Systematic Review

Does Conservative Treatment Change the Brain in Patients with Chronic Musculoskeletal Pain? A Systematic Review

Jeroen Kregel, MSc[1,2,3], Iris Coppieters, PT, MSc[1,3], Robby DePauw, PT, MSc[1], Anneleen Malfliet, PT, MSc[1,2,3], Lieven Danneels, PhD[1], Jo Nijs, PhD[2,3], Barbara Cagnie, PhD[1], and Mira Meeus, PhD[1,3,4]

From: [1]Department of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium; [2]Department of Physiotherapy, Physiology and Anatomy, Faculty of Physical Education & Physiotherapy, Vrije Universiteit Brussel, Brussels, Belgium; [3]"Pain in Motion" international research group, www.paininmotion.be; [4]Department of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

Address Correspondence:
Mira Meeus, PhD
Department of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Health Sciences,Ghent University
St Pietersnieuwstraat 33
9000 Ghent, Belgium
Email: mira.meeus@ugent.be

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Background: Chronic musculoskeletal pain is characterized by maladaptive central neuroplastic changes. Many observational studies have demonstrated that chronic pain states are associated with brain alterations regarding structure and/or function. Rehabilitation of patients with chronic musculoskeletal pain may include cognitive, exercise, or multimodal therapies.

Objective: The current review aims to provide a constructive overview of the existing literature reporting neural correlates, based on brain magnetic resonance imaging (MRI) techniques, following conservative treatment in chronic musculoskeletal pain patients.

Study Design: Systematic review of the literature.

Methods: The current review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Literature was searched from 3 databases and screened for eligibility. Methodological quality across studies was assessed with Cochrane Collaboration's tool for assessing risk of bias and quality of evidence was determined applying the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.

Results: A total of 9 eligible studies were identified with a predominant high risk of bias. Cognitive behavioral therapy induced several structural and functional changes predominantly in prefrontal cortical regions and a shift from affective to sensory-discriminative brain activity after behavioral extinction training. Multidisciplinary treatment in pediatric complex regional pain syndrome facilitated normalization of functional connectivity of resting-state networks and the amygdala, and increased gray matter in prefrontal and specific subcortical areas. Exercise therapy led to specific for resting-state functional connectivity and a trend towards pressure-induced brain activity changes.

Limitations: A very small number of studies was available, which furthermore exhibited small study samples. Moreover, only 2 of the included studies were randomized controlled trials.

Conclusions: It is likely that conservative treatments may induce mainly functional and structural brain changes in prefrontal regions in patients with chronic musculoskeletal pain. Due to the relatively high risk of bias across the included studies, future studies with randomized designs are needed to confirm the current findings. In addition, more research evaluating the treatment-induced effects on white matter and whole-brain network dynamics are warranted.

Key words: Chronic pain, musculoskeletal pain, MRI, functional MRI, therapy, rehabilitation, cognitive behavioral therapy, exercise therapy

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Research regarding pain perception has progressed through the recent decades. Old theories of merely passive transmission from peripheral structures to the cortex have been abandoned, while the current view on pain perception yields a dynamic process, influenced by the effects of past experiences (1). Within this perspective, it is recognized that pathological pain states involve central neuroplasticity. Maladaptive neuroplasticity is also a prominent characteristic in the etiology of chronic musculoskeletal pain. The amount of research focusing on structural and/or functional brain alterations regarding chronic pain is increasing. Certain brain regions known to be active in pain processing exhibit morphological alterations in chronic pain patients compared to pain-free healthy people. Still, results remain inconclusive regarding the direction of these gray matter alterations (decrease or increase) in many specific brain regions (2,3). One of these brain regions, the dorsolateral prefrontal cortex (DLPFC), received particular interest due to its role in controlling pain perception by modulation of cortico-subcortical and cortico-cortical pathways (4). Gray matter volume or thickness of the DLPFC was shown to be decreased in multiple cross-sectional studies comparing chronic low back pain, fibromyalgia, and complex regional pain syndrome (CRPS) patients with healthy controls (5-9). In general, gray matter decreases are often associated with longer pain duration across chronic pain populations (5,10,11). On the other hand, gray matter increases were also documented, indicating that the interrelationship between chronic pain and brain morphology may not be a one-dimensional association, and comorbidities of chronic pain, including fatigue and cognitive and emotional impairments should be taken into account (12).

Besides structural changes, functional reorganization is also increasingly documented in several chronic pain populations. The corresponding brain imaging technique, functional magnetic resonance imaging (fMRI), is based on the blood oxygen level dependent (BOLD) signal, which measures inhomogeneities in the magnetic field due to changes in the level of oxygen in the blood (13). Since neural activity requires a hemodynamic response, the BOLD signal is considered a surrogate measure of neural activity. The specific regional activity in chronic pain states is supposed to be different from the brain areas active in acute pain processing. In a study that evaluated brain activations as a result of spontaneous pain intensity fluctuations in patients with chronic back pain, activation of the medial prefrontal cortex corresponded with high intensity pain (14). This area was not activated during thermal pain induction, indicating a substantial contribution of emotion-related circuitry to the chronic pain state. This was furthermore confirmed in a longitudinal study, where brain activity in acute/subacute back pain was limited to regions involved in acute pain processing, whereas activity in persistent back pain increased over time towards emotion-related circuitry (15).

Parallel to the morphological and functional connectivity changes, resting-state brain activity is also altered in chronic pain patients. In resting-state fMRI, which measures the functional connectivity in a task-free state, brain areas that have a strong temporal, low-frequency correlation can be identified (16). Resting-state fMRI may be a particularly convenient technique in evaluating chronic pain states. It gives insight in global brain network dynamics, which is relevant since chronic pain-related neuroplasticity may not be limited to individual brain regions. A specific network of brain areas that is active in this task-free state, the default mode network, has been shown to be disrupted in multiple chronic pain states (17-20).

The knowledge on brain alterations in chronic pain becomes particularly interesting when the ability of translating it into clinical practice arises. Regarding therapy, several conservative treatment methods are available for the rehabilitation of chronic musculoskeletal pain disorders. A common applied treatment is cognitive behavioral therapy (CBT). The usage of the term CBT varies widely and the therapy content may include self-instructions, relaxation or biofeedback, development of coping strategies, changing maladaptive beliefs about pain, and goal setting (21). A Cochrane meta-analysis concluded that CBT treatment for chronic pain resulted in reduced disability and catastrophizing and a small effect for pain (22). Second, the benefits of exercise therapy are well known for patients with chronic pain. Acute effects of exercise interventions for chronic pain patients show conflicting results regarding the activation of endogenous pain inhibition (23). Nevertheless, the long-term responses to exercise therapy seem to be effective for a wide variety of chronic pain diagnoses (24). A third and promising treatment strategy is pain neuroscience education, which focusses on reconceptualizing the patient's perception of pain by teaching about the role of the hypersensitivity of the central nervous system in causing their presenting symptoms (25). An effective treatment of chronic pain

may be multimodal, including several of the aforementioned approaches or other treatments.

