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The relationship between structural and functional brain changes and altered emotion and cognition in chronic low back pain: A systematic review of MRI and fMRI studies.

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Abstract

Objectives: Chronic low back pain (CLBP) is a major health issue, yet its underlying mechanisms remain unknown. Studies have demonstrated the importance of emotion and cognition in chronic pain, however, the relevant brain physiology in magnetic resonance imaging (MRI) studies are unclear in CLBP populations. Therefore, this review aimed to identify MRI brain changes and examine their potential relationship with emotional and cognitive processes in CLBP.

Method: A systematic search was conducted in 5 databases. Studies that recruited adult, chronic low back pain populations, and used brain MRI protocols were included.

Results: Fifty-five studies met the inclusion criteria. Of the structural MRI studies, 10 of 15 studies found decreased gray matter and 7 of 8 studies found white matter changes in CLBP groups compared to controls. Fourteen resting-state functional MRI (fMRI) studies all reported differences between CLBP and control groups in the default mode network. Interestingly, only 3 of 10 fMRI studies observed significant differences during noxious stimulation between CLBP and control groups, while 13 of 16 studies observed significant brain activation differences in CLBP groups during various external tasks. Finally, there were 3 studies that observed a degree of recovery in functional connectivity following intervention.

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Discussion: The brain changes in CLBP groups were mainly observed in areas and networks important in emotion and cognition, rather than those typically associated with nociception. This supports the understanding that emotional and cognitive processes may be the core contributor to the CLBP experience, however, future studies need to explore these processes further.

Keywords: Chronic low back pain, fMRI, MRI, emotion, cognition, brain

Introduction

Low back pain (LBP) is the leading cause of disability worldwide [1]. Reports have shown that LBP is accountable for 10.7% of years lived with disability (YLD; 83.1 million YLD) globally [2] with significant economic costs [3, 4]. While the majority of LBP cases tend to resolve within the first 6 weeks [5], approximately 10% of individuals develop chronic low back pain (CLBP) [3, 6-8]. However, 85% of these cases do not have a specific physiological cause (i.e., referred to as *non-specific)* [9, 10], making the development of effective treatments and pathways to recovery extremely challenging. While multidisciplinary pain treatment programs are effective in pain relief in CLBP, the effects seen in studies have been small and short-term [10, 11]. Despite the lack of clear pathology in non-specific CLBP, the absence of a physiological cause supports the notion that pain is not a purely sensory-dependent process [12].

Pain is a multifaceted subjective construct [13]. The prominent theoretical model of pain, known as the neuromatrix theory of pain, was developed to conceptualize the complexity of pain. It identified 3 main dimensions: sensory, emotional and cognitive components [13]. Recent pain studies using magnetic resonance imaging (MRI) techniques have identified a network of brain regions, collectively referred to as the *pain matrix* [14] that are in conjunction with the 3 dimensions of pain. The sensory component has been associated with

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the primary and secondary somatosensory cortices of the brain [15]. The emotional component included the cingulate cortex, insula, and areas of the limbic system which influences the perceived unpleasantness of pain stimuli [14, 16]. For instance, studies have demonstrated that induced negative mood can increase the unpleasantness of a pain stimulus but not the intensity [15, 17-20]. Finally, the cognitive aspect of pain showed activation in the frontal and parietal regions of the brain [16, 21]. It is involved in the degree of attention on stimuli, and interprets the meaning of the overall pain experience [16, 21]. For example, diverting attention away from noxious stimuli by engaging in an attention-demanding task can result in reduced pain intensity [22, 23]. The widespread activation in the pain matrix across these domains clearly suggests that emotional and cognitive factors play a fundamental role in how pain is experienced [21].

Cross-sectional studies have shown cognitive deficits in individuals with CLBP, independent of depression and anxiety, include delayed information processing [24], impaired memory [25], decision-making [26] as well as poorer cognitive function in neuropsychological tasks [27]. Studies have also shown that individuals with CLBP have shown disrupted emotional processes as they have a significantly higher prevalence of mood disorders such as depression than the general population (i.e., pain-free individuals) [28, 29]. Therefore, this suggests that CLBP is linked to changes in emotional and cognitive function, however, the underlying neuroanatomy and brain function associated in these relationships are not well understood. This is however, an important area of enquiry as the development and maintenance of persistent pain may be associated with changes in brain regions that make up the pain matrix. Indeed, the consequences of this change, whether the cause or the result of persistent pain, alter the experience of pain and the related cognitive and emotional functions [21, 30]. Recent reviews have examined cognitive modulation on overall pain perception [31], identified MRI brain activations [32] as well as brain alterations in various chronic pain conditions [33]. A

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review also examined the brain changes specifically in CLBP groups [34], however, their findings largely focused identified general changes with an absence of the discussion regarding the implications on emotional and cognitive processes and a lack of integration of the qualitative assessment of the studies. Therefore, the aim of this review was to examine the evidence for the structural and functional changes in the brain and identify how these changes may be associated with emotional and cognitive processes in CLBP. It also included assessment for risk of bias.

Methods

Search strategy

A computerized search was conducted up to the 11th August 2016 using the databases Medline, PsycINFO, Cinahl, Embase and Scopus. The following key search terms used in title and abstracts (* = truncated, ADJ1 = retrieves words that are within 1 word of each other): (Magnetic resonance imaging [Mesh] OR (functional ADJ1 (MRI* or magnetic resonance imaging))) AND (brain [Mesh] OR brain*) AND (back pain [explode]).

Study selection

Studies were included if they met the following criteria: (i) population consisted of human subjects; (ii) adult sample only (age above 18 years of age); (iii) included individuals with chronic low back pain (CLBP) patients (defined as low back pain where the duration is clearly identified as more than 3 months); (iv) used brain MRI techniques; (v) peer-reviewed original research with full-text available (reviews, systematic reviews, and meta-analyses were excluded); and (vi) published in English. Studies were excluded if they did not meet all the inclusion criteria. In the first phase, all studies were evaluated for eligibility based on the title and abstract. In the second phase, full-text articles of potential eligible studies were retrieved and further screened.

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Data extraction

Study information on author, year, study design, definition of CLBP, sample size, mean (SD) age, percentage of females, analysis method (see Table 1), as well as stimulus or task event, follow-up periods (in cohort studies only), main findings, and conclusions were extracted from all eligible studies (Table 2-5).

Assessment of risk of bias

Two independent reviewers (S.K.N. and S.M.H) independently assessed the methodological quality of the selected studies using an adapted scoring system of the Lievense criteria [35]. The Lievense criteria consists of 15 items that were scored either positive (1) or negative (0) (see Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/CJP/A453). Results were then compared and where reviewers disagreed and consensus could not be achieved, a third reviewer (D.U.) gave final judgement. The results of this assessment were used to determine the risk of bias which was assessed using a tool adapted from the Cochrane Collaboration for cohort studies [36]. This risk of bias assessment was based on 4 items for cross-sectional studies and 5 items for cohort studies. Each item was rated as "low", "moderate", or "high" based on specific item scores from the Lievense criteria (see Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/CJP/A453) and these contributed to an overall assessment of the risk of bias for each study; low (all items rated low), low-moderate (1 item rated moderate), moderate (2 items rated moderate), or high (more than 2 items rated moderate or any of the items rated high).

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Results

Study selection

The literature search yielded a total of 1,003 papers from the 5 databases. After the removal of duplicates, there were 715 unique articles remaining. After the first phase of screening based on title and abstracts, 633 articles were excluded with a further 27 articles excluded when screened using full-text based on the inclusion criteria. During the second screening phase, articles were excluded if full-texts could not be found, or if they were conference abstracts. After the 2 screening phases, 55 papers were included. The process of study selection is represented in a PRISMA flowchart [37] in Figure 1.

Study characteristics

The study characteristics of the yielded papers are presented in Table 1. The group size of CLBP patients ranged from 8 to 111. All studies consisted of both males and females, except 1 study that only recruited females [38]. Two studies also had controls groups that were all males that were compared to CLBP groups with individuals of both genders [39, 40]. The mean age of CLBP groups were 47.1 years of age. Two studies did not report mean age [41, 42].

There were 46 studies that compared CLBP patients to healthy controls, while 4 studies compared the effects of treatments within CLBP groups [43-46] and 1 study compared subacute back pain (SBP) with CLBP [47]. There were 6 studies that explored within-CLBP group differences including 3 studies that compared CLBP patients that exhibit pain behaviors with those who did not [48-50], 2 studies that compared disabled and non-disabled CLBP patients [51, 52] and 1 study that compared neuropathic and non-neuropathic CLBP groups [53]. Finally, there were two longitudinal studies that followed CLBP [47] and SBP [54] over the course of 1 year and compared back pain recovery outcomes (i.e., groups that recovered from back pain and those who had persistent back pain).

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Most CLBP patients were selected based on self-reported low back pain every day or almost every day that ranged from at least 3 months to 10 years with pain intensity rating of at least more than 2 out of 10, or were diagnosed according to the IASP criteria by a clinician. There were 19 studies that also targeted specific types of LBP: 12 studies recruited non-specific CLBP [38, 39, 48-50, 55-61], 2 studies with lumbar disc herniation [62, 63], 2 studies with failed back surgery syndrome (FBSS) [46, 64], and 3 studies with a discogenic component [65-67].

Risk of Bias

The risk of bias results are presented in Tables 2 to 5. Of the 55 studies included in this review, 32 studies and the cross-sectional component of a cohort study (59%) had a low to moderate risk of bias and 22 studies and the cohort component of another study (40.9%) had a high risk of bias. Analysis of the risk of bias assessments revealed that 98.2% of studies achieved low risk of bias scores on the selection of participants (Cochrane criteria item 3) and 61.5% of cohort studies obtained a low score for adequate follow-up procedures (Cochrane criteria item 6) (see Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/CJP/A453). The majority of studies obtained a moderate risk of bias score in the "assessment of exposure" (76.4%; Cochrane criteria item 2) and the "assessment of outcome" (89.1%; Cochrane criteria item 5). A total of 16 studies obtained a high risk of bias score for statistical adjustment for potential confounding variables (Cochrane criteria item 4). There were only 13 (23.6%) cohort studies and 4 (7.3%) intervention-based studies. However, there was considerable consistency in the evidence for our findings, particularly from noxious stimulation and resting-state studies, despite the various cohorts and methodologies employed.

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MRI structural changes

Gray matter (GM)

There were 15 studies that examined changes in structural gray matter (GM) with 3 studies that had low-moderate risk of bias [65, 68, 69], 6 studies that had a moderate risk of bias [40, 53, 56, 62, 70, 71] and 6 studies that had a high risk of bias [63, 72-76]. The findings of these studies are presented in Table 2. In terms of global GM volume, 5 studies (2 with low-moderate, 1 moderate, and 2 high risk of bias) did not observe any significant differences between CLBP and healthy controls [56, 65, 68, 74, 75], while 3 other studies (2 moderate and 1 high risk of bias) found reduced global GM in CLBP patients compared to controls [53, 70, 73]. There were 5 studies with a low to moderate risk of bias that observed decreased regional GM volumes in areas including the dorsolateral prefrontal cortex (DLPFC) [53, 69], insula [69, 70], temporal lobes [70], cuneus [71], thalamus [53], medial prefrontal cortex (mPFC) [69], posterior cingulate cortex (PCC) [68], as well as the pre- and post-central regions [70, 71] in CLBP groups compared to controls. Five high risk of bias studies observed similar findings with decreased GM in the DLPFC [73-75], insula [75], temporal lobe [63, 74, 75], cuneus [76], thalamus [73], and pre- and post-central regions [63]. On the contrary, 2 studies observed increased GM volume in the DLPFC, temporal lobe [76] and the thalamus [74], although these studies were of high risk of bias. Furthermore, mixed results in the cingulate cortex [63, 73, 75] and S1 [74-76] were observed in a number of high risk of bias studies. Furthermore, within-group comparisons in 1 study did not find any significant GM volume differences between neuropathic and non-neuropathic CLBP groups [53].

