal nociceptive circuitry. Scandinavian journal of psychology. 2002;43(2):153-9.
36. Brosschot JF. Cognitive-emotional sensitization and somatic health complaints. Scandinavian journal of psychology. 2002;43(2):113-21.
37. Seminowicz DA, Davis KD. Cortical responses to pain in healthy individuals depends on pain catastrophizing. Pain. 2006;120(3):297-306.
38. Ploghaus A, Becerra L, Borras C, Borsook D. Neural circuitry underlying pain modulation: expectation, hypnosis, placebo. Trends in cognitive sciences. 2003;7(5):197-200.
39. Seifert F, Maihofner C. Central mechanisms of experimental and chronic neuropathic pain: findings from functional imaging studies. Cellular and molecular life sciences : CMLS. 2009;66(3):375-90.
40. W. W. Hyperalgesia and Allodynia. New York: Raven Press; 1992.
41. Nijs J, Van Houdenhove B, Oostendorp RA. Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice. Manual therapy. 2010;15(2):135-41.
42. Peters ML, Schmidt AJ. Differences in pain perception and sensory discrimination between chronic low back pain patients and healthy controls. Journal of psychosomatic research. 1992;36(1):47-53.
43. Burns PB, Rohrich RJ, Chung KC. The Levels of Evidence and their role in Evidence-Based Medicine. Plastic and reconstructive surgery. 2011;128(1):305-10.
44. Clauw DJ, Williams D, Lauerman W, Dahlman M, Aslami A, Nachemson AL, et al. Pain sensitivity as a correlate of clinical status in individuals with chronic low back pain. Spine. 1999;24(19):2035-41.
45. Giesecke T, Gracely RH, Grant MA, Nachemson A, Petzke F, Williams DA, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis and rheumatism. 2004;50(2):613-23.
46. Giesbrecht RJ, Battie MC. A comparison of pressure pain detection thresholds in people with chronic low back pain and volunteers without pain. Physical therapy. 2005;85(10):1085-92.
47. 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. European journal of pain. 2005;9(3):267-75.
48. O'Neill S, Manniche C, Graven-Nielsen T, Arendt-Nielsen L. Generalized deep-tissue hyperalgesia in patients with chronic low-back pain. European journal of pain. 2007;11(4):415-20.
49. 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. Journal of rehabilitation medicine. 2010;42(9):884-90.
50. Lautenbacher S, Galfe G, Karlbauer G, Moltner A, Strian F. Effects of chronic back pain on the perception of experimental heat pain. Perceptual and motor skills. 1990;71(3 Pt 2):1283-92.
51. Derbyshire SW, Jones AK, Creed F, Starz T, Meltzer CC, Townsend DW, et al. Cerebral responses to noxious thermal stimulation in chronic low back pain patients and normal controls. NeuroImage. 2002;16(1):158-68.
52. Arntz A, Merckelbach H, Peters M, Schmidt AJ. Chronic low back pain, response specificity and habituation to painful stimuli. Journal of Psychophysiology. 1991;5:177-88.
53. Kleinbohl D, Holzl R, Moltner A, Rommel C, Weber C, Osswald PM. Psychophysical measures of sensitization to tonic heat discriminate chronic pain patients. Pain. 1999;81(1-2):35-43.
54. Flor H, Knost B, Birbaumer N. The role of operant conditioning in chronic pain: an experimental investigation. Pain. 2002;95(1-2):111-8.
55. Diers M, Koeppe C, Diesch E, Stolle AM, Holzl R, Schiltenwolf M, et al. Central processing of acute muscle pain in chronic low back pain patients: an EEG mapping study. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society. 2007;24(1):76-83.
56. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain. 2005;114(1-2):295-302.
57. Hoffman MD, Shepanski MA, Mackenzie SP, Clifford PS. Experimentally induced pain perception is acutely reduced by aerobic exercise in people with chronic low back pain. Journal of rehabilitation research and development. 2005;42(2):183-90.
58. 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(2):177-87.
59. Kosek E, Ordeberg G. Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. Pain. 2000;88(1):69-78.
60. Pielsticker A, Haag G, Zaudig M, Lautenbacher S. Impairment of pain inhibition in chronic tension-type headache. Pain. 2005;118(1-2):215-23.
61. Le Bars D. The whole body receptive field of dorsal horn multireceptive neurones. Brain research Brain research reviews. 2002;40(1-3):29-44.
62. Le Bars D, Willer JC, De Broucker T. Morphine blocks descending pain inhibitory controls in humans. Pain. 1992;48(1):13-20.
63. Chitour D, Dickenson AH, Le Bars D. Pharmacological evidence for the involvement of serotonergic mechanisms in diffuse noxious inhibitory controls (DNIC). Brain research. 1982;236(2):329-37.
64. Willer JC, Le Bars D, De Broucker T. Diffuse noxious inhibitory controls in man: involvement of an opioidergic link. European journal of pharmacology. 1990;182(2):347-55.
65. Koltyn KF, Arbogast RW. Perception of pain after resistance exercise. British Journal of Sports Medicine. 1998;32(1):20-4.
66. Millan MJ. Descending control of pain. Progress in neurobiology. 2002;66(6):355-474.