Added to the knowledge about brain alterations and the effectiveness of different treatment strategies, increasing research has been conducted regarding the effects of treatment on these neural correlates in chronic pain. A constructive overview of current evidence is however lacking. Insight in these effects is crucial to understand the mechanism of chronic pain and its treatment. This way, we may increase the knowledge on the direction and reversibility of the relationship between chronic pain and brain changes and how to approach chronic pain patients. The aim of this systematic review was therefore to provide a constructive overview of the existing literature reporting neural correlates, based on brain MRI techniques, following conservative treatment in chronic musculoskeletal pain patients. Corresponding associations with clinical measures of changes in pain, disability, and psychosocial correlates were furthermore evaluated.

Methods

Information Sources and Search Strategy

The current review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (26). An extensive search of the online databases PubMed (www.ncbi.nlm.nih.gov/pubmed), Web of Science (www.webofknowledge.com/), and Embase (www.embase.com) was conducted in October 2015. The search strategy was based on the Population, Intervention, Comparator, Outcome (PICO) framework and was conducted to find studies evaluating the effect of conservative treatment approaches (I) on changes in brain structure and function, assessed with MRI techniques (O) in chronic musculoskeletal pain patients (P), compared to no treatment, passive information provision, or patients compared with pain-free healthy controls (C). The following search terms were used for each of the databases: chronic pain AND (brain OR cortex OR insula OR amygdala OR thalamus) AND ("diagnostic imaging" OR medical imaging OR MRI OR fMRI OR morphology OR DTI OR neuroimaging) AND (mirror therapy OR exercise therapy OR "Electric Stimulation Therapy" OR electrical stimulation OR physical therapy OR psychotherapy OR behavioral therapy OR cognitive therapy OR psychological treatment OR education OR exercise OR physical activity OR physical treatment) AND (brain AND (treatment outcome OR change* OR altered OR alteration* OR reduction* OR amelioration OR increase* OR treatment effect)). If available, corresponding MeSH terms were added for each search term in PubMed.

Eligibility Criteria and Study Selection

To be included, studies had to meet the following inclusion criteria: (1) the study sample was human, not animal; (2) patients were diagnosed with a chronic musculoskeletal disorder; (3) a comprehensive combination of conservative physical, psychological, or exercise therapy was conducted; (4) at least one structural or functional brain MRI technique was used; (5) articles had to be written in English, Dutch, or German; (6) full-text articles of original research had to be available; and (7) reviews, systematic reviews, or meta-analyses were not allowed. If not fulfilling each of the inclusion criteria, a study was not considered for inclusion.

Study selection was performed in 2 screening phases: Inclusion criteria were applied to title and abstract in the first phase and on the full-text for the remaining studies. Reference lists of included studies were furthermore screened to control for potentially eligible studies not identified by the predefined search strategy.

Qualification of Searchers and Raters

Study selection was performed by J.K., a PhD candidate working on rehabilitation in chronic neck and low back pain. Study selection was supervised by M.M. and B.C., both PhDs experienced in pain research and conducting systematic reviews in the field of chronic pain. Methodological quality was independently assessed by J.K. and I.C., and discussed afterwards until consensus was reached. In cases of disagreement, the opinion of a third reviewer (M.M.) was requested to reach a decision.

Data Items and Collection

Important information from each study was selected and reported in an evidence table (Table 1). The evidence table is composed of the following items: (1) study, (2) patient group characteristics, (3) control group characteristics, (4) experimental intervention, (5) Control interventions, (6) Evaluations, (7) Outcomes, (8) Main MRI findings, and (9) associations with clinical measures.

Risk of Bias in Individual Studies and Quality of Evidence

The Cochrane Collaboration's tool for assessing risk of bias was used to assess the methodological quality of each included study (http://handbook.cochrane.org/

chapter_8/8_assessing_risk_of_bias_in_included_studies.htm). In this tool, the following domains were assessed: (1) the randomization process, (2) treatment allocation, (3) blinding of participants and personnel, (4) blinding of outcome assessors, (5) completeness of the outcome data, (6) reporting of results, and (7) other sources of bias. Since the current tool was developed to assess risk of bias in randomized controlled trials (RCTs), item 7 was specified to detect selection bias in cohort studies. This was done by examining the procedures of recruitment of patients and controls, diagnosis of patients, and history of disease in healthy controls. Each study was examined on each of the 7 domains and considered a low risk of bias, unclear risk of bias, or high risk of bias.

After clustering the results based on relevant outcome measures, interventions, or subpopulations, the quality of evidence was determined by applying the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (27). This procedure of grading the quality of a body of evidence for a specific outcome is characterized by assigning a quality rating based on the study designs (ranging from very low quality of evidence for case reports to high quality of evidence for RCTs), which can either be downgraded or upgraded by several factors.

Results

Study Selection

A total of 749 records were identified through the database search. Following 2 consecutive screening phases on title/abstract and full text, 7 eligible studies remained. After hand searching the reference lists of the identified articles, 2 more eligible articles were identified for inclusion, resulting in a total of 9 studies. The corresponding flowchart is shown in Fig. 1.

Risk of Bias

Detailed information on the individual risk of bias can be found in Fig. 2. The raters agreed on 90.3% (65 of 72 items) of the items. Of the 9 included studies (28-36), 2 studies were RCTs and 7 studies were controlled cohort studies. The RCTs provided insufficient information about the allocation concealment. All studies exhibited a high risk of bias for the lack of blinding participants and personnel. Only one study specified clearly that outcome assessors were blinded. The cohort studies shared a common high risk of bias regarding their study design and thus resulting in negative scores on random sequence generation and allocation concealment. The item "incomplete outcome data" was graded a low risk of bias in 8 out of 9 studies.

Study Characteristics

The number of patients in each study varied from 10 to 25 patients. In 2 studies, only women were included (30,32), whereas the other studies included both men and women. Another 3 studies included pediatric patients (28,35,36). The mean age of the patient population in all included studies was 36.9 years and the mean age ranged from 13.5 years to 52.1 years.

