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Association between sensorimotor impairments and functional brain changes in patients with low back pain: a critical review

Nina Goossens MSc,[1] Sofie Rummens MD,[2] Lotte Janssens PhD,[1,3] Karen Caeyenberghs PhD,[4] Simon Brumagne PhD[1]

[1] KU Leuven – University of Leuven, Department of Rehabilitation Sciences, Tervuursevest 101, box 1501, B-3001 Leuven, Belgium

[2] University Hospitals Leuven, Department of Physical Medicine and Rehabilitation, Herestraat 49, B-3000 Leuven, Belgium

[3] Hasselt University, BIOMED, REVAL, Agoralaan, B-3590 Diepenbeek, Belgium

[4] School of Psychology, Faculty of Health Sciences, Australian Catholic University, Melbourne Campus (St Patrick), Locked Bag 4115, Fitzroy MDC, VIC 3065, Australia

Correspondence:

Nina Goossens

Mailing address: KU Leuven – University of Leuven, Department of Rehabilitation Sciences – Musculoskeletal Rehabilitation Research Group, Tervuursevest 101, box 1501, B-3001 Leuven, Belgium

Phone number: +32 16 37 90 40, Fax number: +32 16 32 91 97

Email address: Nina.Goossens@kuleuven.be

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Abstract

Low back pain (LBP) coincides with sensorimotor impairments, e.g., reduced lumbosacral tactile and proprioceptive acuity and postural control deficits. Recent functional magnetic resonance imaging (fMRI) studies suggest that sensorimotor impairments in LBP may be associated with brain changes. However, no consensus exists regarding the relationship between functional brain changes and sensorimotor behavior in LBP. Therefore, this review critically discusses the available fMRI studies on brain activation related to non-nociceptive somatosensory stimulation and motor performance in individuals with LBP. Four electronic databases were searched, yielding nine relevant studies. Patients with LBP showed reduced sensorimotor-related brain activation and a reorganized lumbar spine representation in higher-order (multi)sensory processing and motor regions, including primary and secondary somatosensory cortices, supplementary motor area and superior temporal gyrus. These results may support behavioral findings of sensorimotor impairments in LBP. Additionally, patients with LBP displayed widespread increased sensorimotor-evoked brain activation in regions often associated with abnormal pain processing. Over-activation in these regions could indicate an over-responsiveness to sensory inputs that signal potential harm to the spine, thereby inducing over-generalized protective responses. Hence, functional brain changes could contribute to the development and recurrence of LBP. However, future studies investigating the causality between sensorimotor-related brain function and LBP are imperative.

Keywords

Low back pain; Functional MRI; Proprioception; Movement

Introduction

Low back pain (LBP) is a highly prevalent health condition[1,2] characterized by recurring episodes and a high risk of chronification.[3-7] Currently, LBP has been identified as the main cause of disability worldwide.[8,9] The majority of LBP complaints are "non-specific", meaning that the pain cannot be ascribed to a recognizable specific pathology such as an inflammatory disorder or vertebral fracture.[10] This highlights the need to elucidate the mechanisms that underlie the development and recurrence of LBP.[11]

Sensorimotor impairments have been identified as possible key factors in the development and recurrence of non-specific LBP.[12,13] For example, patients with LBP show a disrupted body schema of the trunk[14,15] and a decreased tactile and proprioceptive acuity at the lumbar spine compared to healthy controls.[16-20] To compensate for the less accurate lumbosacral proprioceptive signals, patients with LBP predominantly use ankle muscle proprioception during postural control.[21-23] This altered use of proprioception in patients with LBP resulted in increased postural sways during challenging postural conditions[23,24] and was related to a worse sit-to-stand-to-sit performance compared to healthy subjects.[25] Altogether, this vast body of behavioral work indicates that patients with LBP show sensorimotor impairments, which can be present prior to the emergence of pain.[12,13] Unfortunately, the mechanisms underlying these sensorimotor impairments are very poorly understood. Since optimal sensorimotor behavior depends on the adequate central processing and integration of sensory signals,[26-28] investigating the relation between brain function and sensorimotor behavior in patients with LBP could elucidate the neural mechanisms of sensorimotor impairments in LBP.

The recently increased use of magnetic resonance imaging (MRI) in LBP research revealed that patients with LBP display structural and functional brain changes (for reviews, see [29,30]). For example, resting-state functional MRI (fMRI) studies have convergently shown an increased functional connectivity (FC) in the primary somatosensory cortex (S1), primary motor cortex (M1), insula, medial prefrontal cortex, cingulate cortex and amygdala, and abnormal FC within the default mode network in patients with LBP at rest (for reviews, see [29,30]). Additionally, task-related fMRI studies reported altered brain activation patterns during the processing of specific stimuli in patients with LBP. The majority of these studies focused on the processing of nociceptive stimuli. They showed that patients with LBP display increased brain activation during nociceptive processing in e.g., S1, S2, insula, prefrontal cortices, anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC) compared to healthy controls.[31-34]

However, very few task-related fMRI studies investigated brain activation related to sensorimotor behavior, i.e. the processing of non-nociceptive somatosensory stimuli and motor performance in individuals with LBP. Consequently, no consensus exists on whether subjects with LBP display functional brain changes related to sensorimotor behavior. However, such knowledge could guide clinicians towards optimizing the evidence-based diagnosis and treatment of LBP. Therefore, this review systematically summarizes and critically discusses the existing fMRI-based findings on brain function during somatosensory processing and motor performance in individuals with LBP. Moreover, methodological considerations for future studies and implications for clinical practice will be discussed.

