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STRUCTURAL AND FUNCTIONAL BRAIN ABNORMALITIES IN CHRONIC LOW BACK PAIN: A SYSTEMATIC REVIEW

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ABSTRACT

Objectives: The purpose of this systematic review is to analyze the available literature on structural and functional brain abnormalities in chronic low back pain (CLBP) using several brain magnetic resonance imaging (MRI) techniques.

Methods: PubMed and Web of Science were systematically screened for relevant literature using different combinations of keywords regarding structural and functional brain imaging techniques in patients with CLBP. Reference lists of included articles were hand-searched for additional literature. Eligible articles were assessed on risk of bias and reviewed by two independent researchers.

Results: The search query returned 27 articles meeting the inclusion criteria. Methodological quality varied from poor to good. Ten studies evaluated structural gray matter changes. There is conflicting evidence in global gray matter changes, with both increases and decreases shown in different studies. Gray matter changes were demonstrated in specific brain regions. Structural white matter changes were reported in five studies. There is conflicting evidence in total white matter volume due to both increases and unchanged white matter. Several regional differences were identified in which white matter changes were shown. Functional organization during rest was evaluated in ten studies. CLBP patients showed increased activation in specific regions, together with a disrupted default mode network. A total of six studies evaluated brain activity in response to a nociceptive stimulus. Findings suggest that patients demonstrated increased activity in pain related regions, and decreased activity in analgesic regions.

Conclusions: Overall, there is moderate evidence for regional changes in gray and white matter, together with an altered functional connectivity during rest and increased activity in pain related areas following painful stimulation, evidencing an upregulated pain matrix. More longitudinal research is needed to clarify the temporal relationship regarding pain and neuroplastic changes and integration of different brain imaging techniques is warranted.

Keywords: (rs)-fMRI, diffusion tensor imaging, chronic pain, back pain, pain matrix, gray matter, white matter, brain activity, functional connectivity

1. Introduction

Chronic low back pain (CLBP) is the most common and important clinical, social, economic, and public health problem of all chronic pain disorders across the world [1]. Unlike acute pain, a peripheral cause is often absent in chronic pain and the exact underlying central mechanisms are still not fully understood. An interesting mechanism in the human central nervous system is its capacity for plasticity. Although neuroplasticity has various positive (adaptive) characteristics, it can be maladaptive in chronic pain syndromes.

Due to the increasing evidence of maladaptive neuroplastic changes in CLBP and other chronic pain disorders [2], analyzing brain properties may be of great value. A number of non-invasive structural and functional brain imaging techniques can be used to gain more insights into the location and characteristics of brain responses to both acute pain and plasticity associated with chronic pain [3].

Regarding structural brain properties, gray matter (GM) and white matter (WM) volumes can be quantified. A commonly used method to measure GM is voxel-based morphometry (VBM). With this volumetric technique, the brain is registered to a template, smoothed, and GM density in cortical and subcortical regions is statistically compared [4]. Another method to analyze structural changes in GM can be done with the software package FreeSurfer. Some of the advantages over VBM are the geometric basis to do inter-subject registration and the possibility to look at volume by calculating thickness and surface area separately (http://surfer.nmr.mgh.harvard.edu).

Although WM volumes can be quantified by both VBM and FreeSurfer, the WM tracts can be visualized using diffusion tensor imaging (DTI). DTI is an MRI-technique based on the restricted diffusion of water molecules in the brain, thereby measuring the macroscopic axonal organization in the brain [5]. One of the most frequently used DTI measures is

fractional anisotropy (FA) [6]. FA values range between 0 (no restriction in diffusion) and 1 (complete anisotropic diffusion; complete ordering), which gives an indication of the white matter integrity [6, 7].

Besides structural properties of the brain, brain activity can be measured in the human brain using functional MRI (fMRI). With fMRI, the blood oxygen level-dependent (BOLD) response, which is a measure of the proportion of oxy- to deoxy-hemoglobin in the blood volume, an indirect measure of brain activity can be assessed [8]. Using this technique, functional connectivity can be assessed, which refers to the finding that brain areas show temporal correlation at <0.1 Hz [9]. The default mode network is the first network shown to have functional connectivity in a task-free "resting state" [10-12]. In addition, a fairly new technique, arterial spin labeling (ASL), assessing regional cerebral blood flow (rCBF) can be used to obtain task-free information according to the ongoing brain activity that may reflect spontaneous pain characteristics of chronic pain patients [3]. The major difference between BOLD-techniques and ASL is that BOLD examines networks that exhibit very slow frequency interregional synchronizations, and ASL examines focal neuronal activity based on rCBF [3].

So far, there is increasing knowledge of structural and functional neuroplastic changes in CLBP. However, due to a great variability in used techniques and brain regions of interest, the results are difficult to interpret. The present systematic review summarizes the available evidence on structural and functional brain differences in CLBP.

2. Methods

2.1 Information sources and search strategy

A search of the online databases Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/) and Web of Science (www.webofknowledge.com/) was conducted in the period from February to April 2014.

