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Critical Review

Relations Between Brain Alterations and Clinical Pain Measures in Chronic Musculoskeletal Pain: A Systematic Review

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Abstract: **Compelling evidence has shown chronic widespread and exaggerated pain experience in chronic musculoskeletal pain (MSKP) conditions. In addition, neuroimaging research has revealed morphological and functional brain alterations in these patients. It is hypothesized that brain alterations play a role in the persistent pain complaints of patients with chronic MSKP. Nevertheless, lack of overview exists regarding the relations between brain alterations and clinical measures of pain. The present systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines, to investigate the relations between structural or functional brain alterations, using magnetic resonance imaging scans, and clinical pain measures in patients with chronic MSKP. PubMed, Web of Science, Cinahl, and Cochrane databases were searched. First, the obtained articles were screened according to title and abstract. Second, the screening was on the basis of full-text. Risk of bias in included studies was investigated according to the modified Newcastle-Ottawa Scale. Twenty studies met the inclusion criteria. Moderate evidence shows that higher pain intensity and pressure pain sensitivity are related to decreased regional gray matter (GM) volume in brain regions encompassing the cingulate cortex, the insula, and the superior frontal and temporal gyrus. Further, some evidence exists that longer disease duration in fibromyalgia is correlated with decreased total GM volume. Yet, inconclusive evidence exists regarding the association of longer disease duration with decreased or increased regional GM volume in other chronic MSKP conditions. Inconclusive evidence was found regarding the direction of the relation of pain intensity and pressure pain sensitivity with microstructural white matter and functional connectivity alterations. In conclusion, preliminary to moderate evidence demonstrates relations between clinical pain measures, and structural and functional connectivity alterations within brain regions involved in somatosensory, affective, and cognitive processing of pain in chronic MSKP. Nevertheless, inconclusive results exist regarding the direction of these relations. Further research is warranted to unravel whether these brain alterations are positively or negatively correlated to clinical pain measures.**

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Perspective: ***Structural and functional brain alterations within regions involved in somatosensory, affective, and cognitive pain processing play a crucial role in the persistent pain of chronic MSKP patients. Accordingly, these brain alterations have to be taken into account when assessing and treating patients with chronic MSKP.***

Key words: *Chronic musculoskeletal pain, magnetic resonance imaging, brain alterations, pain intensity, pain duration.*

Chronic musculoskeletal pain (MSKP) is defined as pain in muscles, tendons, joints, and ligaments for >3 months.[24] Additionally, this condition is frequently characterized by disproportional pain, meaning that pain severity and dysfunction are disproportionate to the nature and extent of the musculoskeletal damage/deficit.[77] Accordingly, increasing evidence suggests that most of these chronic MSKP syndromes are related to disturbed central pain processes and not strict to peripheral structures.[75] Chronic MSKP conditions include temporomandibular disorders, idiopathic chronic low back pain, fibromyalgia, chronic pelvic pain, and chronic whiplash-associated disorders, among others.[14,17]

Chronic MSKP affects hundreds of millions of people worldwide and is one of the most common forms of chronic pain.[95] This chronic pain condition can cause a profound negative effect on an individual's physical, emotional, and social well-being and thus on quality of life.[90,95] Additionally, MSKP syndromes result in a major burden on health systems, and social care systems, resulting in substantial financial costs.[95]

Accumulating research has shown that features of central sensitization are often present in these chronic MSKP conditions.[20,25,29,81,92] Central sensitization can be defined as an augmented responsiveness of the central nervous system to nociceptive as well as non-nociceptive stimuli (eg, pain, electrical stimuli, pressure, and temperature).[76,80] This exaggerated responsiveness can cause allodynia, hyperalgesia, hypersensitivity of senses unrelated to the musculoskeletal system, and referred pain across multiple spinal segments, leading to chronic widespread pain.[66] Clinical measures/symptoms of central sensitization are for example widespread pain, heightened pain intensity, generalized hyperalgesia, and allodynia.[77]

Approximately 30 years ago noninvasive human brain imaging techniques emerged.[2] This advent provided the opportunity to examine brain structure and function in clinical chronic pain states. During the past decade, the role of the brain in chronic pain conditions has been gradually elucidated.[82] This neuroimaging research has shown neuronal plasticity in the brain, which can lead to maladaptive changes due to sustained abnormal nociceptive input.[3,26] Specifically, the brain of patients suffering from chronic pain displays alterations with respect to brain structure,[5,56] function,[44] and chemistry.[33] In addition, neuroplastic brain remodeling can lead to persistence of pain, even in the absence of (further) nociceptive input.[3,11] Emerging evidence suggests that chronic pain is associated with a distinct representation in the brain, which is often referred to as the neural pain signature.[54]

Magnetic resonance imaging (MRI) has been one of the most influential techniques that has led to an improved understanding of pain perception, modulation, and chronification.[26,82] Brain MRI techniques can be roughly divided into structural and functional MRI (fMRI).

Structural MRI has the ability to measure gray matter (GM) and white matter (WM) morphology in vivo. High-resolution T1-weighted images can be used to assess global measures, such as whole brain volume, GM volume,[30] as well as regional features, including surface area,[31] cortical thickness,[30] and regional GM volume.[6] Voxel-based morphometry is frequently used to examine GM volume and is a voxel-wise comparison of the local concentration of GM between different groups.[6] FreeSurfer is used to render construction of cortical surface models, volumetric segmentation of brain structures, and mapping of cortical GM thickness (http://freesurfer.net, v5.3.0).[30] Three-dimensional mapping of cortical thickness is also possible using the Laplace equation method.[47]

Diffusion MRI is an innovative technique to investigate WM properties and microstructural WM changes.[7] Diffusion imaging data are used to map the 3-dimensional diffusion of water molecules in the brain. Currently, diffusion tensor imaging (DTI) is the most widely used method for assessing WM orientation and integrity. The diffusion tensor characterizes the degree, the magnitude of anisotropy, and the orientation of directional diffusion.[1] This technique provides measures such as fractional anisotropy (FA) and mean-, radial-, and axial diffusivity (AD).[87] Nevertheless, it recently became clear that this tensor model is invalid in voxels containing crossing fibers.[89] Therefore, various methods have been developed that are capable to extract multiple fiber orientations from the diffusion-weighted imaging signal, thereby overcoming the limitation of DTI.[45]