Individual study results were clustered based on treatment type and corresponding MRI outcomes. A total of 4 studies reported brain changes following CBT: 2 RCTs looked at resting-state fMRI (29) and pain-induced fMRI (32), one cohort study evaluated the changes in structural gray matter (34), and a single cohort study evaluated the effects of behavioral extinction training with pain-induced fMRI (31). One research group, focussing on rehabilitation of pediatric CRPS, conducted 3 studies in which a multidisciplinary treatment, consisting of physical, occupational, and psychological (CBT) therapy was performed (28,35,36). Becerra et al (28) evaluated the changes in multiple resting-state networks pre-to-post-treatment, Simons et al (36) investigated functional connectivity changes, and Erpelding et al (35) looked at gray matter morphological changes as well as functional connectivity changes. Lastly, 2 studies applied exercise therapy; Flodin et al (30) evaluated the effects of exercise therapy with resting-state fMRI within fibromyalgia patients and Micalos et al (33) evaluated the effects of exercise therapy with pressure-induced fMRI in chronic musculoskeletal pain patients.

Cognitive Behavioral Therapy

Resting-state and Pain-induced fMRI

Shpaner et al (29) found changes in the anterior default mode network functional connectivity with the amygdala and periaqueductal gray (PAG) and increased functional connectivity of the basal ganglia with the right somatosensory cortex following CBT, compared with an educational materials intervention in patients with chronic musculoskeletal pain. Jensen et al (32), on the other hand, showed that patients with fibromyalgia exhibited no differences in pain-induced activation pre-treatment, yet an increased pain-evoked activation was found in the prefrontal cortex following CBT, compared with waiting list controls. These fMRI studies ap-

Table 1. *Evidence table.*

Study	Patient group	Control group	Experimental intervention	Control intervention	Evaluations	Outcomes	Main MRI findings	Associations with clinical measures
RS-fMRI								
Becerra et al, 2014 (28) Cohort study	Pediatric CRPS: 9 ♀ and 1 ♂ 14.1y (SEM = 0.72y)	HC: age and sex-matched	Multidisciplinary: 3-week intensive physical, occupational, psychological (CBT) therapy	/	Before and after intervention (matched time for HC)	MRI: • Intrinisic brain network connectivity Clinical: • CDI • MASC • FDI • LEFS	Pre-treatment differences with HC: • ↑ FC in SN, CEN, DMN, RFPN • ↓ FC in LFPN • Both ↓ & ↑ FC in SMN Post-treatment differences with HC: • ↓ FC in SN, DMN, SMN, LFPN • Both ↓ & ↑ FC in CEN, RFPN Pre-to-post-treatment FC changes within patients are shown in the next column as these were encompassed in the correlational analyses. No pre-to-post FC differences found in HC	Correlations of VAS with FC in brain networks pre- to post-treatment for DMN, SN, CEN, SMN, RFPN, Cer. No differences in LFPN. In parallel, significant improvements in psychophysical, functional disability, motor function, depressive, and anxiety symptoms.
Shpaner et al, 2014 (29) RCT	Chronic musculoskeletal pain: 16 ♀ and 3 ♂ 43.6 ± 13.7y	Chronic musculoskeletal pain: 13 ♀ and 6 ♂ 39.2 ± 14.1y	CBT: 90 min/wk, 11 weeks	Educational materials intervention	Before and after intervention	MRI: • Intrinsic brain network connectivity • Whole-brain changes in fALFF Clinical: • Subscales TOPS • BDI • Chronic pain self-efficacy scale • PCS, CSQ	Pre-to-post-treatment changes with control intervention: • ↓ FC between anterior DMN and amygdala, PAG • ↑ FC between BG and r. S2 • ↑ fALFF in cerebellum, PCC No ↓ FC between DMN and l. amygdala, dorsal PAG in control intervention	Treatment-related FC changes correlated with measures of self-efficacy for coping with symptoms, pain management, pain symptoms, passive coping, self-efficacy for pain management. Treatment-related fALFF changes correlated with total pain experience, self-efficacy for pain management, perceived family disability, total pain symptoms.
Simons et al, 2014 (29) Cohort study	Pediatric CRPS: 9 ♀ and 3 ♂ 14.1y (SEM = 0.72y)	HC: age and sex matched	Interdisciplinary treatment of physical, occupational, psychological therapy (indidual/ group-based CBT): 8 hrs/day, 5 days/ wk, 3 weeks	/	Before and after intervention Therapy length of stay based on individual patient progress; typical length was 3 weeks	MRI: • Seed-based FC (amygdala) Clinical: • NRS11 • FOPQ	Pre-treatment differences with HC: • ↑ FC between l. amygdala and prefrontal cortex, motor cortices, parietal lobe, bilateral middle cingulate, basal ganglia, bilateral thalamus, bilateral cerebellum • ↓ FC between l. amygdala and l. precuneus, occipital lobe • ↑ FC between r. amygdala and r. parietal lobe, r. occipital lobe, temporal lobe, r. cerebellum • No regions with ↓ FC with r. amygdala Pre-to-post-treatment changes in pediatric CRPS: • ↓ FC between l. amygdala and prefrontal cortex, motor cortex, parietal lobe, bilateral cingulate, bilateral anterior insula, lobule IX of cerebellum • No ↓ FC r. amygdala or ↑ FC bilateral amygdala Pre-to-post-treatment changes in HC: • ↑ FC between l. amygdala and r. thalamus, bilateral cerebellum • No ↑ FC for r. amygdala or ↓ FC for bilateral amygdala	Treatment-related decrease of fear of pain correlated with decreased FC of amygdala with motor- and somatosensory, cortex, cingulate, frontal areas. No correlations for r. amygdala with fear of pain. No correlations for l./r. amygdala, NRS11.