The search strategy was based on the PICO-framework. The following search terms were entered: (low back pain OR lower back pain OR back ache OR lumbago) AND ("brain imaging" OR "fMRI" OR "rs-fMRI" OR "Voxel-Based Morphometry" OR VBM OR "diffusion tensor imaging" OR DTI).

2.2 Study selection

The retrieved articles needed to fulfill a number of inclusion criteria: (1) subjects had to be human, not animals; (2) patients had to be diagnosed with CLBP, with a duration of at least 3 months, not diagnosed with systemic diseases(P; patient population); (3) one or more structural or functional MRI-techniques had to be used (I; diagnostic instrument); (4) articles had to be written in English, Dutch, or German; (5) and articles had to be a full-text of original research. Articles not fulfilling each of the above mentioned criteria were excluded.

In the first phase of screening, articles were selected based on title and abstract. The potentially eligible articles were retrieved in full text. In case the abstract did not provide sufficient information, the full text was also retrieved. In the second phase, full text articles were evaluated again on meeting the inclusion criteria. The first and second phases were conducted by the first author, supervised by 2 independent reviewers (MM and BC). In case of uncertainty about inclusion/exclusion, a decision was made in a separate consensus meeting starting from the 3 independent opinions. Furthermore, the reference lists of included articles were searched for potentially eligible articles that were missed by the predefined search strategy.

2.3 Qualification of searchers/raters

Literature was searched and screened by J.K., PhD candidate working on rehabilitation in chronic neck- and low back pain, supervised by B.C. and M.M., both PhDs experienced in pain research and conducting systematic reviews in the field of chronic pain. Assessment of methodological quality of individual studies was done by J.K., independently from a second rater, A.M., also a PhD candidate working on rehabilitation in chronic neck- and low back pain.

2.4 Data items and collection

Relevant information from each included article was extracted and structurally presented in an evidence table (Table 1), containing following items: (1) study; (2) sex and age of the CLBP group; (3) sex and age of the control group; (4) main findings; (5) and remarks.

2.5 Risk of bias in individual studies

Given the design of studies in the current review, the Newcastle-Ottawa Scale (NOS, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) for case-control and cohort studies was used to determine the methodological quality of individual studies. The NOS is a recommended quality assessment tool of observational studies by the Cochrane Collaboration group (http://www.cochrane.org/). The NOS is divided into three subcategories (selection, comparability, and exposure/outcome) with a maximum score of nine points, representing highest methodological quality. Some modifications were applied in both scoring forms. A study earns one point when controlling for age or sex in the 'Comparability' section and an additional point when controlling for another factor. For 'Outcome' in the cohort studies a

point was given when follow-up was at least six months (following IASP criteria for chronic pain; http://www.iasp-pain.org). Furthermore, the loss to follow-up was set at maximum 20%.

The methodological quality assessment was performed by two reviewers independently (J.K. and A.M.). Afterwards, the results were compared and differences were discussed to reach consensus.

Based on study design and methodological quality, each study received a level of evidence, according to the 2005 classification system of the Dutch Institute for Healthcare Improvement CBO (http://www.cbo.nl/Downloads/632/bijlage_A.pdf). After clustering studies with comparable interventions, a level of conclusion was determined based on the same CBO-classification, accounting for the study designs and the risk of bias.

3. Results

3.1 Study selection

The search yielded 168 results in total from both databases. After deduplication, 135 unique articles were left. Consecutively, after both screening phases and the additional hand search, 27 articles were included. A flowchart of the screening process can be found in figure 1.

3.2 Risk of bias and level of evidence

Results of the assessment of methodological quality using the NOS are shown in supplementary table S1. It should be noted that in three of the cohort studies, item number three was not scored due to the lack of exposure in the concerning articles [13-15]. In the majority of items, an equal score was given by both raters (209/241; 87,1%). The differences were discussed to reach a definitive score.

It is striking that in most of the case-control studies, the ‘Selection’ category showed low scores. This was mainly due to an incomplete description of ‘Representativeness of the cases’, ‘Selection of controls’, and ‘Definition of controls’. In the cohort studies, none of the included studies satisfied the ‘Adequacy of follow up of cohorts’. A strength of most of the included studies is the matching for age and gender. Controlling for an additional factor (e.g. medication) was done in a few studies.

All included studies were given a level of evidence B, since only case-control and cohort studies were included, see supplementary table S1.

3.3 Study characteristics

For each individual study, the characteristics of the CLBP group, control group, main findings, and remarks can be found in the evidence table (Table 1). The number of patients varied between 8 and 59. All studies investigated both men and women. The age of each patient group was on average 46.6 years old. 25 studies compared patients with healthy controls, one study compared chronic back pain with sub-acute back pain [14], and one study compared disabling CLBP with non-disabling CLBP [16]. The majority of the included studies recruited patients with non-specific CLBP. However, a total of five studies only included patients with a specific pathology, including CLBP with a discogenic component [17-19], lumbar disk herniation [20], and failed back surgery syndrome [21].