There were 4 longitudinal studies (2 moderate and 2 high risk of bias) that observed GM changes over time. The 2 moderate risk of bias studies found increased GM in areas including the basal ganglia [62], inferior frontal gyrus, caudal pons, and the cingulate cortex [40], as well as decreased GM in the hippocampus [40, 62], rostroventral pons, and medial orbital

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gyrus [40] in CLBP patients following treatment. Of the high risk of bias studies, 1 found increased GM in the DLPFC following treatment in CLBP patients [75]. The other study observed significant decreased global as well as regional GM volume in the striatum, insula, S1, and the primary motor cortex (M1) as subacute back pain persisted (SBPp) after 1 year [72]. Overall, 10 of the 15 studies, including 2 low-moderate risk of bias studies, found decreased global or regional GM in CLBP groups. These findings show that there are specific regions that consistently show decreased GM volumes, despite the risk of bias assessments. The longitudinal studies also demonstrate a degree of recovery in GM volume following treatment.

White matter (WM)

There were a total of 8 studies that explored changes in structural white matter (WM) (see Table 2) where 1 study had low-moderate risk of bias [68], 1 study had moderate risk of bias [52], 5 studies had high risk of bias [51, 63, 73, 75, 77] and 1 study with a cross-sectional and cohort component, was of moderate and high risk of bias respectively [41]. Of these studies, two studies (1 moderate and 1 high risk of bias) did not find any significant differences in global WM between CLBP patients and controls [68, 75] whereas Ivo [73] (high risk of bias) found significantly reduced global WM in the CLBP group. While 1 study with moderate risk of bias found no significant differences in regional WM in the left insula [41], two studies (1 low-moderate and 1 high risk of bias) found decreased WM volume in cingulate superior to middle corpus callosum [68], and anterior limb of the internal capsule [63]. Furthermore, two studies (1 moderate and 1 high risk of bias) compared within CLBP groups in those who were disabled and those who were not disabled by their LBP. They found that the disabled CLBP group had reduced WM integrity in the splenium of the corpus callosum as well as increased WM hyperintensities in the left hemisphere, including the anterior thalamic radiation, lower

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cingulate, inferior longitudinal fasciculus, and superior longitudinal fasciculus compared to the non-disabled CLBP group [52].

Finally, two longitudinal studies found that CLBP patients exhibited increase in WM integrity in the left insula following treatment [41] and denser WM connections in the dorsal mPFC-amygdala-nucleus accumbens (NAc) network in SBP groups increased the likelihood of developing persistent back pain [77] but these studies had high risk of bias. Overall, 7 of the 8 studies found changes in WM properties in CLBP groups compared to controls. However, these results should be approached with caution as various methodologies have been used with 6 of the studies, as well as the cohort component of another study [41] obtaining high risk of bias assessments.

Resting-state studies

A total of 14 studies examined functional connectivity during resting-state in CLBP groups, predominantly in the default mode network (DMN). Of these studies, 1 study had low-moderate risk of bias [58], 6 studies had moderate risk of bias [56, 61, 64, 66, 78, 79], 6 studies that had high risk of bias [51, 67, 80-83] and 1 study, with a cross-sectional and cohort component, was of moderate and high risk of bias respectively [41]. Their results are presented in Table 3. There were 6 studies with low to moderate risk of bias that showed increased brain activity in CLBP groups within various DMN areas including the superior, middle and inferior regions of the frontal gyri [58, 64], cingulate cortex, inferior parietal gyrus [56, 64], precentral gyrus [58, 61], angular gyrus [64], mPFC [78], as well as increased DMN functional connectivity to the insula, pregenual anterior cingulate cortex, and inferior parietal lobule [66] compared to controls. Increased activity in the angular gyrus [81], orbital region of the middle frontal cortex [82], and the mPFC [83] in CLBP groups was also observed in high risk of bias studies. On the contrary, two moderate risk of bias studies

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observed decreased brain activity in the cingulate cortex [64], and precentral gyrus [58], while two high risk of bias found decreased ACC activity [82] and reduced mPFC connectivity to posterior areas of the DMN [83]. Additionally, 3 studies (1 low-moderate and 2 moderate risk of bias) found decreased DMN brain activity in CLBP groups areas including the S1 and M1 [56], supramarginal parietal gyrus, temporal lobes [64], and the SMA [58] compared to controls. Furthermore, within-CLBP group comparisons found increased mPFC and decreased lateral prefrontal cortex in the disabled CLBP group compared non-disabled CLBP group in a high risk of bias study [51].

Two studies explored the resting-state modular network connectivity (i.e., the integrated connectivity of neurons that define the DMN) and found that CLBP patients differed to controls. One study with moderate risk of bias, found that CLBP patients had increased connectivity between the NAc and subcortical regions while controls had more between the NAc and frontal cortical areas [79]. Changes in the resting-state connectivity were observed in the frontal and temporal regions, the sensorimotor cortex, basal ganglia and ACC, resulting in a change in the overall network in a high risk of bias study [80].

Three moderate risk of bias studies [56, 61, 66] and 1 high risk of bias study [67] compared resting brain activity before and after clinical pain-inducing maneuvers. Compared to controls, the moderate risk of bias studies found CLBP groups showed decreased functional connectivity in in the superior frontal gyrus [56], and between the DMN and mPFC [66], as well as increased superior temporal gyrus, precentral gyrus, dorsal cingulate cortex and posterior insula activity [61] after the maneuvers. Furthermore, while Yu [61] did not find any significant differences before and after the maneuvers, Kong [56] observed decreased activity in the inferior parietal lobule, cuneus, and middle occipital gyrus, as well as increased activity in S1, M1, and superior frontal cortex. Increased activation in the S1 and M1 was also observed in a study with high risk of bias [67]. Therefore, of the 14 resting-state studies,

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8 studies, including 5 with low to moderate risk of bias, observed increased activity or connectivity in areas within the DMN in CLBP groups.

Event-related studies

Noxious stimulation studies

Ten studies explored differences in nociceptive pain processing in CLBP groups, using noxious thermal [49, 54, 59, 84, 85], electrical [46, 48, 86] and mechanical [39, 55] stimulation. The results are presented in Table 4. Six of the 10 studies, including 1 low-moderate risk of bias studies [48], 4 moderate risk of bias studies [54, 55, 84, 85] and 1 high risk of bias study [59] did not observe significant differences in brain activity between CLBP groups (including CLBP with high pain behaviors based on Waddell's sign, WS-H in 1 study [48]) and control groups during noxious stimulation. However, the 5 studies with low to moderate risk of bias observed activation in common areas including the thalamus [54, 84], insula [54, 84], S1 [55], S2 [55, 84], parietal operculum, midcingulate cortex and M1 [85] and the ventrolateral prefrontal cortex [48]. Similar results were observed in the high risk of bias study in the thalamus, insula, and the S1 [59]. Only 3 studies (1 low-moderate and 2 high risk of bias) observed significantly greater activation in the SMA, insula, PCC [39], and inferior parietal cortex [86], in CLBP groups, and superior parietal lobe only in CLBP patients that exhibited low pain behaviours (WS-L; based on Waddell's sign) [48], during noxious stimulation compared to controls. Similarly, 6 of these studies did not find any significant differences in reported pain ratings or thresholds between CLBP and control groups in both fixed [84] and adjusted [48, 54, 59, 85, 86] noxious stimulations. Another 2 studies found that the pain threshold for CLBP groups were significantly lower than the control groups [39, 55].

Moreover, within-CLBP group differences were compared in two studies with low-moderate risk of bias. They found that, compared to the CLBP WS-L group, CLBP patients WS-H had

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decreased activity in the posterior retrosplenial cingulate cortex and inferior parietal cortex during noxious stimulation [48] as well as increased activity in the inferior frontal gyrus, superior mid-temporal gyrus and amygdala during noxious stimulation (compared to warm stimuli) [49]. Importantly, both studies also reported no significant differences in pain threshold between WS-H and WS-L groups, suggesting that the differences in brain activity may be related to the observed pain behaviors (i.e., Waddell's signs) in CLBP. Finally, 1 high risk of bias study observed that there was increased activity in the inferior temporal cortex and cerebellar cortex in CLBP patients during simultaneous spinal cord and heat noxious stimulation compared to when each stimulation occurred alone [46]. Overall, 6 of the 10 studies, 5 of which were of low to moderate risk of bias, did not find significant differences, between CLBP and healthy controls, however, identified several consistent areas that activated following noxious stimuli, despite their risk of bias.

Task-related studies

There was a total of 16 studies (9 moderate and 7 high risk of bias) that looked at brain processes during various external tasks in CLBP patients (see Table 4). Seven of these studies examined brain activity while participants were continuously rating the spontaneous fluctuations of their back pain (i.e., back pain in the absence of an external stimuli) with 3 moderate risk of bias studies [47, 78, 87] and 4 high risk of bias studies [72, 77, 88, 89]. Of the cross-sectional moderate risk of bias studies, they found that CLBP patients had activation in the mPFC [78, 87], and when compared to SBP patients, exhibited increased mPFC and amygdala and decreased insula and thalamus activity [47] during the spontaneous pain rating task. Furthermore, a high risk of bias study showed that CLBP patients experiencing spontaneous back pain exhibit significantly distinct fractal properties compared to during thermal noxious stimuli as well as imagined pain in controls [88]. A longitudinal study with moderate risk of bias observed that increased activation in the amygdala, and basal

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ganglia when SBP persisted after a year (SBPp) [47]. There were 3 other longitudinal studies [72, 77, 89], that found increased NAc connectivity to the basal ganglia [72] and mPFC [72, 89] but decreased connectivity to the insula [77] in SBPp compared to SBP patients who recovered (SBPr) groups, however, all had high risk of bias.

Of the 16 task-related studies, there were only 3 studies that examined brain activity during cognitive tasks. One of the studies (moderate risk of bias) used a monetary gambling task but did not observe any significant brain activity differences between CLBP and control groups [79]. The other two studies (1 moderate and 1 high risk of bias) used an attention task, the multi-source inference task (MSIT) [75, 90]. They showed that CLBP groups had decreased activation in the DLPFC [75], amygdala, dorsal anterior and para-cingulate cortex, superior parietal cortex, precuneus and the pre- and post-central cortices [90] compared to controls. There were two studies with moderate risk of bias that explored the brain activity during a simple visual task [91, 92]. They found that CLBP groups demonstrated increased activity in areas within the DMN including the mPFC [91] and hippocampus [92] compared to controls. Interestingly, the longitudinal component of the Mutso [92] study showed that the SBPp group had decreased hippocampal connectivity to mPFC and cingulate cortex compared to SBPr group.

Finally, there were four studies (2 moderate and 2 high risk of bias) that used other various tasks. Two studies (1 moderate and 1 high risk of bias) did not observe apparent differences between CLBP and control groups when viewing pain-evoking images [38, 42]. The third study, with moderate risk of bias, used a motor imagery task and found CLBP patients exhibited decreased activity in the SMA and superior temporal sulcus compared to controls [60]. Finally, a study using a pain anticipation task found increased activation in the precentral gyrus, PCC and superior parietal lobe in CLBP with pain behaviors (WS-H) compared to CLBP without (WS-L), although it had a high risk of bias [50]. Overall, 13 of

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the 16 studies, including 9 moderate risk of bias studies, demonstrated significant differences in brain activity during various external tasks in CLBP groups.

Intervention studies

There were 4 studies that examined the effects of various treatments on brain activity in CLBP patients with 1 study with low-moderate risk of bias [43], 2 studies with moderate risk of bias [44, 45] and 1 studies with high risk of bias [57] (Table 5). Of the moderate risk of bias studies, 1 study showed that the functional connectivity between mPFC and the insula predicted the probability of a placebo response [44], while the other study did not report any significant differences in brain activity before and after the use of lidocaine. Instead, they reported a 50% placebo effect in the overall participant group, regardless of the intervention type [45]. Increased activity in the middle temporal cortex was found in a low-moderate risk of bias study [43] after an intervention. Finally, the high risk of bias study observed increased connectivity in CLBP groups in various regions of the cingulate cortex [57] following intervention. Overall 3 of the 4 identified studies, regardless of their risk of bias but including the low-moderate risk of bias study, showed changes in connectivity that might suggest recovery in CLBP individuals with the various interventions examined.

Relationship between brain changes, and emotional and cognitive measures

Across the 58 selected studies in this review, 15 studies explored the correlational relationships between brain changes, and emotional and cognitive behavioral measures. These include 8 MRI studies examining structural brain changes and volumes, including 2 low-moderate risk of bias studies [65, 68], 3 moderate risk of bias studies [53, 70, 71] and 3 high risk of bias studies [51, 72, 73]. Of these 8 studies, 4 did not find any significant relationships with depression and anxiety measures [65, 70-72] while another study only observed significant negative correlations between anxiety and anterior cingulate and left lingual gyrus GM density but no significant correlations with depression [73]. Another 2

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studies did not find any significant associations between GM volumes and neuropsychological assessment tasks [51, 68]. One study observed a significant negative correlation between affect dimension of the short form of the McGill Pain Questionnaire (SF-MPQ) with DLPFC GM density, and also predicted DLPFC GM change in both neuropathic and non-neuropathic CLBP group. Furthermore, the lateral ventricle size and change in lateral ventricle size showed a positive correlation with the affective dimension of the SF-MPQ [53].

