In the spine or in the brain? Recent advances in pain neuroscience applied in the intervention for low back pain

J. Nijs[1-3], J. Clark[1,2,4,5], A. Malfliet[1-3,7], K. Ickmans[1-3], L. Voogt[1,2,6], S. Don[1,2,6], H. den Bandt[1,2,6], D. Goubert[1,2,7], J. Kregel[1,2,7], I. Coppieters[1,2,7], W. Dankaerts[8]

[1]Pain in Motion International Research Group, www.paininmotion.be;
[2]Dept. of Physiotherapy, Human Physiology and Anatomy, Faculty of Physical Education and Physiotherapy, Vrije Universiteit Brussel, Belgium;
[3]Department of Physical Medicine and Physiotherapy, University Hospital Brussels, Belgium;
[4]Faculty of Health, Psychology and Social Care, Manchester Metropolitan University, UK;
[5]The Physio Shed, private practice for Physiotherapy, Omokoroa, New Zealand;
[6]Dept. of Physiotherapy, University of Applied Sciences Rotterdam, The Netherlands;
[7]Dept. of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Health Sciences, Ghent University, Belgium;
[8]Musculoskeletal Rehabilitation Research Unit, Dept. of Rehabilitation Sciences, Faculty of Kinesiology and Rehabilitation Sciences, University of Leuven, Belgium.

Jo Nijs, PT, MT
Jacqui Clark, PT, MT
Anneleen Malfliet, MSc, MT
Kelly Ickmans, PhD, MT
Lennard Voogt, PhD, MT
Sanneke Don, MSc, PT
Hester den Bandt, MSc, PT
Dorien Goubert, PhD, MT
Jeroen Kregel, MSc, PE
Iris Coppieters, PhD, MT
Wim Dankaerts, PhD, PT, MT

Please address correspondence to:
Dr Jo Nijs,
Vrije Universiteit Brussel,
Building F-Kima, Laarbeeklaan 103,
BE-1090 Brussels, Belgium.
E-mail: jo.nijs@vub.be

Received and accepted on September 1, 2017.

Clin Exp Rheumatol 2017; 35 (Suppl. 107): S108-S115.

Key words:
Pain, low back pain, neuroplasticity, clinical reasoning, exercise therapy

Funding information on page S-113.

Competing interests: none declared.

ABSTRACT

Conservative, surgical and pharmacological strategies for chronic low back pain (CLBP) management offer at best modest effect sizes in reducing pain and related disability, indicating a need for improvement. Such improvement may be derived from applying contemporary pain neuroscience to the management of CLBP. Current interventions for people with CLBP are often based entirely on a "biomedical" or "psychological" model without consideration of information concerning underlying pain mechanisms and contemporary pain neuroscience. Here we update readers with our current understanding of pain in people with CLBP, showing that CLBP is not limited to spinal impairments, but is also characterised by brain changes, including functional connectivity reorganisation in several brain regions and increased activation in brain regions of the so-called 'pain matrix' (or 'pain connectome'). Indeed, in a subgroup of the CLBP population brain changes associated with the presence of central sensitisation are seen. Understanding the role of these brain changes in CLBP improves our understanding not only of pain symptoms, but also of prevalent CLBP associated comorbidities such as sleep disturbances and fear avoidance behaviour. Applying contemporary pain neuroscience to improve care for people with CLBP includes identifying relevant pain mechanisms to steer intervention, addressing sleep problems and optimising exercise and activity interventions. This approach includes cognitively preparing patients for exercise therapy using (therapeutic) pain neuroscience education, followed by cognition-targeted functional exercise therapy.

Introduction

Chronic low back pain (CLBP) is the most common and important clinical, social, economic, and public health problem of all chronic pain disorders across the world (1). It is a complex disorder which is difficult to treat (2-5). The global point prevalence of LBP was estimated at 9.4% in 2010, with the highest prevalence of 15% in Western Europe (3), a significant proportion of whom develop CLBP. The prevelance of CLBP has been shown to be increasing in the United States of America, *e.g.*, from 3.2% in 1992 to 10.2% in 2006 in North Carolina (6). Conservative and pharmacological strategies for CLBP management offer at best modest effect sizes in reducing pain and related disability (7-9), suggesting the need for improvement.

Improvement in management of CLBP may emerge from applying contemporary pain neuroscience. Current intervention strategies for people with CLBP are often based on a biomedical (*e.g.*, neuromuscular training, myofascial treatment) or cognitive behavioural model (*i.e.*, graded exposure, graded activity) without accounting for the underlying pain mechanisms and our present understanding of contemporary pain neuroscience (10). Interventions often focus either on input (treating muscles and joints) or output mechanisms (motor control), while there is less attention paid to the well documented impairments in central nociceptive processing mechanisms (11-15). Here we update readers with our current knowledge of pain in people with CLBP, including recent advances in understanding impairments in central nociceptive processing mechanisms (11-15). First, we will show that CLBP is also characterised by differences in the morphology and functionality of the brain. Understanding these brain changes in CLBP improves our understanding not only of pain symptoms, but also of prevalent CLBP comor-

bidities like sleep disturbances and fear avoidance behaviour. The second part of the paper explains how clinicians can apply our current understanding of contemporary pain neuroscience to improve care for people with CLBP. This approach includes identifying relevant pain mechanisms to steer intervention, optimising exercise and activity and addressing sleep problems in people with CLBP.

Understanding brain changes in chronic low back pain

Central sensitisation in people with chronic low back pain

Modern pain neuroscience has advanced our understanding about pain, including the role of central sensitisation (or central hyperexcitability) in the presence and amplification of (persistent) pain experiences. Central sensitisation is defined as "an amplification of neural signaling within the central nervous system (CNS) that elicits pain hypersensitivity" (16) and as "an increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input" (17). Many people with CLBP lack a clear origin of nociceptive input, or this input is not severe enough to explain the experienced pain severity, related disability and other symptoms. In such patients (estimated at 25% of the CLBP population), central sensitisation often dominates the clinical picture. It is now well-established that sensitisation of the CNS is an important feature in many people with chronic pain, including those with CLBP (15).