3.4 Structural organization

3.4.1 Gray matter

Structural organization of GM was assessed in ten studies [17, 20, 22-29]. Global GM was reported in seven studies; three studies found a decrease in global GM volume in CLBP [22,

23, 25], whereas the other four studies did not find differences in global GM volume [17, 24, 28, 30].

Multiple studies found reduced GM in CLBP in the dorsolateral prefrontal cortex (DLPFC) [22, 25, 28, 29], temporal lobes [20, 23, 28, 29], insula [23, 29], and cuneus [27, 30]. On the other hand, both DLPFC and the right temporal lobe showed increased GM in a study of Ung et al. [30]. Two studies found an increase of GM in the putamen, a structure of the basal ganglia [27, 28]. Mao et al. [27] also found an increase of GM in two other structures of the basal ganglia; the pallidum and the right caudate nucleus. Luchtmann et al. [20] however, found reduced GM in the right caudate nucleus. Inconsistent results were also found in several other brain regions. For the thalamus, Apkarian et al. [22] and Ivo et al. [25] found a decrease, while Schmidt-Wilcke et al. [28] found an increase in GM. In the primary somatosensory cortex (S1), a decrease of GM was found in three studies [27-29], whereas an increase of GM (somatotopically associated with the lower back) was found by Kong et al. [26] and Ung et al. [30]. The amygdala, a key structure in the limbic system, showed a GM increase in the left hemisphere in the study of Mao et al. [27], whereas an area adjacent to the right amygdala showed a decrease in the study of Ung et al. [30].

Furthermore, both increases and decreases of GM were found in the right cerebellum [20, 30]; right anterior cingulate cortex (ACC) [20, 29]; left precuneus [20, 27]; brainstem (pons) [20, 28]; and secondary somatosensory cortex (S2) [23, 30].

In conclusion, there is indistinct evidence in global GM changes, with three studies demonstrating decreased global GM changes and another three studies reporting no changes in CLBP. There is reasonable evidence that GM changes occur in CLBP in specific brain regions, including DLPFC, temporal lobes, insula, and S1 (strength of conclusion 2).

3.4.2 White matter

A total of five studies reporting WM changes in CLBP were identified [15, 16, 20, 24, 25]. Two studies analyzed global WM volumes, in which one reported decreased global WM volume in CLBP [25] and the other reported no difference between CLBP and healthy subjects [24].

Two studies reported WM structural changes in the middle part [24] and the splenium [16] of the corpus callosum (CC). In the latter study, decreased WM FA was found in disabling CLBP, compared to non-disabling CLBP. Additionally, adjacent decreased cingulate WM was found superior to the middle CC of the left hemisphere [24]. Luchtmann et al. [20] found a decrease of WM in the anterior limb of the left internal capsule (IC). This result is in accordance with the study of Mansour et al. [15], in which a lower FA was found in the left retro-lenticular and the left anterior limb of the IC.

In conclusion, there is conflicting evidence in total WM volume in CLBP due to both decreased and unchanged WM. Several regional differences were identified in which WM changes were shown. These regions include the corpus callosum and WM superior to the corpus callosum, and the internal capsule (strength of conclusion 2).

3.5 Functional organization

3.5.1 fMRI during rest

Functional organization during rest was assessed in ten studies [13, 14, 16, 18, 19, 21, 26, 31-33]. Results of these studies are highly consistent, reporting functional connectivity reorganization in several regions in CLBP. Overall, patients showed increased activation in the medial prefrontal cortex (medial PFC) [13, 14, 16, 31, 32], cingulate cortex [14, 21, 32], amygdala [14, 32], and insula [21, 33]. An increased activity in bilateral medial and dorsolateral PFC, insula and ACC was also found in the study of Wasan et al. [19] during an

fMRI session following back pain-exacerbating physical maneuvers. In the same study, an increased activity in S1, primary motor cortex (M1), and S2 was found after physical maneuvers. This result is in accordance with the study of Kornelsen et al. [21], where an increased activity in sensory motor integration regions was shown also in a single fMRI session without back pain-exacerbating maneuvers. In a third back pain exacerbating fMRI study, S1 activity was increased in the high pain condition, compared to the low pain condition [26].

Four studies reported a disrupted default mode network connectivity in CLBP [18, 21, 32, 33]. In the study of Loggia et al. [18], the default mode network connectivity was compared between patients and controls following physical maneuvers. At baseline, patients showed stronger default mode network connectivity to the insula and less to the pregenual ACC. Following physical maneuvers, an increase in low back pain was associated with an increase in default mode network-right insula connectivity.

In conclusion, there is decent evidence that CLBP patients show increased activation in medial PFC, cingulate cortex, amygdala, insula, and sensory motor integration regions, together with a disrupted default mode network (strength of conclusion 2).