Table 1 (cont.). *Evidence table.*

Study	Patient group	Control group	Experimental intervention	Control intervention	Evaluations	Outcomes	Main MRI findings	Associations with clinical measures
Flodin et al, 2015 (30) Cohort study	FM: 14 ♀ 48.4y (range 25-64y)	HC: 11 ♀ 41.8 (range 20 – 63y)	Exercise therapy: 2 x 60 min/wk, 15 weeks	/	Before and after intervention	MRI: • FC of 6 pairs of seed regions located in pain regions Clinical: • Bodily subscale of SF36 • FIQ	Pre-to-post-treatment changes in FM: • ↑ FC between r. anterior insula and l. S1/M1*, r. supramarginal gyrus and r. S1/M1, r. supramarginal gyrus and l. inferior PFC • ↓ FC between supramarginal gyrus and cerebellum Pre-to-post-treatment changes in HC: • ↑ FC between supramarginal gyrus and cerebellum *Only this FC was significantly more affected by the intervention compared to HC	No treatment-related correlations found with bodily pain subscale of SF36 and FIQ.
Pain-induced fMRI								
Diers et al, 2012 (31) Cohort study	FM: 9 ♀ and 1 ♂ 52.1 ± 6.08y	/ (Only HCs for pain thresholds; not compared to MRI outcomes)	BET: 120min/wk, 12 weeks	/	Before and after intervention	MRI: • Brain activation to mechanical painful stimulation of the index finger Clinical: • Pain-related interference and pain severity from MPI • CESDS	Pre-treatment pain-induced activations in FM: • In bilateral anterior insula, MCC, bilateral caudate nucleus/striatum. Post-treatment pain-induced activation in FM: • In contralateral S1, bilateral S2, MCC, bilateral caudate nucleus/striatum, bilateral posterior insula. No significant post-pre contrast was found in pain-induced activations	Treatment-related positive correlation between pain interference/severity and posterior insula, ipsilateral caudate nucleus / striatum, contralateral lenticular nucleus of basal ganglia, l. thalamus, contralateral S1. No correlation with changes in depression.
Jensen et al, 2012 (32) RCT	FM: 25 ♀ 44.5y (SEM = 1.5y)	FM: 18 ♀ 46.9y (SEM = 1.1y)	Experimental: CBT (ACT): 90 min/wk, 12 weeks	Waiting list	fMRI / questionnaires before and after intervention + 3month follow-up questionnaires	MRI: • Brain activation to mechanical painful stimulation of the thumbnail Clinical: • PGIC • BDI • STAI-S	Pre-treatment differences in experimental, compared to control group: • No differences in pain-induced activations Post-treatment differences in experimental, compared to control group: • ↑ activity in vlPFC, OBFC • ↑ vlPFC-thalamic connectivity In the control group, no regions detected where activity was increased post-treatment and no regions that showed increased vlPFC connectivity	Positive correlation of change in anxiety with vlPFC activity after CBT, but not in control group. No correlations of brain activation with clinical treatment effects or depression. VAS rating and experimental pain not improved after CBT.
Micalos et al, 2014 (33)	Chronic musculoskeletal pain: 9 ♀ and 2 ♂ 50.0 ± 12	HC: 7 ♀ and 1♂ 49.6y ± 10	Exercise therapy: 2 x 20min/wk, 12 weeks	HCs performed same exercise therapy	Before and after intervention	MRI: • Brain activation to standardized somatic pressure stimulation on r. anterior mid-thigh Clinical: • Perceptual pain pressure rating	Differences in experimental, compared to control group: • Trend differences for superior temporal gyrus, thalamus, caudate Pre-to-post-treatment differences total group: • Trend differences for superior temporal gyrus, thalamus, caudate Pre-to-post-treatment group by time interaction: • Trend differences for superior temporal gyrus, caudate	/

Table 1 (cont.). *Evidence table.*

Study	Patient group	Control group	Experimental intervention	Control intervention	Evaluations	Outcomes	Main MRI findings	Associations with clinical measures
Structural MRI								
Seminowicz et al, 2013 (34) Cohort study	Chronic pain: 10 ♀ and 3 ♂ 51.4 ± 11.8y	HC: 10 ♀ and 3 ♂ 51.6 ± 11.9 + 6 ♀ and 4 ♂ 36.0 ± 9.73y Chronic pain subtypes: low back (n = 6), myofacial (n = 2), headache (n = 2), FM (n = 1), upper body (n = 1), pelvic floor (n = 1)	CBT: 90 min/wk, 11 weeks	/	Chronic pain: intake, 11 weeks Healthy subjects 1: intake Healthy subjects 2: intake, 6 months	MRI: • VBM measures of GM volume/ density Clinical: • SFMPQ, TOPS pain symptoms • SF36 mental and physical subscales, TOPS total pain experience • BDI • CSQ	Pre-treatment differences with HC: • No differences Pre-to-post-treatment changes in patients: • ↑ GM in l. inferior PPC, r. premotor/M1/S1, r. HIC, r. DLPFC, l. S1, l. subgenual. ACC/OBFC, l. superior PPC, l. inferior temporal cortex, S2/M1, r. premotor/IFG, l. inferior temporal • ↓ GM in SMA/pre-SMA Post-treatment differences in patients, compared to HC: • ↑ GM in l./r. DLPFC, ventral/dorsal l. PPC, r. HIC No longitudinal changes found in subgroup of HC's at 2 time points over 6 months	Treatment-related negative correlation of Catastrophizing with change in PPC (S1/S2), l. DLPFC, IFG/VLPFC, bilateral posterior ACC/medial PFC. Positive correlation with change in r. HIC, r. DLPFC. Treatment-related negative correlation of Pain control with change in HIC. Positive correlation with change in r. motor cortex. Treatment-related positive correlation of Physical ability with change in r. middle temporal gyrus. No correlations for depression, mental subscale SF36, total pain experience. No significant reductions in pain/physical health.
RS-fMRI + structural MRI								
Erpelding et al, 2015 (35) Cohort study	Pediatric CRPS, cross-sectional: 12 ♀ and 9 ♂ 13.3 ± 2.5y Pediatric CRPS, longitudinal: 13 ♀ and 7 ♂ 13.5 ± 2.4y	HC: age and sex matched	Interdisciplinary treatment of physical, occupational, psychological therapy (individual/group-based CBT): 8 hrs/day, 5 days/wk, 3 weeks	/	Before and after intervention	MRI: • Cortical thickness • VBM measures of subcortical GM volume/ density • FC of DLPFC-PAG Clinical: • NRS11 • CDI • MASC • PCS-C • FOPQ • FDI	Pre-treatment structural differences with HC: • ↓ cortical thickness in M1, PMC, SMA, paracentral lobule, middle temporal gyrus, OBFC, DLPFC, anterior/posterior MCC, DPCC, fusiform gyrus, precuneus • No ↑ cortical thickness in any region • ↓ subcortical GM in caudate, putamen, nucl. accumbens, anterior thalamus, amygdala, anterior HIC • ↑ subcortical GM in mediodorsal thalamus, posterior HIC Pre-to-post-treatment structural changes in pediatric CRPS • ↑ cortical thickness in DLPFC • ↑ subcortical GM in putamen, caudate, parahippocampal gyrus, hypothalamus, mediodorsal thalamus + cluster including HIC, amygdala • No ↓ GM in any region or changes in overall GM volume in caudate, putamen, thalamus, HIC, amygdala Pre-to-post-treatment FC changes in pediatric CRPS: • Negative correlation between DLPFC-PAG activity pre-treatment → positive correlation post-treatment	Treatment-related negative correlation between depression and change in DLPFC thickness. Positive correlation between catastrophizing pre- and post-treatment and caudate GM. Positive correlation between catastrophizing pre- and post-treatment and hippocampal GM. No correlation with pain intensity found.