Central sensitisation encompasses various related dysfunctions within the CNS, including altered sensory processing in the brain (13). Functional magnetic resonance studies revealed that people with CLBP have functional connectivity reorganisation in several brain regions: increased activation in the medial prefrontal cortex (11, 18-21), cingulate cortex (19, 20, 22), amygdala (19, 20), and insula (22, 23), and a disrupted default mode network connectivity (19, 22-24). When reviewing studies that explored the brain responses to noxious stimuli in people with CLBP, it was concluded that most studies found increased activation in brain regions involved in somatosensory-discriminative, affective, and cognitive processing of pain (the so-called "pain matrix") (25), including the primary/secondary somatosensory cortex, anterior and posterior cingulate, insula, prefrontal cortices, and the thalamus (14). On a side note, the term 'pain matrix' should be used with caution (26), as it remains unclear whether such a 'limited network' represents the full perception of pain. Pain perception possibly arises from a spatiotemporal signature of brain network communication that represents the integration of all cognitive, affective, and sensorimotor aspects of pain, referred to as the 'pain connectome' (27). Prospective cohort studies are needed to examine whether such brain alterations were not present before the onset of back pain, and whether they are specific for CLBP only.

Functional brain changes can be treated in people with chronic low back pain

Increasing evidence supports the idea that the functional brain changes found in people with CLBP are not permanent, and can be reversed by effective interventions (28). For instance, one study found changes in the anterior default mode network functional connectivity with the amygdala and periaqueductal gray and increased functional connectivity of the basal ganglia with the right somatosensory cortex following cognitive behavioural therapy, compared with an educational materials intervention in people with chronic musculoskeletal pain (29). The available evidence provides low level evidence favouring both functional and structural changes in prefrontal areas following cognitive behavioural therapy, including increased pain-evoked activation and increased grey matter volume in people with chronic musculoskeletal pain (28). The respective structural brain changes were associated with intervention-related improvements of coping with pain symptoms, pain management, anxiety, catastrophising, and cognitive speed (28), which underscores the clinical importance of these brain changes. Preliminary evidence was found for a shift of pain-induced activations from more affective brain regions towards sensory-discriminative regions, including the posterior insula and primary somatosensory cortex, following behavioural extinction training (28).

The amygdala as a key target for exercise therapy in people with chronic low back pain

One key brain area involved in the pain (neuro)matrix is the amygdala, often referred to as the fear-memory centre of the brain. The amygdala has an important role in negative emotions, and takes part of the central fear network in the brain, together with the anterior cingulate cortex (30). The amygdala's role includes negative emotions (*e.g.* anger), pain-related memories (31) and represents – together with the anterior cingulate cortex – the central fear network in the brain (30). Moreover, the amygdala has been identified as a facilitator of chronic pain development, including sensitisation of CNS pain pathways (30-35). On the other hand, the amygdala, together with the somatosensory cortex and insula, show less activity during pain delivery in case of positive treatment expectations (36).

Another crucial aspect of the amygdala entails its role in the development of pain memories as a result of operant learning processes (37), including memories of painful movements, for which the amygdala closely collaborates with the hippocampus and the anterior cingulate cortex. The development of such a pain memory applies to all movements that once provoked pain, and results in protective behaviours (*e.g.*, antalgic postures, antalgic movement patterns, including altered lumbopelvic motor control, and/or avoidance of particular movements like forward bending) in people with CLBP (38). Preparing for such 'dangerous' movements is enough to evoke an activation of the fear-memory centre in the brain and hence to produce pain (without peripheral nociceptive input), and employ an altered (protective) motor control strategy (39). Even visualisation of such 'dangerous' movements can trigger feelings of discomfort and pain, together with increased activation of pain

and memory related areas of the brain (40, 41). Exercise therapy can address this by applying the 'exposure without danger' principle (37), which is further explained below.

Glial overactivity as an underlying mechanism of central sensitisation in people with chronic low back pain

Despite our increased understanding of the mechanisms explaining (hypersensitivity) symptoms in people with CLBP, there is much to learn about the development of (chronic) LBP, including the aetiological mechanisms underlying central sensitisation as a facilitator of chronicity and severe disability (42) in this population. The question is, why do some pain people with LBP develop central sensitisation while others do not? Or is central sensitisation innate? Recent studies indicate that glial cells, to a greater extent than neurons, might play a key role in answering this question (43).

Glia are non-neuronal cells that reside within the nervous system. An increasing number of studies suggest that aberrant glial activation might explain the establishment and/or maintenance of central sensitisation, and persistent pain (44-48). In the acute or subacute phases of injury and pain, glial activation likely plays an adaptive role, as it favours tissue healing and restoring homeostasis. Glial activation produces inflammatory mediators and when glial activation does not resolve, and becomes chronic, it can become pathogenic leading to collateral damage of nearby neurons and other glia (49) (*i.e.*, gliopathy). Such increased glial activation has been found in people with CLBP (47). Prospective cohort studies are needed to examine whether such glial activation is genetic, innate or specific for CLBP.

Aberrant glial activity has the potential to initiate central sensitisation through several mechanisms. Activated microglia have been identified as a major source for the synthesis and release of brain-derived neurotrophic factor, which is responsible for increasing neuronal excitability by causing disinhibition in dorsal horn neurons in the spinal cord (50, 51). Aberrant glial activity is accompanied by increased TNF-α availability, which in turn induces long-term potentiation (52) and consequent enhanced synaptic efficacy (53) and pain sensitisation (52). Long-term potentiation and enhanced synaptic efficacy are possibly coordinated by glial overactivity and are (partly overlapping) key mechanisms underlying increased excitability of the CNS (54-56) and the formation of (maladaptive) pain memories (38, 57) in people with chronic pain and central sensitisation.