3.5.2 Mechanical stimulation

Functional connectivity during mechanical induced pain was assessed in three studies [34-36]. Increased activity in S1 and S2 was reported in both studies by Giesecke et al. [34, 35]. In their first study, Giesecke et al. [35] reported also an increased activity in the lateral orbitofrontal cortex and a decreased activity in the periaqueductal gray (PAG) compared to healthy controls. In their second study, an increased activity was also found in the inferior parietal lobe and cerebellum [34]. The study of Kobayashi et al. [36] reported an increased activity in de posterior cingulate cortex (PCC), insula, and supplementary motor cortex.

In conclusion, there is some evidence that patients show increased activity in pain related regions (S1, S2, PCC, and insula), and decreased activity in the PAG following mechanical stimulation (strength of conclusion 3).

3.5.3 Thermal stimulation

Two studies of Baliki et al. assessed the cerebral activation after thermal stimulation [37, 38]. In the first study of Baliki et al. [37], thermal stimulation was compared with spontaneous pain in chronic back pain (CBP) patients. Their main results were that sustained spontaneous high-intensity pain resulted in increased activity in the medial PFC. On the other hand, thermally induced pain resulted in increased activity in the insula in both patients and controls. Furthermore, activation of medial PFC and DLPFC were negatively correlated during high pain [37]. In the second study, nucleus accumbens activity was recorded during thermal stimulation. Nucleus accumbens activity distinguished between patients and controls perfectly. Furthermore, a strong connectivity with medial PFC cortex was found during thermal stimulation and a strong connectivity with medial PFC/amygdala during a pain rating task without thermal stimulation [38].

In conclusion, there is moderate evidence for a substantial role of the medial PFC in sustained spontaneous pain in CLBP and a role for the insula in induced thermal pain in both CLBP and controls. Furthermore, nucleus accumbens activity seems to differentiate between CLBP and controls in reaction to thermal stimulation (strength of conclusion 3).

3.5.4 Electrical stimulation

Only one study used electrical stimulation of the lower back to induce an intense and unpleasant stimulus [39]. CLBP patients were differentiated on the basis of Waddell signs [40]. Patients with a low degree of pain-related illness (WS-L) were compared with patients

with a high degree of pain-related illness (WS-H). WS-L patients showed an increased activity in posterior cingulate and extrastriate cortex and left posterior parietal lobe compared to WS-H patients.

There is some evidence that patients coping well with their pain, activate different cortical regions than patients showing exaggerated pain-related illness behavior (strength of evidence 3).

4. Discussion

The main goal of the current study was to identify structural and functional neuroplastic changes in CLBP by systematically reviewing the literature. Although there was great variability in used brain imaging techniques and study designs, several important results were identified and are discussed below.

Global GM reduction in patients compared to healthy controls was found in three studies [22, 23, 25], whereas the other four studies demonstrated no difference [17, 24, 28, 30]. An important note to this finding is that two of the studies showing a global GM decrease in the patient group, performed their analyses on neocortical GM volume [22, 23]. These calculations exclude the cerebellum, deep GM, and brainstem.

A considerable part of the included studies found corresponding results regarding regional structural changes in CLBP. Reasonable evidence was found for GM reduction in specific brain regions, including DLPFC, temporal lobes, insula, and S1. The DLPFC plays an important role in active control on pain perception by modulating corticosubcortical and corticocortical pathways [41]. Furthermore, others found that the DLPFC has an influence in placebo analgesia [42-44] and is less activated in healthy individuals exhibiting higher pain catastrophizing scores during moderate intensity pain [45].

Interesting results were found regarding GM changes in S1. Three studies found a GM reduction [27-29], while two other studies found a GM increase [26, 30]. It should be noted that these studies included patients with varying underlying pathologies. The two latter studies tested subjects with only non-specific CLBP [26] and medication-free and non-neuropathic subjects [30], whereas two of the other studies included subjects with disk pathology changes [28, 29].

Overall, a statement regarding GM changes in CLBP is hard to establish, since a considerable variation in the direction of changes has been demonstrated. The evidence of GM changes in CLBP, regardless of an increase or decrease is more obvious, as well as the specific regions in which these changes occur.

WM differences in CLBP are less studied than GM differences. Following global GM volume, there is also ambiguity about the global WM volumes in patients compared to healthy controls. Only two studies performed DTI analyses in CLBP [15, 16]. Results of regional WM changes are rather consistent, with lower WM integrity in the splenium and middle part of the corpus callosum [16, 24] and anterior limb of the internal capsule [15, 20]. It should be noted that the former studies are from the same research group. When looking for WM changes in other chronic pain populations, some similarities exist. Lower FA in the corpus callosum was also found in chronic complex regional pain syndrome patients [46] and temporomandibular disorder patients [47]. In a more recent study however, higher FA was found in regions of the corpus callosum in irritable bowel syndrome [48]. Due to the low number of studies analyzing WM changes in chronic pain patients, rigid conclusions are hard to establish.

There is reasonable evidence that functional connectivity during rest is disrupted in CLBP. Higher activation of the medial PFC, cingulate cortex, amygdala, insula, and a disrupted default mode network were identified. These results are partly in concordance with a study in

fibromyalgia, where a higher default mode network-connectivity with the insula compared to controls was found [49]. Another study with partially comparable results reported that chronic pain patients with several underlying pathologies showed altered spatial connectivity between insulae and anterior cingulate cortex, implying a divergent activity of the affective pain-processing areas [50].