RS fMRI = resting-state functional MRI; RCT = randomized controlled trial; CRPS = complex regional pain syndrome; FM = fibromyalgia; HC = healthy controls; CBT = cognitive behavioral therapy; BET = behavioral extinction training; ACT = acceptance and commitment therapy; l = left; r = right; FC = functional connectivity; SN = salience network; CEN = central executive network; DMN = default mode network; RFPN = fronto-parietal network - right; LFPN = fronto-parietal network - left; SMN = sensorimotor network; VAS = visual analogue scale; Cer = cerebellum network; BG = basal ganglia network; MCC = medial cingulate cortex; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; MPI = West Haven-Yale multidimensional pain inventory; GM = gray matter PPC = posterior parietal cortex; M1 = primary motor cortex; PMC = premotor cortex; HIC = hippocampus; PFC = prefrontal cortex; DLPFC = dorsolateral prefrontal cortex; ACC = anterior cingulate cortex; DPCC = dorsal posterior cingulate cortex; IFG = inferior frontal gyrus; SMA = supplementary motor area; VLPFC = ventrolateral prefrontal cortex; OBFC = orbitofrontal cortex; PAG = periaqueductal gray; fALFF = fractional amplitudes of low frequency fluctuations; PCC = posterior cingulate cortex; n = nucleus; CDI = children's depression inventory; MASC = multidimensional anxiety scale for children; FDI = functional disability inventory; LEFS = lower extremity functional scale; TOPS = treatment outcomes in pain survey; BDI = Beck depression inventory; PCS = pain catastrophizing scale; CSQ = coping strategies questionnaire; NRS11 = 11-point numerical rating scale; FOPQ = fear of pain questionnaire; SF36 = short form health survey 36 items; FIQ = fibromyalgia impact questionnaire; MPI = multidimensional pain inventory; CESDS = center for epidemiological studies depression scale; PGIC = patient global impression of change; STAI-S = Spielberger state-trait anxiety inventory; SFMPQ = short form McGill pain questionnaire; PCS-C = pain catastrophizing scale – child version

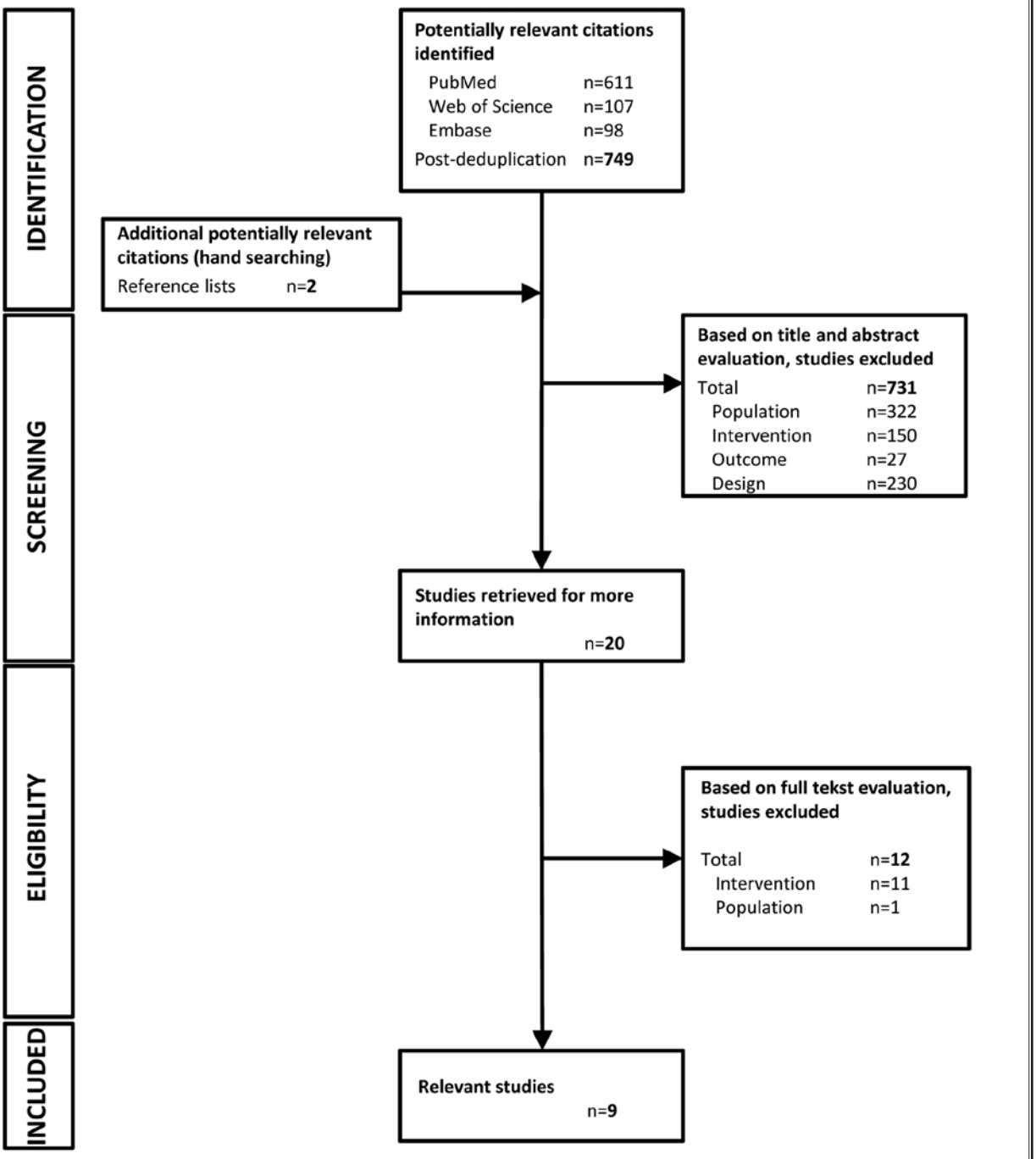

Fig. 1. *PRISMA flowchart of study selection.*

plied different imaging techniques and outcomes, but both studies found correlations of pre-to-post-treatment activity changes with clinical measures of coping with pain symptoms and pain management (29), and anxiety (32).

Diers et al (31) conducted a study to evaluate the brain responses to behavioral extinction training with pain-induced fMRI. The results showed that pre-treatment pressure stimuli elicited activation in the bilateral anterior insula, medial cingulate cortex, and bilateral caudate nucleus/striatum. These activations shifted towards more posterior locations post-treatment, including the contralateral primary somatosensory cortex, bilateral secondary somatosensory cortices, medial cingulate cortex, bilateral caudate nucleus/striatum, and bilateral posterior insula. An important note is that no significant pre-to-post contrast was found. These treatment-related changes of more activation in the bilateral posterior insula, contralateral primary somatosensory cortex, and ipsilateral caudate nucleus/striatum were correlated with less interference or pain severity. A reduction in interference from pain was furthermore associated with more bilateral activation in the posterior insula, contralateral primary somatosensory cortex, and ipsilateral caudate nucleus/striatum.