Compelling structural MRI research has shown alterations in GM morphology and WM properties in various chronic MSKP conditions, including patients with fibromyalgia, chronic low back pain, and chronic temporomandibular disorders,[20,52,61,68] within brain regions involved in somatosensory, affective, and cognitive modulation of pain, such as the somatosensory cortex (S1, S2), medial and dorsolateral prefrontal cortex, anterior (ACC) and posterior cingulate cortex (PCC), insula, amygdala, hippocampus, and periaqueductal gray.[8,19-21,27,37,52,82,83]

Functional MRI (fMRI) is used to evaluate human brain function in vivo and is on the basis of measuring the

blood oxygen-level dependent (BOLD) contrast.[15] fMRI is able to analyze changes in BOLD contrast during a task or during rest.[13] During task-based fMRI, the BOLD contrast shows the hemodynamic brain changes after enhanced neural brain activity while performing a specific task.[59,78] When a person is at rest (no task), spontaneous low-frequency (<.1 Hz) fluctuations of the BOLD signal occur throughout the brain.[38] This signal exposes temporal correlations in spatially distinct brain regions. Certain patterns appear consistently and are referred to as resting-state functional networks.

Resting-state fMRI research aims to generate statistical maps of these significant temporal BOLD correlations between brain areas.[13] These correlations of signal fluctuations between distinct brain regions are calculated as an index of functional connectivity (FC).[34] The default mode network (DMN) and the salience network are examples of resting-state (no task) functional networks in the brain.[54] Recently, various research groups have shown reorganized connectivity patterns within various resting-state functional networks such as the DMN and salience network in chronic pain patients.[9,40,55,64] Resting-state fMRI and FC analyses have improved our knowledge on how brain regions work together as networks to modulate pain and how these networks may be modified in the presence of persistent pain.[18,82]

fMRI research has shown alterations in (resting-state) functional activity and connectivity within various brain regions involved in somatosensory, affective, and cognitive modulation of pain in patients with various chronic MSKP.[9,10,20,52]

During the past years, the relationship between brain alterations and clinical features of pain has been frequently hypothesized and studied.[26] Scientific evidence for underlying central mechanisms of pain processing has become increasingly necessary. Imaging studies investigating the relation between brain alterations and clinical behavioral measures in chronic MSKP patients have been published during the past years.[82] In particular, accumulating research investigating the relationship between clinical measures of pain such as pain duration, pain intensity, pressure pain sensitivity, and brain alterations has been published.[37,48,60] Evaluation of clinical pain measures is highly important and is often used in clinical assessment, therapy, and research in patients with chronic MSKP to evaluate the nature and extent of symptoms as well as the evolution of pain.[36,57] A systematic review has shown that clinical pain outcome measures, used in research to assess chronic MSKP, are very heterogeneous.[57] In particular, various dimensions of pain, different types of scales/questionnaires and descriptors, and varying reporting periods of pain (eg, current pain intensity, mean pain intensity during past week or past month) are examined in chronic MSKP research. Overall, clinical pain measures can be subdivided into self-reported pain measures such as pain intensity and pain duration, and more objective experimental pain measures such as pressure pain sensitivity and hypersensitivity for various stimuli.[57]

Unfortunately, currently no clear overview exists on how brain alterations are related to clinical correlates of pain in various chronic MSKP conditions. However, knowledge on this relationship is important to integrate neuroimaging findings into clinical practice and to further unravel the underlying mechanisms of persistent pain. Therefore, the aim of the present systematic review was to investigate the relations between structural and functional brain alterations and clinical pain measures in chronic MSKP patients, examined with structural and functional brain MRI techniques.

Methods

Research Questions

This systematic review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.[70] The Patient, measurement Instrument, Comparison, Outcome (PICO) approach was applied to formulate the following research questions: 1) 'What are the relations between structural brain alterations (O = outcome) and clinical pain measures (O) in chronic MSKP patients (P = patient), examined with structural brain MRI techniques (I = measurement instrument)? 2) 'What are the relations between functional brain alterations (O) and clinical pain measures (O) in chronic MSKP patients (P), examined with functional brain MRI techniques (I)?

Eligibility Criteria

Eligibility assessment was performed by screening the obtained articles on the basis of the inclusion and exclusion criteria (Table 1). To be included, articles had to investigate a relation or association between structural or functional brain alterations and clinical measures/correlates of pain (ie, pain duration, pain intensity, pain perception, pressure sensitivity, hyperalgesia, hypersensitivity, allodynia, referred pain) (O) by using brain MRI techniques (I) in patients with chronic MSKP (P).

Eligibility assessment of the obtained articles was performed by 2 independent researchers (I.C. and B.C.), who have published systematic reviews and were trained in conducting a systematic review by the second author (M.M.). After deduplication, a first screening was performed on the basis of the title and abstract of the remaining articles. If any of the inclusion criteria were not met, the article was excluded. In the second phase, publications were screened on the basis of the full-text and fulfilment of the inclusion criteria was ensured.

Literature Search Strategy

A systematic search of relevant literature was conducted by the authors. The electronic databases PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Web of Science (http://isiwebofknowledge.com), Cinahl (https://health.ebsco.com/products/cinahl-complete), and Cochrane (http://onlinelibrary.wiley.com/cochranelibrary/search) were searched through on September 7, 2015 to identify relevant articles. To make the search as complete as possible, reference lists of the included articles were screened. The search strategy consisted of a combination

Table 1. Inclusion and Exclusion Criteria

	Inclusion	Exclusion
Population	• Human study • Patients with chronic MSKP • Adults (≥18 y of age)	• Animal study • Children and adolescents (<18 y of age)
Instrument	• At least 1 brain MRI technique is applied: T1 MRI, DTI, DWI, fMRI, rs-fMRI	• SPECT, PET, EEG, MEG, MR spectroscopy
Outcome 1	• At least 1 clinical pain measure was examined: pain intensity, pain perception, pain duration, allodynia, hyperalgesia, referred pain, pressure sensitivity	• Not examining the relation, association, or correlation between a clinical pain measure and structural or functional brain alterations
Outcome 2	• At least 1 type of brain change was examined: structural or functional alterations	• Not examining the relation, association or correlation between a clinical pain measure and brain alterations
Type of report	• Clinical • Full-text	• Nonclinical: review, systematic review, meta-analysis, letter to the editor • Full-text not available, abstracts, posters
Language	• English, German, Dutch, French	• All other languages

Abbreviations: T1 MRI, T1-weighted MRI; DWI, diffusion weighted imaging; rs-fMRI, resting-state fMRI; SPECT, single photon emission computed tomography; PET, photon emission tomography; EEG, electroencephalography; MEG, magnetoencephalography; MR, magnetic resonance.

of free text words on the basis of the eligibility criteria. The complete search strategy is shown in Table 2.