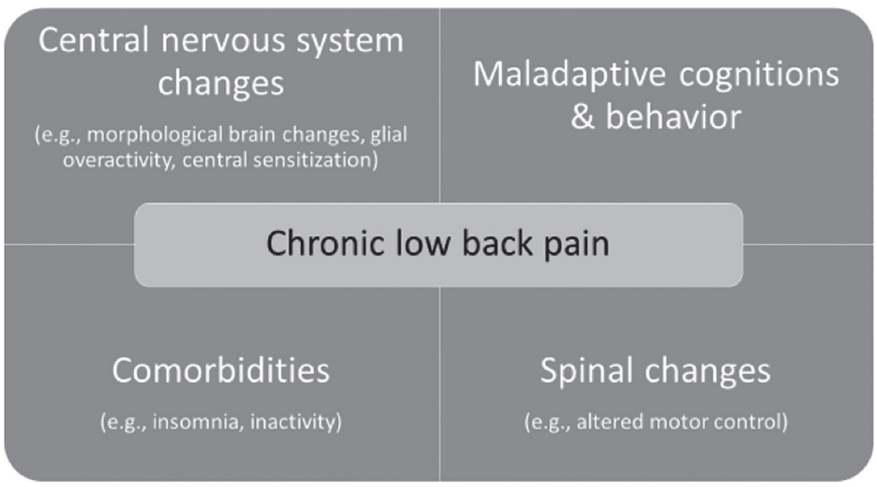

Fig. 1. Multimodal features of people with chronic low back pain.

Poor sleep, glial overactivity and central sensitisation in people with chronic low back pain

Poor sleep is one possible trigger for glial overactivity. Sleep deprivation results in low-grade inflammatory responses (58-60), including increased levels of IL-6, prostaglandin E2 (59, 60) and nitric oxide (61) possibly mediated by cerebral microglia (61). This may in part explain why a single night of total sleep deprivation in healthy people can induce generalised hyperalgesia and increase state anxiety (62, 63). Taken together, poor sleep sustains the underlying mechanisms of central sensitisation in people with CLBP, a notion that may require addressing during intervention (43).

Applying modern pain neuroscience for a better management of chronic low back pain

From what is presented above, it becomes clear the CLBP entails much more than spinal changes (summarised in Figure 1). The application of contemporary pain neuroscience to clinical practice for a better management of people with CLBP requires three important considerations, discussed here. Firstly, identification of relevant pain mechanisms in people with CLBP is explained; secondly issues relating to the retraining of pain memories using cognition-targeted functional exercise therapy for people with CLBP will be discussed; thirdly, interventions that target sleep disturbances in people who have CLBP and comorbid insomnia.

Identifying relevant pain mechanisms in chronic low back pain

Available evidence indicates that central sensitisation is present in a subgroup of the CLBP population (42, 64, 65). This potentially impacts upon clinical practice, as CLBP patients with a predominant central sensitisation pain type require intervention targeted at the CNS rather than the lower back region (15, 66, 67). Therefore awareness is growing that people with CLBP should be stratified clinically as experiencing either predominantly nociceptive, neuropathic or central sensitisation pain (42, 68) in order to target intervention strategies appropriately. A practical guide is available elsewhere (69), and is summarised below.

Following identification of red flags, excluding the possibility of a back disorder with neuropathic pain is often the first step (70, 71) that can be taken by applying international guidelines for

the stratification of neuropathic pain (72, 73). Examples of a back disorder with neuropathic pain include radicular pain with several patho-anatomical dysfunctions in case of compression of the dorsal root ganglion (direct) or the spinal nerve (indirect) (17). Possible dysfunctions that could induce such compression include foraminal stenosis (*e.g.*, due to osteophytes), prolapsed intervertebral disk, radiculitis (*e.g.*, caused by a viral infection like herpes zoster), etc. Although the presence of neuropathic pain does not exclude a predominant central sensitisation underlying mechanism, if neuropathic pain is excluded two options remain: predominantly either nociceptive or central sensitisation LBP. To differentiate between predominant nociceptive and central sensitisation LBP, clinicians are advised to use the algorithm presented in Figure 2. This algorithm guides the clinician through the screening of three major stratification criteria (69):

1) the severity of LBP must be disproportionate to the nature and extent of the injury or pathology (*i.e.*, tissue damage or structural impairments which might cause nociceptive LBP);
2) the pain pattern lacks a neuroanatomically distribution, *e.g.*, one that is not neuroanatomically plausible for the presumed sources of (lumbar) nociception;
3) a score of 40 or higher on part A of the Central Sensitisation Inventory (CSI) (74), which assesses symptoms common to central sensitisation, with the total score ranging from 0 to 100 and a recommended and validated cutoff score of 40 (75, 76).

In addition to the above guide for stratification of LBP patients according to the dominant pain mechanism, thorough clinical examination including the use of screening questionnaires is required (78), but is beyond the scope of the present paper.

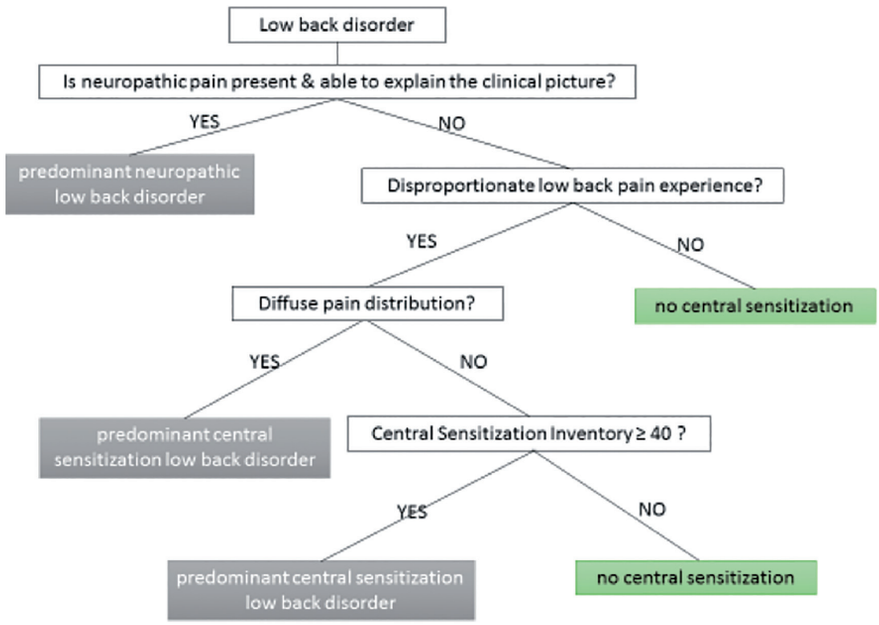

Fig. 2. Algorithm for the differential diagnosis of predominant nociceptive *versus* central sensitisation low back disorder (modified from Nijs *et al*. (77)).