Structural MRI

Seminowicz et al (34) found increased gray matter in bilateral DLPFC. This corresponds with the results of the study of Jensen et al (32), which found an increased pre-to-post-treatment pain-evoked activation of prefrontal cortical areas. It should be noted that the latter study was an RCT, in which CBT was compared to waiting list controls. This morphological change in the DLPFC was associated with improvements in catastrophizing (34).

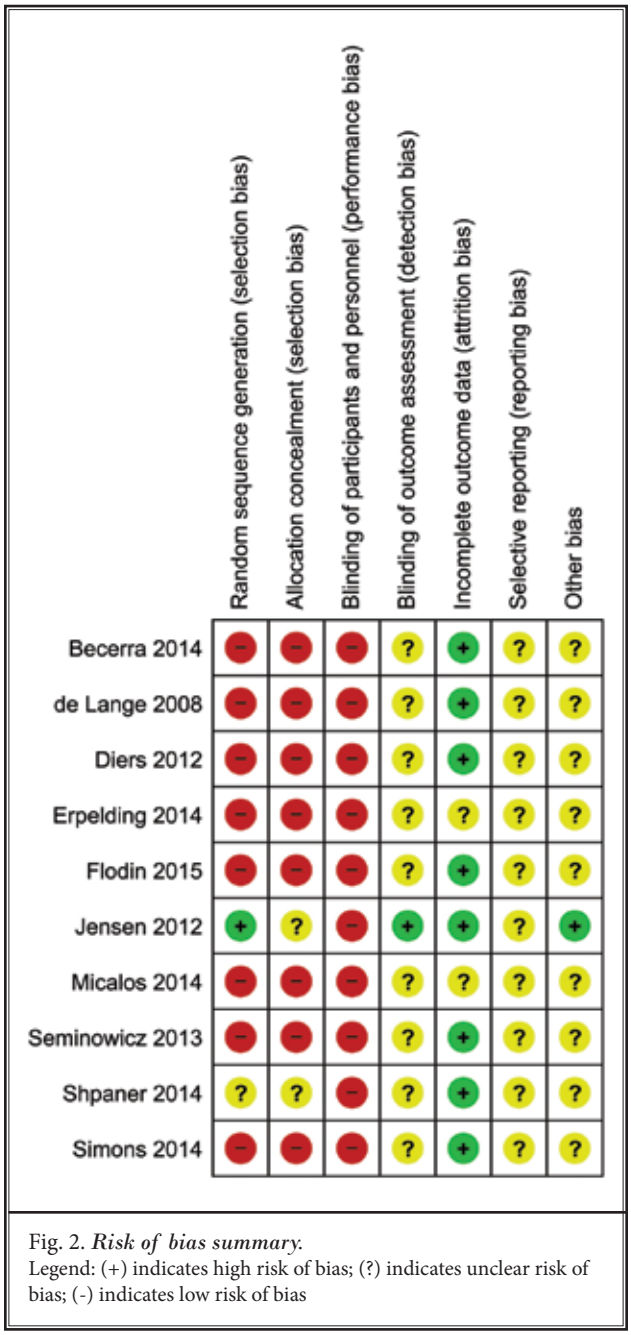

Fig. 2. *Risk of bias summary.*
Legend: (+) indicates high risk of bias; (?) indicates unclear risk of bias; (-) indicates low risk of bias

These results indicate a low level of evidence regarding both functional and structural changes in prefrontal areas following CBT, including increased pain-evoked activation and increased gray matter volume in patients with chronic musculoskeletal pain. The respective brain changes were associated with treatment-related improvements of coping with pain symptoms, pain management, anxiety, and catastrophizing. Preliminary evidence was found for a shift of pain-induced activations from more affective brain regions towards sensory-discriminative regions, including the posterior insula and primary somatosensory cortex, following behavioral extinction training.

Multidisciplinary Treatment in Pediatric Patients with Complex Regional Pain Syndrome

Resting-state fMRI

Resting-state fMRI findings in the study of Becerra et al (28) exhibited a pre-treatment increased functional connectivity of several brain networks, including the fronto-parietal, salience, default mode, central executive, and sensorimotor networks compared to healthy controls. From these networks, the connectivity within the salience, central executive, default mode, and sensorimotor networks was decreased pre-to-post-treatment. In addition, Simons et al (36) found that the pre-treatment hyperconnectivity of the left amygdala with the motor cortex, parietal lobe, and cingulate cortex was normalized after multidisciplinary physical, occupational, and psychological (CBT) treatment. Erpelding et al (35) evaluated the functional connectivity of the DLPFC and the PAG, which was negatively correlated pre-treatment, but changed to a positive correlation post-treatment.

The pre-to-post-treatment functional connectivity decreases of resting-state networks in Becerra et al (28) were associated with pre-to-post-treatment visual analogue scale (VAS) changes. Another association was found in the study of Simons et al (36), in which the pre-to-post-treatment decreased left amygdala functional connectivity with several other brain areas was associated with decreased pain-related fear after treatment.

Structural MRI

Only Erpelding et al (35) investigated morphological brain changes in pediatric CRPS following multidisciplinary treatment. The patients in this study exhibited reduced pre-treatment cortical thickness and subcortical gray matter compared to healthy controls in several regions. Following treatment, increased cortical thickness in patients was found for the DLPFC, and increased volumes for the amygdala, basal ganglia, thalamus, and hippocampus. No decreased gray matter changes pre-to-post-treatment were found.

The gray matter increase in the hippocampus was associated with reduced pain catastrophizing, yet this was negatively correlated with increased gray matter in the left DLPFC. The change of the DLPFC thickness was furthermore negatively correlated with depression post-treatment.

A low level of evidence was found regarding the normalization of the resting-state network functional connectivity and decreased connectivity of the amygdala with several other brain regions following multidisciplinary treatment in pediatric CRPS. Based on the single study results of morphological changes, a low level of evidence indicates a treatment-induced prefrontal cortical thickness increase, and increased subcortical volumes in areas associated with sensation, emotion, cognition, and pain modulation. The changes in brain function were associated with an improvement of subjective pain rating and pain-related fear, whereas the morphological changes were associated with changes in pain catastrophizing and depression.