Risk of Bias in Individual Studies

Methodological quality of all included studies was assessed by 2 independent reviewers (I.C. and J.K.), both PhD candidates working with chronic MSKP patients in the research field of brain MRI. Both reviewers were trained by M.M., a PhD experienced in conducting systematic reviews. Risk of bias was evaluated using the Newcastle-Ottawa Scale (NOS) for case control studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).[93] The NOS applies a star rating system to judge methodological quality on the basis of 3 subcategories: selection of groups, comparability, and ascertainment of exposure. This checklist is recommended for case-control studies[99] and has frequently been used by the Cochrane Collaboration (www.cochrane.org). The criterion on response rate could not be scored because this item was not applicable for the articles on the current research topic. Therefore, item 9 was replaced by a self-constructed additional subcategory, 'MRI data quality and preprocessing' that includes 2 items, which was chosen specifically for the current systematic review. Item 9 scores whether the researchers performed visual inspection of the MRI data quality (eg, head motion). Item 10 scores whether manual exclusion in case of low data quality and/or data adjustment was included in the preprocessing pipeline. Subsequently, each study could reach a maximum score of 10 on the modified NOS, representing the highest methodological quality. A study earned 1 point when controlling for sex or age in the 'comparability' section and an additional point when controlling for another factor (eg, medication use, collecting cardiorespiratory data).

On the basis of study design and methodological quality, each individual study received a level of evidence, according to the 2005 classification system of the Dutch Institute for Healthcare Improvement (CBO) (Supplementary Table 1). Subsequently, strength of conclusion was determined after clustering studies with comparable experimental methods and research aims, accounting for the study design and the risk of bias (Supplementary Table 2). Strength of conclusion 2 was assigned when there were at least 2 independently conducted studies of evidence level B. Strength of conclusion 3 was assigned when there was at least 1 study of evidence level B. Strength of conclusion 4 was given in case of inconclusive or inconsistent results between various studies.

Table 2. The Search Terms (Free Text Words) Used for the Literature Review

Patients	and	Measurement Instrument	and	Outcome	and	Outcome
Musculoskeletal pain syndrome		Brain imaging		White matter		Allodynia
Chronic low back pain		Diffusion tensor imaging		Cortical thickness		Hyperalgesia
Fibromyalgia		Diffusion weighted imaging		Gray matter		Heightened sensitivity
Chronic fatigue syndrome		Magnetization transfer contrast		Gray matter		Hypersensitivity
Temporomandibular disorders		Magnetization transfer ratio		Gray matter volume		Referred pain
Osteoarthritis		T1		Gray matter volume		Pain duration
Chronic knee pain		Voxel-based morphometry		Functional connectivity		Pain severity
Chronic pelvic pain syndrome		fMRI		Structural connectivity		Pain intensity
Chronic ankle pain		fMRI		Resting state activity		
Chronic neck pain		Resting-state fMRI		Resting state connectivity		
Chronic whiplash-associated disorder		Resting state fMRI		Cortical morphology		
Chronic epicondylalgia		Tractography				
Myofacial pain syndrome						

Data Extraction Process

The following information was extracted from each included study and is shown in the evidence table (Supplementary Table 3): 1) patients, 2) control group, 3) brain MRI technique, 4) clinical pain measures, 5) correlations, relations, associations, 6) main results, and 7) correlation coefficients, t-scores, Z-scores. The data were obtained by the first author (I.C.) and a second reviewer (R.D.P.) checked the extracted data. Noteworthy, the evidence table only includes the MRI techniques and clinical pain measures, which were used to evaluate possible relations. In addition, the main results regarding relations between clinical pain measures and brain alterations in chronic MSKP patients are summarized whereas the results among the healthy control group are not shown.

Results

Study Selection

The selection process of relevant articles is presented in Figure 1. The initial search resulted in 137 articles. After removing the duplicates, 91 articles remained. Two articles[32,37] were found by manual search: these articles were found in the reference list of included studies. The entire selection process resulted in 20 eligible articles.

Study Characteristics

All included studies (n = 20) applied a case-control design, comparing chronic MSKP patients with healthy pain-free individuals. The characteristics of each study were extracted and presented in the evidence table (Supplementary Table 3). Articles were divided on the basis of the applied MRI technique. Six articles compared clinical pain measures with GM alterations,[22,37,53,67,71,97] 4 articles with WM alterations,[48,56,61,68] and 11 articles observed relations with functional brain alterations.[9,22,28,32,43,44,49,51,60,74,98]

Risk of Bias Within Studies and Level of Evidence

The risk of bias and level of evidence is shown in Table 3. All studies scored a level of evidence B. Methodological quality was moderate to good, varying between 5 of 10 (50%) and 9 of 10 (90%). Most studies lost points on 'representativeness of the cases' (80%), 'selection of controls' (85%), and 'definition of controls' (60%), either because authors did not mention the required information or the information was not adequate. Nevertheless, most studies were awarded for taking into account confounding factors (eg, matching for age and sex), ascertainment of exposure, and for using the same method of ascertainment for cases and controls. All studies

