ORIGINAL ARTICLE

Network Connectivity in Chronic Musculoskeletal Pain: A Systematic Review of Resting State Functional Magnetic Resonance Imaging Studies

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Abstract

Central mechanisms of chronic musculoskeletal pain, specifically disruption of network connectivity, are poorly understood. This systematic review analyzes the current understanding of functional network connectivity in chronic pain, with a focus on resting state functional magnetic resonance imaging studies in chronic musculoskeletal pain. The search terms included terms and synonyms that represent resting state neuroimaging of functional connectivity combined with terms and synonyms that represent chronic pain and related disorders. The search was limited to studies performed in the past twenty years, involving adult, human subjects in whom functional connectivity was measured either before, after or independently of treatment. Connectivity was typically aberrant in regions related to default mode network, salience network and sensorimotor network. Aberrant connectivity was also conspicuous within primary visual network, brainstem regions (nucleus accumbens, periaqueductal gray matter), and the striatal network that governs emotion, motivation and reward. The findings from the literature on functional magnetic resonance imaging in chronic back pain patients are heterogeneous, precluding any clear identification of reliable patterns that can be used as diagnostic or treatment biomarkers. Future studies that take into account neurodevelopmental co-morbidities, emotional processing traits, and function of the adrenergic system are needed in order to better understand the central nervous system mechanisms underlying disability in chronic pain.

Abbreviations:
Anterior Cingulate Cortex (ACC), Attention Deficit Hyperactivity Disorder (ADHD), Blood Oxygen Level-Dependent (BOLD), Default Mode Network (DMN), Electroencephalogram (EEG), Federal Drug Administration (FDA), Frontal Cortex (FC), Functional Magnetic Resonance Imaging (fMRI), Irritable Bowel Syndrome (IBS), Learning Disorder (LD), Medial Frontal Cortex (mFC), Medial Prefrontal Cortex (mPFC), Periaqueductal Gray (PAG), Position Emission Tomography (PET), Rostral Anterior Cingulate Cortex (rACC), Sensorimotor Setwork (SMN), Single-Shoton Emission Computerized Tomography (SPECT), Visual Analog Scale (VAS), Ventromedial Prefrontal Cortex (vmPFC).

Introduction

Patients with pain disorders often display atypical patterns of functional connectivity. Atypical patterns of functional connectivity occur because of two reasons in chronic pain. First, re-organization of the cerebral cortex caused by chronic pain signals leads to adaptive changes in overall network connectivity (Pelletier *et al.* 2015). Second, imbalances in the adrenergic (parasympathetic vs. sympathetic) system can influence cerebral hemodynamics as well as clinical symptoms (Benson *et al.* 2019; Hsieh *et al.* 1996). These adaptive changes in functional connectivity are potentially reversible with treatments that target the adrenergic system (Benson *et al.* 2019). In fact, successful treatment of pain is associated with resolution of atypical patterns of functional connectivity (Kano *et al.* 2018). Changes in functional connectivity occur across a host of pain disorders with different etiological causes of pain. For example, neuropathic pain, which is caused by pain in peripheral nerve endings, is centrally regulated, possibly within the thalamus (Henderson *et al.* 2013). Therefore, targeting functional connectivity may be a useful approach for patients with different causes of chronic pain disorders (Li *et al.* 2014).