Two of the 15 studies, both of high risk of bias, explored the relationship between resting-state, and emotional and cognitive measures. One study did not find any significant correlations between functional connectivity and depression [83]. The other study observed a positive correlation between the performances in Trail Making Test A and the left lateral prefrontal cortex activity [51].

Another 2 of the 15 studies, with a low-moderate risk of bias studies explored the relationship brain activation during noxious stimulation and between emotional and cognitive measures in a CLBP group with high pain behaviors (WS-H) compared to another with low pain behaviors (WS-L). One study found there was a significant negative correlation between the magnitude of the blood-oxygen-level dependent (BOLD) response and the catastrophizing in the WS-L group [48]. The other study found a correlation between the percentage of change in BOLD responses with the anxiety and catastrophizing scores in the WS-H group but no significant relationships in the WS-L group [49].

The remaining 4 of the 15 studies, utilized task-related fMRI studies. Two of the studies (moderate risk of bias), using simple visual tasks, did not observe any significant relationships between brain activity and depression or anxiety [91, 92]. A high risk of bias study looking at spontaneous back pain fluctuations found a significant positive correlation

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between the number of NAc connections with the affect dimension of the SF-MPQ in SBPp groups [72]. The fourth study with high risk of bias used a pain anticipation task and found anxiety and rumination scores positively covaried with the BOLD responses in multiple brain areas when comparing the green vs yellow cue conditions, green vs red cue conditions as well as in response to the green cue. Finally, 1 intervention study (moderate risk of bias) observed a positive correlation between the affect dimension of the SF-MPQ and the brain connectivity between the dorsomedial prefrontal cortex and anterior insula [44].

Discussion

Overall findings

This review aimed to examine MRI evidence of structural and functional brain changes observed in individuals with CLBP and identify how these changes may be associated with emotional and cognitive processes in CLBP. We found that there were widespread brain changes in CLBP groups compared to healthy pain-free controls, although this was no present in all studies. These alterations were seen across both structural and functional MRI protocols. Structural MRI studies generally showed decreased GM volume compared to controls. There was some evidence of reduced WM structures in CLBP individuals, however, there were only a limited number of studies. In fMRI studies, individuals with CLBP did not show significant differences in brain activation during noxious stimulation, although, they did have lower pain thresholds compared to controls. Furthermore, as the brain activity during spontaneous back pain did not activate the areas of the pain matrix typically seen in noxious pain, it supports the notion that chronic pain may not be caused by nociceptive process [16, 21]. Instead, CLBP groups exhibited altered functional connectivity during resting-state, particularly in the DMN, as well as during various attention tasks. There have only been 3 studies explicitly looking at cognitive function, specifically in attention and decision-making in external tasks

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while 15 studies examined the correlational relationship between the brain changes observed and emotional and cognitive behavioral measures in CLBP. Furthermore, 56% of the selected studies reported low to moderate risk of bias based on stringent criteria, indicating relatively sound studies. Taken together, this review therefore demonstrates widespread brain changes in both structural and functional MRI studies, however, there is a lack of functional MRI studies specifically examining the emotional and cognitive processes that are associated with CLBP, even though they have been shown to be important in the chronic pain experience.

Beyond nociception: Chronic ≠ nociception

Research has clearly established that pain is comprised of sensory, emotional and cognitive components. Despite this review highlighting extensive brain changes in CLBP, significant differences during noxious stimulation were not generally observed between CLBP and healthy control groups. These contrasting findings suggest that sensory pain processes in nociception remain intact in CLBP patients. Interestingly, brain activity during spontaneous fluctuations of back pain did not exhibit activation of typically identified pain matrix areas. Instead, there were several studies that observed increased activity in the mPFC, an area involved in emotional processes [93], such as processing negative emotions, reappraisal, self-referential thoughts [30, 94, 95] as well as the self-regulation of emotions that influences pain perception of acute noxious stimuli [96]. Furthermore, a direct comparison between nociceptive and spontaneous pain showed distinct networks with no overlap in brain regions that showed nociceptive pain was associated with insula activity while spontaneous back pain correlated with the mPFC [87, 88]. Taken together, this might suggest that the spontaneous pain experienced in CLBP may be driven by emotional processes. Indeed, recent research has demonstrated behavioral emotional and cognitive deficits in CLBP [24-29]. However, there has been an absence of studies exploring the underlying brain physiology that may explain the altered emotional and cognitive processes.

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Implications on understanding mechanisms underpinning emotional and cognitive processes in CLBP

There are limited studies in the current literature that have used MRI techniques to explore the specific emotional and cognitive processes that may be affected in CLBP; however, this review may indicate some of the potential networks involved. Here, we suggest that CLBP may be associated with disrupted functional connectivity in the DMN. The DMN refers to a network of brain areas, consisting primarily of the mPFC, precuneus, PCC and the inferior parietal lobule, that are active during resting-state (i.e., when an individual is not engaged in any externally-focused tasks) [97]. This network typically deactivates as individuals shift their cognitive resources to externally-focused tasks or their environment [97]. While previously thought to be a passive network [98], recent studies have shown that the DMN is involved in various internal or self-referential thought processes such as recalling episodic or semantic information, personal introspection, planning for the future as well as the cognitive assessment and regulation of emotions (i.e., appraisal and reappraisal) [97, 99, 100]. Self-regulation of emotions is an important process in the perception of noxious pain [96] as well as coping and managing the negative affect of pain [101]. Therefore, altered DMN connectivity may reflect impaired self-regulation processes [97] necessary to cope with CLBP.

Indeed, the findings from this review support a previous study by Woo [96], who observed a distinct network, including the mPFC, involved in self-regulation processes that influences nociceptive pain perception. Specifically, Woo and colleagues propose that there is an "evaluative" functional network that interacts with the pain matrix in order to produce the overall pain experience. Taken together with the findings of the current review, the DMN may be involved in the evaluative network that becomes impaired in CLBP (depicted in Figure 2).

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The disruption of connectivity in the DMN may also interrupt the function of other interconnected networks, including the cognitive networks involved in externally-focused tasks. There were task-related studies from this review that found inefficient deactivation of the DMN [91], as well as reduced activation of the network involved in executive function during attention tasks [90]. Interestingly, a recent study observed the opposite effect during resting-state with increased connectivity between subregions of the amygdala and the central executive network (CEN) but reduced amygdala-DMN connectivity in CLBP. The increased CEN connectivity at rest also correlated with pain catastrophizing while the DMN did not show significant associations with catastrophizing, depression or anxiety [103]. Taken together, this may reflect the inability to engage in the appropriate mental resources and networks during internal and external processes in CLBP. However, the current literature in this review presented mixed findings where there was no consistency in the relationship between the observed brain changes, and emotional and cognitive processes assessed through task performance and self-report measures. For example, some studies found that CLBP groups showed altered brain connectivity, although, there were no differences in task performance differences [75, 91], while others showed task performance differences but no functional brain changes compared to controls [79]. We also reported contrasting findings where a number of studies who have found significant correlations between structural GM density [53], functional connectivity during tasks [50, 72] and BOLD responses during noxious stimulation [48, 49] with various negative affect and catastrophizing measures. Although, other studies did not find any significant associations in structural brain volumes [65, 70-72], resting-state [83] or tasks [91, 92] with behavioral measures. Overall, these findings demonstrate our understanding of the implications of brain changes on emotional and cognitive processes in CLBP remains unclear. Therefore, the relationship between

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cognitive function and brain activity as well as the degree of interaction between the DMN and other cognitive networks needs to be determined.

Theoretical implications on Neuromatrix of pain

This review may have some implications on the theoretical understanding of the neuromatrix theory of pain and the related pain matrix areas involved. As spontaneous back pain and acute nociceptive pain exhibit different patterns of brain activity, it may indicate that the sensation of pain is not exclusively produced by activation of the pain matrix. In addition, other studies have demonstrated that other non-painful sensory stimuli can also produce a pain matrix response, suggesting the pain matrix is not exclusively for pain [104, 105]. Instead, there may be another distinct evaluative network, in addition to the pain matrix that has the ability to produce the pain experience which demonstrates that the brain regions in pain may be more extensive than previously thought. Furthermore, while spontaneous back pain in CLBP may not be a nociceptive process, it may be possible for sensory input to influence the CLBP experience. Sustained postural activity, such as prolonged sitting, has been found to exacerbate some types of CLBP [106]. However, further research would be required to understand how sensory processes may contribute to the CLBP experience. Therefore, the pain matrix may interact with the evaluative network that influence both the inputs and outputs of pain processes and it is important to further explore the role of this network in CLBP.

Limitations

One of the major limitations of the current literature was the absence of studies exploring specific emotional and cognitive processes that may be contribute to or influence CLBP, despite their importance in pain. Furthermore, while the current evidence does support the involvement of emotional and cognitive processes, it is likely that there is also large inter-

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individual variability in terms of their contribution. Between individuals, emotional and cognitive processes may differ according to age [107, 108], gender [109, 110], and psychosocial factors [111-113]. For example, studies have shown that normal aging results in changes in the structural and functional properties of the brain [114-116] which are associated with changes in cognition [117, 118]. Additionally, neuroimaging studies have indeed found that inter-individual factors are associated with differences in brain activity during the perception of pain [119-125], although, these studies have largely investigated healthy populations. However, other studies have reported individual differences within chronic pain groups, in terms of pain coping strategies, subjective mood, perceived health, and emotional processing in self-report measures [126-128]. Thus, it is likely that differences in the findings presented here may be impacted by inter-individual variability within and between study samples.

In addition, there is substantial variability in the different MRI methodologies used in the studies presented within this review. For instance, new equipment and techniques for data acquisition have been introduced over time in addition to changes in data analyses approaches. This has led to differences in how data has been acquired or analyzed across the studies presented here. For example, acquiring scans on a 1.5T MRI scanners compared to 3T scanners include differences in sensitivity [129, 130], signal-to-noise ratios [131] as well as spatial and spectral resolution [132]. Furthermore, the type of data analyses used (i.e., whole brain and region of interest) may impact the reported results. For instance, whole-brain analysis allows an exploratory approach that can identify new regions involved in a certain process [133]. However, it may be at risk of Type I errors due to the increased number of multiple comparisons and thus, corrections [134]. Alternatively, region of interest analysis is often a hypothesis-driven approach and has a smaller number of comparisons, and therefore increased statistical power [133, 134], yet it may not detect potentially new areas involved

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outside the regions of interest. While comparing the various imaging parameters and data analyses are beyond the scope of this review, it is important to note their potential influence in the results presented within this review.

Finally, while our review presents a body of work linking CLBP to structural and functional brain changes, the causality between the two cannot be clearly determined. As the majority of the studies were cross-sectional designs, data is only collected at a single time point and therefore, difficult to determine the order of events (i.e., CLBP or brain changes) [135, 136]. The majority of the longitudinal studies in this review predominantly examined the effects pre- and post-intervention in CLBP groups. Only 5 studies were observational studies that explored brain changes over time [47, 72, 77, 89, 92], however, they were all in SBP samples. Therefore, these studies demonstrated there were brain changes associated the chronicity of pre-existing pain. However, it remains unclear whether there are underlying structural and functional brain abnormalities apparent prior to the onset of pain and thus, contribute to its development.

Other limitations include that the tasks used in the fMRI studies of this review were relatively simple tasks. The lack of differentiation between CLBP and control groups in task performance may be due to the simplicity of the task given, as 1 study found performance declined in individuals with CLBP as the task became more complex [90], although, further investigations are needed. The definition of CLBP also varied between the selected studies. It is important to distinguish differences in duration and cause of CLBP as it may influence brain changes differently; however, these differences were not clearly established in the studies included in this review. Finally, to assess risk of bias we used a tool adapted from the Cochrane collaboration which applies a stringent scoring system (i.e., studies needed to obtain a "low" assessment for *all* criteria to be considered low risk) and as a result the majority of selected studies in this review were rated moderate to high risk of bias.