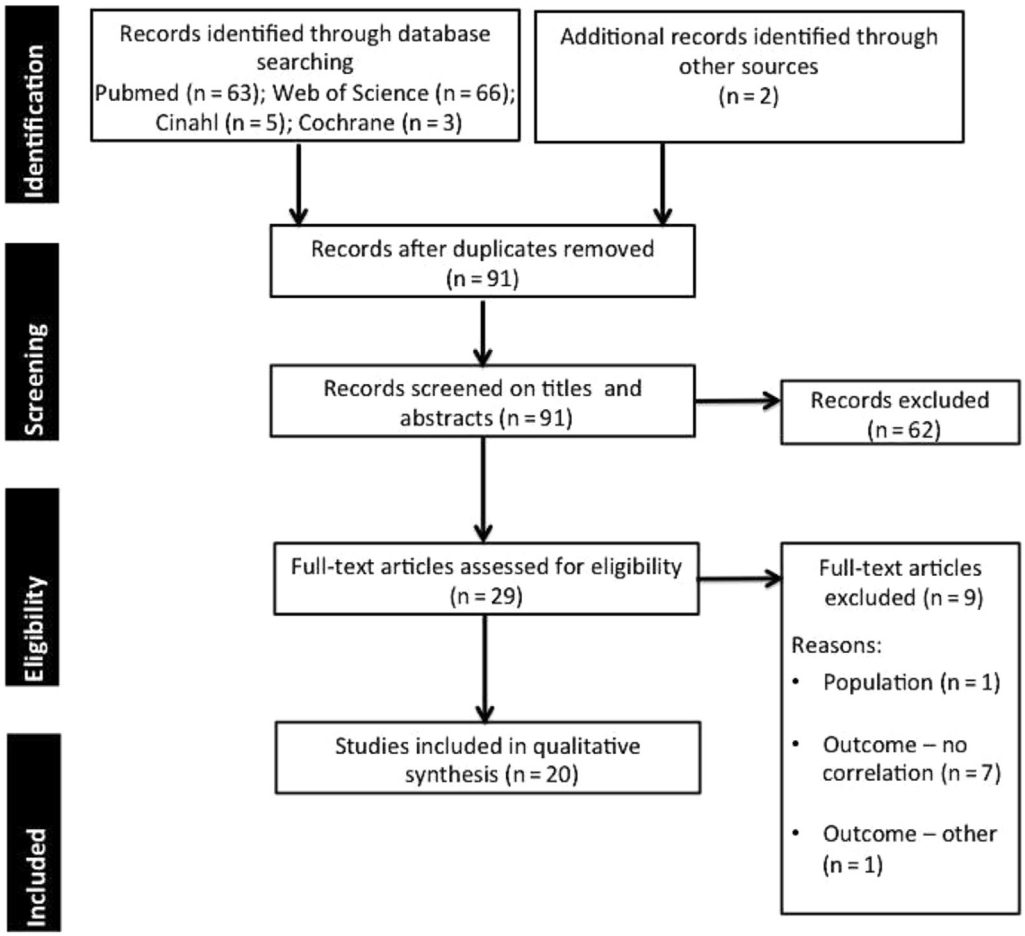

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram of the conducted search.

Table 3. Methodological Quality for Case-Control Studies

	Selection				Comparability		Exposure		MRI Data Quality and Preprocessing			
Study	1	2	3	4	5	6	7	8	9	10	Total Score (%)	LOE
Kim et al[48]	–	+	+	+	+	+	+	+	+	+	9/10 (90)	B
Moayedi et al[68]	+	/	–	+	+	+	+	+	+	+	8/10 (80)	B
Ichesco et al[44]	+	–	–	+	+	+	+	+	+	+	8/10 (80)	B
Ichesco et al[43]	+	–	–	+	+	+	+	+	+	+	8/10 (80)	B
Gerstner et al[37]	+	–	–	+	+	+	+	+	–	+	8/10 (80)	B
Lutz et al[61]	+	/	–	+	+	+	+	+	+	+	8/10 (80)	B
Moayedi et al[67]	+	–	–	+	+	+	+	+	–	+	7/10 (70)	B
Kim et al[49]	+	–	–	+	+	+	+	+	–	+	7/10 (70)	B
Lopez-Sola et al[60]	+	/	–	–	+	+	+	+	+	+	7/10 (70)	B
Baliki et al[9]	+	+	–	–	+	+	+	+	–	+	7/10 (70)	B
Mordasini et al[71]	+	–	–	–	+	+	+	+	+	+	7/10 (70)	B
Yu et al[98]	+	–	+	–	+	+	+	–	–	+	7/10 (60)	B
Ceko et al[22]	+	–	–	–	+	+	+	+	–	+	7/10 (70)	B
Kong et al[51]	+	–	+	–	+	+	+	–	+	+	7/10 (70)	B
Flodin et al[32]	–	–	–	–	+	+	+	+	+	+	6/10 (60)	B
Farmer et al[28]	+	+	–	–	+	+	+	+	–	+	6/10 (60)	B
Lieberman et al[56]	+	–	–	–	+	–	+	+	+	+	6/10 (60)	B
Younger et al[97]	+	+	–	–	+	–	/	+	–	+	5/10 (50)	B
Napadow et al[74]	–	–	–	–	+	+	+	+	–	+	5/10 (50)	B
Kuchinad et al[53]	–	–	–	–	+	+	+	+	–	+	5/10 (50)	B

Abbreviations: LOE, level of evidence; –, score not fulfilled; +, score fulfilled; /, answer is unclear.
NOTE. Newcastle-Ottawa Quality Assessment Scale: case-control studies: 1 = Is the case definition adequate?; 2 = Representativeness of the cases; 3 = Selection of controls; 4 = Definition of controls; 5 = Study controls for age or sex; 6 = Study controls for any additional factor; 7 = Ascertainment of exposure; 8 = Same method of ascertainment for cases and controls; 9 = Visual inspection of the MRI data quality; 10 = Manual exclusion in case of low data quality and/or automated data adjustment included in preprocessing pipeline.

were awarded for manual exclusion in case of low data quality and/or inclusion of automated data adjustment in the preprocessing pipeline.

In most cases (90.5% or 181 of the 200 items), the 2 reviewers (I.C. and J.K.) agreed. After a second review and a comparison of the 19 differences, the reviewers reached a consensus for 197 items. For the 3 remaining items, a third investigator was consulted (R.D.P.). The final score of each study is presented in Table 3.