Chronic pain affects approximately 20% of adults, with 8% of adults reporting high-impact pain (Dahlhamer *et al.* 2018). The most common conditions associated with chronic pain in the United States are lower back pain, osteoarthritis, and rheumatoid arthritis (Johannes *et al.* 2010). No current, Federal Drug Administration (FDA)-approved treatments for pain are designed to target functional connectivity. Also, no current FDA-approved treatments, other than opiate-based treatments, are designed to target central mechanisms common to different types of chronic pain. Current FDA-approved treatments for chronic pain target either the opiate system, inflammation, neuruopathic pathology or neurotransmitters. Current novel agents for chronic pain, currently under study in Phase II and Phase III clinical trials, including gabapentin (Ribeiro 2020; Schuster 2020), opioids (Kuzla 2020; University of Minnesota 2020), cannabidiol (Lakin 2020), ketamine (Lim 2019), oxytocin (Curry 2020; Eisenach 2020), cabergoline (DiVasta 2019), Transforming Growth Factor (TGF)-alpha/epiregulin monoclonal antibody (Lilly 2020a, 2020b), D-cycloserine (Schnitzer 2020), nortriptyline (Nackley 2020), oxcarbazepine (Ribeiro 2020), brivaracetam (Falci 2020), and minocycline (Loggia 2020), are targeting similar mechanisms to current FDA-approved treatments. These are critical research gaps since chronic pain is 1) common, 2) debilitating, and 3) difficult to treat.

This paper updates what is known about functional connectivity in chronic pain since the last systematic review of studies up to August 2016 (Ng *et al.* 2018). The previous review included 14 resting state fMRI studies. The current study includes 24 such studies. This updated review was important due to the recent surge in publications on the topic. Six studies included in the previous review also met criteria for the current study. This review expands beyond the prior review in that It includes studies of chronic musculoskeletal pain in other locations such as the neck and shoulder.

The primary aim of this study is to review what is known about resting state brain network connectivity in chronic musculoskeletal pain. If the aims of this study are achieved, a central framework for understanding functional connectivity in chronic pain can be formulated. Approaching central mechanisms of pain may be significant for understanding different chronic pain disorders. Furthermore, findings from chronic pain may translate to disorders hallmarked by psychological pain. Functional Magnetic Resonance Imaging (fMRI) has become an objective method to understand the properties of not only chronic pain but also autism, depression, schizophrenia and others (Biswal *et al.* 2010). In fact, the cerebral mechanisms for pain are common to both physical and psychological pain (Vachon-Presseau *et al.* 2016). A new functional connectivity framework for chronic pain may also lead to new interventions to fight the opiate epidemic. The United States Pain Foundation, the American Academy of Pain Medicine, and the National Institute of Health (i.e. the "HEAL" Initiative), are commonly advocating for increased development safer, more effective pain treatments (National Institutes of Health 2020).

Methods

This study includes all English language studies published in Pubmed or Medline over the past twenty years from October 01, 2000 to October 26, 2020, involving adult, human subjects suffering from any cause of chronic musculoskeletal pain in whom functional network connectivity was measured either before, after or independently of treatment. Studies were included if they compared patients to themselves before and after treatment, and also if they compared patients to a reference group without pain. Studies were also included if there was no intervention. The search terms included terms and synonyms that represent resting state neuroimaging of functional network connectivity combined with terms and synonyms that represent chronic musculoskeletal pain and related disorders.

The exact search term used was:

(((((("functional magnetic resonance imaging") AND (chronic pain)) OR ("pain clinics")) OR ("low back pain")) OR ("back pain")) AND ("resting state")

Studies of chronic migraine, which is outside of the scope of this review, were excluded as is common in chronic pain studies due to its unique and complex pathology as well as treatment (Williams *et al.* 2020). Studies of chronic headache or orofacial pain were