Brain activation during somatosensory processing and motor performance in individuals with low back pain: search strategy and selection of articles

This critical review using a systematic approach was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[35] and reports the required information accordingly (see PRISMA checklist, Supplemental Digital Content 1, http://links.lww.com/PHM/A520). The protocol was registered in the PROSPERO database with registration number CRD42016053053. Electronic databases Pubmed, CINAHL, Web of Science, and Embase were searched systematically from inception onwards, with the latest search performed on May 26th, 2017. The following research question was formulated: "Do individuals with LBP exhibit functional brain changes related to somatosensory processing and/or motor performance, as examined with fMRI techniques?" To promote comparability of results across studies, only studies using resting-state and task-related fMRI (vs. e.g., electroencephalography) were included. The search strategy was formulated, with the assistance of a librarian, by using the PICOS framework. MeSH terms in Pubmed, Emtree terms in Embase and free text words for LBP, fMRI, brain, sensory stimuli (e.g. touch, proprioception) and motor tasks were combined (see Supplemental Digital Content 2, http://links.lww.com/PHM/A521, for a detailed search strategy). No limitations for article type or time of publication were applied.

The obtained articles were entered in EndNote. After de-duplication, two reviewers (NG and SR) independently screened the titles and abstracts of all retrieved articles for eligibility. Then, full-texts of all relevant articles were screened. In case of disagreement, a third researcher (LJ) screened the article and consensus was reached. To be eligible, studies had to (1) include patients with LBP or healthy individuals with experimentally induced LBP, (2) assess brain function with

task-related or resting-state fMRI and (3) assess brain activation during or correlate functional brain outcomes with a non-nociceptive somatosensory stimulus or motor task. Studies using stimuli or motor tasks to explicitly induce (more) pain, to investigate the direct effect of pain on brain function, were excluded. Although noxious stimuli and the performance of pain-aggravating movements may activate sensorimotor brain areas in addition to pain-related areas, studies using such stimuli or movements were excluded to distinguish articles on pain-evoked brain activation from studies on sensorimotor-evoked brain activation. Moreover, studies in healthy subjects with experimentally induced LBP were included only if (1) LBP was induced prior to fMRI scanning to create a "baseline" condition of LBP, and (2) brain activation was then studied during a somatosensory stimulus or motor task that did not aim to elicit (more) pain. Finally, articles had to be written in English, Dutch, French or German (See Table 1 for an overview of the eligibility criteria).

As presented in Figure 1, the systematic search yielded 217 unique articles. The first phase of eligibility screening resulted in 22 citations. Hand-searching the reference lists of these articles did not yield any additional articles. Screening the full-texts of the 22 articles resulted in nine articles to be included.

Two researchers (NG and SR) independently extracted relevant information from each article: (1) LBP group: type of LBP, number, age and gender of participants, (2) healthy group: number, age and gender of participants, (3) fMRI technique and somatosensory stimulus or motor task, (4) main group differences, (5) correlations and (6) remarks. The nine included studies showed

great variability in terms of participant's characteristics, fMRI (analysis) techniques, studied regions-of-interest (ROIs) and used somatosensory stimuli and motor tasks (See Table 2).

Two researchers (NG and SR) independently assessed risk of bias in each study with the validated Downs and Black tool[45] as recommended by The Cochrane Collaboration. The Downs and Black tool consists of 27 items rating reporting bias, external validity and internal validity and has high internal consistency and inter-rater reliability.[46] Because this review only included observational studies, a modified version of the Downs and Black tool was employed. This modified version has been used in other reviews.[47,48] Questions related to the validity of the methodological design associated with an intervention were omitted (items 4, 8, 9, 13, 14, 15, 17, 19, 23, 24, 26 and 27) and case-series and case studies were not assessed on items related to a control group (items 5, 21, 22 and 23). Differences in scoring were discussed until consensus was reached. Both reviewers gave equal scores in 91% of the cases (131/144). Scores ranged from 45 to 85% between studies (see Table 3). Most articles scored low on external validity, as they provided insufficient information on the representativeness of participants who were willing and eligible to participate. While the majority of studies controlled for confounding factors, e.g. by matching groups on age and gender, only a few reported whether patients with LBP and healthy controls were recruited from a similar population and during a similar period. Finally, no study indicated if they performed analyses that were not planned a priori. Hence, none received a score on 'data dredging'.

Decreased brain activation in regions involved in higher-order sensory processing and motor control in low back pain

Two task-related fMRI studies revealed that patients with chronic LBP showed decreased brain activation in S2 during the processing of simultaneously applied tactile and proprioceptive stimuli at the lumbar spine,[39] and in supplementary motor area (SMA) and superior temporal gyrus (STG) during motor imagery of daily life activities.[44] Additionally, one resting-state fMRI study demonstrated decreased resting-state FC in S1, SMA, M1 and cerebellar lobules IV-V in patients with non-specific LBP compared to healthy subjects.[42] This decreased resting-state FC in M1 and cerebellar lobules IV-V correlated significantly with a worse sensorimotor performance (more time to perform five sit-to-stand-to-sit movements when blindfolded) in patients with LBP and healthy subjects combined.[42]

Above-mentioned brain regions are important in different aspects of sensorimotor control. S1 processes unimodal sensory signals and integrates them with motor signals to guide movement.[49] S2 integrates bilateral, multimodal sensory inputs[50] and is key in sensorimotor integration through its connections with premotor planning areas.[51,52] The STG contributes to the kinesthetic perception of joint movements[53,54], higher-order sensory integration, and the formation of a body schema.[55-57] The SMA is crucial for adequate motor planning,[58-61] whereas M1 controls movement execution by generating motor commands. Finally, the cerebellum is considered important for sensorimotor and postural control,[62-64] as it co-ordinates the acquisition of sensory signals on which motor systems depend.[62]