Optimising exercise and activity interventions for people with chronic low back pain

Applying contemporary pain neuroscience to exercise interventions for people with CLBP includes preparing patients for exercise therapy using (therapeutic) pain neuroscience education. Pain neuroscience has taught us that pain is often present without tissue damage, is often disproportionate to tissue damage, and that tissue damage (and nociception) does not per se result in the feeling of pain. Pain neuroscience education intends to transfer that knowledge to patients, allowing them to understand their pain and hence to cope effectively with their pain. The main goal of pain neuroscience education is to improve the patient's pain beliefs and decrease the threatening nature of pain, including possible acute pain flares following exercises or daily physical activity. Guidelines for enabling clinicians to apply pain neuroscience education in clinical practice are available (79, 80), and imply the use of an information leaflet, an explanatory handbook [*e.g.*, Explain Pain (81)] and websites (retrainpain.org) designed specifically for explaining pain to patients with persistent pain. Preceding therapeutic exercise interventions with a preparatory phase using pain neuroscience education enhances deep learning and reconceptualisation of pain(10, 38) with the intention of improving exercise outcomes. Mounting evidence supports the use of pain neuroscience education for the intervention of CLBP (82-85), although at present effect sizes are often small and it remains to be examined whether effects are independent from socioeconomic status and cultural background.

The pain neuroscience education prepares the CLBP patient for cognition-targeted exercise therapy (10) that aims at systematic desensitisation. This includes graded and repeated exposure to fearful movements in order to generate a new memory of safety in the brain, and to replace or bypass the old and maladaptive movement-related pain memories (38). Hence, such an approach directly targets the brain circuitries orchestrated by the amygdala detailed above. The mechanism of long-term potentiation of brain synapses is crucial for (re)learning and developing new (pain/movement-related) memories, and hence for altering pain memories in the brain (38). Part of these intervention principles are in line with graded exposure *in vivo* (86), a cognitive behaviour intervention that has yielded good outcomes in people with CLBP (87, 88). Whether such a combined approach of pain neuroscience education with cognition-targeted exercise therapy is superior over standard evidence based care in people with CLBP is currently under investigation (89), but preliminary results are promising.

'Cognition-targeted' implies a time-contingent ("Perform this exercise 10 times regardless the symptoms it might induce") rather than pain-contingent ("Stop or adapt the exercise as soon as symptoms occur") approach to exercise interventions (10), and should account for the individual (pain) cognitions and apply the reconceptualisation of pain to exercises and daily physical activities (*e.g.,* walking, cycling, gardening and lifting heavy objects) (38). Thorough questioning and discussion of the patient's perceptions about the exercise (before, during and following the exercise) is required (38), including discussion of the anticipated consequences of the exercises.

Therapists should try to decrease the anticipated danger (threat level) of the exercises/physical activities by challenging the nature of, and reasoning behind the patients' fears, assuring the safety of the exercises, and increasing confidence in a successful accomplishment of the exercise (38). This can be done by applying graded exposure *in vivo* experiments (87). After performing the exercise/physical activity, the therapist discusses the patient's experience with the exercises, including the threatening nature of the exercise/physical activity. The experienced difference between the anticipated (pre-exercise) pain increase and the actual experience most often decreases the threat value of the exercise/physical activity.

In addition, within cognitive functional therapy control over maladaptive provocative patterns of maladaptive pain behaviour is also included (90). Cognitive functional therapy represents an individually targeted behaviourally-orientated intervention for people with CLBP, which directs at the identification of the modifiable and no-modifiable factors associated with the disorders (90). CFT provides a personalised bio-psycho-social understanding of pain, enhances pain controllability, targets behavioural and lifestyle change and positive adaptation (90).

Addressing sleep problems for a comprehensive management of chronic low back pain

Insomnia is an important yet seldom addressed comorbidity within current interventions for CLBP. Indeed, people suffering from CLBP are eighteen times more likely to experience clinically defined insomnia (91). If present, insomnia contributes substantially to CLBP severity and related disability (91). Whether insomnia or the back pain is the chicken or the egg (cause and effect) probably varies from patient to patient, but regardless of that, if insomnia is left untreated, it represents a barrier for effective CLBP management (92).

Cognitive behavioural therapy for insomnia (CBT-I) is the standard evidence-based care for treating chronic primary insomnia (93), but evidence supporting the use of CBT-I in people with CLBP is scarce. A proof of concept study found that CBT-I was successful in improving sleep and the extent to which pain interfered with daily functioning in people with CLBP, with moderate to large effect sizes and clinically important improvements (94).

CBT-I typically includes changing negative thoughts about sleep, sleep hygiene, sleep restriction therapy, and teaching relaxation skills (94-96). Improving thoughts about sleep includes "decatastrophisation" to address the perception of dire consequences of sleep loss (94). Sleep hygiene implies promoting good sleep habits and may include stimulus control to establish a strong association between the bedroom and sleep by allowing for sleep to occur uniquely in association with the bedroom (94). Some authors propose sleep restriction therapy in which the amount of time spent in bed is limited to an amount equal to their average sleep time for a week (92). This has been shown to enhance homeostatic sleep drive (93) in which the mechanisms which induce sleep are made more efficient. Once sleep becomes more efficient, total sleep time is incrementally increased on a week-to-week basis (92). Relaxation skills can be applied to improve falling asleep and learn people to adequately cope with high levels of arousal before falling asleep (96).