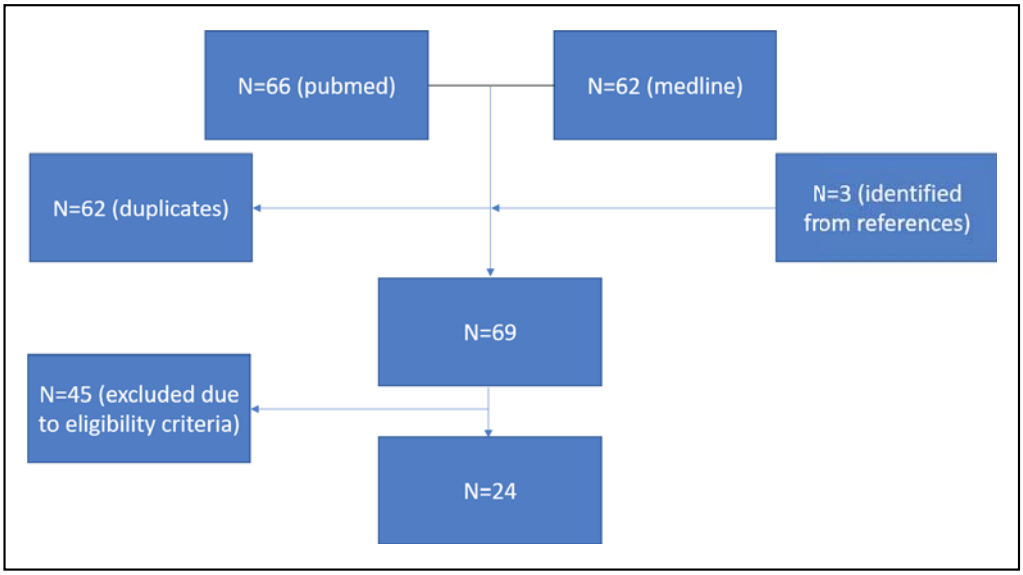

Fig. 1.

also excluded due to their potential inter-relation with migraine. Case reports of individual patients, task-based studies, and review articles were excluded; all other study types were included. Other chronic pain populations such as genitourinary pain, fibromyalgia, somatic symptom disorder, spinal cord injury, and neuropathic pain were excluded..

Two independent investigators reviewed the titles of all citations from each database. Duplicates identified from separate databases were excluded. Remaining studies were screened individually by each reviewer separately by reading the abstract. Studies that did not meet inclusion criteria after review of abstract were excluded. The remaining citations were retrieved in full text and reviewed independently by each reviewer. Full text articles revealing additional exclusion criteria were further excluded. References of every citation were reviewed to identify additional citations.

Primary outcome measures included the number of studies describing the relationship between functional network connectivity and pain disorders. Also, this study collects key framework factors including specific chronic pain etiology, type of pain scales used, biomarkers assessed, and functional neuroimaging findings, as well as measures of key study biases including accounting of clinical co-morbidities.

Results

Study Selection

A total of 66 titles resulted from the search in Pubmed. A total of 62 titles resulted from the search in Medline. 62 were excluded as duplicates and an additional 3 eligible articles were identified in the references of these articles. 69 titles were screened for eligibility. 45 full text articles were further excluded based on eligibility criteria. 24 quantitative studies were included in the final analysis. (See Figure 1)

Study Characteristics

Twenty-four studies examined functional connectivity via resting state fMRI in patients with chronic musculoskeletal pain, including chronic low back, neck, and shoulder pain. Table 1 lists the authors, sample size, pain population type and key findings for each of the studies.

Results of Individual Studies

A cross-sectional resting state fMRI study of 18 patients with chronic low back pain, compared to 18 healthy controls, found chronic low back pain patients have increased connectivity between periaqueductal gray matter (PAG) and ventromedial prefrontal cortex (vmPFC); the functional connectivity between the PAG and the vmPFC decreases as pain intensity increases in high pain conditions. Duration of pain was negatively correlated with PAG–posterior insula and PAG–amygdala functional connectivity (Yu *et al.* 2014).

A resting state fMRI study of 11 patients with failed laminectomy syndrome, compared to 11 healthy controls, showed that patients with failed laminectomy syndrome show overall reduction of functional connectivity in all Default Mode Network (DMN) regions, as well as increased connectivity in regions involved in sensory-motor integration, and pain modulation (Kornelsen *et al.* 2013).

A resting state fMRI study of 64 older adults with chronic pain, compared to 64 older healthy controls, using patients from the Rush Memory & Aging Project, showed that older adults with chronic pain show greater functional connectivity of the posterior cingulate to the left insula, to the superior temporal gyrus, and to

Tab. 1.