Taken together, these results could suggest a reduced sensorimotor-related brain activation and decreased resting-state FC in higher-order sensory processing and motor regions in patients with LBP. In these studies, it was proposed that a decreased brain activation in these regions might negatively affect sensorimotor behavior in patients with LBP through e.g., a down-regulated higher-order processing of multimodal (e.g. tactile and proprioceptive) sensory signals originating in the spine, a disrupted body schema of the trunk and impoverished motor planning.[39,44] However, Pijnenburg et al. (2015) were the only researchers who directly correlated functional brain outcomes with sensorimotor performance. Therefore, above-mentioned putative mechanisms warrant further study.

Cortical reorganization in the primary and secondary somatosensory cortices in low back pain

Two studies revealed changes in the cortical representation of the lumbar spine in patients with long-lasting LBP.[40,44] Lloyd et al. (2008) reported that patients with chronic LBP who show aberrant pain-related illness behavior displayed a medially shifted S1 activation during tactile vibration at the lower back compared to healthy controls and well-coping patients with LBP.[40] This was consistent with previous findings of a medially shifted lumbar spine representation in S1 in patients with chronic LBP compared to healthy subjects.[65] Moreover, Hotz-Boendermaker et al. (2016) revealed that the cortical representations of three lumbar vertebrae in S2 (not in S1) was blurred in patients with chronic LBP, whereas clearly distinct representations in S2 were found in healthy subjects.[44] The difference in findings of a reorganized lumbar spine representation in S1[40,65] compared to in S2[44] could be explained by the nature of the applied stimuli, i.e. painful[65] and intense[40] versus non-painful[44].

Taken together, these findings might suggest a reorganized lumbar spine representation in S1 and S2 in patients with chronic LBP. Bearing in mind that these regions are important for (multi)sensory processing,[49,50] these results might corroborate behavioral findings of an impaired trunk perception and reduced lumbosacral tactile and proprioceptive acuity in patients with LBP.[16,18,20,29] Moreover, since adequate sensory processing and integration are indispensable for optimal motor control,[26-28] a reorganized lumbar spine representation may disturb spinal and postural control in patients with LBP. However, none of the studies above assessed trunk perception, tactile sensitivity, proprioceptive acuity or motor control. Consequently, direct conclusions on the behavioral implications of a reorganized trunk representation in S1 and S2 in LBP cannot be drawn.

Increased brain activation in low back pain as maladaptive response

Four task-related and two resting-state fMRI studies revealed patterns of increased sensorimotor-related brain activation in patients with LBP.[36,38,40-42,44] Interestingly, these patterns were found in studies using a whole-brain approach[40,41] and studies using predefined ROIs during fMRI analysis.[38,42,44]

Patients with chronic LBP showed increased brain activation during the appliance of pressure on their thumbnail in contralateral S1, bilateral S2 and ipsilateral inferior parietal lobule and cerebellum compared to healthy controls, who only activated S2 contralaterally.[38] Moseley (2004a) reported a similar result in his case study, where a patient with chronic LBP displayed widespread activation in S1, ACC, insula, parietal association areas and frontal cortices during

abdominal muscle contractions. Furthermore, patients with chronic LBP exhibited widespread increased FC during motor imagery of daily life activities across the majority of the motor imagery network compared to healthy controls.[44] This network consisted of left SMA, inferior parietal lobule and thalamus and bilateral M1, superior parietal lobules, supramarginal gyri, putamina, middle and inferior frontal gyri and insulae.[66] Interestingly, no group differences were found in a control region, suggesting that the increased motor imagery-driven FC in LBP was task-specific and not due to an overall enhanced FC.[44] Additionally, patients with non-specific LBP demonstrated increased resting-state FC in lobule VI of the cerebellar vermis and right superior and middle frontal gyri compared to healthy subjects.[42] Finally, compared to elderly with non-disabling chronic LBP, elderly with disabling chronic LBP exhibited increased resting-state FC in the medial prefrontal cortex.[36]

Up to now, it remains unclear whether these patterns of increased brain activity in LBP indicate (1) a diffuse, non-specific recruitment of brain regions during task performance due to loss of neural specialization (i.e. "dedifferentiation")[67,68] or (2) a compensatory increase in brain activation to support performance[69-71]. Results from Moseley (2004a) support the "dedifferentiation" hypothesis. In this study, contracting specific abdominal muscles initially induced widespread brain activation.[41] Interestingly, this motor-evoked activation reduced markedly after the patient received pain physiology education, although quality of task performance remained unchanged.[41] This might suggest that the initially diffuse over-activation was non-functional and irrelevant for performing the motor task.