CBT-I cannot be a standalone intervention for CLBP, but instead should provide an added value to available evidence-based intervention for CLBP. The results from 2 small scale pilot trials supports combining CBT-I with a more pain management-focused (cognition-targeted) intervention for chronic pain: the combined approach was feasible to deliver and produced significant improvements in sleep, disability from pain, pain interference, depression and fatigue (92, 97). Importantly, the combined intervention appeared to have a strong advantage over more pain management-focused (cognition-targeted) intervention alone and modest advantage over CBT-I alone in reducing insomnia severity in chronic pain patients (92). The gains in insomnia severity and pain interference were maintained at one- and six-months follow-up (97).

Taken together, increasing evidence supports the application of CBT-I for people with CLBP with comorbid insomnia as a way of applying our current understanding of pain neuroscience, including the role of insomnia in sustaining central sensitisation, to clinical practice. Still, larger multicentre trials and collecting outcome data in usual care are required to confirm these promising findings.

Conclusions

It is now well established that CLBP is not limited to spinal impairments, but can also be characterised brain changes. The latter include functional connectivity reorganisation in several brain regions and increased activation in brain regions of the so-called "pain matrix". Increasing evidence supports the idea that these functional brain differences found in people with CLBP are not permanent, and can be reversed by effective interventions (28). Understanding these brain changes in CLBP improves our understanding not only of pain symptoms, but also of prevalent CLBP comorbidities like sleep disturbances. Poor sleep sustains the underlying mechanisms of central sensitisation in people with CLBP, which can be addressed by including CBT-I in a comprehensive intervention programme.

The brain changes seen in people with CLBP are in line with the presence of central sensitisation in a subgroup of the CLBP population. Identifying relevant pain mechanisms in people with

CLBP is required to steer intervention. In addition to addressing comorbidities like insomnia, applying our current understanding of pain neuroscience to the management of people with CLBP includes optimising exercise interventions. This includes preparing patients for exercise therapy using (therapeutic) pain neuroscience education, followed by cognition-targeted exercise therapy (10) that aims at systematic desensitisation, or graded, repeated exposure to generate a new memory of safety in the brain, replacing or bypassing the old and maladaptive movement-related pain memories (38).

For the application of contemporary pain neuroscience to clinical practice for a better management of people with CLBP, three important issues were discussed here: the clinical recognition of predominant central sensitisation pain, the application of exercise therapy and treating insomnia in people with CLBP. Space limits hinder a more comprehensive coverage of other ways to implement contemporary pain neuroscience in the management of CLBP. Other issues that hold great potential to diminish the sensitivity of the nervous system include pre- and post-surgical pain neuroscience education (85), the incorporation of (mindfulness-based) stress management [stress is another established glia activator (53)], and pharmacological targeting of neurotrophic factors (*e.g.,* brain-derived neurotrophic factor) (98). Importantly, intervention for people with CLBP should also aim at modifying lifestyle factors such as sedentary behaviour, and behavioural factors such as fear avoidance beliefs and maladaptive pain behaviour.

Further research is required, and is ongoing, to test the validity and clinical utility of the suggested approach of applying recent advances in pain neuroscience in the intervention for people with CLBP. In addition to CLBP, this approach may have utility across a range of musculoskeletal disorders with similar CNS changes, comorbidities and cognitive-behavioural issues.

Funding

A. Malfliet is a PhD research fellow funded by the Research Foundation Flanders (FWO), Belgium. K. Ickmans and D. Goubert are post-doctoral researchers funded by the Applied Biomedical Research Programme, Institute for the Agency for Innovation by Science and Technology, Belgium (IWT-TBM project no. 150180). I. Coppieters is a postdoctoral researcher funded by the Research Foundation Flanders (FWO), Belgium (FWO project no. G007217). J. Kregel is a PhD research fellow funded by the Applied Biomedical Research Programme, Institute for the Agency for Innovation by Science and Technology, Belgium (IWT-TBM project no. 130246). J. Nijs is holder of the Chair 'Exercise immunology and chronic fatigue in health and disease' funded by the Berekuyl Academy/European College for Decongestive Lymphatic Therapy, the Netherlands.