Citation (PMID)	Sample size of active patients	Primary Pain Scale Measure	Study Design	Key Findings	Specific Cause of Pain	Co-Factors	Key Limitations / Strengths
25379421	N=18 Chronic Low Back Pain N=18 HC	Visual Analog Scale; The Brief Pain Inventory	Cross-Sectional	Chronic low back pain patients have increased connectivity between periaqueductal gray matter and ventromedial prefrontal cortex; the Frontal Cortex (FC) between the PAG and the vmPFC decreases as pain intensity increases in high pain conditions. Duration of pain was negatively correlated with PAG–posterior insula and PAG–amygdala FC.	Chronic low Back Pain	Age, Gender, Race, Beck Depression Inventory, Duration of Pain	Didn't use cardiac gating with fMRI; relatively small seed region; didn't account for medications.
22985900	N=30 Chronic Back Pain	Visual Analog Scale; McGill Pain Questionnaire; Neuropathic Pain Scale	Randomized, 2 weeks	The extent of functional connectivity between left medical PFC and bilateral insula accurately predicts clinical placebo response. At baseline, higher left dorsolateral prefrontal cortex activity is associated with treatment outcomes.	Chronic back pain	Handedness, Age, Gender, Duration, Beck Anxiety Inventory, Beck Depression Inventory, Medication Quantification Scale	Half of patients had lidocaine patches; did not account for rescue medications.
27725689	N=40 CP, 22 CRPS, 12 sub-acute BP, 40 OA, 75 HC	Short Form McGill Pain Questionnaire; Western Ontario and McMaster Universities Index	Cross-Sectional	Regardless of the etiology of pain, exhibited a similar disruption of degree rank order in functional networks of relatively equal magnitude (approximately 20% reduction). The extent of degree rank order disruption correlated with extent of clinical pain.	Prolonged chronic back pain, complex regional pain syndrome, osteoarthritis	Beck Depression Inventory	Unique clinical cohorts with different types of chronic pain; longitudinal measurements of the transition from subacute back pain to chronic pain; age and gender-matched healthy control population derived form an off-site data set; rat neuropathic pain model used to support cross-species generalizability of findings; analysis with depression.
32322322	N=28 CP, N=25 HC	Visual Analog Scale	Cross-sectional	Chronic pain patients showed abnormal low-frequency fluctuations and abnormal cerebral blood flow in the posterior cerebellum, middle orbitofrontal gyrus, medial superior frontal gyrus, middle temporal gyrus, precuneus, cingulate gyrus, middle occipital gyrus, middle frontal gyrus, pre- and post-central gyrus and superior parietal gyrus . The low frequency fluctuation within medial superior frontal gyrus correlated with pain score, as measured by visual analog scale.	Chronic neck and shoulder pain	Disease Duration	Did not assess emotional state such as anxiety, depression.
24280949	N=20 CP; N= 10 HC	Visual Analog Scale	Longitudinal	At baseline, chronic low back pain patients demonstrated less connectivity within the default mode network (dorsolateral prefrontal cortex, medial prefrontal cortex, anterior cingulate gyrus and precuneus) . Four weeks of acupuncture normalized connectivity. The normalization of connectivity was associated with clinical reduction of pain as measured by visual analog scale.	Chronic low back pain	Handedness, Disease Duration	Comparison to age and gender matched healthy controls; multiple treatment sessions analyzed long term treatment response over 4 weeks; exclusion of certain medications