In contrast, results of Vrana et al. (2015) may support the second "compensation" hypothesis. In this study, patients with LBP showed diffusely spread increases in motor imagery-driven FC

compared to pain-free controls.[44] However, motor imagery performance did not differ between groups, suggesting that, although patients with LBP had retained their ability to perform motor imagined movements, they needed extra neural resources to preserve performance compared to controls.[44]

Compensatory increases in brain activation may initially be adaptive. This was evident in the study of Lloyd et al. (2008). They revealed that well-coping patients with chronic LBP activated the right PCC and left posterior parietal lobe more during intense tactile stimulation at the lumbar spine compared to patients with chronic LBP showing abnormal pain-related illness behavior.[40] Interestingly, this increased sensory-evoked activation correlated significantly with lower levels of catastrophizing in the well-coping patients, suggesting a neural mechanism of successful adjustment to and coping with pain.[40] However, compensatory mechanisms of over-activation may become maladaptive over time, thereby potentially leading to sensorimotor impairments. This was suggested by Buckalew et al. (2010), who showed an increased resting-state FC in the medial prefrontal cortex in elderly with disabling chronic LBP compared to peers with non-disabling chronic LBP. The medial prefrontal cortex is suggested to be involved in expectation and top-down inhibition of negative emotions[72-74] and inhibits motor planning areas when activated.[75] The authors suggested that suppressing negative emotions and expectations of pain in patients with disabling chronic LBP could activate the medial prefrontal cortex, thereby inhibiting motor planning and inducing disability over time.[36]

Unfortunately, none of the studies mentioned above decisively showed whether the increased brain activation patterns in LBP indicate a dedifferentiated brain activation during sensorimotor processing or a compensatory increase in brain activity to preserve sensorimotor behavior. This

question could be solved by correlating functional brain outcomes with sensorimotor behavior, with positive correlations indicating a compensatory increased brain activation and negative correlations supporting the dedifferentiation hypothesis.[71] However, only two included studies correlated brain function (i.e. resting-state FC) with sensorimotor behavior, respectively in patients with LBP and healthy controls combined, and in elderly with disabling and non-disabling chronic LBP combined. [36,44] Thus, more studies that directly correlate functional brain outcomes with sensorimotor behavior in patients with LBP are urgently needed to elucidate the neural correlates of sensorimotor impairments in LBP. For instance, studying brain activation during the processing of proprioceptive signals (e.g., by applying muscle vibration during fMRI[76]) and correlating this with proprioceptive use during postural control, could clarify the neural underpinnings of postural control deficits in patients with LBP.

Neuroimaging studies could also unravel the causal relationship between sensorimotor-related brain changes and LBP. Unfortunately, all included studies were cross-sectional. Moreover, only two of the nine studies investigated, and did not find, correlations between brain function (i.e. resting-state FC) and duration of LBP (total amount of months with LBP)[36], and between sensorimotor performance and LBP intensity.[44] Therefore, until confirmed by longitudinal research, a bidirectional relationship between functional brain changes and LBP can be hypothesized. First, ongoing LBP might lead to maladaptive, widespread brain changes that could predispose patients to further pain chronification. Alternatively, sensorimotor-related brain changes might already be present prior to the emergence of LBP.[77] For example, altered brain activation patterns in regions involved in higher-order sensory processing and motor planning, present prior to LBP, might negatively affect trunk movement patterns, thereby inducing hyper-

or hypo-activity of trunk muscles.[78] Such suboptimal trunk movement patterns may in turn lead to excessive lumbar movements beyond the normal range of mechanical stability,[79] abnormal loading of the lumbar spine and (recurrence of) LBP. A recent longitudinal behavioral study supports this latter causal direction.[13] In this study, young pain-free individuals who predominantly used ankle muscle proprioception instead of lumbosacral proprioceptive signals during postural control showed an increased risk of developing or maintaining LBP within two years.[13] However, longitudinal neuroimaging studies that directly investigate associations between brain function, sensorimotor behavior and LBP are highly needed to clarify the causality between sensorimotor-related functional brain changes and LBP.

Do we need to think outside the "pain matrix" box when observing individuals with low back pain?

Three included studies used the "pain matrix" concept to design the experiments, analyze the obtained fMRI data and/or interpret study results.[37,38,41] The "pain matrix" has been described as a network of brain areas that are involved in different aspects of pain perception, such as sensory-discriminative aspects (S1, S2, insula, thalamus), affective-attentional aspects (amygdala, ACC, posterior parietal and prefrontal cortices), motor responses to pain (SMA, cerebellum, striatum) and top-down inhibition of pain (periaqueductal gray) (for reviews, see [80,81]). In the past, researchers have proposed that the conscious perception of pain arises from "pain matrix" activity during the processing of nociceptive inputs.[80,81] Some authors even suggested to use "pain matrix" activity to objectively measure whether or not patients actually experience pain.[82] However, caution might be needed when using the "pain matrix" concept to set up experiments, analyze and interpret fMRI data in LBP research.

For example, some studies considered LBP as the result of persistent abnormal pain processing, similar to e.g., fibromyalgia and irritable bowel syndrome. This might have influenced the experimental set-up and fMRI analysis. For instance, Giesecke et al. (2004) and Gay et al. (2014) narrowed their search volume to only "pain-related" brain regions. They based their selection on a previous study on pressure pain sensitivity in healthy subjects[83] and previous fMRI studies showing increased brain responses to painful stimuli in patients with LBP[32,84], respectively. However, as many of these "pain-related" regions are also shown to play an important role in sensorimotor control (e.g. S1[49]; S2[50-52]; M1; SMA[58,59,61]; cerebellum[62]; STG[53,54]), they cannot be viewed as merely "pain-specific" regions. This was evident in some of the included studies. While Giesecke et al. (2004) and Gay et al. (2014) considered SMA, M1, inferior parietal lobule, thalamus, basal ganglia, middle frontal gyrus and insula as "pain-related", two other studies viewed the same regions as "sensorimotor-related".[39,44] Therefore, findings of increased sensory- or motor-evoked brain activation in these brain regions in patients with LBP might suggest an altered sensorimotor processing in LBP, in addition to abnormal pain processing.