References

1. MANCHIKANTI L, SINGH V, DATTA S *et al.*: Comprehensive review of epidemiology, scope, and impact of spinal pain. *Pain physician* 2009; 12: E35-70.
2. HOY D, BAIN C, WILLIAMS G *et al.*: A systematic review of the global prevalence of low back pain. *Arthritis Rheum* 2012; 64: 2028-37.
3. HOY D, MARCH L, BROOKS P *et al.*: The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014; 73: 968-74.
4. VAN MIDDELKOOP M, RUBINSTEIN SM, KUIJPERS T *et al.*: A systematic review on the effectiveness of physical and rehabilitation interventions for chronic non-specific low back pain. *Eur Spine J* 2011; 20: 19-39.
5. VOS T, BARBER RM, BELL B *et al.*: Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 386: 743-800.
6. FREBURGER JK, HOLMES GM, AGANS RP *et al.*: The rising prevalence of chronic low back pain. *Arch Intern Med* 2009; 169: 251-8.
7. HENSCHKE N, OSTELO RW, VAN TULDER MW *et al.*: Behavioural treatment for chronic low-back pain. *Cochrane Database Syst Rev* 2010; 7: Cd002014.
8. WILLIAMS AC, ECCLESTON C, MORLEY S: Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev* 2012; 11: Cd007407.
9. CHEUNG CW, QIU Q, CHOI SW *et al.*: Chronic opioid therapy for chronic non-cancer pain: a review and comparison of treatment guidelines. *Pain Physician* 2014; 17: 401-14.
10. NIJS J, MEEUS M, CAGNIE B *et al.*: A modern neuroscience approach to chronic spinal pain: combining pain neuroscience education with cognition-targeted motor control training. *Phys Ther* 2014; 94: 730-8.
11. BALIKI MN, PETRE B, TORBEY S *et al.*: Corticostriatal functional connectivity predicts transition to chronic back pain. *Nat Neurosci* 2012; 15: 1117-9.
12. FLOR H, BRAUN C, ELBERT T, BIRBAUMER N: Extensive reorganization of primary somatosensory cortex in chronic back pain patients. *Neurosci Lett* 1997; 224: 5-8.
13. GIESECKE T, GRACELY RH, GRANT MA *et al.*: Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis Rheum* 2004; 50: 613-23.
14. KREGEL J, MEEUS M, MALFLIET A *et al.*: Structural and functional brain abnormalities in chronic low back pain: A systematic review. *Semin Arthritis Rheum* 2015; 45: 229-37.
15. ROUSSEL NA, NIJS J, MEEUS M, MYLIUS V, FAYT C, OOSTENDORP R: Central sensitization and altered central pain processing in chronic low back pain: fact or myth? *Clin J Pain* 2013; 29: 625-38.
16. WOOLF CJ: Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011; 152: S2-15.
17. MERSKEY H BOGDUK N: PART III: Pain Terms, A Current List with Definitions and Notes on Usage. *In*: H. MERSKEY N. BOGDUK editor. Classification of chronic pain. Second Ed. Seattle, USA: IASP Press; 1994; 209-14.
18. BALIKI MN, BARIA AT, APKARIAN AV: The cortical rhythms of chronic back pain. *J Neurosci* 2011; 31: 13981-90.
19. BALIKI MN, GEHA PY, APKARIAN AV *et al.*: Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. *J Neurosci* 2008; 28: 1398-403.
20. HASHMI JA, BALIKI MN, HUANG L *et al.*: Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain* 2013; 136: 2751-68.
21. BUCKALEW N, HAUT MW, AIZENSTEIN H *et al.*: Differences in brain structure and function in older adults with self-reported disabling and nondisabling chronic low back pain. *Pain Med* 2010; 11: 1183-97.
22. KORNELSEN J, SBOTO-FRANKENSTEIN U, MCIVER T *et al.*: Default mode network functional connectivity altered in failed back surgery syndrome. *J Pain* 2013; 14: 483-91.
23. TAGLIAZUCCHI E, BALENZUELA P, FRAIMAN D *et al.*: Brain resting state is disrupted in chronic back pain patients. *Neurosci Lett* 2010; 485: 26-31.
24. LOGGIA ML, KIM J, GOLLUB RL *et al.*: Default mode network connectivity encodes clinical pain: An arterial spin labeling study. *Pain* 2013; 154: 24-33.
25. MOISSET X, BOUHASSIRA D: Brain imaging of neuropathic pain. *Neuroimage* 2007; 37 (Suppl. 1): S80-8.
26. BALIKI MN, APKARIAN AV: Nociception, Pain, Negative Moods, and Behavior Selection. *Neuron* 2015; 87:474-91.
27. KUCYI A, DAVIS KD: The dynamic pain connectome. *Trends Neurosci* 2015; 38: 86-95.
28. KREGEL J, COPPIETERS I, DEPAUW R *et al.*: Does conservative treatment change the brain in patients with chronic musculoskele-