Citation (PMID)	Sample size of active patients	Primary Pain Scale Measure	Study Design	Key Findings	Specific Cause of Pain	Co-Factors	Key Limitations / Strengths
21957259	N=15 CP, n=15 HC	McGill Short Form Pain Questionnaire	Cross-Sectional	Increased high-frequency BOLD oscillations within medial prefrontal cortex and parts of the default mode network (posterior cingulate cortex, lateral parietal). The medial prefrontal cortex exhibited increased correlation with anterior cingulate cortex, right insular cortex and secondary somatosensory cortex. The increased BOLD oscillations in medial prefrontal cortex correlated with spontaneous pain ratings.	Chronic back pain	Handedness; Beck Depression Inventory; Medication Quantification Scale	Age and gender matched healthy controls; psychiatric disease, including mild to moderate depression, used as exclusion criteria; The Medication Quantification Scale
25180885	N=18 CP, N=19 CPRS, N=14 Knee Osteoarthritis, N=36 HC	Visual Analog Scale; Short Form McGill Pain Questionnaire	Cross-sectional	All chronic pain groups showed decreased connectivity of medial prefrontal cortex to posterior constituents of the DMN, with increased connectivity to the insular cortex, in proportion to intensity of pain.	Chronic Pain	Beck Depression Inventor-II; Medication Quantification Scale	The Medication Quantification Scale
31107712	N=50 Chronic Pain, 44 HC	Visual Analog Scale (the LBP Severity Assessment)	Cross-Sectional	Chronic pain patients have decreased functional connectivity between default mode network and Medial Frontal Cortex (mFC)/rACC, with increased functional connectivity between mFC/rACC and sensorimotor network. Duration of pain, but not pain intensity, was associated with abnormality in functional connectivity.	Chronic Pain	PROMIS 29 (pain, health, social disability, sleep disturbance, fatigue, depression and anxiety)	Inclusion of PROMIS measures; inclusion of a validation set
31404104	N=20 CP, N= 20 HC	Visual Analog Scale	Cross-Sectional	Patients with chronic neck pain show aberrant functional connectivity particularly between right dorsolateral prefrontal cortex and other brain regions. Connections with right precuneus and right anterior insular cortex were significantly associated with Kinesiophobia.	Chronic neck pain	Handedness, Age, Gender, Fear Avoidant Belief (Tampa scale for Kinesiophobia)	Patients were on medications; cross-sectional design
31430270	N=108 CP	Ecological momentary assessments entered twice daily using smart phone; in-lab numeric rating scale, McGill Pain Questionnaire	Cross-Sectional	A cluster of traits related to pain, and a cluster of traits related to emotion, were associated with back pain characteristics and could be related to distinct distributed functional networks. Income in particular was associated with traits and functional networks.	Chronic neuropathic low back pain	Positive and Negative Affect Scale; Beck Depression Index; 12-item short form physical health; self-reported income, race/ethnicity, education, gender	Low sample size for dimensional analysis; No controls
23498869	N=11 CP, N=11 HC	Mcgill Pain Questionnaire	Cross-Sectional	Patients with failed laminectomy syndrome show overall reduction of functional connectivity in all default mode network regions, as well as increased connectivity in regions involved in sensory-motor integration, and pain modulation.	Failed back surgery syndrome	Beck Depression Inventory, Beck Anxiety Inventory, Fear of Pain Questionnaire	Strengths: Comparison to age and gender matches healthy controls; psychological measured including depression and anxiety; inclusion of lateralization. Limitations: Homogenous patient group not generalizable to all chronic pain; concurrent medication.