Second, new insights support that the functional significance of the "pain matrix" needs to be reinterpreted (for reviews, see [85,86]). For instance, studies showed that several "pain matrix" regions are not solely activated during nociceptive stimulation, but also during non-nociceptive somatosensory, auditory and visual stimulation (e.g., S2, insula and ACC).[87] This indicates that any type of stimulus, independent of the modality, can elicit the majority of brain responses to nociceptive stimuli.[87] Moreover, "pain matrix" responses to nociceptive stimuli are larger when the presented stimuli are novel and unpredictable.[88] Finally, patients with congenital analgesia

(or insensitivity to pain) appear to activate the same "pain matrix" regions as healthy subjects during the presentation of noxious stimuli that were perceived as painful by the healthy subjects.[89]

Taken together, these recent findings suggest that the "pain matrix" does not merely present a cortical representation of pain. However, it might serve as a defensive salience detection system that detects, processes, orients attention towards and reacts upon salient sensory inputs.[85,86] As such, both nociceptive and non-nociceptive stimuli could trigger responses in the salience detection system if their salience content is sufficiently high, e.g. because they contrast greatly from their surroundings, are entirely new or diverge from expectations based on previous experiences.[85,86]

Thus, findings of increased sensorimotor-evoked brain activation within regions of the so-called "pain matrix" in LBP might need to be reappraised. Giesecke et al. (2004) interpreted increased sensory-evoked brain activation in S1, S2, inferior parietal lobule and cerebellum (parts of the "pain matrix") in patients with LBP as "augmented pain processing", although the sensory stimuli were non-noxious and applied at a pain-free body site (thumbnail). Moreover, Moseley (2004a) stated that abdominal muscle contractions activated regions of the "pain matrix" (S1, ACC, insula, parietal and frontal cortices) in a patient with LBP, even though she did not perceive the motor task as painful. Taken together, these findings of increased sensorimotor-evoked brain activation may indicate that patients with LBP are over-responsive/over-attentive towards salient sensory inputs that signal possibly back-threatening events and require action, thereby inducing over-generalized motor responses to protect the spine. Such protective responses have been identified in patients with LBP, i.e. they appeared to over-activate lumbar

paravertebral and abdominal muscles during normal trunk and limb movements and during walking.[78,90-92] Protective motor responses may initially be adaptive. However, they often lose their protective function over time, e.g., through a vicious cycle of decreased lumbar movement and increased muscular stress, which induces (more) pain and disability and reduces physical activity further.[93] Recent work supports that increased brain responses to non-nociceptive stimuli, leading to over-generalized protective motor responses, may induce LBP.[77] However, longitudinal studies are highly needed to clarify the causality between sensorimotor-related functional brain changes and LBP. Such studies could also help to optimize LBP management, which nowadays mainly targets symptoms and musculoskeletal dysfunctions (vs. addressing brain changes) with e.g., massage, lumbar traction or manipulation, but has no to only small-modest effects (e.g. reviews [94-97]).

Targeting functional brain changes in patients with low back pain with therapy

The included studies revealed overall that patients with LBP display altered patterns of brain activation related to somatosensory processing and motor performance. Interestingly, studies have shown that maladaptive functional brain changes are reversible with treatment (e.g., with motor training).[98,99] Therefore, more efforts are being made to develop interventions that target brain changes in patients with LBP. The current review on the association between functional brain changes and sensorimotor behavior in patients with LBP may provide additional insights into which interventions could be valuable in the management of LBP.

First, performing motor-imagined movements might help to restore disrupted brain activation patterns in LBP.[44] Motor imagery activates largely the same brain regions as motor

execution[100,101] without requiring the patient to actually perform the movements. Therefore, it can be particularly advantageous in anxious or fearful patients. Motor imagery has already been proven effective to improve trunk dynamics in ballet dancers with LBP,[102] and to diminish pain and to improve movement in patients after lumbar surgery.[103] However, future studies investigating the effect of graded motor imagery training on brain activation patterns in patients with LBP are needed. Moreover, studying the effect of "kinesthetic imagery" (imaging the sensations of muscular contraction, relaxation and stretching during specific movements) in patients with LBP might be valuable.[104]

Second, Moseley (2004a) highlighted the potential of pain physiology education to normalize brain activation during motor performance (e.g., by reducing the perceived threat related to the motor task[41)] in addition to its proven effect on reducing pain and improving physical performance in LBP.[105]

Third, the importance of improving pain coping strategies in patients with LBP was revealed by Lloyd et al. (2008). In this study, well-coping patients with chronic LBP showed increased sensory-evoked brain activation in PCC and posterior parietal lobe, which correlated with lower catastrophizing scores.[40] In contrast, patients with chronic LBP who showed poor pain coping were not able to activate these brain regions, and reported higher current pain scores and higher levels of catastrophizing and depression.[40] Coping strategies can be improved with cognitive behavioral therapy, which has already been proven effective on the long-term in patients with non-specific LBP.[106]

In addition to above-mentioned strategies, other top-down and bottom-up interventions have been shown promising to improve pain and function and normalize brain changes in patients

with LBP (for recent reviews, see [107-110]). For example, specific motor control training of trunk muscles normalized cortical reorganization in M1 and trunk muscle recruitment patterns in patients with LBP,[99] while sensory discrimination training (or recognizing the location and type of different stimuli) significantly improved pain and functioning in LBP.[108] Moreover, peripheral magnetic stimulation of deep abdominal muscles restored M1 intracortical inhibition mechanisms and improved postural control in LBP.[111] Finally, well-considered combinations of different top-down and bottom-up interventions may yield additive effects in the treatment of LBP. For example, providing education on pain physiology prior to specific motor control exercises may reduce cortical over-activation during the exercises.[41] Peripheral electrical stimulation combined with transcranial direct current stimulation over M1, or combining peripheral magnetic stimulation of trunk muscles with motor control training might reduce pain more and improve motor learning.[111,112] However, further studies are imperative to optimize the evidence-based management of LBP.