tal pain? a systematic review. *Pain Physician* 2017; 20: 139-54.
29. SHPANER M, KELLY C, LIEBERMAN G *et al*.: Unlearning chronic pain: A randomized controlled trial to investigate changes in intrinsic brain connectivity following cognitive behavioral therapy. *Neuroimage Clin* 2014; 5: 365-76.
30. KATTOOR J, GIZEWSKI ER, KOTSIS V *et al*.: Fear conditioning in an abdominal pain model: neural responses during associative learning and extinction in healthy subjects. *PloS One* 2013; 8: 26.
31. LI Z, WANG J, CHEN L *et al*.: Basolateral amygdala lesion inhibits the development of pain chronicity in neuropathic pain rats. *PloS One* 2013; 8.
32. HADJIKHANI N, WARD N, BOSHYAN J *et al*.: The missing link: Enhanced functional connectivity between amygdala and viscerоceptive cortex in migraine. *Cephalalgia* 2013; 29: 29.
33. KIM JY, KIM SH, SEO J *et al*.: Increased power spectral density in resting-state pain-related brain networks in fibromyalgia. *Pain* 2013; 154: 1792-7.
34. SCHWEDT TJ, SCHLAGGAR BL, MAR S *et al*.: Atypical resting-state functional connectivity of affective pain regions in chronic migraine. *Headache* 2013; 53: 737-51.
35. SIMONS LE, MOULTON EA, LINNMAN C *et al*.: The human amygdala and pain: Evidence from neuroimaging. *Hum Brain Mapp* 2012; 25: 22199.
36. SCHMID J, THEYSOHN N, GASS F *et al*.: Neural mechanisms mediating positive and negative treatment expectations in visceral pain: A functional magnetic resonance imaging study on placebo and nocebo effects in healthy volunteers. *Pain* 2013; 16: 00381-3.
37. ZUSMAN M: Mechanisms of musculoskeletal physiotherapy. *Phys Ther Rev* 2004; 9: 39-49.
38. NIJS J, LLUCH GIRBES E, LUNDBERG M *et al*.: Exercise therapy for chronic musculoskeletal pain: Innovation by altering pain memories. *Man Ther* 2015; 20: 216-20.
39. TUCKER K, LARSSON AK, OKNELID S *et al*.: Similar alteration of motor unit recruitment strategies during the anticipation and experience of pain. *Pain* 2012; 153: 636-43.
40. SHIMO K, UENO T, YOUNGER J *et al*.: Visualization of painful experiences believed to trigger the activation of affective and emotional brain regions in subjects with low back pain. *PLoS One* 2011; 6: e26681.
41. TAYLOR AM, HARRIS AD, VARNAVA A *et al*.: A functional magnetic resonance imaging study to investigate the utility of a picture imagination task in investigating neural responses in patients with chronic musculoskeletal pain to daily physical activity photographs. *PLoS One* 2015; 10: e0141133.
42. SMART KM, BLAKE C, STAINES A, DOODY C: Self-reported pain severity, quality of life, disability, anxiety and depression in patients classified with 'nociceptive', 'peripheral neuropathic' and 'central sensitisation' pain. The discriminant validity of mechanisms-based classifications of low back (± leg) pain. *Man Ther* 2012; 17: 119-25.
43. NIJS J, LOGGIA ML, POLLI A *et al*.: Sleep disturbances and severe stress as glial activators: key targets for treating central sensitization in chronic pain patients? *Expert Opin Ther Targets* 2017; 21: 817-26.
44. AGOSTINI S, EUTAMENE H, CARTIER C *et al*.: Evidence of central and peripheral sensitization in a rat model of narcotic bowel-like syndrome. *Gastroenterology* 2010; 139: 553-63, 563 e1-5.
45. AUSTIN PJ, MOALEM-TAYLOR G: The neuroimmune balance in neuropathic pain: involvement of inflammatory immune cells, immune-like glial cells and cytokines. *J Neuroimmunol* 2010; 229: 26-50.
46. BJURSTROM MF, GIRON SE, GRIFFIS CA: Cerebrospinal fluid cytokines and neurotrophic factors in human chronic pain populations: a comprehensive review. *Pain Pract* 2016; 16: 183-203.
47. LOGGIA ML, CHONDE DB, AKEJU O *et al*.: Evidence for brain glial activation in chronic pain patients. *Brain* 2015; 138: 604-15.
48. SORGE RE, MAPPLEBECK JC, ROSEN S *et al*.: Different immune cells mediate mechanical pain hypersensitivity in male and female mice. *Nat Neurosci* 2015; 18: 1081-3.
49. SPIELMAN LJ, LITTLE JP, KLEGERIS A: Physical activity and exercise attenuate neuroinflammation in neurological diseases. *Brain Res Bull* 2016; 125: 19-29.
50. SMITH PA: BDNF: No gain without pain? *Neuroscience* 2014; 283: 107-23.
51. FERRINI F, DE KONINCK Y: Microglia control neuronal network excitability via BDNF signalling. *Neural Plast* 2013; 2013: 429815.
52. GAO YJ, JI RR: Activation of JNK pathway in persistent pain. *Neuroscience Lett* 2008; 437: 180-3.
53. DELPECH JC, MADORE C, NADJAR A *et al*.: Microglia in neuronal plasticity: Influence of stress. *Neuropharmacology* 2015; 96: 19-28.
54. JI RR, KOHNO T, MOORE KA, WOOLF CJ: Central sensitization and LTP: do pain and memory share similar mechanisms? *Trends Neurosci* 2003; 26: 696-705.
55. ZHOU LJ, YANG T, WEI X *et al*.: Brain-derived neurotrophic factor contributes to spinal long-term potentiation and mechanical hypersensitivity by activation of spinal microglia in rat. *Brain Behav Immun* 2011; 25: 322-34.
56. ZHUO M: A synaptic model for pain: long-term potentiation in the anterior cingulate cortex. *Mol Cells* 2007; 23: 259-71.
57. APKARIAN AV, MUTSO AA, CENTENO MV *et al*.: Role of adult hippocampal neurogenesis in persistent pain. *Pain* 2016; 157: 418-28.
58. MULLINGTON JM, SIMPSON NS, MEIER-EWERT HK, HAACK M: Sleep loss and inflammation. *Best Pract Res Clin Endocrinol Metab* 2010; 24: 775-84.
59. HAACK M, LEE E, COHEN DA *et al*.: Activation of the prostaglandin system in response to sleep loss in healthy humans: potential mediator of increased spontaneous pain. *Pain* 2009; 145: 136-41.
60. HAACK M, SANCHEZ E, MULLINGTON JM: Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. *Sleep* 2007; 30: 1145-52.
61. WISOR JP, SCHMIDT MA, CLEGERN WC: Cerebral microglia mediate sleep/wake and neuroinflammatory effects of methamphetamine. *Brain Behav Immun* 2011; 25: 767-76.
62. ONEN SH, ALLOUI A, GROSS A, ESCHALLIER A, DUBRAY C: The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *J Sleep Res* 2001; 10: 35-42.
63. SCHUH-HOFER S, WODARSKI R, PFAU DB *et al*.: One night of total sleep deprivation promotes a state of generalized hyperalgesia: a surrogate pain model to study the relationship of insomnia and pain. *Pain* 2013; 154: 1613-21.
64. SMART KM, BLAKE C, STAINES A, THACKER M, DOODY C: Mechanisms-based classifications of musculoskeletal pain: part 1 of 3: symptoms and signs of central sensitisation in patients with low back (± leg) pain. *Man Ther* 2012; 17: 336-44.
65. SMART KM, BLAKE C, STAINES A, THACKER M, DOODY C: Mechanisms-based classifications of musculoskeletal pain: part 3 of 3: symptoms and signs of nociceptive pain in patients with low back (± leg) pain. *Man Ther* 2012; 17: 352-7.
66. NIJS J, MEEUS M, VAN OOSTERWIJCK J *et al*.: Treatment of central sensitization in patients with 'unexplained' chronic pain: what options do we have? *Expert Opin Pharmacother* 2011; 12: 1087-98.
67. NIJS J, MALFLIET A, ICKMANS K, BAERT I, MEEUS M: Treatment of central sensitization in patients with 'unexplained' chronic pain: an update. *Expert Opin Pharmacother* 2014; 15:1671-83.
68. SMART KM, BLAKE C, STAINES A, DOODY C: The Discriminative validity of "nociceptive," "peripheral neuropathic," and "central sensitization" as mechanisms-based classifications of musculoskeletal pain. *Clin J Pain* 2011; 27: 655-63.
69. NIJS J, APELDOORN A, HALLEGRAEFF H *et al*.: Low back pain: guidelines for the clinical classification of predominant neuropathic, nociceptive, or central sensitization pain. *Pain physician* 2015; 18: E333-46.
70. WADDELL G: The back pain revolution. Edinburgh: Churchill Livingstone; 1998.
71. KOES BW, VAN TULDER MW, OSTELO R, KIM BURTON A, WADDELL G: Clinical guidelines for the management of low back pain in primary care: an international comparison. *Spine* 2001; 26: 2504-13; discussion 13-4.
72. TREEDE RD, JENSEN TS, CAMPBELL JN *et al*.: Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 2008; 70: 1630-5.
73. HAANPÄÄ M TR: Diagnosis and classification of neuropathic pain. *Pain Clinical Updates* 2010; XVII(7).
74. MAYER TG, NEBLETT R, COHEN H *et al*.: The development and psychometric validation of the central sensitization inventory. *Pain Pract* 2012; 12: 276-85.
75. NEBLETT R, COHEN H, CHOI Y *et al*.: The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. *J Pain* 2013; 14: 438-45.
76. NEBLETT R, HARTZELL MM, COHEN H *et al*.: Ability of the Central Sensitization Inventory to identify central sensitivity syndromes