Citation (PMID)	Sample size of active patients	Primary Pain Scale Measure	Study Design	Key Findings	Specific Cause of Pain	Co-Factors	Key Limitations / Strengths
23124844	N=64 CP, N=64 HC	Number of Joints and Duration of Pain	Cross-Sectional	Older adults with chronic pain show greater functional connectivity of the posterior cingulate to left insula, superior temporal gyrus and cerebellum, after controlling for total gray matter volume.	Chronic musculoskeletal pain	Gray Matter Volume, age, education, gender, MMSE, global cognition, CES-D depression, use of pain medications, number of pain medications	Accounted for several co-factors; Used only self-report measure of pain; seed of interest was only posterior cingulate
30677731	N=25 CP, N=26 HC	Visual Analog Scale; Japanese Orthopedic Association Back Pain Evaluation Questionnaire	Cross-Sectional	Patients with low back-related leg-pain show increased connectivity in bilateral precuneus, left medial prefrontal cortex and bilateral inferior parietal lobule belonging to default mode network. Connectivity differences were not correlated with clinical indices such as duration of disease, etc.	Low back pain; related leg pain	Fugl-Meyer assessment for sensorimotor impairment; Two-Point Tactile Discrimination Test	Leg pain related back pain is more specific.
29697536	N=51 CP, N=51 HC	Clinical Pain scale 0-10; Bath Ankylosing Spondylitis Disease Activity Index	Cross-Sectional	The level of clinical pain in patients with spondylarthritis is associated with the extent of increased cross-network connectivity between DMN and SMN.	Ankylosing Spondylitis	25-Item Resilience Scale	Strengths: Limited medications to NSAIDs and TNF-alpha inhibitors; dietary limitations including caffeine and alcohol before testing; subgroup analysis of high versus low/no pain. Limitations: E Patients with chronic pain were significantly older; only men included; exclusion of psychiatric or neurological disorders; only assessed chronic pain due to AS.
24167119	N=14 CP, N=19 Depression 21 healthy controls	Visual Analog Scale	Longitudinal	Patients with chronic low back pain showed increased activation in the thalamus, amygdala, midcingulate cortex and sensorimotor regions. Depression patients without chronic back pain showed less activation in midbrain and brainstem areas.	Chronic Pain	Chronic low back pain	Experimentally induced pain; did not include chronic back pain with depression
20800649	N=12 CP, N= 20 HC	None	Cross-Sectional	Patients with chronic back pain show increased connectivity between bilateral insular, middle frontal gyrus and three out of four regions of the default mode network.	Chronic Pain	Chronic back pain	Comparison to controls; possible "bleed through effect" due to subjects primed from participation in a previous study involving a task
30927604	N=90 CP, N=74 HC	Visual Analog Scale, Pain Bothersome Scale	Cross-Sectional	Increased connectivity between the primary visual network and somatosensory motor network in the pain group. This association was inversely related to duration of pain. Changes in the primary visual system were able to classify pain vs. non-pain controls with approximately 79% accuracy.	Chronic low back pain	Age, Gender, Duration, Beck Depression Inventory	Non-generalizability beyond back pain; healthy controls did not have a BDI score

Citation (PMID)	Sample size of active patients	Primary Pain Scale Measure	Study Design	Key Findings	Specific Cause of Pain	Co-Factors	Key Limitations / Strengths
28222620	N=25, N=25	Visual Analog Scale	Cross-Sectional	Increased regional homogeneity in bilateral middle frontal gyrus, decreased in left insula, superior frontal gyrus, middle cingulate gyrus, supplementary motor area, right postcentral gyrus, and superior parietal lobule.	Chronic neck and shoulder pain	Handedness, Gender, Age, Education	Did not assess specific components of pain such as duration, attack frequency, intensity
32312809	N=40 subacute back pain, N=28 CBP, N=30 HC	Short Form McGill Pain Questionnaire; Neuropathic Pain Scale; Pain Catastrophizing Scale	Longitudinal	Patients with chronic pain display smaller nucleus accumbens volume at baseline. Loss of power spectral density within low-frequency (0.01 to 0.027 Hz) oscillations at rest in the nucleus accumbens developed only after the onset of the chronic pain phase.	Chronic and subacute back pain	Beck Depression Beck Anxiety	Patients dichotomized into recovered or persistent 1 year follow up; measurements of transition from acute to chronic pain; comparison to healthy control; three testing sites; exclusion of psychiatric disease
31176295	N=50 (25 active, 25 sham acupuncture)	Visual Analog Scale	4- week, Randomized	Functional connectivity between medial prefrontal cortex, insula, putamen, caudate and angular gyrus significantly predicted real acupuncture treatment responses, while functional connectivity between medial prefrontal cortex and dorsal ACC, superior parietal lobule and paracentral lobe were predictive of sham treatment response.	Chronic low back pain	Age, Gender, Duration of Pain, PROMIS pain interference, physical health, social disability, sleep disturbance, fatigue, depression, anxiety and pain intensity	Strengths: Measured many co-factors; included control group; longitudinal; Limitations: Limited duration, small sample size, participants maintained on prior treatments during stud, single-blinded design, duration between the last treatment and the MRI
32074111	N=10 CP, N=12 HC	Visual Analog Scale	Cross-Sectional	Decreased functional connectivity between the striatum network and six other brain networks. The extent of connectivity loss between striatum network and the other networks was inversely associated with pain symptoms. The study also found decreased functional connectivity between periaqueductal gray matter and amygdala, with increased functional connectivity between periaqueductal gray matter and sensorimotor cortex and cingulate gyrus.	Failed back surgery syndrome	Age, Sex, Pain Duration, Pain Location, Time from latest surgery, Time from stimulator trial	Physiological significance of amplitude low frequency fluctuations is still under investigation
30417246	N=20 CBP, N=17 HC	Visual analog scale	Cross-sectional	Longer path lengths as well as lower clustering co-efficients, lower global efficiency and lower local efficiency, with decreased functional connectivity in anterior/middle/posterior cingulate cortex, inferior frontal gyrus, middle temporal gyrus, occipital gyrus, post/precentral gyrus, supplementary motor area, thalamus, fusiform, caudate and cerebellum.	Chronic low back pain	Age, gender	No clinical co-morbidities assessed