Syntheses of Results

Structural Brain MRI

Overall, 10 studies investigated the relationship between structural brain alterations and clinical pain measures in chronic MSKP patients.[22,37,48,53,56,61,67,68,71,97] Six of 10 articles used voxel-based morphometry,[22,37,53,67,71,97] 1 article performed cortical thickness analysis,[67] and 4 articles applied DTI.[48,56,61,68]

GM Alterations Related to Clinical Pain Measures

Pain Intensity. Three studies examined the relation between clinical pain intensity and alterations in regional GM volume.[67,71,97]

Mordasini et al[71] and Younger et al[97] reported a significant relation between pain intensity and regional GM volume. Increased pain intensity in patients with chronic temporomandibular disorders was associated with decreased GM volume in the right rostral ACC, right PCC, precuneus, and superior frontal and superior temporal gyrus.[97] Mordasini et al[71] reported correlations between higher chronic pelvic pain intensity and decreased GM volume in the left ACC.

In conclusion, there is moderate evidence that higher clinical pain intensity in chronic MSKP patients is related to decreased GM volume in pain processing regions such as the ACC[71,97] (strength of conclusion 2).

Moayedi et al[67] reported a negative correlation between pain intensity in temporomandibular disorders patients and GM thickness in the anterior midcingulate cortex and the ventrolateral aspect of the primary motor cortex. Furthermore, they reported that increased pain unpleasantness was associated with decreased GM thickness in the lateral orbitofrontal cortex.

In conclusion, there is some evidence that increased pain intensity and pain unpleasantness in chronic temporomandibular disorders patients is correlated with decreased GM thickness in pain, motor, and cognitive processing regions of the brain (strength of conclusion 3).

Pressure Pain Sensitivity

Two studies reported an association between pressure pain sensitivity and regional GM volume alterations.[22,97]

Younger et al[97] reported a negative association between pressure pain sensitivity and GM volume in the trigeminal nuclei in chronic temporomandibular disorders patients. Furthermore, Ceko and colleagues[22] observed significant relations between increased pressure pain sensitivity and decreased GM volume in the left anterior insula and PCC in fibromyalgia patients.

In conclusion, there is moderate evidence that increased pressure pain sensitivity in chronic MSKP patients is associated with decreased GM volume in somatosensory, pain, and affect-cognitive processing brain regions (strength of conclusion 2).

Pain Duration

Four articles[37,53,67,97] reported an association between the duration of chronic MSKP and GM volume alterations. Three articles described a relation with regional GM volume[37,67,97] and 1 article showed a relation with total GM volume.[53] A negative correlation was reported by Gerstner et al,[37] who observed that longer pain duration in chronic temporomandibular disorders patients was correlated with decreased GM volume in the right superior and middle temporal gyrus. Kuchinad et al[53] reported that longer disease duration in fibromyalgia patients was correlated with decreased total GM volume. In contrast, Younger et al[97] and Moayedi et al[67] described a positive relation between duration of temporomandibular disorders and regional GM volume. Increased GM volume was found in the PCC and midbrain bilaterally, in the right hippocampus and in the right middle cerebellar peduncle.[97] Further, longer temporomandibular disorders disease duration was correlated with increased GM volume in the sensory thalamus.[67]

In conclusion, there is moderate evidence that regional GM volume alterations are correlated with chronic MSKP duration (strength of conclusion 2). However, inconclusive evidence exists regarding the relation between longer disease duration and decreased or increased regional GM volume (strength of conclusion 4).

Additionally, there is some evidence that longer disease duration in fibromyalgia patients is correlated with decreased total GM volume (strength of conclusion 3).

WM Alterations Related to Clinical Pain Measures

Pain Intensity. Four studies[48,56,61,68] investigated the relationship between clinical pain correlates and structural alterations in WM using DTI as an MRI technique. Kim and colleagues[48] and Moayedi and colleagues[68] reported a correlation between higher pain intensity and lower FA in the corpus callosum,[48] internal, external and extreme capsules,[68] and the thalamus.[68] Moayedi et al[68] also detected a negative correlation between pain unpleasantness and FA in the right internal capsule. In contrast, Lutz et al[61] and Lieberman et al[56] have reported positive correlations between higher pain intensity and increased FA values in the WM of the right superior frontal gyrus[61] and between higher total pain experience score and increased FA in the left uncinate fasciculus.[56]

In conclusion, there is moderate evidence that higher pain intensity is correlated with FA alterations in regional WM tracts involved in transmission of somatosensory, pain, and affective and cognitive information (strength of conclusion 2). However, there is inconclusive evidence as to whether greater pain intensity is related to decreased or increased FA values in these WM tracts (strength of conclusion 4).

Subjective Pain Scores

Lieberman et al[56] reported positive correlations in chronic MSKP patients between higher total pain experience scores and increased AD in the left anterior and posterior limb of the internal capsule. Additionally, increased typical pain scores on the McGill pain questionnaire were positively correlated with increased AD in the left anterior limb.

In conclusion, there is some evidence that increased subjective pain scores in chronic MSKP patients are correlated with increased AD in WM tracts involved in transmission of information through the anterior and posterior limb of the internal capsule (strength of conclusion 3).

Functional Brain MRI

Overall, 11 articles described interrelations between clinical pain correlates and functional brain alterations using fMRI and/or resting-state fMRI in chronic MSKP patients.[9,22,28,32,43,44,49,51,60,74,98] Six studies examined fibromyalgia patients, 1 article included chronic pelvic pain patients, 3 articles assessed chronic low back pain patients, 1 article investigated osteoarthritis patients, and 1 article included patients with temporomandibular disorders.

FC Alterations Related to Clinical Pain Measures

Pain Intensity. Most studies investigated relations between clinical pain measures and FC alterations.[9,22,32,43,44,49,51,73,74,98] Napadow et al[74] reported in fibromyalgia patients a positive association between higher current pain intensity and increased FC between the DMN and right middle and anterior insula, cerebellum, dorsolateral prefrontal cortex, and subgenual ACC. Further, a positive covariation was reported between higher current pain intensity and increased FC between the right executive attention network and right anterior, left middle, and posterior insula and putamen.

In contrast, Napadow et al[74] reported higher current pain intensity to be related to decreased FC between the right executive attention network and the hippocampus, periaqueductal gray, nucleus cuneiformis, and the pontine raphe. A negative relation was shown in temporomandibular disorders patients between pain intensity and FC between the left anterior insula and rostral ACC during resting-state fMRI by Ichesco et al.[43] Ichesco et al,[44] reported in fibromyalgia patients higher pain intensity to be related to increased FC between the right anterior insula and superior temporal gyrus. Kong et al[51] reported positive relations between pain intensity changes after exercises and FC at the left insula, precuneus, amygdala, and fusiform in chronic low back pain patients.