Exercise Therapy

Flodin et al (30) performed resting-state fMRI before and after exercise therapy in fibromyalgia patients and assessed the functional connectivity in 6 pairs of seed regions associated with pain processing. Several changes pre-to-post-treatment were reported, however, only increased functional connectivity of the right anterior insula with left primary sensory and motor cortices was significantly affected, compared to healthy controls. No correlation with bodily pain of the SF-36 or with the fibromyalgia impact questionnaire of was found.

Micalos et al (33) assessed brain activity as response to innocuous somatic pressure stimulation before and after an aerobic exercise intervention for both chronic musculoskeletal pain patients and healthy controls. No significant changes in brain activity were found pre-to-post-treatment, however, trend differences in the group by time interaction were detected for the activity of the superior temporal gyrus and caudate nucleus. No comparison with clinical measures was made.

These findings indicate preliminary evidence for regional changes in resting-state functional connectivity and pressure-induced activation following exercise therapy. The resting-state and pressure-induced fMRI findings did not provide any evidence for correlations with clinical parameters.

Discussion

The aim of the present systematic review was to provide an overview of the existing literature regarding functional and structural brain changes following

conservative treatment in patients with chronic musculoskeletal pain. The included studies were characterized by a dominant high risk of bias, particularly explained by the high contribution of cohort studies, in which the control group was a healthy control group not undergoing any therapy. Nevertheless, the results of the studies that applied CBT imply that treatment-related morphological and functional changes occurred most prominently in prefrontal brain areas. Brain changes after multidisciplinary treatment in pediatric CRPS focused on normalization of resting-state network and amygdala functional connectivity, together with regional gray matter morphology increases. The results of the studies that applied exercise therapy point out preliminary evidence of brain changes, which indicated modest, yet specific, resting-state functional connectivity changes and only trends towards pressure-induced brain activity changes.

A major part of the included studies applied CBT as (part of) their treatment. In previous research, CBT has been demonstrated effective for several (non-)musculoskeletal chronic pain disorders (37-43), for which the most efficacious effects were found on psychological functioning and pain intensity. Consequently, improvements of several psychological outcomes were found in the included studies in the present review. This is important since the interaction between chronic pain, psychosocial functioning, and brain processes remains largely unknown. Demonstrated associations of brain changes with psychological measures following therapy may represent the clinical implications of changes in brain activity or morphology. The CBT studies found associations with pain coping/management (29), anxiety (32), catastrophizing, and pain control (34). Common brain areas that showed changes following CBT that correlated with these psychological measures were localized in prefrontal areas. Shpaner et al (29) found pre-to-post-treatment functional connectivity changes of the anterior default mode network with the amygdala and PAG, Jensen et al (32) found increased pain-induced activity in the ventrolateral prefrontal cortex (VLPFC), and Seminowicz et al (34) showed that gray matter volume in the DLPFC was increased following CBT. The DLPFC and VLPFC have been extensively studied for their role in descending pain modulation (44-46) and an increased activation or increased gray matter volume in these regions may indicate an improvement of descending pain modulation. The DLPFC has previously been shown to exhibit decreased gray matter density in chronic pain patients (5) and has a well-established role in the recruitment of endogenous pain modulation through projections on the rostral anterior cingulate cortex and the PAG – rostral ventromedial medulla – dorsal horn pathway. Also, the VLPFC is involved, but this region has been associated with reappraisal of the emotional significance of a stimulus (44). The decreased functional connectivity with the PAG following CBT in the study of Shpaner et al (29) may be difficult to interpret; however, the authors themselves stated that this discrepancy may have arisen from the task-related fMRI in previous studies, while functional connectivity between the DLPFC and PAG in their study was examined during resting-state fMRI. Functional connectivity between regions may therefore differ under various circumstances.

Another interesting finding of the 5 included studies that applied CBT as single therapy was that 3 studies did not find a reduction in pain intensity (31,32,34), while the other studies did not implement measures of pain intensity. A plausible explanation for the lack of effect on pain intensity may be that pain intensity in these studies was measured directly after completing therapy, whereas CBT aims to change pain behaviors rather than pain intensity. It is therefore possible that a significant pain intensity decrease may develop during a longer timeframe, or even after completion of therapy, induced by behavioral changes. This effect was also seen in a study that applied a relapse prevention program after CBT in chronic musculoskeletal pain patients, which showed a significant decrease in pain intensity at 4 months follow-up, compared with pain intensity immediately after completion of CBT (47).

The results from the study of Diers et al (31) concentrated on activations in the insula and primary somatosensory cortex, more specifically in response to behavioral extinction training evaluated by mechanical pain-induced fMRI. Their results included a shift from anterior insula activations pre-treatment to activations in the posterior insula and primary somatosensory cortex post-treatment. Although this study lacked a significant pre-post contrast, the change in activity correlated with pain-related interference and pain severity. In addition, activation in the anterior insula has been linked with anticipation of high pain intensity (48) and has been identified as a possible key region in cognition-emotion integration (49). Recent findings of a study that applied intracerebrally recorded nociceptive laser evoked potentials in the insula indicated that nociceptive stimuli are first processed in the posterior insula for pain intensity and anatomical location, then forwarded to the anterior

insula for the emotional integration (50). The findings of Diers et al (31) therefore imply that behavioral extinction training in patients with fibromyalgia reduces the emotional involvement of processing painful stimuli, and induces a shift to a more sensory-discriminative way of pain processing post-treatment.

Three of the included studies evaluated brain changes in pediatric patients with CRPS following a multi-disciplinary treatment consisting of physical, occupational, and psychological (CBT) treatment (28,35,36). When considering these results, it should be taken into account that children's brains are in development, and although not similar as in adults, the foundations of resting-state networks can already be recognized in premature children (51,52). Becerra et al (28) found a substantial overlap of healthy children's resting-state networks with those reported in adult literature. Their main findings included hyper-connectivity in resting-state networks before treatment and reductions of functional connectivity in salience, central executive, default mode, and sensorimotor networks that correlated with reductions of pain intensity (VAS) following treatment. In adult patients with CRPS, however, the default mode network showed mainly reduced functional connectivity compared to healthy controls (53). In addition, specific reductions in amygdala functional connectivity following treatment in pediatric patients with CRPS were found in the study of Simons et al (36). Baseline results included a hyper-connectivity of the amygdala with several cortical, subcortical and cerebellar regions, compared to healthy controls, whereas functional connectivity following treatment was reduced between the left amygdala and motor cortex, parietal lobe, and cingulate cortex. The role of the amygdala in chronic pain states has been evaluated in previous research, which has shown altered amygdala functional connectivity in chronic low back pain (15,17) and fibromyalgia (54,55), but also in migraine (56) and irritable bowel syndrome (57). The amygdala is well-known for its pain-related processing of fear, anxiety, and fear memory, and plays a crucial role in the development of a chronic pain state (58). The results of the study of Simons et al (36) was another confirmation of the crucial role for the amygdala, since a decreased amygdala functional connectivity coincided with a decrease in fear of pain.