67. Hoffman MD, Shepanski MA, Ruble SB, Valic Z, Buckwalter JB, Clifford PS. Intensity and duration threshold for aerobic exercise-induced analgesia to pressure pain. Archives of physical medicine and rehabilitation. 2004;85(7):1183-7.
68. Sandrini G, Serrao M, Rossi P, Romaniello A, Cruccu G, Willer JC. The lower limb flexion reflex in humans. Progress in neurobiology. 2005;77(6):353-95.
69. Willer JC. Comparative study of perceived pain and nociceptive flexion reflex in man. Pain. 1977;3(1):69-80.
70. Flor H, Braun C, Elbert T, Birbaumer N. Extensive reorganization of primary somatosensory cortex in chronic back pain patients. Neuroscience letters. 1997;224(1):5-8.
71. Meyer K, Tschopp A, Sprott H, Mannion AF. Association between catastrophizing and self-rated pain and disability in patients with chronic low back pain. Journal of rehabilitation medicine. 2009;41(8):620-5.
72. Waxman SE, Tripp DA, Flamenbaum R. The mediating role of depression and negative partner responses in chronic low back pain and relationship satisfaction. The journal of pain : official journal of the American Pain Society. 2008;9(5):434-42.
73. Vlaeyen JW, Kole-Snijders AM, Boeren RG, van Eek H. Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. Pain. 1995;62(3):363-72.
74. Crombez G, Vlaeyen JW, Heuts PH, Lysens R. Pain-related fear is more disabling than pain itself: evidence on the role of pain-related fear in chronic back pain disability. Pain. 1999;80(1-2):329-39.
75. Gheldof EL, Crombez G, Van den Bussche E, Vinck J, Van Nieuwenhuyse A, Moens G, et al. Pain-related fear predicts disability, but not pain severity: a path analytic approach of the fear-avoidance model. European journal of pain. 2010;14(8):870.e1-9.
76. Lethem J, Slade PD, Troup JD, Bentley G. Outline of a Fear-Avoidance Model of exaggerated pain perception--I. Behaviour research and therapy. 1983;21(4):401-8.
77. Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain. 2000;85(3):317-32.
78. Arendt-Nielsen L, Graven-Nielsen T. Translational musculoskeletal pain research. Best practice & research Clinical rheumatology. 2011;25(2):209-26.
79. Sterling M, Jull G, Vicenzino B, Kenardy J. Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. Pain. 2003;104(3):509-17.
80. Schliessbach J, Siegenthaler A, Streitberger K, Eichenberger U, Nuesch E, Juni P, et al. The prevalence of widespread central hypersensitivity in chronic pain patients. European journal of pain. 2013;17(10):1502-10.
81. Flor H. The modification of cortical reorganization and chronic pain by sensory feedback. Applied psychophysiology and biofeedback. 2002;27(3):215-27.
82. Lotze M, Moseley GL. Role of distorted body image in pain. Current rheumatology reports. 2007;9(6):488-96.
83. Peters ML, Schmidt AJ, Van den Hout MA. Chronic low back pain and the reaction to repeated acute pain stimulation. Pain. 1989;39(1):69-76.
84. Flor H. Cortical reorganisation and chronic pain: implications for rehabilitation. Journal of rehabilitation medicine. 2003(41 Suppl):66-72.
85. Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, et al. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature. 1995;375(6531):482-4.
86. Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2004;24(46):10410-5.
87. Wand BM, O'Connell NE. Chronic non-specific low back pain - sub-groups or a single mechanism? BMC musculoskeletal disorders. 2008;9:11.
88. Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. Nature reviews Rheumatology. 2010;6(10):599-606.
89. Neblett R, Cohen H, Choi Y, Hartzell M, Williams M, Mayer TG, et al. The Central Sensitization Inventory (CSI): Establishing Clinically-Significant Values For Identifying Central Sensitivity Syndromes In An Outpatient Chronic Pain Sample. The journal of pain : official journal of the American Pain Society. 2013;14(5):438-45.