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Future studies

There are several avenues future research can pursue to further our understanding of the brain in CLBP. Studies need to investigate the specific emotional and cognitive processes affected in CLBP, particularly during complex tasks that target functions associated with the DMN, such as self-regulation of emotion. These studies could also investigate how brain changes may affect the various aspects of pain (i.e., pain intensity vs. pain unpleasantness) as well as the ability to shift to the appropriate neural networks from resting-state to externally-driven tasks. Future research should also investigate the potential inter-individuality, as well as specifically explore the impact of age, gender and biopsychosocial factors on cognitive and emotional processes that may influence CLBP using neuroimaging techniques. Longitudinal studies will also help establish the causal relationship between brain changes and CLBP in order to determine if psychological interventions are possible as an effective treatment. Developing effective coping strategies may result in better self-regulation processes in order to cope with persistent pain. Additionally, these results of studies can be further validated by recruiting a larger sample size, particularly in fMRI studies to increase statistical power.

Furthermore, the relationship between structural and functional brain changes needs to be clarified as changes in neuroanatomical structures may not necessarily correlate with brain function. This review showed that individuals with CLBP had decreased GM volume in pain matrix regions; however, the functional brain activity during noxious stimuli remained relatively comparable with the controls. Decreased GM may be a consequence of frequent nociceptive input [137] as reduced GM has been associated with pain duration [53] and recovery of GM volume was observed following effective pain relief [75]. Although, the components of GM is comprised of not only neurons but also includes astrocytes, glial cells, interstitial space and vasculature [138]. Therefore, decreased GM but normal functional

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connectivity in the pain matrix may reflect shrinkage of the various brain tissue components, rather than neuronal atrophy [53], hence future studies need to explore this relationship.

Conclusion

This study has systematically reviewed the literature demonstrating that there are widespread structural and functional brain changes in individuals with CLBP. Interestingly, brain activity during spontaneous back pain and altered functional network connectivity were consistently identified in brain areas associated with emotional processing and self-regulation, rather than the pain matrix regions involved in nociception. The activation of these areas may suggest there is another distinct evaluative network responsible for emotional and cognitive function that contributes to the overall experience of pain, which may be the network responsible for facilitating CLBP. Pain has proven to be a complex process and further research, particularly in the specific emotional and cognitive processes is necessary to understand CLBP.

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Figure Legend

Figure 1. PRISMA flowchart showing systematic study selection.

Figure 2. Chronic low back pain is associated with the activation of common regions of the default mode network [100, 102] (blue) rather than the pain matrix areas involved in nociception [14, 105] (red) (ACC = anterior cingulate cortex; IPL = inferior parietal lobule; mPFC = medial prefrontal cortex; MTL = medial temporal lobe (including hippocampus); PCC = posterior cingulate cortex).

Table 1. Study characteristics of selected studies.

Author	Year	Study methods	Definition of CLBP	CLBP		Healthy controls	
				N (% of F)	Age (M ± SD)	N (% of F)	Age (M ± SD)
Apkarian [53]	2004	Structural	Diagnosed according to IASP criteria by clinician, had pain >1 year localised to the lumbosacral region including buttocks and thighs, with or without pain radiating to the leg. *Neuropathic:* Significant radiculopathy, with or without presence of musculoskeletal pain (large component of back pain was from unilateral leg pain (>40%), that may radiated to foot or toes and accompanied by numbness or paraesthesias. *Non-neuropathic:* Leg pain component was minimal	**Neuropathic** No flow: 7 (28.6%) Fast: 4 (100%) **Non-Nu** No flow: 10 (70%) Fast: 5 (60%)	43.3 ± 12.4 43.3 ± 8.2 47.0 ± 12.6 38.0 ± 12.1	7 (28.6%) 4 (100%) 10 (70%) 5 (60%)	42.3 ± 10.0 43.8 ± 6.8 45.5 ± 14.5 40.0 ± 11.9
Baliki [87]	2006	Event-related	Clinically diagnosed with CBP.	**Group 1** 13 (92.3%) **Group 2** 11 (54.5%)	49.2 ± 17.2 50 ± 12	11 (54.5%)	48.7 ± 11.2
Baliki [91]	2008	Event-related	Same as Baliki [87]	15 (46.7%)	43.8 ± 4.11	15 (46.7%)	39.6 ± 3.43
Baliki [43]	2008	Treatment	CBP fulfilled IASP criteria; reported pain >3 months with pain intensity >30/100.	8 (42.9%)	48 (N/A)		
Baliki [84]	2010	Event-related	Clinically diagnosed by clinician.	16 (50%)	45.06 ± 12.0	16 (50%)	38.8 ± 12.5
Baliki [78]	2011	Resting-state, event-related	Clinically diagnosed by clinician, had pain intensity >20/100 and duration >1 year.	15 (33.3%)	49.9 ± 9.90	15 (33.3%)	51.9 ± 8.26
Baliki [70]	2011	Structural	Diagnosed according to IASP by clinician.	36 (36.1%)	48.2 ± 11.4	46 (56.5%)	38.8 ± 12.5

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Baliki [72]	2012	Structural, event-related	**SBP:** Diagnosed by clinician for back pain with pain intensity >40/100 and duration <16 weeks. Recovered (SBPr) when 20% reduced pain intensity at follow-up.	**SBP** 39 (51.3%)	40.9 ± 2.3	17 (41.2%)	37.7 ± 1.8
Baliki [83]	2014	Resting-state	Diagnosed according to IASP criteria diagnosed by clinician.	18 (27.7%)	51.6 ± 1.87	36 (66.7%)	41.4 ± 2.05
Balenzuela [80]	2010	Resting-state	Recruited from Baliki [87].	12 (N/A)	51.2 ± 11.2	12 (N/A)	40.2 ± 12.7
Barke [38]	2012	Event-related	Non-specific LBP for >6 months and pain intensity >5/10 over the previous 4 weeks.	30 (100%)	46.8 ± 9.8	15 (100%)	45.1 ± 9.1
Berger [79]	2014	Resting-state, event-related	LBP for >1 year with no other pain co-morbidities.	22 (45.5%)	45.9 ± 7.8	21 (38.1%)	36.6 ± 6.94
Buckalew [68]	2008	Structural	LBP least moderate intensity every day or almost every day >3 months.	8 (50%)	74.5 ± 4.2	8 (37%)	69.9 ± 3.9
Buckalew [51]	2010	Structural, resting-state	Reported CLBP every day or almost every day for ≥3 months of at least moderate pain. **Disabling:** Significant disruption to daily activities or being bed bound during some days of ≥6 weeks in the past 6 months. **Non-disabling:** Pain that had limited function for <6 weeks over the past 6 months.	**Disabling** 8 (50%) **Non-disabling** 8 (25%)	74.1 ± 6.4 75.1 ± 7.3		
Buckalew [52]	2013	Structural	Self-reported LBP every day or almost every day for ≥3 months of at least moderate intensity. **Disabling:** Significant disruption to daily activities or being bed bound during some days of ≥6 weeks in the past 6 months. **Non-disabling:** Pain that had limited function for <6 weeks over the past 6 months.	**Disabled** 8 (50%) **Non-disabled** 8 (25%)	74.1 ± 6.4 75.1 ± 7.3	8 (50%)	82.3 ± 1.7
Callan [86]	2014	Event-related	Diagnosed by physician with LBP for > 6 months.	13 (69.2%)	51.8 ± 1.9	13 (69.2%)	48.7 ± 2.37
Čeko [41]	2015	Structural	CLBP with intensity of >4/10 for >1 year.	14 (N/A)	(N/A)	16 (gender-matched with CLBP group)	Age-matched with CLBP group
Dolman [65]	2014	Structural	CLBP of ≥3/10 pain intensity for at least 6 months with significant discogenic component to their pain syndrome, confirmed by clinical evaluation and lumbar MRI (excluded purely non-specific or myofascial causes).	14 (64.3%)	46.9 ± 14.6	14 (64.3%)	45.9 ± 12.9
Foss [88]	2006	Event-related	Fulfilled IASP criteria with unrelenting pain for >1 year (did not distinguish various etiologies).	11 (81.8%)	37 (N/A)	23 (65.2%)	34 (N/A)

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Fritz [69]	2016	Structural	Experienced continuous back pain for >3 months and have not recovered at time of study.	111 (70.3%)	53.12 ± 11.8	432 (42.8%)	48.9 ± 14.0
Giesecke [55]	2004	Event-related	Diagnosed with idiopathic CLBP for >12 months (excluded evidence of fracture or malignancy, inflammatory joint disease).	11 (72.7%)	44 ± 13	11 (36.3%)	41 ± 7
Hashmi [45]	2012	Treatment	Diagnosed by a clinician with CLBP for >4/10 pain intensity at baseline for >1 year (same sample as Hashmi [44])	**Overall** 30 (46.7%) **Placebo** 15 **Treatment** 15	51.4 ± 9.08 Groups were age and gender-matched		
Hashmi [44]	2012	Treatment	Diagnosed by a clinician with CLBP for >4/10 pain intensity at baseline for >1 year (same sample as Hashmi [45])	**CBPp** 15 (46.6%) **CBPd** 15 (46.6%)	52.6 ± 2.6 50.1 ± 2.1		
Hashmi [47]	2013	Structural, event-related	Diagnosed by clinician according to IASP criteria. **CLBP:** Reported pain intensity >40/100 for >6 months. **SBP:** Reported single intense episode of back pain of >40/100 pain intensity for 4-16 weeks with no prior back pain for >1 year.	59 (42.4%) **SBP** 94 (51.1%)	48.8 ±1.2 42.1 ± 1.15		
Ivo [73]	2013	Structural	Suffering from CLBP of ≥4/10 pain intensity for >1 year according to IASP criteria.	14 (57.1%)	54 (N/A)	14 (57.1%)	54 (N/A)
Kobayashi [39]	2009	Event-related	Having idiopathic LBP >3 months with pain intensity >3/10 with no structural abnormalities in lumbar spine.	8 (37.5%)	33 (N/A)	8 (0%)	29 (N/A)
Kong [56]	2013	Structural, resting-state	Diagnosed with non-specific CLBP for >6 months by clinic evaluation with the use of X-ray/MRI where available.	18 (66.7%)	36.1 ± 9.9	18 (66.7%)	37.1 ± 9.2
Kornelsen [64]	2013	Resting-state	Diagnosed with CLBP with FBSS by physician.	11 (45.5%)	52.7 ± 14.3	11 (45.5%)	53.5 ± 15.0
Li [57]	2014	Treatment	Reported non-specific low back pain for >3 months and pain intensity of ≥5/10	20 (50%)	38.1 ± 6.4	10 (50%)	37.7 ± 5.1
Lloyd [48]	2008	Event-related	CLBP for >6 months, without sciatica and no structural spinal abnormalities other than degenerative change in no more than 3 lumbar discs. Waddell signs: Major pain behaviour (**WS-H**; Waddell score	**WS-H** 30 (46.7%) **WS-L** 17 (52.9%)	45 ± 12.2 31 ± 8.1		