An interesting finding in the mechanical pain-induced findings is that when equal pressures were applied, CLBP patients showed augmented activation in similar regions, while no differences were found during subjective equally painful pressure [34-36]. An important difference between the studies of Kobayashi et al. [36] and Giesecke et al. [35] is the lack of activation in S1 and S2 in the former. A possible explanation is the different stimulus site in both studies. Giesecke et al. [35] performed pressure at the thumbnail, while Kobayashi et al. [36] performed pressure at the low back. In the study of Giesecke et al. [34] a decreased activation of the periaqueductal gray was also found, indicative for a maladaptive endogenous analgesia system.

Several of the pain inducing brain imaging studies reported increased activation in the so-called “pain matrix” [51], including S1/S2 [26, 34, 35], insula [36, 37], and prefrontal cortices [16, 37]. Activation of the pain matrix-associated regions thalamus and ACC was not different from that of healthy controls in the included pain-inducing studies.

Limitations and suggestions for further research

It should be noted that the methodological quality of the studies was moderate, with a level of evidence B as mainly case-control studies were included. Secondly, in functional brain imaging studies, a variety of pain-inducing methods were used. Therefore, comparing results from different studies is not always legitimate. An important limitation of a large

proportion of the included studies is the small sample size, which is characteristic for brain imaging studies. Furthermore, a large variety in the patient population used for the present review possibly exists. The vast majority of included studies only included non-specific low back pain , whereas others included patients with specific pathology, including CLBP with a discogenic component, lumbar disk herniation, and failed back surgery syndrome [17-21]. It may be possible that different pathology leads to different neuroplastic changes.

It would be interesting for further research to combine different imaging techniques. For instance, earlier studies found that WM properties have been linked to GM function [46, 52], structural connectivity has been linked with resting state functional connectivity [53] and a relationship between anatomical connectivity and functional connectivity has been established [54-57]. Given these relationships, more combined structural and functional brain imaging studies could provide more insight in understanding the underlying mechanisms in CLBP.

For better understanding of the temporal relationship regarding pain and neuroplastic changes in CLBP, more longitudinal research is warranted. In addition, further research investigating the effect of treatment on structural and functional brain properties seems warranted.

5. Conclusion

There is moderate evidence that CLBP patients show structural brain differences in specific cortical and subcortical areas. Furthermore, CLBP patients show altered functional connectivity during rest and increased activity in pain related areas following painful stimulation, evidencing an upregulated pain matrix. Future research should focus on longitudinal designs to clarify the temporal relationship regarding pain and neuroplastic changes. Furthermore, research on integration of different brain imaging techniques is warranted.

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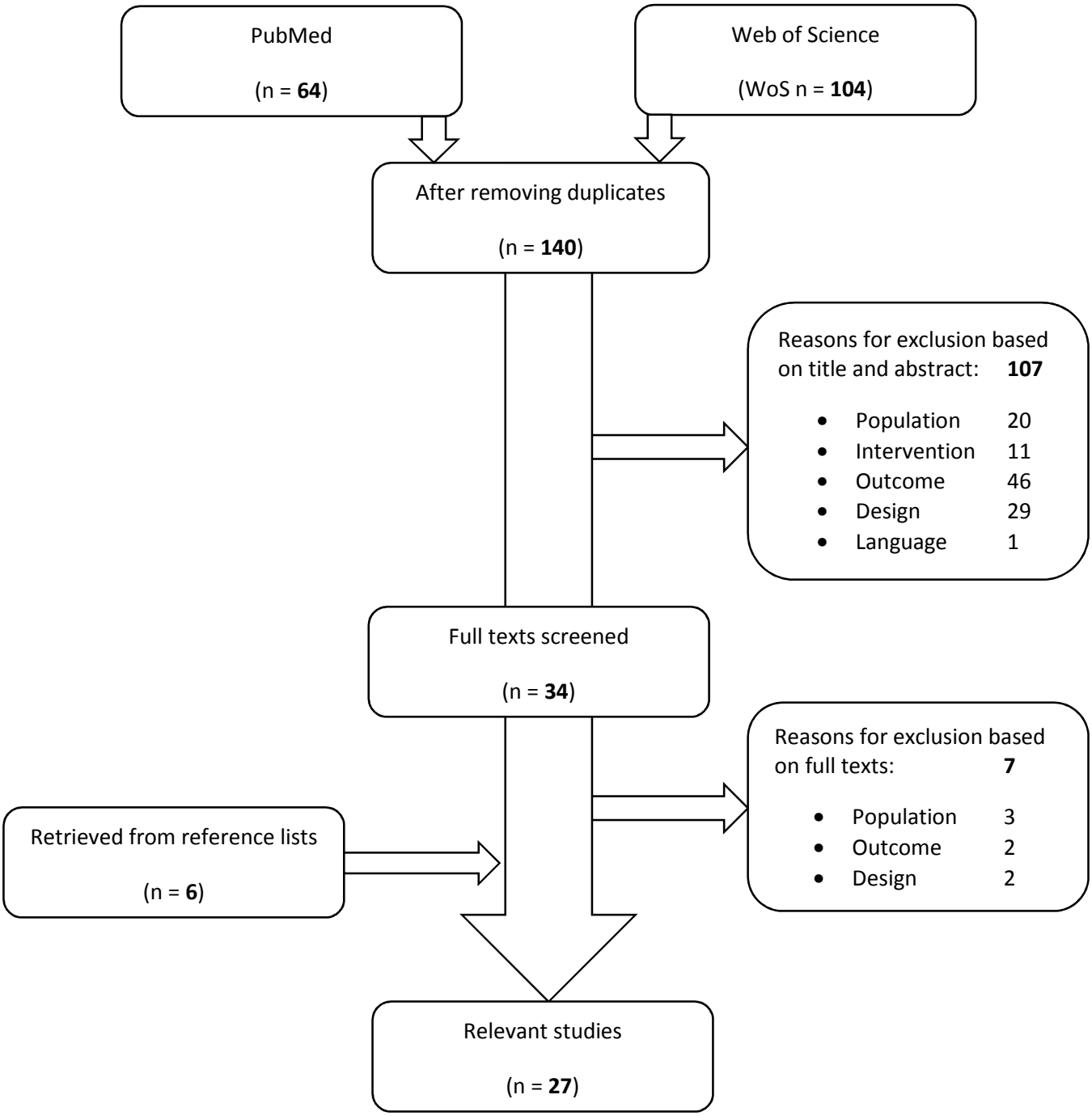