Methodological considerations and future studies

The following section discusses methodological considerations regarding functional brain research in LBP, including the recruitment of participants, the preprocessing of resting-state fMRI data, the added value of combining structural and functional brain imaging techniques and the need for longitudinal studies.

First, only three studies accounted for possible confounding factors during the recruitment of participants.[36,38,43] Buckalew et al. (2010) excluded individuals with disorders with well-known effects on brain function (e.g. diabetes, depression, anxiety or multiple sclerosis) and subjects

who were or had been taking psychotropics. Giesecke et al. (2004) asked participants to discontinue the intake of antidepressants up to four weeks before the tests and excluded patients who were taking long-term opioid medication. Shi et al. (2015) only included participants who had no psychiatric illnesses or did not take any drugs within the last month. However, in the other six studies, medication use nor the presence of psychiatric/neurological disorders was questioned, despite a wealth of studies demonstrating their effect on brain function.[113-116] Thus, future studies should screen participants more rigorously for confounding factors. Additionally, to obtain more homogenous groups of patients with ongoing LBP, researchers might also consider subgrouping individuals with LBP, e.g., based on recurrent versus chronic LBP. However, since considerable heterogeneity exists even within the subgroup of patients with chronic LBP (e.g. in terms of pain duration, psychosocial profile and potential underlying mechanisms), a more thorough clinical examination of patients with LBP prior to inclusion might be warranted.

Second, the preprocessing of resting-state fMRI data differed between studies. Gay et al. (2014) determined resting-state FC by calculating bivariate correlations between the time series of two ROIs, whereas Buckalew et al. (2010) used a seed-based approach. Pijnenburg et al. (2015) analyzed resting-state fMRI data with two different techniques: (1) independent component analysis that decomposed fMRI data into spatially independent resting-state networks[117] of which the sensorimotor network was retained for final analysis and (2) FC density mapping to calculate long- and short-range FC density in the sensorimotor network[118]. The differences in preprocessing hampered the integration of findings on resting-state FC in LBP across studies.

Third, only one study combined structural (high-resolution anatomical imaging and diffusion tensor imaging) and functional MRI techniques (resting-state fMRI) to investigate brain alterations in LBP.[36] Future studies incorporating different structural and functional neuroimaging techniques are imperative to improve our in-depth understanding of neural alterations associated with impaired sensorimotor behavior in patients with LBP.

Fourth, because of the relatively small number of participants in the included studies (ranging from one to 45), results should be generalized with caution.

Finally, future studies might consider using graph theory to analyze brain function and structure from a network perspective. Graph theory differs from more traditional approaches that examine individual components of the brain, such as cortical regions, by quantifying different topological properties of functional and structural brain networks. In this way, graph theory can be used to study the efficiency of information transfer between brain regions. To the best of the author's knowledge, only one study used graph theory, thereby revealing a disrupted white matter network organization (i.e. decreased local efficiency and increased connectivity degree in M1) in patients with non-specific LBP compared to healthy controls.[119] Moreover, this study showed a significant correlation between decreased global efficiency and a worse sensorimotor performance in the patients with LBP.[119]

Conclusions

This review revealed the presence of functional brain changes associated with sensorimotor behavior and at rest in patients with long-lasting LBP compared to healthy subjects. Patients with LBP demonstrated decreased sensorimotor-evoked brain activation and a reorganized lumbar spine representation in brain regions involved in higher-order sensory processing and motor

control compared to healthy subjects. These results could support behavioral findings of a disturbed body schema of the trunk, reduced lumbosacral tactile and proprioceptive acuity, impaired sensorimotor performance and postural control deficits in LBP. Additionally, patients with LBP showed widespread increases in brain activation during non-nociceptive external (i.e. pressure) as well as bodily-induced stimuli (i.e. motor tasks) in regions of the so-called "pain-matrix". In the past, these findings were often interpreted as abnormal pain processing in LBP. However, findings of this review support an urgent need to reinterpret these results. Specifically, they may indicate that patients with long-lasting LBP are over-responsive to sensory inputs that potentially signal danger to the body, thereby inducing maladaptive, over-generalized motor responses to protect the spine. Hence, functional brain changes associated with sensorimotor behavior may lead to (recurrences of) LBP. However, longitudinal studies are crucial to elucidate the causality between functional brain changes, sensorimotor behavior and LBP and to investigate the effect of targeted training interventions addressing these specific brain changes in patients with LBP.

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Figure legends

Fig. 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses flow chart of the study selection process