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			of 4-5); No pain behaviour (**WS-L;** Waddell score 0-1). Intermediate scores of 2-3/5 were excluded.				
Lloyd [49]	2014	Event-related	CLBP for >6 months without sciatica and no structural spinal abnormalities other than degenerative change in no more than 3 lumbar discs. Waddell signs: Major pain behaviour (**WS-H**; Waddell score of 4-5); No pain behaviour (**WS-L;** Waddell score 0-1). Intermediate scores of 2-3/5 were excluded.	**WS-H** 11 (54.5%) **WS-L** 11 (46.2%)	44 ± 12.8 49 ± 19.9		
Lloyd [50]	2016	Event-related	CLBP for >6 months, without sciatica and no structural spinal abnormalities other than degenerative change in no more than 3 lumbar discs. Waddell signs: Major pain behaviour (**WS-H**; Waddell score of 4-5); No pain behaviour (**WS-L;** Waddell score 0-1). Intermediate scores of 2-3/5 were excluded.	**WS-H** 13 (46.2%) **WS-L** 16 (43.75%)	45 ± 10.2 47 ± 13.1		
Loggia [66]	2013	Resting-state	CLBP and radicular pain with ongoing pain intensity of >3/10 of >6 months with discogenic component to their syndrome confirmed by lumbar MRI.	16 (69%)	47.4 ± 7.4	16 (69%)	46.7 ± 6.5
Luchtmann [63]	2014	Structural	Experiencing LBP >3 months and diagnosed with an isolated LDH at either L4-5 or L5-S1, using spinal MRI.	12 (N/A)	43.9 ± 12.9	12 (gender-matched with CLBP)	Age-matched with CLBP
Luchtmann [62]	2015	Structural	Experiencing LBP >3 months and diagnosed with an isolated LDH at either L4-5 or L5-S1, using spinal MRI.	12 (50%)	43.9 ± 12.9	12 (50%)	Age-matched with CLBP group
Mao [71]	2013	Structural	Diagnosed with CLBP according to IASP criteria.	30 (66.7%)	51.6 ± 8.6	30 (66.7%)	50.2 ± 5.8
Mao [90]	2014	Event-related	Diagnosed with CLBP according to the IASP criteria.	36 (58.3%)	50.3 ± 10.6	36 (58.3%)	49.4 ± 8.9
Mutso [92]	2014	Event-related	**CBP**: Pain intensity >40/100 for >10 years. **SBP:** Diagnosed by clinician for back pain with pain intensity >40/100 and duration <16 weeks (same as Baliki [72]).	**SBP** 32 (50%) **CBP** 17 (41.2%)	40.8 ± 11 41.24 ± 7.3	15 (40%)	38.5 ± 8.0
Petre [89]	2015	Structural, event-related	Back pain for >5 years. **SBP:** Back pain last 4-12 weeks with no prior back pain for >1 year. Recovered (SBPr) when 20% reduced pain intensity at follow-up.	32 (43.8%) **SBP** 160 (50%)	45.1 ± 1.3 42.1 ± 0.86	35 (57.1%)	36.2 ± 1.3
Pijnenburg [58]	2016	Resting-state	Non-specific and disabling LBP for >6 months.	17 (64.7%)	33.3 ± 7.9	17 (70.6%)	31.8 ± 8.2

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Schmidt-Wilcke [74]	2006	Structural	Seven weeks of pain from onset and pain persisted >1 month beyond course of acute disease.	18 (50%)	50.4 ± 6.8	18 (50%)	49.9 ± 8.7
Seminowicz [75]	2011	Structural, event-related	CLBP patients with pain intensity of >4/10 for >1 year.	18 (55.6%)	46 ± 10.6	16 (50%)	40 ± 13.2
Stancak [46]	2008	Event-related	Patients scheduled to receive spinal cord stimulation for intractable neuropathic back pain after failed back surgery.	8 (37.5%)	48 (N/A)		
Tagliazucchi [81]	2010	Resting-state	Participants taken from Baliki [91].	12 (N/A)	51.2 (N/A)	20 (N/A)	38.4 (N/A)
Tagliazucchi [82]	2011	Resting-state	Participants taken from Baliki [91].	12 (N/A)	51.2 (N/A)	20 (N/A)	38.4 (N/A)
Ung [76]	2014	Structural	Axial LBP without radicular symptoms persisting for >6 months.	47 (46.8%)	37.7 ± 7.8	47 (46.8%)	37.3 ± 12.2
Vachon-Presseau [59]	2013	Event-related	Reported idiopathic CLBP for >6 months.	21 (52.4%)	36 (N/A)	21 (52.4%)	36 (N/A)
Vachon-Presseau [85]	2013	Event-related	Reported CLBP for >6 months.	21 (52.4%)	36 (N/A)	21 (52.4%)	36 (N/A)
Vachon-Presseau [42]	2013	Event-related	Experiencing LBP for >6 months.	21 (47.6%)	N/A	20 (50%)	N/A
Vachon-Presseau [54]	2016	Event-related	Experiencing back pain symptoms for >6 months.	14 (50%)	36 ± 10.90	16 (43.75)	36 ± 10.9
Vachon-Presseau [77]	2016	Structural, event-related	**SBP:** Diagnosed by a clinician with back pain between 4-16 weeks with pain intensity >40/100. Recovered (SBPr) when 20% reduced pain intensity at follow-up of 1 year.	1 year follow-up: 69 (49.3) SBPp: 39 SBPr: 30 3 years: 39 (46.2)	43.1 ± 10.4 44.2 ± 11.3	1 year follow-up: 20 (45%)	37.4 ± 7.5
Vrana [60]	2015	Event-related	Experiencing non-specific LBP for >6 months.	15 (26.7%)	39.7 ± 13.5	14 (64.3%)	33.6 ± 12.6
Wasan [67]	2011	Event-related	Reported ongoing pain intensity of >3/10 of >6 months with discogenic component to their syndrome confirmed by lumbar MRI.	16 (69%)	47.4 ± 7.4	16 (69%)	46.7 ± 6.5
Younger [40]	2011	Treatment	Had chronic, moderate-to-severe, non-radicular low back pain who had not responses to other non-opioid treatments.	10 (60%)	47 ± 11	9 (0%)	30 ± 10
Yu [61]	2014	Resting-state	Non-specific CLBP for >6 months by clinic evaluation with the use of X-ray/MRI where available.	18 (66.7%)	36.1 ± 9.9	18 (66.7%)	37.1 ± 9.2

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CLBP = chronic low back pain; CT = computed tomography; DEP = depressed patients; FBSS = failed back surgery syndrome; FMS = fibromyalgia; IASP = International Association for the Study of Pain; LBP = low back pain; LDH = lumbar disc herniation; MRI = magnetic resonance imaging; N/A = not available or reported; Non-Nu = Non-neuropathic group; Nu = Neuropathic group; OA = osteoarthritis; SBP = subacute back pain; SBPp = persistent subacute back pain; SBPr = recovered subacute back pain; UBP = upper back pain; WS-H = high pain behaviour (according to Waddell's signs); WS-L = no or low pain behaviour (according to Waddell's signs).

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Table 2. Main findings and risk of bias assessment of structural MRI studies in chronic low back pain populations.

Author	Year	Brain analysis methods and behavioural measures	Main findings (CLBP compared to control groups[#])	Risk of bias
Apkarian [53]	2004	Whole-brain and regional GM volume: VBM Pain: SF-MPQ Depression: BDI Anxiety: BAI	↓ 5-11% GM volume and global GM density ↓ GM in bilateral DLPFC, and right thalamus ↓ GM volume was related to pain duration Positive correlation between lateral ventricle size and change in ventricle size, with negative affect dimension of SF-MPQ Neuropathic vs non-neuropathic CBP No significant differences in GM volume between nuCBP and non-nuCBP groups Affect dimension of SF-MPQ predicted DLPFC GM density in CLBP but the opposite effect observed between nuCBP and non-nuCPB groups.	M
Baliki [70]	2011	Whole-brain and regional GM density: VBM Depression: BDI Anxiety: BAI	↓ global GM volume ↓ GM in bilateral posterior insula, S2, pre- and post-central regions, hippocampus, and temporal lobes No significant correlations between GM density and pain duration, intensity, depression and anxiety scores	M
Buckalew [68]	2008	Regional GM and WM density: VBM Neuropsychological testing: Digit span, digit symbol substitution, letter-number sequencing, trail making) Depression: Geriatric depression screen	No differences in percent global GM or WM, prefrontal GM or thalamic volume between CLBP and HC ↓ GM in PPC ↓ WM in cingulate superior to the middle CC of left hemisphere CLBP performed worse on forward digit span task (attention-demanding task) No significant relationships between forward digit span task and brain volumes	LM
Buckalew [51]	2010	WM: DTI Neuropsychological testing: Repeatable Battery for the Assessment of Neuropsychological Status, Trail making test A and B, Letter-Number Sequencing	CLBP disabling compared to CLBP non-disabling ↓ WM integrity of the SCC WM integrity of SCC negatively correlated with pain duration Right centrum semiovale positively correlated between pain duration No significant correlations between WM integrity and neuropsychological task performance	H
Buckalew [52]	2013	WMH localization and segementation	CLBP disabling compared to CLBP non-disabling and HC ↑ WMH in left hemisphere	M

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Dolman [65]	2014	GM: Cortical thickness and VBM Depression and anxiety: HADS	No significant differences in whole-brain cortical thickness ↑ cortical thickness in right rostral middle frontal gyrus Significant clusters became non-significant after controlling for age Significant different HADS scores between CLBP and HC No significant relationships between HADS scores and cortical thickness in ROI and whole-brain analyses	LM
Fritz [69]	2016	GM volume: VBM	↓ VLPFC, DLPFC, ventral and dorsal mPFC, and anterior insula Negative correlation between pain intensity and GM volume in VLPFC, DLPFC, and ACC	LM
Ivo [73]	2013	Regional GM and WM volume: VBM Depression: BDI Anxiety: BAI	↓ global GM and WM volume ↓ GM in DLPFC, thalamus, middle cingulate cortex CLBP had significantly higher BDI and BAI scores than HC group Regional brain analyses: No significant correlations between anxiety and depression scores, and brain regions (in DLPFC, middle cingulate cortex, thalamus) in CLBP group Whole brain analyses: No correlation between BDI scores and brain region. Significant negative correlation between BAI scores and anterior cingulate and left lingual gyrus	H
Kong [56]	2013	GM volume: Cortical thickness and VBM	No differences in total GM ↑ cortical thickness in bilateral S1 ↑ GM in top third of bilateral post-central gyrus No differences when comparing whole volume, middle and bottom third of the post-central gyrus bilaterally	M
Luchtmann [63]	2014	GM and WM volumes: VBM	↑ GM in right dorsal ACC, left precuneal cortex, left fusiform gyrus, and right brainstem ↓ GM in right ALPFC, right temporal lobe, left premotor cortex, right CN, and right cerebellum ↓ WM volume in anterior limb of left internal capsule	H
Mao [71]	2013	GM volume: VBM and ROI analyses Cognition: Montreal Cognitive Assessment Depression: HAMD Anxiety: HAMA	Whole brain analysis ↓ Left pre-central and post-central cortices, bilateral cuneal and left precuneal cortices ROI-analysis ↑ GM in bilateral putamen and accumbens, right pallidum, right caudate nucleus, and left amygdala ↓ GM in left post-central gyrus, left precuneus, and bilateral cuneal cortex Significantly higher depression and anxiety scores in CLBP group than HC CLBP group had lower Montreal Cognitive Assessment scores than HCs No significant correlations between GM abnormalities and psychometric variables in CLBP group	M
Schmidt-	2006	GM volume: VBM	No significant differences in global GM volume	H

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Wilcke [74]			↑ GM in bilateral basal ganglia, and left posterior thalamus ↓ GM in brainstem, DLPFC and somatosensory cortex Negative correlation between GM in brainstem and left somatosensory cortex, with pain intensity Positive correlation between pain intensity and GM in left thalamus and putamen	
Ung [76]	2014	GM density patterns: VBM and SVM	SVM analyses ↑ GM in right cerebellum, regions of temporal lobe (bilateral middle temporal gyrus and left occipital-temporal lobe), left S1 and S2, left M1, right calcarine sulcus, and right DLPFC ↓ GM in right amygdala, left medial orbital gyrus, and right cuneus VBM analyses ↑ Left M1 and S1/S2 ↓ Right middle occipital lobe SVM classifier characterised a pattern of regional GM density that distinguished CLBP from HC with 76% accuracy	H
Longitudinal studies				
Baliki [72]	2012	Followed-up SBP group: SBPp vs SPBr Whole-brain GM volume and regional GM density: VBM Pain: SF-MPQ Mood: PANAS Depression: BDI	Follow-up vs baseline (within SBPp group): ↓ global GM volume ↓ GM density bilateral striatum and insula, and left sensorimotor cortex in whole-brain analyses ↓ GM in right NAc and right insula in ROI analyses No significant differences over time in SBPr group. Higher affect dimension of SF-MPQ score in SBPp than SBPr at baseline At follow-up, SBPr showed decreased scores in all measures except BDI and PANAS positive scores	H
Čeko [41]	2015	CLBP pre-treatment vs 6 months post-treatment (spine surgery or zygapophysical (facet) joint block) WM: DTI	No significant differences in left insula white matter pre-treatment CLBP patient compared to HC Post-treatment CLBP patients had ↑ FA in left insula white matter, compared to pre-treatment patients No significant differences observed in white matter in right insula (or in any other regions of the brain) FA values in insula post-treatment negatively correlated with reduced pain intensity	CS: M CH: H
Luchtmann [62]	2015	CLBP pre-treatment vs 4 weeks post-treatment (microsurgical lumbar discectomy) GM volume: VBM	Post-surgery, compared to pre-surgery ↑ Right basal ganglia (pallidum and putamen) ↓ Left hippocampus GM volume changes in hippocampus correlated with preoperative pain intensity (but not duration of chronic pain)	M
Seminowicz [75]	2011	CLBP pre-treatment vs 6 months post-	No differences in global GM, WM Pre-treatment, compared to HC ↓ GM in left DLPFC, bilateral anterior insula/frontal	H