The study of Erpelding et al (35) was the only study evaluating morphological gray matter changes following multidisciplinary treatment in pediatric CRPS. Cortical thickness and subcortical gray matter volumes were predominantly smaller, compared with healthy controls, in sensory, motor, emotional, cognitive, and pain modulatory regions. Cortical thickness of the DLPFC and subcortical volumes of the thalamus, basal ganglia, amygdala, and hippocampus increased after treatment. This was partly in accordance with the study of Seminowicz et al (34), which, however, did not show pre-treatment morphological differences between adult chronic pain patients and healthy controls, but found pre-to-post-treatment increased gray matter in the DLPFC and hippocampus in the patient group. Furthermore, a treatment-related change in functional connectivity between the DLPFC and PAG was found, which was negatively correlated pre-treatment and positively correlated post-treatment (35). This may indicate that top-down modulation of pain processes was improved due to the treatment (44).

Two of the included studies applied physical exercise therapy (30,33). Flodin et al (30) included fibromyalgia patients, which were evaluated by resting-state functional connectivity of 6 predefined seed regions. Only a significant normalization was found of the connectivity between the right anterior insula and left primary somatosensory cortex, which showed a decreased pre-treatment connectivity compared to healthy controls. This functional connectivity change did not correlate with changes in clinical symptoms. The normalization of resting-state functional connectivity is partly comparable to results of the CBT (29) and multidisciplinary treatment studies (36), which, however, mainly demonstrated treatment-related decreased functional connectivity of the prefrontal and limbic regions. Where the former psychological-based treatment studies showed normalization of cognitive-emotional regions, the current exercise intervention study showed a normalization of sensory integration through regions such as the insula and primary somatosensory cortex. A reduced functional connectivity of the bilateral insula was previously shown in fibromyalgia patients (59).

The study of Micalos et al (33) did not show any statistically significant pressure-induced brain activity changes following exercise therapy in a sample of chronic musculoskeletal pain patients. Only group by time trends towards activity changes in the superior temporal gyrus and caudate nucleus were shown. It should therefore be concluded that much more research is needed to provide evidence for brain changes after exercise therapy in chronic musculoskeletal pain patients.

The findings of the current review, with several treatment-related changes in prefrontal areas, limbic

structures, and corresponding clinical improvements, may indicate that the applied therapies have a certain effect on the cerebral processes of maintaining a chronic pain state. A recently proposed theory of Baliki and Apkarian (60) regarding predisposing factors, transition to, and maintenance of chronic pain states, draws attention to the limbic system. According to this theory, limbic brain properties may be a risk factor for developing chronic pain and may furthermore be involved in the shift of the threshold delineating unconscious nociception to conscious pain perception, referred to as the corticostriatal threshold. After a specific injury, activation of corticostriatal circuitry either leads to coping with the injury and recovery over time or leads to further lowering the corticostriatal threshold, which enhances afferent signals resulting in a chronic pain state. It is, however, unclear what the exact underlying processes leading to brain changes in reaction to treatment are. Furthermore, it remains to be elucidated to what extent these treatments induce a true reversal of the chronic pain state or just lead to adaptive brain changes in order to cope with chronic pain.

Some limitations should be noted in the present review. First, relatively few studies were identified that evaluated brain responses to conservative treatment in musculoskeletal chronic pain patients. Since the included studies were characterized by a fair amount of heterogeneity with different types of treatment and imaging modalities, clustering of the results and deduction of conclusions were limited. However, to our knowledge, the current review is the first attempt to systematically provide an overview of the methodological characteristics and results of the available studies on this subject matter. As there were at least 2 studies available for each therapy modality, it was possible to determine levels of evidence, although these were relatively low.

Furthermore, clustering of results might have been biased by the inclusion of studies on patients with chronic musculoskeletal pain, rather than specific chronic pain patients. Although the literature describes many corresponding findings regarding MRI outcomes in chronic pain patients, a study of Baliki et al (61) found specific morphological reorganization differences between chronic back pain, CRPS, and knee osteoarthritis.

A study-specific limitation was the inclusion of relatively low numbers of patients across studies, with most of the studies including between 10 and 20 patients. Although this is a common limitation of MRI studies, more studies with larger sample sizes are required to gain high quality evidence regarding effective treatment approaches for chronic pain and corresponding brain responses. Furthermore, most studies evaluated their patients at intake and immediately after therapy. It was already shown in a sample of patients with chronic posttraumatic headache that specific regional gray matter decreases were found 3 months after the accident, while these changes resolved after one year, in parallel with the cessation of the headache (62). Rehabilitation of chronic pain is a complicated and long-lasting process, which may have treatment effects long after finishing therapy. Lastly, only 2 RCTs were identified in the current review. An RCT is the only study design able to detect causal relationships and to identify characteristics of people who respond to therapy in a heterogeneous sample (63). Future clinical trials should therefore examine the long-term effects of conservative treatment on brain changes in sufficiently powered study samples of patients with chronic musculoskeletal pain.

Future research should also focus on other brain MRI modalities in response to treatment for patients with chronic musculoskeletal pain. To our knowledge, no studies have evaluated the effects of treatment on white matter fiber properties in this patient group. Previous studies, however, found white matter abnormalities compared to healthy controls in patients with chronic musculoskeletal pain (7,64-66). Correspondingly, little research has been done on whole-brain network dynamics in chronic pain patients. As it is more accepted that pain and the effects of chronic pain are not limited to specific brain regions, but affect the whole brain, Kucyi and Davis (67) introduced the dynamic pain connectome, which describes "the spatiotemporal signature of brain network communication that represents the integration of all aspects of pain." In addition to the current knowledge, future studies on whole-brain network dynamics might reveal more comprehensive effects on the interaction between chronic pain and the brain, and may facilitate the development of disorder-specific and personalized treatments.

Conclusion

To conclude, it is likely that conservative treatments for patients with chronic musculoskeletal pain may induce both functional and morphological changes to predominantly prefrontal brain regions. Most brain changes were associated with several psychosocial outcome measures. Since the evidence is based on a limited number of mainly non-randomized studies, with limited patient numbers, several limitations should be noted. Future research requires adequately powered randomized designs to either

confirm or refute the preliminary findings currently available in the literature. In addition to the current evidence, more research should be conducted to evaluate the effects of conservative treatments on properties of white matter structure and whole-brain network dynamics in patients with chronic musculoskeletal pain.

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