Figure 1. Study selection process

Table 1. Evidence table of structural and functional brain MRI in CLBP

Study	CLBP group (age in years)	Control group (age in years)	Main findings	Remarks
Structural				
[22]	16 ♀ and 10 ♂; CBP (11 NP and 15 non-NP)	16 ♀ and 10 ♂; HC	*Global differences* · ↓Neocortical GM volume *Regional differences* · ↓ GM volume bilateral DLPFC and right thalamus	· Pain duration predicts decreased neocortical GM volume · Regional GM volume strongly related to pain characteristics in a distinct pattern for NP and non-NP CBP
[24]	3 ♀ and 5 ♂; CLBP (age: 69.9 ± 3.9)	4 ♀ and 4 ♂; HC (age: 74.5 ± 4.2)	*Global differences* · No difference *Regional differences* · ↓ GM volume PPC · ↓ middle CC volume (WM, non-significant trend) · ↓ cingulate WM volume superior to middle CC of left hemisphere	· No correlations between pain severity, pain duration or education with manual tracing brain volumes · No correlations between pain severity/ duration and GM/WM with VBM brain volumes
[17]	9 ♀ and 5 ♂; discogenic CLBP (age: 46.9 ± 14.6)	9 ♀ and 5 ♂; HC (age: 45.9 ± 12.9)	*Global differences* · No difference *Regional differences* · ↑ cortical thickness right paracentral lobule (S1) (non-significant trend) · ↑ cortical thickness right rostral middle frontal gyrus (DLPFC)	· Results non-significant after including age as covariate · In contrast with HC, no age-related cortical thinning CLBP
[25]	8 ♀ and 6 ♂; CLBP (age: 54, range 41-73)	14 subjects; HC (gender- and age-matched)	*Global differences* · ↓ GM volume · ↓ WM volume *Regional differences* · ↓ GM density in middle cingulate gyrus, thalamus and DLPFC	· No correlations between structural changes and depression · Negative correlation between anterior cingulate/left lingual gyrus and anxiety
[20]	12 patients; CLBP (age: 43.9 ± 12.9)	12 subjects; HC (gender- and age-matched)	*Regional differences* · ↓ GM volume in ALPFC, right temporal lobe, left PMC, right CN, right cerebellum · ↑ GM volume in right dorsal ACC, left precuneus, left fusiform gyrus, right brainstem	· No information on gender distribution