Baliki et al[9] reported in chronic low back pain and osteoarthritis patients positive correlations between current

pain intensity and medial prefrontal cortex/insula FC. Further, Ceko et al[22] reported in fibromyalgia positive relations between current pain intensity and FC of the left anterior insula to the primary somatosensory cortex (S1) and primary motor cortex. In addition, Kim et al[49] reported a correlation between higher pain intensity and increased changes (from the pain phase through the rest phase) in S1 leg connectivity to the anterior insula in fibromyalgia patients. Additionally, increased temporal summation of pain was correlated with increased changes in S1 leg connectivity to the right anterior/middle insula in fibromyalgia patients. In contrast, higher clinical pain intensity was related to decreased resting-state FC within S1.

Ichesco et al[44] examined associations between pain rating index scores and FC in fibromyalgia patients. Higher FC, between insula and superior temporal gyrus, was associated with higher affective scores. Higher sensory scores were correlated with greater FC between the right middle insula and bilateral precuneus. In contrast, Yu et al[98] observed in chronic low back pain patients a negative relationship between increased low back pain ratings and FC between periaqueductal gray and left ventromedial prefrontal cortex/rostral ACC after a pain-inducing maneuver.

In conclusion, there is moderate evidence that greater clinical pain intensity is related to alterations in FC in chronic MSKP patients (strength of conclusion 2). However, inconclusive evidence exists regarding the direction of the relation within somatosensory, pain, and affect-cognitive processing regions/networks in chronic MSKP patients. Positive[9,22,32,44,51,73,74] and negative[32,43,49,73,74,98] relations between pain intensity and FC alterations were found (strength of conclusion 4).

Pressure Pain Sensitivity

Three studies investigated the relation between pressure pain sensitivity and FC alterations.[32,43,44]

Flodin et al[32] reported that increased pressure pain sensitivity in fibromyalgia was correlated with decreased FC between the right inferior orbitofrontal regions and right associative visual cortex. In contrast, they also reported a relation between increased pressure pain sensitivity and increased FC between pain-related regions (ie, the left insula and dorsal PCC, the left Rolandic operculum, left parahippocampal gyrus, and thalamus and prefrontal cortex).

Ichesco et al[44] investigated correlations between FC and pressure pain thresholds at different intensities. In fibromyalgia patients, a negative correlation was detected between lower pressure pain thresholds, hence increased pressure pain sensitivity and higher FC. Higher FC was reported between the right posterior insula and PCC during a faint, mild, and slightly intense stimulus. A slightly intense stimulus correlated with FC between the left middle insula and left middle cingulate cortex. When a faint stimulus was given, higher FC was reported between the left middle insula and right middle cingulate cortex and between the right posterior insula and left middle ACC. Ichesco et al[43] reported that increased pressure pain sensitivity was related to decreased FC between the left anterior insula and the right ACC and medial frontal gyrus in chronic temporomandibular disorders patients.

In conclusion, there is moderate evidence that pressure pain sensitivity is related to alterations in FC within somatosensory, pain, and affect-cognitive processing brain regions/networks in chronic MSKP patients (strength of conclusion 2). However, inconclusive evidence exists regarding the direction of the relation between increased pressure pain sensitivity and FC alterations in chronic MSKP patients. Positive[32,43] and negative[32,44] relations between pressure pain sensitivity and FC alterations were found (strength of conclusion 4).

Functional Activity Alterations Related to Clinical Pain Measures

Pain Intensity. Farmer et al[28] reported a positive correlation between pain intensity and activity in the anterior insula in men with chronic pelvic pain. Lopez-Sola et al[60] observed negative correlations between pain intensity in fibromyalgia patients and activation in primary and secondary visual cortical areas. Furthermore, hypersensitivity to tactile stimulation (ie, allodynia) was related to decreased activation in the superior middle temporal gyri.

In conclusion, there is some evidence that higher pain intensity and allodynia are associated with decreased functional brain activation in fibromyalgia patients (strength of conclusion 3). Further, there is some evidence that greater pain intensity is related to increased functional activity in the anterior insula in men with chronic pelvic pain (strength of conclusion 3).

Discussion

The purpose of this systematic review was to summarize the evidence regarding relations between structural and functional brain alterations and clinical pain measures in chronic MSKP patients, examined with brain MRI techniques. Most studies reported significant relations between structural and functional alterations in the brain and various clinical pain correlates such as pain intensity, pain duration, and pressure pain sensitivity. Overall, the included studies examined a wide range of brain regions involved in somatosensory, cognitive, and affective processing of pain. Remarkably, the direction of the relations (eg, increased or decreased GM volume related to higher pain measures) often differed between and within various studies. This might be due to a variety of conditions that are classified as chronic MSKP, together with the multiple MRI acquisition and analytical techniques that have been applied to measure alterations in the brain. Furthermore, the different standardized scales and questionnaires that have been used to measure clinical features of pain could have influenced the direction and nature of the observed relations as well as the specific brain regions that were investigated. Nevertheless, several conclusions can be made and are summarized in Table 4. In addition, a glossary

of important terms regarding MRI analysis of brain alterations is presented in Table 5.

Twenty case-control studies met the inclusion criteria. All studies scored a level of evidence B. Methodological quality was moderate to good, varying between 5 of 10 (50%) and 9 of 10 (90%). Moderate evidence shows that higher pain intensity and pressure pain sensitivity are related to decreased regional GM volume in brain regions encompassing the cingulate cortex, the insula, and the superior frontal and temporal gyrus.[22,71,97] Further, some evidence exists that longer disease duration in fibromyalgia patients is correlated with decreased total GM volume. Yet, inconclusive evidence exists regarding the association of longer disease duration with decreased or increased regional GM volume in other chronic MSKP conditions.[37,67,97] Moreover, moderate evidence is present for a correlation between higher pain intensity and FA alterations in regional WM tracts[48,56,61,68] and FC alterations.[9,22,32,43,44,49,51,73,74,98] However, inconclusive evidence was found regarding the direction of the relation of pain intensity and pressure pain sensitivity with microstructural WM[48,56,61,68] and FC[9,22,32,43,44,49,51,73,74,98] alterations in chronic MSKP.