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		treatment (spine surgery or zygapophysical (facet) joint block) GM and WM volume: Cortical thickness	operculum, left mid/posterior insula, left S1, left medial temporal lobe, and right anterior cingulate cortex Post-treatment, compared to pre-treatment ↑ cortical thickness left DLPFC Recovery of cortical thickness in left DLPFC and S2/posterior insula correlated with reduced pain and improved physical disability Increased thickness in M1 was associated with reduced physical disability Increased thickness in right anterior insula was associated with reduced pain	
Vachon-Presseau [77]	2016	Followed-up SBP group: SBPp vs SPBr (3 years) WM: DTI	Denser WM connections were observed in the corticolimbic network in the SBPp group SBPp consistently had ↑ WM connections in the dorsal mPFC-amygdala-NAc module over the SBP groups and over the 3 years Other WM networks in the ventral mPFC-amygdala and OFC-amygdala-hippocampus networks did not differ between SBPp and SBPr Predisposed corticolimbic WM connections increased likelihood of transition to CLBP	H
Younger [40]	2011	CLBP pre-treatment vs 1 month post-treatment (daily oral morphine) GM volume: TBM	Post-treatment vs pre-treatment ↓ GM in right hippocampus, bilateral rostroventral pons, left medial orbital gyrus ↑ GM in left inferior frontal gyrus, dorsal posterior cingulate, right hypothalamus, bilateral mid-cingulate, bilateral ventral posterior cingulate, right caudal pons, and dorsal anterior cingulate Higher dosage correlated with volumetric decrease in right amygdala. Higher dosage correlated with volumetric increase in right hypothalamus, left inferior frontal gyrus, right ventral posterior cingulate, and right caudal pons.	M

ACC = anterior cingulate cortex; ALPFC = anterolateral prefrontal cortex; BAI: Beck Anxiety Inventory; BDI = Beck Depression Inventory; CC = corpus callosum; CLBP = chronic low back pain; CN = caudate nucleus; DLPFC = dorsolateral prefrontal cortex; DTI = diffusion tensor imaging; FA = fractional anisotropy; GM = gray matter; HADS = Hospital Anxiety and Depression Scale; HAMD = Hamilton Rating Scale for Depression; HAMA = Hamilton Anxiety Rating Scale; HC = healthy controls; M1 = primary motor cortex; mPFC = medial prefrontal cortex; NAc = nucleus accumbens; OFC = orbital frontal cortex; PANAS = Positive and Negative Affect Schedule; PHQ9 = Patient Health Questionnaire; PPC = posterior parietal cortex; ROI = region of interest; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; SBPp = persistent subacute back pain; SBPr = recovered subacute back pain; SCC = splenium of corpus callosum; SF-MPQ = short form of McGill Pain Questionnaire; SVM = support vector machine analysis; TBM = tensor-based morphometry; VBM = voxel-based morphometry; VLPFC = ventrolateral prefrontal cortex; WM = white matter; WMH = white matter hyperintensities.

[#]Unless otherwise specified

Risk of bias: L = low, LM = low-moderate, M = moderate, H = high.

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Table 3. Main findings and risk of bias assessment of fMRI studies in resting-state studies in chronic low back pain populations.

Author	Year	Brain analysis methods and behavioural measures	Main findings (CLBP compared to healthy pain-free control groups[#])	Risk of bias
Balenzuela [80]	2010	Modular connectivity	Modular reorganisation in frontal and temporal regions, sensorimotor cortex, basal ganglia, and ACC ↑ FC in caudate nucleus and ACC	H
Baliki [78]	2011	Resting-state fMRI (low, mid and high frequency BOLD oscillations)	↑ High-frequency BOLD oscillation within mPFC and parts of the DMN CBP showed (spectral analysis) increased power for high-frequency BOLD oscillations in mPFC, PCC, lateral parietal cortex.	M
Baliki [83]	2014	Resting-state Depression: BDI-II	↑ High-frequency oscillations in DMN regions, especially mPFC, and precuneus ↓ mPFC and its FC to other areas of DMN, especially the precuneus ↓ FC between mPFC with other parts of the DMN was directly related to ↑ FC between mPFC and bilateral insula ↑ correlation of the DMN, specifically the mPFC with insular cortex No significant relationships between BDI-II and functional parameters	H
Berger [79]	2014	Modular connectivity of NAc during resting-state	NAc module: ↑ 20-30% FC between NAc and subcortical regions including the *hippocampus* and *amygdala* ↓ 15-20% FC between NAc and frontal regions NAc and frontal regions correlated more to reward behaviour than connectivity between NAc and subcortical structures CBP patients' brains resembled highly-impulsive subjects, while HC resembled intermediately-impulsive	M
Buckalew [51]	2010	Resting-state Neuropsychological testing: Repeatable Battery for the Assessment of Neuropsychological Status, Trail making test A and B, Letter-Number	CLBP disabling compared to CLBP non-disabling ↑ right mPFC ↓ left lateral PFC Positive correlation between Trail Making test A (motor speed) and left lateral prefrontal cortical activation at rest	H

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		Sequencing		
Čeko [41]	2015	Resting-state of cognitive network and DMN Longitudinal (6-month f/up)	Pre-treatment compared to HC ↓ FC between left anterior-mid insula and bilateral anterior insula/frontal operculum, bilateral DLPFC, bilateral VLPFC/frontal pole, left SMA/anterior mid-cingulate cortex, PCC/precuneus, left PMC, left PPC, bilateral S1/M1, bilateral temporal and visual regions ↓ DLPFC Post-treatment compared to pre-treatment (CLBP) ↑ FC between left anterior-mid insula and left frontal operculum/anterior insula, right DLPFC, left VLPFC, right SMA/mPFC, PCC/precuneus, right temporal and visual regions ↑ FC between DLPFC and posterior mid-cingulate cortex, bilateral S1/M1, right PMC, right PPC, left cerebellum, left temporal, bilateral fusiform, bilateral visual ↓ subgenual ACC/vmPFC ↑ connectivity of insula to DLPFC and other TPN and TNN areas were related to treatment-related pain reduction Partial recovery in bilateral insula connectivity (TPN and TNN areas) and left DLPFC connectivity (to TPN areas) post-treatment	CS: M CH: H
Kong [56]	2013	FC in resting-state before and after pain-inducing exercise manoeuvres	CLBP at baseline (before manoeuvres) vs HC: ↑ FC in left fusiform gyrus, occipital gyrus, right posterior cingulate cortex, and inferior parietal gyrus ↓ FC in right S1 and M1 CLBP after manoeuvres vs HC: ↓ FC in left superior frontal gyrus After vs before manoeuvres (within CLBP groups): ↑ Bilateral S1 and M1, left superior frontal cortex ↓ Right inferior parietal lobule, cuneus, middle occipital gyrus Positive correlation between FC and LBP rating changes at left insula, precuneus, amygdala, and fusiform Negative correlation between FC and LBP rating changes at S1 Positive correlations between FC changes and LBP rating changes at left insula and	M

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			amygdala	
Kornelsen [64]	2013	Resting-state	↑ Left angular gyrus, right middle and inferior frontal gyri, left cingulate gyrus, right inferior frontal gyrus extended into right insula, right DLPFC extending into the anterior insula, left precentral gyrus, and right inferior parietal lobule ↓ Right medial frontal gyrus, right precuneus, left supramarginal parietal gyrus, bilateral temporal lobes, left posterior cingulate, and bilateral cerebellum	M
Loggia [66]	2013	FC in resting-state (ASL) before and after clinical manoeuvres or thermal stimulations	CLBP at baseline (before manoeuvres) vs HC ↑ DMN connectivity to pgACC, left inferior parietal lobule, right insula CLBP after manoeuvres vs. HC ↓ FC in DMN-mPFC (including pgACC) Baseline pain positively correlated with connectivity strength between DMN-right insula Baseline pain negatively correlated with connectivity between DMN-pgACC Clinical pain at baseline and greater ↑ in manoeuvre-induced pain was associated with ↑ DMN-right insula connectivity	M
Pijnenburg [58]	2015	Resting-state	↑ Right middle frontal gyrus, right superior frontal gyrus, and lobule VI of vermis ↓ Left SMA, left precentral gyrus, lobule IV and V of left cerebellum In conjunction with performance in sit-to-stand-to-sit (STSTS) task: CLBP required more time to perform STSTS task ↓ FC at rest in precentral gyrus and lobule IV and V of left cerebellum was associated with ↑ duration for STSTS task in both HC and CLBP	LM
Tagliazucchi [81]	2010	Spontaneous activity of eight resting-state networks	↑ Orbital part of the middle prefrontal cortex and bilateral angular gyrus ↑ activity in middle prefrontal and angular gyri correlated with insular cortex	H
Tagliazucchi [82]	2011	Resting BOLD event triggered averages	↑ Orbital part of the middle frontal cortex, and thalamus ↓ ACC	H
Wasan [67]	2011	FC in resting-state (ASL) before and after clinical manoeuvres and	After vs before manoeuvres (within CLBP groups) ↑ Bilateral mPFC, bilateral DLPFC, superior parietal lobules, S1, S2, and M1	H

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		thermal stimulations Catastrophizing: PCS	Differences in CLBP vs differences in HC ↑ Left S1, M1, and superior parietal lobule ↑ activity in mPFC and insular cortices were associated with higher pain intensity CLBP had significantly higher PCS scores	
Yu [61]	2014	FC in resting-state before and after pain-inducing exercise manoeuvres in CLBP vs HC (only scanned once)	Baseline (before manoeuvres) CLBP vs HC ↑ FC between PAG and vmPFC/rACC ↑ Superior temporal gyrus, and precentral gyrus After manoeuvres, CLBP vs HC ↑ FC between PAG and vmPFC/rACC ↑ Lingual gyrus, superior temporal gyrus, precentral gyrus, dorsal cingulate cortex, posterior insula CLBP, after vs before manoeuvres: No significant differences Negative correlations between pain intensity and PAG-vmPFC/rACC in CLBP *after* pain-inducing manoeuvres Negative correlation between duration of CLBP and PAG-insula and PAG-amygdala FC before pain-inducing manoeuvres	M

ACC = anterior cingulate cortex; ASL = arterial spin labelling; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; BOLD = blood oxygen level dependent; CLBP = chronic low back pain; DLPFC = dorsolateral prefrontal cortex; DMN = default mode network; FC = functional connectivity; HC = healthy controls; LBP = low back pain; M1 = primary motor cortex; mPFC = medial prefrontal cortex; NAc = nucleus accumbens; PAG = periaqueductal gray; PCC = posterior cingulate cortex; PCS = Pain Catastrophizing Scale; pgACC = pregenual anterior cingulate cortex; PFC = prefrontal cortex; PPC = posterior parietal cortex; rACC = rostral anterior cingulate cortex; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; SMA = supplementary motor area; TNN = task-negative network; TPN = task-positive network; VLPFC = ventrolateral prefrontal cortex; vmPFC = ventral medial prefrontal cortex.

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Risk of bias: L = low, LM = low-moderate, M = moderate, H = high; CH = cohort component, CS = cross-sectional component.

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Table 4. Main findings and risk of bias assessment of fMRI studies in event-related fMRI studies in chronic low back pain populations.