			· ↑ and ↓ in bilateral OFC, ↓ WM volume adjacent to left PFC, right PMC, anterior limb of left internal capsule.	
[27]	20 ♀ and 10 ♂; CLBP (age: 51.6 ± 8.6)	20 ♀ and 10 ♂; HC (age: 50.2 ± 5.8)	*Regional differences* · ↓ GM volume in left S1, left precuneus, bilateral cuneal cortex · ↑ GM in bilateral putamen, nucleus accumbens, left amygdala, right caudate nucleus, pallidum	
[28]	9 ♀ and 9 ♂; CBP (age: 50.4 ± 6.8)	9 ♀ and 9 ♂; HC (age: 49.9 ± 8.7)	*Global differences* · No difference in GM volume *Regional differences* · ↓ GM volume in right S1, right DLPFC, right temporal lobe · ↑ GM volume in bilateral putamen, left posterior thalamus	· Negative correlation between brainstem/left somatosensory cortex and positive correlation in left thalamus/left putamen with pain intensity · Negative correlation between brainstem/bilateral somatosensory cortex and pain unpleasantness
[23]	13 ♀ and 23 ♂; CBP (age 48.2 ± 11.4)	26 ♀ and 20 ♂; HC (age: 38.8 ± 12.5)	*Global differences* · ↓ total neocortical GM volume *Regional differences* · ↓ GM density in bilateral posterior insula, bilateral S2, pre- and post-central regions, hippocampus, temporal lobes	· Pain duration and whole-brain GM reorganization are interrelated
[15]	22 ♀ and 24 ♂; SBP (age: 42.7, SEM=1.5) 11 ♀ and 13 ♂; CBP (age: 46.0, SEM=1.6)	12 ♀ and 16 ♂; HC (age 37.7, SEM=2.3)	· ↓ FA in temporal part of left SLF, left retro-lenticular part IC and EC, left anterior limb of IC and anterior corona radiata of CC · Abnormal regional FA related to differential structural connectivity to medial vs lateral PFC · Local FA correlated with functional connectivity between medial PFC/nucleus accumbens in persisting SBP	· WM structural abnormalities at baseline predicted pain persistence over next year

[30]	22 ♀ and 25 ♂; CLBP (age: 37.3 ± 12.2)	22 ♀ and 25 ♂; HC (age: 37.7 ± 7.8)	*Global differences* · No difference in GM volume *Regional differences* · ↓ GM volume in area adjacent to right amygdala, left medial orbital gyrus, right cuneus (2nd visual cortex) · ↑ GM volume in right cerebellum, temporal lobe, left S1 and S2, left M1, right calcarine sulcus (1st visual cortex), right DLPFC	· Analyses based on a multivariate machine learning approach to classify CLBP from HC on GM distribution pattern · Accuracy, sensitivity, and specificity were 76%, 76%, and 75% respectively
Functional **Resting state fMRI**				
[13]	20 ♀ and 19 ♂; SBP (age: 40.9 ± 2.3)	7 ♀ and 10 ♂; HC (age: 37.7 ± 1.8)	· ↑ functional connectivity of nucleus accumbens with PFC in persisting SBP	
[31]	5 ♀ and 10 ♂; CBP	5 ♀ and 10 ♂; HC (age: 51.9 ± 8.3)	· ↑ high-frequency BOLD oscillations in medial PFC and parts of DMN · ↑ frequency fluctuations within medial PFC are temporally synchronous with spontaneous pain changes during pain-rating task	
[32]	7 ♀ and 8 ♂; CBP (age: 43.8 ± 4.1)	7 ♀ and 8 ♂; HC (age: 39.6 ± 3.4)	· ↓ deactivation DMN regions (medial PFC, amygdala, PCC)	· fMRI during simple visual attention task
[14]	25 ♀ and 34 ♂; CBP (age: 48.8 ± 1.2)	48 ♀ and 46 ♂; SBP (age: 42.1 ± 1.15)	*Cross-sectional* · SBP showed ↑ activation in anterior to mid bilatateral insula, thalamus, striatum, lateral OFC, inferior cortex, dorsal ACC · CBP showed ↑ activation in perigenual ACC, medial PFC, amygdala *Longitudinal* · In persistent CBP, ↓ activity in acute pain regions, ↑ activity in emotional regions	· Results reported in relation to meta-analytic probabilistic maps related to terms of pain, emotion, and reward · SBP showed ↑ activation in acute pain regions · CBP showed ↑ activation in emotional regions
[21]	5 ♀ and 6 ♂; CLBP (age 52.7 ± 14.3)	5 ♀ and 6 ♂; HC (age 53.5 ± 15.0)	· Overall ↓ connectivity of the DMN · ↑ activation in pain modulation regions (DLPFC, insula) and	· Included patients suffer from CLBP with failed back surgery syndrome