It can be summarized that different chronic MSKP syndromes, which seem to be a heterogeneous group, expose unique (specific for each chronic MSKP condition) anatomical 'brain signatures' and functional reorganization. However, among all included chronic MSKP conditions it seems that brain regions involved in the limbic-affective and cognitive component of pain processing are involved in the observed neuroplastic brain remodeling. On the basis of this compelling evidence it can be stated that chronic MSKP is not only involved with somatosensory processing but also critically involves cognitive and affective-limbic processing in regions such as the ACC, insula, prefrontal cortex, and amygdala.

Important to discuss is that the observed relations (eg, extent and direction) between clinical pain characteristics and brain alterations can be influenced by multiple factors. Research has shown in chronic MSKP and non-MSKP patients the influence on pain and neuroplasticity of sex, age, genetics, environment, preexisting vulnerabilities, previous experiences, medication, culture, and psychosocial factors.[8,16,22,35,41,58,63,65,69,88,96] Accordingly, all of these variables could interfere with the observed relations between brain alterations and clinical pain measures and therefore may explain the incongruence found in this systematic review.

Various hypotheses can be made to explain the relation between clinical pain measures and GM decreases. It has been suggested that GM decrease is associated with long-term nociceptive input and neuroplastic changes.[5,50,84] Furthermore, increased cortical thickness for example in frontal brain regions could be the consequence of increased cognitive load in chronic pain conditions.[67] The frontal pole may process the cognitive dimension of pain, which suggests that pain has a cognitive load and this may require continuous engagement of regions in the frontal cortex and subsequently may lead to cortical thickness. The same theories could be hypothesized for alterations in limbic-affective brain regions.

To put the results of the current systematic review into a broader perspective, scientific studies regarding the relations between brain alterations and clinical pain measures in chronic non-MSKP patients should be reported. Research in other chronic pain syndromes such as irritable bowel syndrome and complex regional pain syndrome has also investigated the relationship between

Table 4. Summary of Evidence Regarding Interrelations Between Brain Alterations and Clinical Pain Measures

Brain Structural and Functional Alterations, Clinical Pain Measures	*Strength of Conclusion*	*Reference*
Interrelations between GM alterations and clinical pain measures in chronic MSKP		
↘ GM volume (ACC), ↗ clinical pain intensity	Moderate evidence (2)	57,75
↘ GM volume (pain processing regions), ↗ pressure pain sensitivity	Moderate evidence (2)	18,75
Δ in regional GM volume (pain processing regions), ↗ pain duration	Moderate evidence (2)	30,53,75
↘ Total GM volume, ↗ pain duration in FM	Preliminary evidence (3)	43
↘ GM thickness (pain processing regions), ↗ pain intensity and unpleasantness	Preliminary evidence (3)	53
Interrelations between WM alterations and clinical pain measures in chronic MSKP		
Δ in FA (WM tracts involved in transmission of somatosensory, pain, affective, and cognitive information), ↗ clinical pain intensity	Moderate evidence (2)	40,46,49,54
↗ AD (WM tracts involved in transmission of information through the basal ganglia), ↗ subjective pain scores	Preliminary evidence (3)	46
Interrelations between FC alterations and clinical pain measures in chronic MSKP		
Δ in FC (brain regions/networks involved in somatosensory, pain, and affect-cognitive processing of pain), ↗ clinical pain intensity	Moderate evidence (2)	11,18,27,35,36,41,42,59,60,76
Δ in FC (brain regions/networks involved in somatosensory, pain, and affect-cognitive processing of pain), ↗ pressure pain sensitivity	Moderate evidence (2)	27,35,36
Interrelations between functional activity alterations and clinical pain measures in chronic MSKP		
↘ Functional activity (temporal, occipital regions), ↗ clinical pain intensity and allodynia	Preliminary evidence (3)	48
↗ Functional activity in anterior insula, ↗ clinical pain intensity	Preliminary evidence (3)	23

Abbreviations: ↘, decreased; ↗, increased; FM, fibromyalgia.

Table 5. Glossary of Important Terms Regarding MRI Analysis of Brain Alterations

DMN	A constellation of brain regions thought to be involved in self-referential thinking.[18,32] The DMN is deactivated during various externally focused task conditions.
ICA	Technique to analyze resting state fMRI data, which allows for the estimation of resting state or FC networks.
EAN	The frontoparietal EAN is a brain network involved in cognitive processing of working memory and attention.[23,70]
FA	FA is a measure of the degree of diffusion anisotropy. The FA is normalized so that it ranges from 0 (diffusion is isotropic) to 1 (diffusion is constrained along 1 axis only). FA is typically much higher in WM structures than in CSF and GM, because of the highly organized and tightly packed myelinated axons in WM. Because of this, FA is often used as a surrogate marker for WM 'integrity.'[14]
AD	AD is a measure of diffusion along the first eigenvector. Decreased AD but unchanged radial diffusivity is typically assumed to indicate axonal damage or a lower axonal density.[14] As such, AD leads to a more specific interpretation of the concept of WM 'integrity' associated with FA.
Z-score	A Z-score is a way of standardizing the scale of 2 distributions. When the scales have been standardized, it is easier to compare scores on one distribution with scores on the other distribution. The mean of a distribution of Z-scores is always 0. The SD of a distribution of Z-scores is always 1.
t-score	The t-score is a measure not of the strength of the association but the confidence with which we can assert that there is an association. A t-score is a standard score Z-shifted and scaled to have a mean of 50 and an SD of 10.

Abbreviations: ICA, independent components analysis; EAN, executive attention network; CSF, cerebrospinal fluid.

structural and functional brain alterations, and clinical pain measures such as pain intensity, pain inhibition, and pain duration.[12,79,91,94] Positive and negative correlations between clinical pain measures and GM morphology alterations have been reported in chronic non-MSKP patients in similar regions involved in somatosensory, affective, and cognitive components of pain processing, as reported in chronic MSKP patients.[12,79,91] The observed relations between brain alterations and clinical pain measures in chronic non-MSKP patients are in accordance with the results of our systematic review, but the direction of the relation was often conflicting.