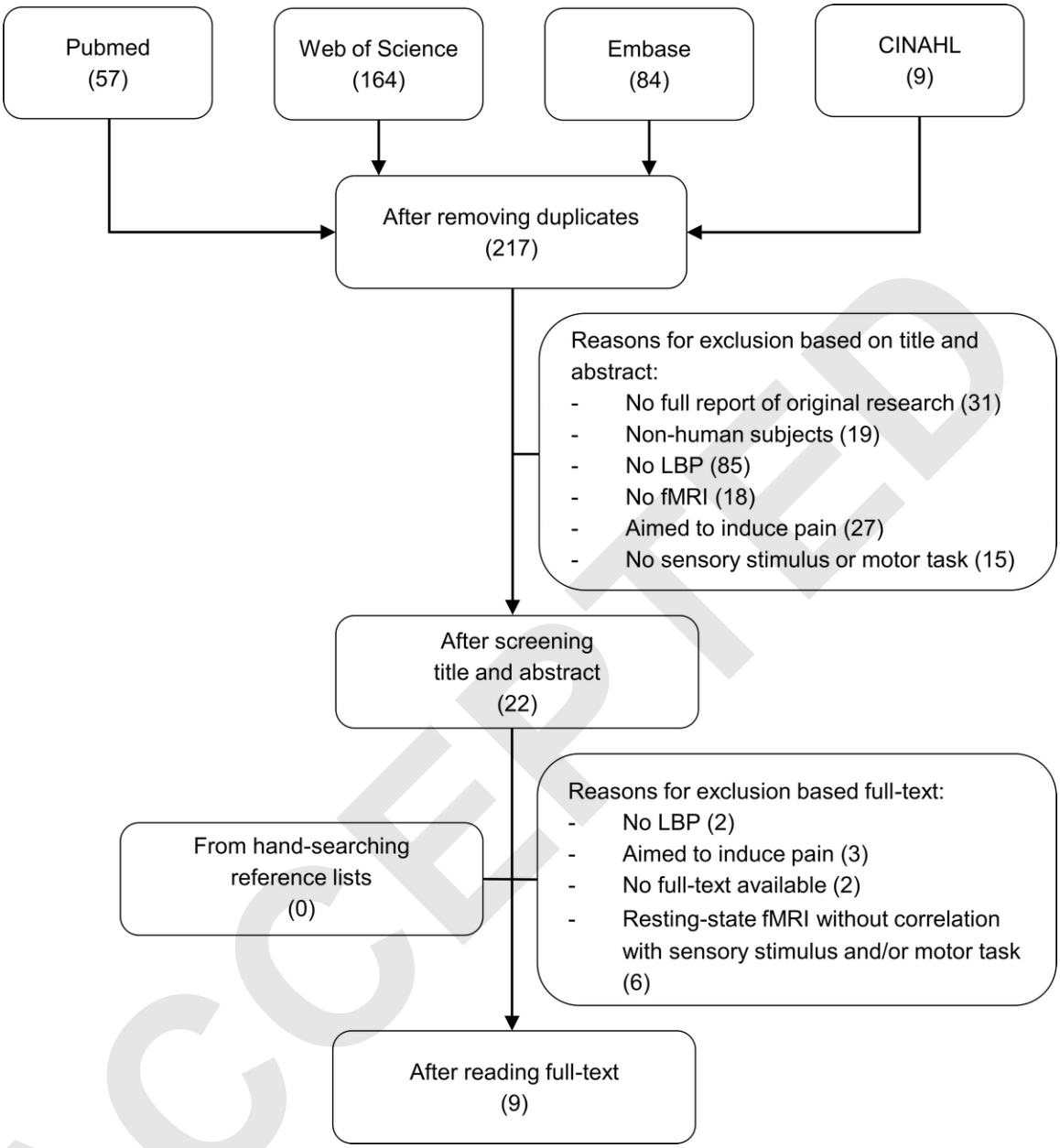

Table 1. Eligibility criteria

	Inclusion criteria	Exclusion criteria
Population	▪ Patients with non-specific LBP ▪ Healthy subjects with experimentally induced LBP	▪ Animals
Instrument	▪ Task-related fMRI with a somatosensory stimulus or motor task ▪ Resting-state fMRI correlated with a somatosensory stimulus or motor task	▪ EEG, MEG, SPECT, PET, fNIRS ▪ Structural MRI
Outcome	▪ Brain activity or FC during a somatosensory stimulus or motor task ▪ Resting-state FC correlated with a somatosensory stimulus or motor task	▪ Brain activity or FC during painful stimulus ▪ Resting-state FC before and after eliciting (more) pain, without correlations with somatosensory stimulus or motor task
Article type	▪ Clinical report ▪ Full-text	▪ Systematic review, meta-analysis, letter ▪ Abstracts, posters
Language	▪ English, Dutch, German, French	▪ All other languages

LBP= low back pain, fMRI= functional magnetic resonance imaging, EEG= electroencephalography, MEG= magnetoencephalography, SPECT= single-photon emission computed tomography, PET= positron emission tomography, fNIRS= functional near-infrared spectroscopy, FC= functional connectivity

Table 2. Summary of evidence on fMRI changes during somatosensory processing or motor performance in subjects with LBP