			sensory motor integration regions (pre- and postcentral gyri)	
[33]	12 CBP (age: 51.2)	20 HC (age: 38.4)	· ↑ activity orbital part of middle frontal gyrus, right and left angular gyri (DMN regions) more correlated with insula compared with HC	· Same cohort as in [32]
[18]	11 ♀ and 5 ♂; CLBP (age: 47.4, 95% CI 40-54.8)	11 ♀ and 5 ♂; HC (age: 46.7, 95% CI 40.1-53.2)	· ↑ Connectivity of DMN to pregenual ACC, left inferior parietal lobule, right insula at baseline · Baseline DMN connectivity predicted maneuver-induced changes in pain and DMN-right insula connectivity	· Brain connectivity before and after physical maneuvers · Baseline clinical pain correlated positively with connectivity strength between DMN and right insula · ASL study
[19]	11 ♀ and 5 ♂; CLBP (age: 47.4, 95% CI 40-54.8)	11 ♀ and 5 ♂; HC (age: 46.7, 95% CI 40.1-53.2)	· ↑ activity bilateral medial and dorsolateral PFC, superior parietal lobules, S1, M1, S2, insula, ACC, presupplementary motor area, supramarginal gyrus	· Brain connectivity before and after physical maneuvers · Same cohort as in [18] · ASL study
Mechanical stimulation				
[34]	8 ♀ and 3 ♂; CLBP (age: 44 ± 13)	4 ♀ and 7 ♂; HC (age: 41 ± 7)	*Subjectively equal pain* · ↓ activation PAG · ↑ activation S1, S2, lateral OFC	· Same cohort as in [35]
[35]	8 ♀ and 3 ♂; CLBP (age: 44 ± 13)	4 ♀ and 7 ♂; HC (age: 41 ± 7)	*Subjectively equal pain* · Equal neuronal activation in both CLBP and HC *Similar pressure* · ↑ activation contralateral S1 and S2, inferior parietal lobe, cerebellum, ipsilateral S2	
[36]	3 ♀ and 5 ♂; CLBP (age: 29, range 22-44)	8 ♂; HC (age: 29, range 22-42)	· ↑ activation PCC, insula, supplementary motor cortex	
Thermal stimulation				
[37]	12 ♀ and 1 ♂; CBP (age:	6 ♀ and 5 ♂; HC (age:	· ↑ activation in medial PFC, correlated with	

	49.2 ± 17.2) 6 ♀ and 5 ♂; CBP (age: 50.0 ± 12.0)	48.7 ± 11.2)	spontaneous pain intensity · Strong negative correlation between DLPFC and medial PFC during high pain · ↑ insular activition during induced pain in both CBP and HC's and correlated with pain intensity during thermal stimulation and with duration of spontaneous back pain	
[38]	8 ♀ and 8 ♂; CBP (age: 45.1 ± 12.0)	8 ♀ and 8 ♂; HC (age: 38.8 ± 12.5)	· Nucleus accumbens activity correlated with different cortical circuitry (medial PFC and amygdala) than in HC · suggesting that acute pain relieves chronic pain	· The relieving effect was confirmed in a psycophysical study in CBP
Electrical stimulation				
[39]	14 ♀ and 16 ♂; CLBP (age: 45 ± 12.2)	9 ♀ and 8 ♂; HC (age: 31 ± 8.1)	· ↑ activation right posterior cingulate, extrastriate cortex, left posterior parietal lobe in WS-L vs WS-H	· Patients were divided into 2 groups using Waddell signs (WS), referring to no/low (WS-L) or high (WS-H) degree of pain-related illness behavior
Functional + structural				
[26]	12 ♀ and 6 ♂; CLBP (age: 36.1 ± 9.9)	12 ♀ and 6 ♂; HC (age: 37.1 ± 9.2)	*Functional differences* · ↓ activity S1 during low intensity pain, compared to HC · ↑ activity S1 during high intensity pain, compared to low intensity pain *Structural differences* · ↑ cortical thickness and volume in bilateral S1 (somatotopically associated with lower back)	· Pain was induced by physical maneuvers
[16]	4 ♀ and 4 ♂; disabling CLBP (age: 74.1 ± 6.4) 2 ♀ and 6 ♂	non-disabling CLBP (age: 75.1 ± 7.3)	*Functional differences* · ↑ activity right medial PFC in disabled CLBP · ↑ activity left lateral PFC in non-disabled CLBP *Structural differences* · ↓ WM volume in splenium of the CC in disabling	· Disabling and non-disabling CLBP in older adults were compared · Negative correlation between duration of CLBP and WM integrity in splenium of the CC

CLBP

[29]	10 ♀ and 8 ♂; CLBP (age: 46 ± 10.6)	8 ♀ and 8 ♂; HC (age 40 ± 13.2)	*Functional differences* · abnormal left DLPFC activity before treatment, normalized after treatment *Structural differences* · ↓ cortical thickness in left DLPFC, bilateral anterior insula/frontal operculum, left mid/posterior insula, left S1, left medial temporal lobe, right ACC before treatment · ↑ cortical thickness in left DLPFC after treatment compared with before treatment	· Longitudinal study measuring effects following treatment · ↑DLPFC thickness correlates with reduction of pain/physical disability · ↑M1 thickness correlates with reduced physical disability · ↑ right anterior insula correlates with reduced pain

CBP = chronic back pain; CLBP = chronic low back pain; HC = healthy controls; SBP = sub-acute back pain; GM = gray matter; WM = white matter; DLPFC = dorsolateral prefrontal cortex; NP = neuropathic; PPC = posterior parietal cortex; CC = corpus callosum; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; SLF = superior longitudinal fasciculus; IC = internal capsule; EC = external capsule; M1 = primary motor cortex; ALPFC = anterolateral prefrontal cortex; PMC = premotor cortex; CN = caudate nucleus; ACC = anterior cingulate cortex; OFC = orbitofrontal cortex; PFC = prefrontal cortex; FA = fractional anisotropy; BOLD = blood oxygenation level dependent; DMN = default mode network; PCC = posterior cingulate cortex; PAG = periaqueductal gray; ASL = arterial spin labeling