in an outpatient chronic pain sample. *Clin J Pain* 2015; 31: 323-32.
77. NIJS J, GOUBERT D, ICKMANS K: Recognition and treatment of central sensitization in chronic pain patients: not limited to specialized care. *J Orthop Sports Phys Ther* 2016; 46: 1024-8.
78. WIJMA AJ, VAN WILGEN CP, MEEUS M, NIJS J: Clinical biopsychosocial physiotherapy assessment of patients with chronic pain: The first step in pain neuroscience education. *Physiother Theory Pract* 2016; 32: 368-84.
79. NIJS J, PAUL VAN WILGEN C, VAN OOSTERWIJCK J, VAN ITTERSUM M, MEEUS M: How to explain central sensitization to patients with 'unexplained' chronic musculoskeletal pain: practice guidelines. *Man Ther* 2011; 16: 413-8.
80. VAN WILGEN CP, KEIZER D: The sensitization model to explain how chronic pain exists without tissue damage. *Pain Manag Nurs* 2012; 13: 60-5.
81. BUTLER D, MOSELEY GL: Explain pain: Adelaide: NOI Group Publishing; 2003.
82. MOSELEY GL: Combined physiotherapy and education is efficacious for chronic low back pain. *Aust J Physiother* 2002; 48: 297-302.
83. MOSELEY GL: Evidence for a direct relationship between cognitive and physical change during an education intervention in people with chronic low back pain. *Eur J Pain* 2004; 8: 39-45.
84. MOSELEY GL, NICHOLAS MK, HODGES PW: A randomized controlled trial of intensive neurophysiology education in chronic low back pain. *Clin J Pain* 2004; 20: 324-30.
85. LOUW A, DIENER I, LANDERS MR, PUENTEDURA EJ: Preoperative pain neuroscience education for lumbar radiculopathy: a multicenter randomized controlled trial with 1-year follow-up. *Spine* 2014; 39: 1449-57.
86. VLAEYEN JWS MS, LINTON SJ, BOERSMA K, DE JONG J: Pain-related fear. Exposure-based treatment of chronic pain. IASP Press Seattle, USA. 2012: 196p.
87. LEEUW M, GOOSSENS ME, VAN BREUKELEN GJ *et al*.: Exposure in vivo versus operant graded activity in chronic low back pain patients: results of a randomized controlled trial. *Pain* 2008; 138: 192-207.
88. VLAEYEN JW, DE JONG J, GEILEN M, HEUTS PH, VAN BREUKELEN G: The treatment of fear of movement/(re)injury in chronic low back pain: further evidence on the effectiveness of exposure *in vivo*. *Clin J Pain* 2002; 18: 251-61.
89. DOLPHENS M, NIJS J, CAGNIE B *et al*.: Efficacy of a modern neuroscience approach versus usual care evidence-based physiotherapy on pain, disability and brain characteristics in chronic spinal pain patients: protocol of a randomized clinical trial. *BMC Musculoskelet Disord* 2014; 15: 149.
90. O'SULLIVAN PD, O'SULLIVAN K, FERSUM K: Multidimensional approach for the targeted management of low back pain. *In*: JULL GMA, FALLA D, LEWIS J, MCCARTHY C, STERLING M (Eds.) Grieve's Modern Musculoskeletal Physiotherapy. Edinburgh, Elsevier, 2015; 465-70.
91. TANG NK, WRIGHT KJ, SALKOVSKIS PM: Prevalence and correlates of clinical insomnia co-occurring with chronic back pain. *J Sleep Res* 2007; 16: 85-95.
92. PIGEON WR, MOYNIHAN J, MATTESON-RUSBY S *et al*.: Comparative effectiveness of CBT interventions for co-morbid chronic pain & insomnia: a pilot study. *Behav Res Ther* 2012; 50: 685-9.
93. FINAN PH, BUENAVER LF, CORYELL VT, SMITH MT: Cognitive-Behavioral Therapy for Comorbid Insomnia and Chronic Pain. *Sleep Med Clin* 2014; 9: 261-74.
94. JUNGQUIST CR, O'BRIEN C, MATTESON-RUSBY S *et al*.: The efficacy of cognitive-behavioral therapy for insomnia in patients with chronic pain. *Sleep Med* 2010; 11: 302-9.
95. RITTERBAND LM, BAILEY ET, THORNDIKE FP, LORD HR, FARRELL-CARNAHAN L, BAUM LD: Initial evaluation of an Internet intervention to improve the sleep of cancer survivors with insomnia. *Psychooncology* 2012; 21: 695-705.
96. CURRIE SR, WILSON KG, PONTEFRACT AJ, DELAPLANTE L: Cognitive-behavioral treatment of insomnia secondary to chronic pain. *J Consult Clin Psychol* 2000; 68: 407-16.
97. TANG NK, GOODCHILD CE, SALKOVSKIS PM: Hybrid cognitive-behaviour therapy for individuals with insomnia and chronic pain: a pilot randomised controlled trial. *Behav Res Ther* 2012; 50: 814-21.
98. NIJS J, MEEUS M, VERSIJPT J *et al*.: Brain-derived neurotrophic factor as a driving force behind neuroplasticity in neuropathic and central sensitization pain: a new therapeutic target? *Expert Opin Ther Targets* 2015; 19: 565-76.