Author, year	LBP group	Control group	fMRI, stimulus and motor task	Main findings on group differences	Correlations	Remarks
Buckalew et al. 2010[36]	• Disabling chronic LBP, 4F/4M, 74±6 y • Non-disabling chronic LBP, 2F/6M, 75±7 y	NA	RS, physical performance	*Disabling LBP*: ↑ FC of medial PFC *Non-disabling LBP*: ↑ FC of lateral PFC *Physical performance*: no difference	No correlation between FC and physical performance	PCC as seed region in RS-fMRI data analysis
Gay et al. 2014[37]	Healthy with induced LBP, 17F/7M, 22±4 y	NA	RS, before and after spinal manipulation, mobilization and touch	*FC changes common to three stimuli* between L PCC - L ant insula, L post insula - L PAG, L S1 - R post insula *Stimuli-dependent FC changes* between R S1 - R ant insula, R S1 - R PAG, R ant insula - L PCC	Small correlations between FC and pain intensity and between FC and pressure pain sensitivity	Only "pain-related" regions and descending pain modulatory region (PAG) analyzed
Giesecke et al. 2004[38]	Chronic non-specific LBP, 8F/3M, 44±13 y	Healthy 4F/7M, 41±7 y	Task-related, 2 kg pressure on L thumb	*LBP*: ↑ activation in R S1, L&R S2, L cerebellum and L inferior parietal lobe *Healthy*: ↑ activation in R S2	NA	Only "pain-relevant" regions analyzed
Hotz-Boendermaker et al. 2016[39]	Chronic non-specific LBP, 5F/8M, 39±15 y	Healthy 5F/9M, 42±18 y	Task-related, manual pressure on 3 lumbar vertebrae	*LBP*: ↓ activation in L&R S2, blurred representation of vertebrae in S2 *Healthy:* distinct representations of vertebrae in S2	NA	Only S1 and S2 analyzed
Lloyd et al. 2008[40]	Chronic non-specific LBP with • low degree of pain-related illness behavior, n=15, 46±13 y • high degree of	Healthy 9F/8M, 31±8 y	Task-related, tactile vibration at lumbar spine	*LBP with low illness behavior* • *vs. healthy*: ↑ activation in L superior parietal lobe, extrastriate cortex, fusiform gyrus • *vs. LBP with high illness behavior:* ↑ activation in R PCC, R extra-striate cortex, L post parietal lobes	*LBP with low illness behavior:* negative correlation between activation in R PCC, L post	NA

	pain-related illness behavior, n=13, 44±12 y			*LBP with high illness behavior* • *vs. healthy and LBP with low illness behavior:* S1 activation medially shifted	parietal lobes and catastrophizing	
Moseley 2004a[41]	Disabling chronic LBP, 1F, 36 y	NA	Task-related, abdominal muscle contraction	*Before pain education*: activation in S1, ACC, insula, parietal association and frontal cortices *After pain education*: ↓ activation in all regions, except for S1	NA	NA
Pijnenburg et al. 2015[42]	Chronic non-specific LBP, 11F/6M, 33±8 y	Healthy 12F/5M, 32±8 y	RS, duration to perform 5 sit-to-stand-to-sit movements when blindfolded	*LBP*: ↓ FC in L SMA, M1, S1 and cerebellar lobules IV-V + ↑ FC in R middle frontal gyrus, superior frontal gyrus, lobule VI of vermis + worse sensorimotor performance	*Total group:* negative correlation between FC of cerebellar lobules IV-V, M1 and task performance	Only sensorimotor network analyzed
Shi et al. 2015[43]	Healthy with induced LBP, 11F/17M, age range 22-30 y	NA	Task-related, real and sham acupuncture at knee	*Acupuncture vs. baseline*: deactivation in somatosensory and limbic system, pain matrix, DMN, thalamus + activation in M1, S1, SMA, insula, midcingulate cortex *Sham versus. baseline*: deactivation in insula, frontal operculum, M1 + activation in somatosensory, limbic and attentional systems, DMN, thalamus, cerebellum, lateral occipital gyrus	NA	NA
Vrana et al. 2015[44]	Chronic non-specific LBP, 4F/11M, 40±14 y	Healthy 9F/5M, 34±13 y	Task-related, motor imagery	*LBP:* ↓ activity in L SMA and R STG, ↑ task-related FC in majority of motor imagery-network *Healthy controls:* ↑ task-related FC in thalamus *Motor imagery performance:* no	NA	Only motor imagery-related regions, STG and primary auditory cortex

Abbreviations: LBP= low back pain, F= female, M= male, y= years, RS-fMRI= resting-state fMRI, fMRI= functional magnetic resonance imaging, ↑= increased, ↓= decreased, FC= functional connectivity, PFC= prefrontal cortex, S1= primary somatosensory cortex, S2= secondary somatosensory cortex, M1= primary motor cortex, SMA= supplementary motor area, STG= superior temporal gyrus, DMN= default mode network, PCC= posterior cingulate cortex, ACC= anterior cingulate cortex, ant= anterior, post= posterior, L= left, R= right

Table 3. Risk of bias in included articles (cfr. modified Downs and Black tool[45,47,48])

	Vrana et al. 2015[44]	Giesecke et al. 2004[38]	Hotz-Boender-maker et al. 2016[39]	Lloyd et al. 2008[40]	Moseley 2004a[41]	Shi et al. 2015[43]	Pijnen-burg et al. 2015[42]	Buckalew et al. 2010[36]	Gay et al. 2014[37]
Reporting									
Aims described	1	0	1	1	1	0	1	1	1
Outcomes described	1	1	1	1	1	1	1	1	1
Patients' characteristics	1	1	0	0	1	0	1	1	1
Distribution of confounders	1	1	1	1	NA	NA	1	1	1
Main findings	1	1	1	1	0	1	1	0	1
Random variability of findings	1	1	1	1	0	1	1	1	1
Actual p-values reported	0	0	1	1	0	1	1	1	0
Validity									
Those asked to participate representative	1	1	0	0	0	0	0	0	1
Those willing to participate representative	0	0	0	0	0	0	0	0	1
Bias									
Data dredging	0	0	0	0	0	0	0	0	0
Appropriate statistical analysis	1	1	1	1	1	1	1	1	1
Accurate outcome measures	1	1	1	1	1	1	1	1	1
Confounding									
Groups recruited from similar population	1	0	0	0	NA	NA	0	1	NA

Groups recruited over same time	0	0	0	0	NA	NA	0	0	NA
Adjusted for confounding	1	1	1	0	NA	NA	1	1	1
Total (%)	**73%**	**60%**	**60%**	**53%**	**45%**	**55%**	**67%**	**67%**	**85%**

NA= not applicable