Clinical Relevance and Implications

To our knowledge, this is the first systematic review summarizing the current evidence regarding relations between brain alterations explored with MRI, and clinical pain correlates (ie, pain duration, pain intensity, pain perception, pressure sensitivity, hyperalgesia, hypersensitivity, allodynia, and referred pain) in patients with chronic MSKP. Regarding the results, it can be stated that structural and functional brain alterations are closely related to clinical aspects of pain perception, modulation, and duration. Increased pain intensity and pressure pain sensitivity seem to be related to decreased GM volume in regions involved in somatosensory, affective, and cognitive processing of pain. In contrast, inconclusive evidence was found regarding the direction of the relation between WM and FC alterations, and increased pain intensity or pressure pain sensitivity.

On the basis of the summarized evidence, we can presume that central pain processing mechanisms of the brain play a crucial role in the persistent pain complaints of patients with chronic MSKP. It is clear that pain is associated with a complex interplay among various brain regions and networks. Therefore, it can be recommended that the rehabilitation of patients with chronic MSKP has to be biopsychosocially-driven and that the central nervous system, including the brain has to be addressed. Recently, Baliki and Apkarian and colleagues concluded in 2 reviews that the activity and neuroplasticity of the limbic system plays a crucial role in the chronification of pain.[4,8] This statement is in accordance with our observations of alterations in brain regions that are often engaged in emotional, motivational, and cognitive processing of pain. However, on the basis of the current systematic review and on the available literature the causality of the relations between brain alterations and chronic pain is not yet clear.

Limitations and Strengths

When interpreting the results, the following study limitations have to be taken into account. First, 50% of included studies did not report visual inspection of the raw MRI data quality. Visual inspection of data quality is, however, extremely important in MRI research.[42] Nevertheless, all included studies adequately reported the application of manual exclusion in case of low data quality and/or included automated data adjustment in the preprocessing pipeline. The latter is equally important to obtain valid and reliable structural and fMRI data results.[46,86] Second, despite the fact that neuroimaging research in chronic pain conditions has not only shown alterations in brain structure[5] and function[44] but also alterations in brain chemistry,[33] we did not include articles on brain chemistry. In addition, studies using other functional neuroimaging techniques such as positron emission tomography, magnetoencephalography, and electroencephalography were not included. However, this was beyond the scope of this systematic review. Further, it is crucial to mention the fact that different MRI analytical techniques were used in the included studies, because the specific MRI acquisition and analytical technique can very much affect the outcome of a study. Next, it should be noted that the included studies used different standardized scales or questionnaires to measure clinical features of pain. This might result in difficulties comparing results of different studies. Last, when interpreting results of correlation analyses it is important to realize that a correlation

between 2 variables does not imply a causal relationship. Therefore, no conclusions can be drawn on the causality of the observed relations. Longitudinal studies are required to unravel the direction of the relations and to answer the question of causality: Are brain alterations the result or the origin of chronic pain or a combination?

Several strengths of this systematic review can be outlined. First, the present study is innovative and has important clinical relevance. Second, the methodological quality of the included studies was moderate to good. Furthermore, the methods used for screening and scoring were completed by 2 independent blinded researchers. Last, the NOS was modified by adding 2 items specifically developed for the topic of the current systematic review. Consequently, the methodological quality and risk of bias of the brain MRI articles could have been evaluated more thoroughly giving a more accurate view on the preprocessing of the MRI analyses.

Recommendations for Further Research

In most included studies, the investigation of interrelations between brain alterations and clinical pain measures was a secondary aspect. Researchers are mostly primarily interested in the differences in brain structure and function between patients with pain and healthy individuals. In future research, it is important to include correlation analyses between clinical pain measures and brain alterations as a primary focus of interest. The current systematic review has not included studies that investigated the relation between brain alterations and pain measures associated with maladaptive pain cognitions such as pain catastrophizing and hypervigilance. Maladaptive pain cognitions could be interesting to include in a future systematic review on this topic.

Many chronic MSKP conditions remain largely unexplored regarding this research topic. It would be valuable in future research to investigate also patients with chronic whiplash and chronic idiopathic neck pain regarding brain alterations and the relation with clinical correlates of pain.

Furthermore, it could be interesting to explore the relation between brain alterations and experimental measures of central pain modulation, such as temporal summation or the efficacy of conditioned pain modulation. Efficacy of pain inhibition and the degree of bottom-up sensitization could then be related to potential brain alterations. The interaction between structural and functional brain alterations would also be a valuable research topic. In addition, it could be interesting to further examine the relationship between structural and functional brain connectivity in chronic MSKP patients. Innovative analytical techniques such as graph theoretical analyses of structural and functional brain networks (ie, connectomics) could be applied in pain research and can contribute to an increased insight in chronic pain. Also, new and more advanced data acquisition and analytic techniques such as multishell diffusion MRI and multitissue constrained spherical deconvolution should be used in future pain research.[45] Further, it will be a challenge for researchers and physicians to integrate brain neuroimaging including structural and fMRI into clinical/radiological practice at the individual level.

Finally, despite existing longitudinal brain research in patients with chronic MSKP[10,23,39,62,72,85] the causality of the relations between brain alterations and chronic pain is not yet elucidated. Further research is warranted to clarify the direction of the relations of structural and functional brain alterations with clinical pain measures. It remains a crucial issue to further explore the underlying mechanisms of pain chronification and the role of brain alterations in this transition. Last, it will be a challenge for researchers to explore the effectiveness of different therapy strategies for chronic MSKP patients by analyzing the effects of specific interventions on brain morphological and functional alterations as well as on clinical measures of pain using a longitudinal design.

Conclusion

Moderate evidence was found for relations between clinical pain measures and structural, regional GM and WM morphology, and FC brain alterations within regions involved in somatosensory, affective-motivational, and cognitive processing of pain in chronic MSKP patients. Nevertheless, inconclusive results were found regarding the direction of these relations. Further research is warranted to unravel whether these brain alterations occur as a result of chronic pain or vice versa and whether these alterations are positively or negatively related to clinical measures of pain.

Supplementary Data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jpain.2016.04.005.

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