Paper	Year	Event and/or task; Groups	Main findings (CLBP compared to control groups[#])	Risk of bias
Pain stimulation				
Baliki [84]	2010	Fixed thermal pain stimulation (baseline: 38°C; peak temps: 47°C, 49°C, 51°C) for 3 durations ranging from 12 to 30 seconds vs visual rating task	No significant brain activity differences Both groups showed activations in thalamus, insula, and S2 ↑ NAc-mPFC connectivity, which was stronger in those with more severe back pain During visual rating task, no significant phasic change was observed in NAc signal in either group Tonic phases during painful stimulation correlated negatively with stimulus duration and, following stimulus cessation, correlated negatively with stimulus pain in HC and positively with CBP No significant differences in mean pain ratings between CLBP and HC groups	M
Callan [86]	2014	Adjusted electrical pain stimulation to highest pain they could withstand (alternating 14 seconds of painful stimulation and 14 seconds of rest)	↑ Left inferior parietal cortex ↓ Somatosensory (two different regions along post-central gyrus in S1) Used patterns of activity to correctly classified 92.3% of CLBP and 92.3% in HC No significant difference between stimulation intensity between CLBP and HC group	H
Giesecke [55]	2004	Fixed mechanical pain stimuli: Starting at 0.5kg/cm^2 and increasing 0.5kg/cm^2 intervals Adjusted mechanical pain stimuli: 36 stimulations delivered at 20 second intervals at random order	CLBP vs HC at equal pressure (at 2kg) ↑ Contralateral S1 and S2, inferior parietal lobule, cerebellum, ipsilateral S2 Equal pain intensities (CLBP and HC groups) ↑ Contralateral S1 and S2, contralateral inferior parietal lobule, ACC, posterior insula and ipsilateral S2, cerebellum in both CLBP and HC groups (but greater magnitude in CLBP groups) CLBP had ↑ pain sensitivity than HC CLBP showed greater increased magnitude of activation in equal pain condition when compared to equal pressure conditions At equal pressure, CLBP rated higher pain than HC At equal pain intensity, pain pressure was lower in the CLBP than the HC group	M
Kobayashi [39]	2009	Adjusted mechanical pain stimulation to pain intensity rating of 3 and 5 (on scale of 0-10 on VAS; 3 blocks of	When VAS = 3 ↑ right insula, bilateral PCC, primary motor cortices, right PMA and right SMA (HC showed right PMA only) When VAS = 5 ↑ activation in right PMA and right thalamus Both groups had activation in right insula, bilateral PCC,	H

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		alternating 30 seconds of painful stimulation and 30 seconds of rest)	right PFC, right SMA (larger clusters in CLBP) CLBP had lower pain thresholds and larger unpleasantness at VAS = 3 and 5 No significant differences in the amplitude of BOLD signals but CLBP showed differences in the size of activation clusters	
Lloyd [48]	2008	CLBP with WS-H vs CLBP with WS-L vs HC Adjusted electrical pain stimulation to pain intensity rating of 7/10 using ABAB block design (A = rest, B = stimulation) for 15 second each block Coping: Pain Coping Strategies Questionnaire Beliefs: Activities subscale of FABQ Questionnaire Depression and anxiety: HADS	No differences between WS-H and HC WS-L vs HC ↑ Left superior parietal lobe, left extrastriate visual cortex, including fusiform gyrus WS-H vs WS-L ↓ Right posterior (retrosplenial) cingulate, extrastriate cortex, left inferior parietal lobe, extending to superior parietal Slight shift in S1 locus (only right S1) in WS-H No significant differences between mean lumbar stimulation tolerance threshold between WS-L, WS-H and HC groups WS-H group had significantly higher scores for the catastrophizing subscale of the Pain Coping Strategies Questionnaire and depression subscale of HADS but not the other measures than the WS-L group Significant negative correlation between the magnitude of the BOLD responses and catastrophizing subscale of Pain Coping Strategies Questionnaire in the WS-L group	LM
Lloyd [49]	2014	CLBP with WS-H vs CLBP with WS-L Adjusted thermal pain stimulation to pain intensity rating of 7/10 using ABAC block design (A = rest at 32°C for 15 seconds, B = painful stimulation for 9 seconds, C = warm stimulation for 9 seconds) Coping: Pain Coping Strategies Questionnaire Beliefs: Activities subscale of FABQ Depression and anxiety: HADS	Noxious thermal vs warm stimuli (within WS-H group) ↑ Right amygdala/parahippocampal gyrus, bilateral temporal pole, cerebellum Noxious thermal vs warm stimuli (within WS-L group) ↑ Bilateral inferior frontal gyrus WS-H vs WS-L (noxious vs warm stimuli) ↑ Right amgydala, right inferior frontal gyrus, extending into insular cortex, right superior mid-temporal gyrus No differences in pain threshold between WS-H and WS-L groups WS-H group had significantly higher depression and anxiety scores, as well as the catastrophizing subscale of Pain Coping Strategies Questionnaire than the WS-L group No significant differences in FABQ Questionnaire Percentage of BOLD signal canges correlated with anxiety scores of HADS and catastrophizing score in the WS-H group (where $p \leq .01$) No significant correlations found in WS-L group	LM
Stancak [46]	2008	SCS (electrical stimuli) vs heat pain vs	SCS alone ↑ medial S1 (corresponds to foot region), posterior insula, S2	H

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		simultaneous SCS and heat pain in CLBP group only Painful heat stimulation from 43°C to 46-49°C for 36 seconds and returning to baseline (32°C) for 36 second rest period	↓ M1, S1 (corresponds to shoulder) Simultaneous SCS and heat pain vs heat/SCS alone ↑ bilateral inferior temporal cortex, cerebellar cortex	
Vachon-Presseau [85]	2013	Adjusted thermal pain stimulation at pain intensity of 75/100, adjusted warm stimulation (control) and baseline at 38°C Alternated warm and pain stimulation (2 second ramp up to stimuli, 5 second pain/warm stimulation, 2 second ramp down).	CBP and HC activity (non-sig.) ↑ Thalamus, S1 and M1, parietal operculum, and insular cortex ↑ Anterior region of midcingulate cortex (compared to warm stimulation) No differences in temperatures, subjective ratings of pain and warm stimuli and pain-related brain regions between CBP and HC	M
Vachon-Presseau [59]	2013	Adjusted thermal pain stimulation at pain intensity of 75/100, adjusted warm stimulation (control) and baseline at 38°C Random warm and pain stimulation order (2 second ramp up, 5 second pain/warm stimulation, 2 second ramp down) with resting period of 18-25 seconds.	Thermal vs warm conditions in CBP and HC (non-sig.) ↑ Thalamus, sensorimotor regions (S1 and M1), lateral parietal operculum, insular cortex, anterior region of midcingulate cortex Those with largest reactive cortisol response reported less pain unpleasantness during scanning No significant differences in painful and warm stimulations between CLBP and HC groups	H
Vachon-Presseau [54]	2016	Adjusted thermal pain stimulation at pain intensity of 75/100, adjusted warm stimulation (control) and baseline at 38°C	Activation in both CBP and HC groups (non-sig) ↑ Pre- and post-central gyri, SMA, cingulate cortex, insula, lateral operculum, thalamus ↓ mPFC, precuneus, medial temporal lobe, occipital cortex No significant differences warm and painful stimulations, and brain activity between CLBP and HC	M

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		Random warm and pain stimulation order (2 second ramp up, 5 second pain/warm stimulation, 2 second ramp down) with resting period of 18-25 seconds.		
Task-related studies				
Baliki [87]	2006	Spontaneous pain rating task (CLBP only) and thermal stimulation in HC	Spontaneous pain ratings (CBP only): *Sustained high pain* resulted in ↑ activity in mPFC (including rostral anterior cingulate) No differences between CLBP and HC during thermal stimulation mPFC activity strongly correlated with CBP intensity Bilateral DLPFC are negatively correlated with mPFC activity (DLPFC activity deactivate before increased mPFC activity)	M
Baliki [91]	2008	Simple visual attention task Depression: BDI Anxiety: BAI	↑ mPFC during task No differences in task performance between CLBP and HC mPFC activity was negatively correlated with the task No significant relationship between fMRI activity and BDI and BAI scores	M
Baliki [78]	2011	Spontaneous pain rating task vs visual rating scans (CBP group only)	↑ high-frequency BOLD oscillation within mPFC and parts of the DMN during pain-rating task No task performance differences Positive correlation between high-frequency oscillations in mPFC BOLD time course and with pain ratings but not visual ratings	M
Barke [38]	2012	Viewing images of aversive movement, neutral movements, general fear-inducing images, neutral images, and spider images in CLBP (low and high fear-avoidance), HC and spider phobic participants	No fear-related activations were found in high or low fear-avoidance CLBP patients when viewing aversive movement images No differences between high and low fear-avoidance CLBP patients or high fear-avoidant CLBP patients and HC Normal fear-related activations were present in high fear-avoidant CLBP patients when viewing the general fear-inducing images	M
Berger [79]	2014	Gambling task	No significant differences in FC during gambling task CBP were more impulsive on gambling task than HC	M
Foss [88]	2006	Spontaneous pain rating task in CLBP vs acute	CLBP exhibited significantly different fractal properties during spontaneous back pain compared to thermal and imagined pain	H

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		thermal pain stimulation vs imaged back pain		
Lloyd [50]	2016	Pain anticipation of pain-inducing leg raise manoeuvre (green light visual cue = 100% leg raise; yellow = 50%; red = 0%) in CLBP with WS-H vs CLBP with WS-L Catastrophizing: PCS Beliefs: FABQ Depression and anxiety: HADS	Red cue vs at rest (within WS-H group): ↑ anterior intraparietal sulcus, extending into posterior supramarginal gyrus, superior parietal lobe, superior lateral occipital cortex, sensorimotor cortex, extending into posterior cingulate gyrus, SMA Yellow cue vs red cue (within WS-L group) ↑ posterior supramarginal gyrus, extending into angular gyrus WS-H vs WS-L during red cue: ↑ precentral and posterior cingulate gyrus, superior parietal lobe, extending into S1 and occipital pole WS-H reported higher anxiety, depression, catastrophizing, and fear-avoidance beliefs than WS-L Positive covariance between anxiety subscale of the HADS and the BOLD responses in right insula, right frontal pole, pregenual ACC and paracingulate gyrus between the WS-H and WS-L groups in response to the green vs yellow cue conditions. Positive covariance between the rumination subscale of PCS and the BOLD response in the left superior parietal lobe/precuneus, extending to superior division of the lateral occipital cortex bilaterally and intracalcarine cortex between the WS-H and WS-L groups in green vs yellow cue conditions. Rumination subscale of PCS also positively covaried with group differences in right premotor cortex, left inferior parietal lobe and left hippocampus in response to the green visual cue as well as the right premotor and sensorimotor cortices, posterior division of right supramarginal gyrus and cuneal cortex	H
Mao [90]	2014	MSIT	↓ Right DLPFC, dorsal ACC, bilateral superior parietal cortex, bilateral precentral cortex, left post-central cortex, paracingulate cortex, bilateral precuneus, left amygdala Negative correlation between back pain intensity and activation of right PFC during MSIT in CLBP Response accuracy was worse in CLBP when task was complex (interference trials)	M
Vachon-Presseau [42]	2013	Response to images of nociceptive agent applied to right hand and foot, and facial expressions of pain, and thermal pain stimulation	No differences between in vicarious brain activity Positive correlation in right insula activity with patients' expressiveness and perceived pain intensity in images	H
Vrana [60]	2015	Motor imagery	↓ Left SMA, and right superior temporal sulcus	M

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		task (presented video clips showing everyday activities) Anxiety: STAI	No significant differences in STAI between CLBP and HC groups	
Longitudinal studies				
Baliki [72]	2012	Followed-up SBP group: SBPp vs SBPr (1 year) Spontaneous back pain rating task Pain: SF-MPQ Mood: PANAS Depression: BDI	↑ FC of NAc-mPFC predicted pain persistence SBPp vs SBPr ↑ FC between NAc with basal ganglia at baseline and follow-up ↓ FC between NAc with insula at follow-up and over time (i.e., SBPp follow-up > SBPp baseline) ↑ FC between NAc and mPFC at baseline and follow-up SBPp had negative correlations of insula with DLPFC and posterior cingulate ↓ FC in insula, DLPFC and precuneus positively correlated with insula GM density and negatively with pain intensity Higher affect dimension of SF-MPQ score in SBPp than SBPr at baseline At follow-up, SBPr showed decreased scores in all measures except BDI and PANAS positive scores. The number of positive NAc links correlated with affect dimension of SF-MPQ at baseline and follow-up.	H
Hashmi [47]	2013	SBP vs HC vs CBP Followed-up SBP: SBPp vs SBPr (1 year) Spontaneous back pain rating vs control visual rating task	CBP vs SBP (non-sig.) No significant regions of comparable magnitude between CBP and early SBP ↓ Thalamus, and insula (during pain rating task but not visual) ↑ Amygdala, and mPFC (during pain rating task but not visual) SBPp vs SBPr (meta-analysis maps): ↓ Acute pain regions (e.g., insula, thalamus, mid-brain, ACC and S1) ↑ Emotion-related circuitry (amygdala, hippocampus, orbitofrontal cortices, operculum, and dorsal, ventral, and rostral regions of mPFC)	M
Petre [89]	2015	Smokers vs non-smokers in SBP vs CBP vs HC Followed-up SBP: SBPp vs SBPr (1 year)	↓ strength in NAc-mPFC from precessation to postcessation of smoking in SBP and CBP (those who stopped smoking) Smoking increases the risk of transitioning from SBP to CBP, which is mediated by NAc-mPFC In SBP, smoking status at baseline was predictive of persistence of back pain after 1 year No significant differences in the positive PANAS scores between SBP, CBP and HC groups at baseline.	H
Seminowicz [75]	2011	MSIT	CLBP before treatment vs HC: ↑ Dorsal mPFC, cerebellum, precentral gyrus, and DLPFC CLBP after vs before treatment: ↓ DLPFC	H