Table 1: Summary of the included studies

Author/ Publication Year	Design	Population studied	Stimulus used	Outcome measures[including Assessment of CS]	Central sensitization Yes CS+/ No CS-	Results of the study	Level of evidence/Limitations of study
Hyperalgesia (mechanical &/or electrical stimuli)							
Peters and Schmidt(42) (1992)	Case control study	20 CLBP 20 HCs	Electrical pain stimulus, Mechanical pressure	Algometry- Pain perception threshold, & Maximum pain tolerance	No	Higher PPT & MPT in CLBP group. Supports adaptation theory/DNIC	Level IV (43)
Clauw et al (44) (1999)	Cross-sectional pilot study	45 CLBP patients	Mechanical pressure	Algometry, MRI, SF-36, Psychosocial variables	Yes	CLBP patients had more tender points (5.2±5.4) in comparison with 1 to 3.5 in general population.	Level IV
Giesecke et al(45) (2004)	Case control study	11 CLBP 16 Fibro-myalgia 11 HCs	Mechanical Pressure	Pressure pain threshold, fMRI	Yes	Low PPT found in CLBP patients	Level IV Small sample size
Giesbrecht and Battie(46) (2005)	Case control study	30 CLBP females 30 HCs female	Mechanical Pressure	Pressure pain threshold (Electronic Algometry)	Yes	Significantly lower PPT in CLBP patients in comparison with HC	Level IV Only females
Laursen et al (47) (2005)	Case control study	40 female patients - 10FM/whiplash, 10 endometriosis, 10 LBP, 10 Rheumatoid arthritis Compared with 41 female HCs.	Mechanical Pressure	Pressure pain threshold (Electronic Algometry), SF-36	Yes	lower values of PPT in CLBP patients in comparison with HC	Level IV Small sample of CLBP patients; Only female patients.
O'Neill et al (48) (2007)	Case control study	12 CLBP 12 HC	Mechanical pressure, Hypertonic saline injection	Pressure pain threshold; Supra-threshold stimulation; Experimentally induced muscle pain.	Yes	Significant difference between LBP and HC in pain threshold or pain tolerance.	Level IV Small sample size. Selection bias
Meeus et al(49) (2010)	Experimental case control study	26 Chronic Fatigue Syndrome 21 CLBP 31 HC	Mechanical pressure, Aerobic exercises	Pressure pain threshold Venous blood sampling (Nitric Oxide level)	No	No difference between LBP and HC in pain threshold	Level IV Selection bias. Individual difference. Duration of exercise

Hyperalgesia (thermal stimuli)							
Lautenbacher et al (50) (1990)	Cross-sectional study	19 CLBP 19 HC	Thermal stimuli, cold	VAS, Tonic & phasic threshold, Somatosensory perception	No	No difference in threshold between CLBP andHCs but SSP is decreased	Level IV Small sample size
Derbyshire et al(51) 2002	Cross-sectional Case control study	16 CLBP 16 HC	Thermal stimuli	Thermal pain perception; Regional cerebral blood flow (rCBF); VAS rating.	Yes	Patients experienced higher VAS score at higher temperature compared with HCs; Small difference between LBP and HCs in rCBF for thermal stimuli	Level IV Small sample size
Wind up							
Arntz et al (52) (1991)	Pre-post repeated measure design	22 CLBP 21 HC	Electrical pain stimulus	VAS	No	Both the groups showed habituation	Level IV Methodological flaw
Kleinbohl et al (53) (1999)	Case control study	15 CLBP 15 headache patients 23 HCs	Tonic & Phasic heat stimuli	Pain threshold Index of Sensitization	Yes	LBP patients showed stronger & early sensitization	Level IV Selection bias
Flor et al (54) (2002)	Case control study	30 CLBP 30 HCs	Electrical pain stimuli; Repeated stimulation at different intensities	Pain threshold; Pain tolerance threshold; Somatosensory perception	Yes	Elevated pain threshold in CLBP group, Decrease in pain threshold in HC Supports CS+	Level IV
Diers et al (55) (2007)	Cross-sectional Case control study	14 CLBP 11 HCs	Electrical intracutaneous & intramuscular stimulus	Pain threshold Pain tolerance	Yes	Sensitization occurs in all CLBP patients but not in HCs	Level IV Small sample size
DNIC							
Julien et al(56) (2005)	Cross-over trial	30 Fibromyalgia30 CLBP 30 HCs	Immersion in noxious cold water at 12ºC	VAS rating during ascending or descending sessions (spatial summation)	No	Deficit of endogenous pain inhibitory systems found in fibromyalgia but not in chronic low back pain.	Level IV Methodological flaw

Endogenous inhibition during exercise							
Hoffman et al (57) (2005)	Repeated measure design/clinical trial	8 CLBP 10 HCs	Mechanical pressure	PPT	No	Pressure pain perception can be reduced after aerobic exercise in LBP patients and HCs	Level IV Small sample size
Flexion reflex							
Peters et al (58) (1992)	Mixed between-within group design	12 CLBP 12 oral surgery 12 HCs	Electrical pain stimulation	Nociceptive flexion reflex threshold	No	No significant difference between CLBP and HCs; No role of DNIC/supports adaptation theory	Level IV Small sample size