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Mutso [92]	2014	CLBP vs SBP vs HC (followed up SBP after 1 year: SBPp vs SBPr) Hippocampal FC during simple visual attention task Mood: PANAS Depression: BDI	SBP and CLBP vs HC ↑ hippocampal connectivity in SBP and CLBP than HC ↑ intrinsic and extrinsic hippocampal connectivity in anterior region of hippocampus in SBP than HC ↑ extrinsic hippocampal connectivity in CLBP than HC Follow-up vs baseline (within SBPp group): ↓ Hippocampal connectivity with mPFC (HG-mPFC), paracentral lobule, and cingulate gyrus Changes in HG-mPFC reflected task performance by SBP (rating pain fluctuations) No significant correlations between BDI scores and connectivity extent at baseline and follow-up.	M
Vachon-Presseau [77]	2016	Followed up SBP: SBPp vs SBPr (3 years) Modular connectivity during spontaneous back pain rating task	SBPp consistently had ↑ FC in dorsal mPFC-amygdala-NAc network compared to other networks and over 56 weeks FC was not maintained over the 3 years (156 weeks) (i.e., SBPp and SBPr did not differ in mPFC-amygdala-NAc network at 156 weeks follow-up Other networks, the ventral mPFC-amygdala and OFC-amygdala-hippocampus networks did not differ in SBP groups The dorsal mPFC-amygdala-NAc may predict transition to CLBP but is not necessary to maintain chronicity	H

ACC = anterior cingulate cortex; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; BOLD = Blood-oxygen-level dependent; CES-D = Center for Epidemiologic Studies Depression Scale; CLBP = chronic low back pain; DLPFC = dorsal lateral prefrontal cortex; DMN = default mode network; FABQ = Fear-Avoidance Beliefs Questionnaire; FC = functional connectivity; HADS = Hospital Anxiety and Depression Scale; HAMD = Hamilton Rating Scale for Depression; HC = healthy controls; mPFC = medial prefrontal cortex; MPQ = McGill Pain Questionnaire; MSIT = multisource interference task; NAc = nucleus accumbens; NHP = Nottingham Health Profile; OFC = orbital frontal cortex; PANAS = Positive and Negative Affect Schedule; PCC = posterior cingulate cortex; PCS = Pain Catastrophizing Scale; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; SBP = subacute back pain; SBPp = persistent subacute back pain; SBPr = recovered subacute back pain; SCS = spinal cord stimulation; SF-36 = 36-item Short Form Survey; SF-MPQ = short form of McGill Pain Questionnaire; SMA = supplementary motor area; STAI = State-Trait Anxiety Inventory; STPI = State-Trait Personality Inventory; VAS = Visual Analogue Scale; WS-H = high pain behaviour (according to Waddell's signs); WS-L = no or low pain behaviour (according to Waddell's signs).

[#]Unless otherwise specified.
Risk of bias: L = low, LM = low-moderate, M = moderate, H = high; CH = cohort component, CS = cross-sectional component.

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Table 5. Main findings and risk of bias assessment of intervention fMRI studies in chronic low back pain populations.

Paper	Year	Task/event, intervention, and comparison groups	Main findings	Risk of bias
Baliki [43]	2008	Spontaneous pain rating task and visual task before and after 2 weeks of treatment (5% lidocaine patches) in CBP.	Before treatment (Pain – visual task) ↑ mPFC, rostral ACC, superior frontal gyrus, NAc, inferior temporal gyrus, PCC After treatment vs before ↑ Middle temporal cortex Significant decrease in pain after treatment mPFC and rostral ACC at level of genu encoded pain intensity in CBP.	LM
Hashmi [45]	2012	Spontaneous pain rating task and visual task before and after 6 hours, and 2 weeks of treatment (5% lidocaine patches treatment vs. placebo) in CBP only	No group differences in pain intensity, sensory or affective qualities of pain or pain-related brain activation. Spontaneous pain ratings correlated with activity in mPFC, extending from medial frontal pole to genual ACC Treated CBP showed significantly greater decrease in pain compared to untreated CBP group 50% of overall patients (both lidocaine and placebo) reported >50% decrease in pain = placebo effect	M
Hashmi [44]	2012	Spontaneous pain rating task and visual task before and after 2 weeks of treatment (lidocaine) in those with persistent CBP (CBPp) and decreasing CBP (CBPd). Pain: MPQ Depression: BDI Anxiety: BAI	No group differences at baseline Baseline functional connectivity between left mPFC and bilateral insula predicted post-treatment group The left DLPFC high-frequency oscillations at baseline predicted treatment outcomes Prefrontal cognitive and pain processing regions predetermine the probability of placebo response in CLBP No significant differences in BDI and BAI scores between CBPp and CBPd Affect dimension of MPQ scores correlated with right dmPFC-left anterior insula connectivity	M
Li [57]	2014	Resting-state before and after 4 weeks after treatment (acupuncture) in CLBP and HC groups.	CLBP before treatment vs HC ↓ DLPFC, mPFC, ACC, precuneus After vs before treatment ↑ DLPFC, mPFC, ACC, precuneus Reductions in clinical pain which correlated with increases in DMN connectivity	H

ACC = anterior cingulate cortex; CBP = chronic back pain; CLBP = chronic low back pain; DLPFC = dorsolateral prefrontal cortex; DMN = default mode network; GM = gray matter; MBSR = mindfulness-based stress reduction treatment; mPFC = medial prefrontal cortex; OA = osteoarthritis; OFC = orbital frontal cortex; PCC = posterior cingulate cortex.

Risk of bias: L = low, LM = low-moderate, M = moderate, H = high.

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Figure 1

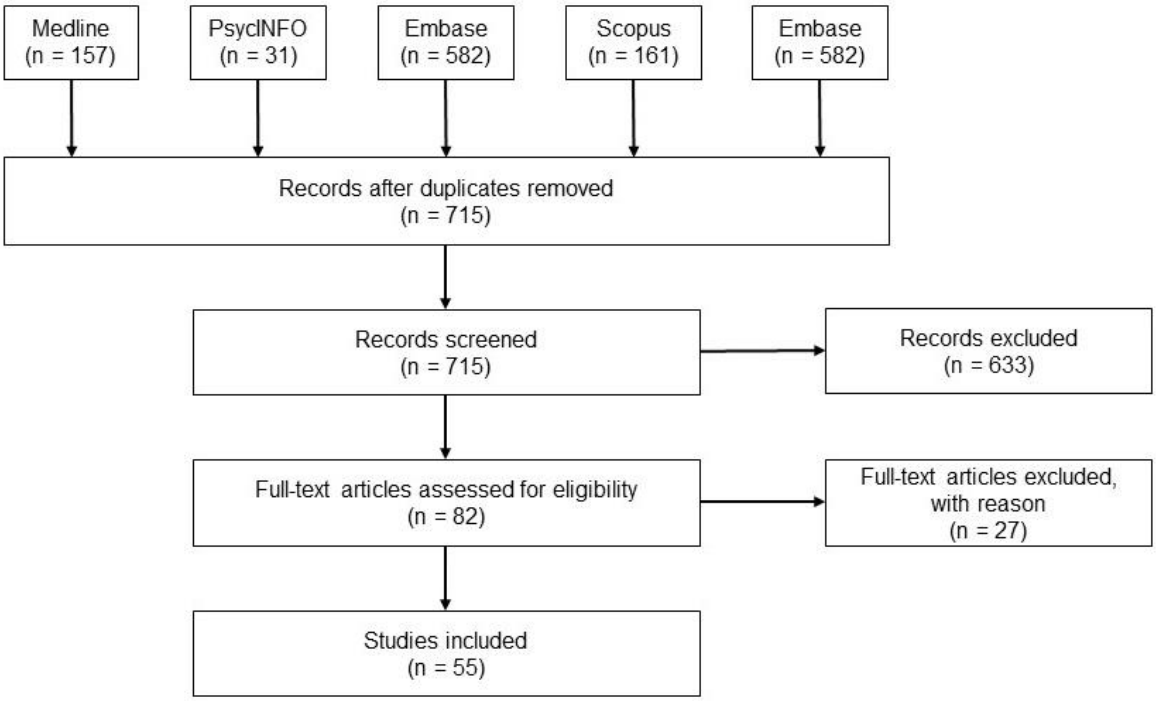

Figure 1. PRISMA flowchart showing systematic study selection.

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Figure 2

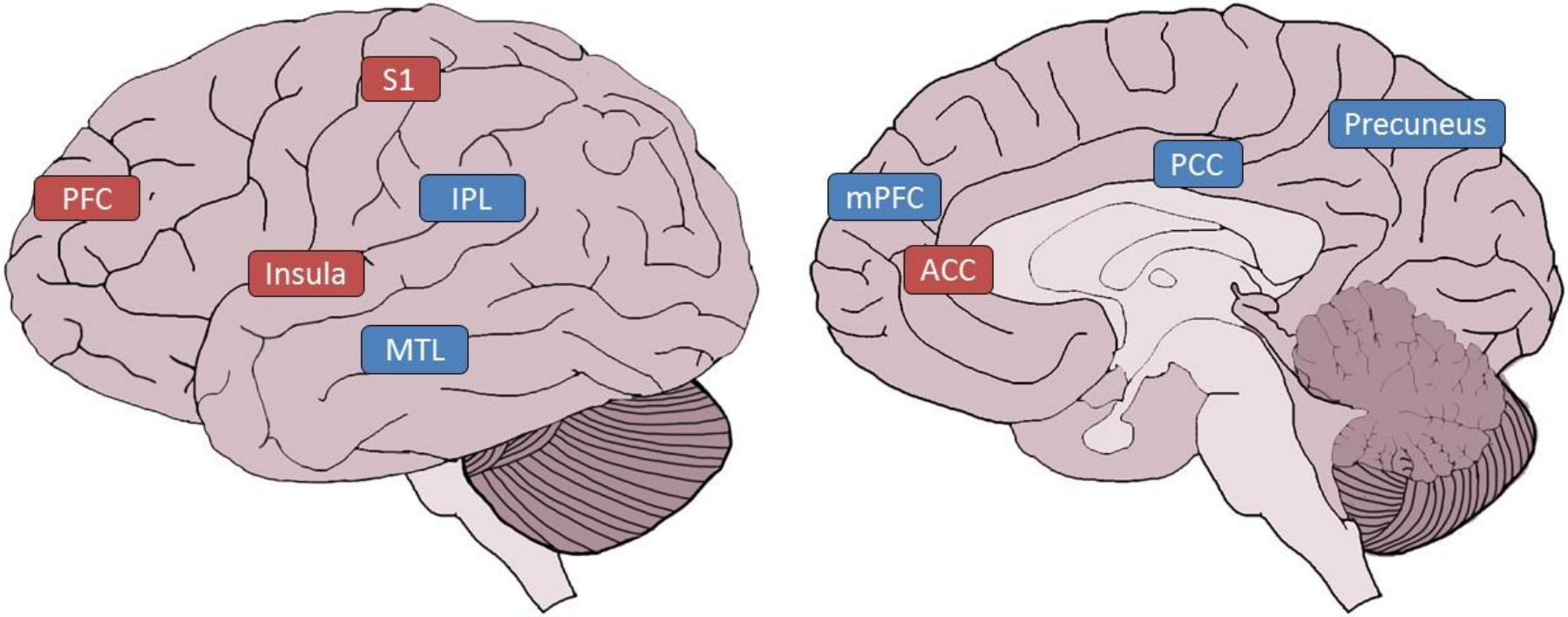

Figure 2. Chronic low back pain is associated with the activation of common regions of the default mode network [100, 102] (blue) rather than the pain matrix areas involved in nociception [14, 105] (red) (ACC = anterior cingulate cortex; IPL = inferior parietal lobule; mPFC = medial prefrontal cortex; MTL = medial temporal lobe (including hippocampus); PCC = posterior cingulate cortex).

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