Citation (PMID)	Sample size of active patients	Primary Pain Scale Measure	Study Design	Key Findings	Specific Cause of Pain	Co-Factors	Key Limitations / Strengths
23965184	N=18 CBP, N=18 HC	Visual Analog Scale	Cross-sectional	Decreased connectivity within right primary somatosensory and motor areas (S1 and M1). Chronic pain patients also had greater connectivity in left fusiform gyrus, occipital gyrus, right posterior cingulate cortex and inferior parietal gyrus. Functional connectivity changes within left insula, left precuneus, left amygdala and right fusiform gyrus correlated within pain intensity.	Quebec Class I or II back pain	Age, Gender, Race, Beck Depression Inventory, Duration	Used Quebec Class I or II classification criteria for inclusion; used race-matched controls
28052444	N=39 headache, N=49 CBP, N=88 controls	Visual Analog Scale	Cross-sectional	Strong inter-regional correlations between left multisensory association area and right S1 cortex, and also between left posterior cingulate cortex and right V1 cortex in both headache and low back pain groups. Two region of interest pairs showed increased connectivity in back pain vs. controls (left multisensory association area with left posterior cingulate cortex, left premotor cortex with left posterior cingulate cortex); two region of interest pairs showed increased connectivity in controls vs. back pain patients (left pre-motor cortex with right V1 cortex, right multisensory association area with right V1 cortex); and two region of interest pairs (left premotor cortex with right V1 cortex, right V2 cortex with right V1 cortex) showed decreased connectivity in chronic pain vs. controls. Interestingly, both chronic pain and headache groups showed similar cortical thickness changes, but the two groups displayed significantly different functional connectivity.	Chronic low back pain (Musculoskeletal and Roland-Morris Questionnaire)	Short Form-36, Beck Depression Inventory, Pittsburgh Sleep Quality Index, Hamilton Depression Rating Scale	Large sample size

the cerebellum, after controlling for total gray matter volume (Duke Han *et al.* 2013).

A resting state fMRI study of 51 spondylarthritis patients and 51 healthy controls found abnormally high cross-network functional connectivity between the DMN and sensorimotor networks in patients with higher pain scores (Hemington *et al.* 2018).

A resting state fMRI study of 25 patients with chronic low back pain with leg pain, compared to 26 healthy controls, found increased connectivity in precuneus, medial prefrontal cortex (mPFC) and bilateral inferior parietal lobule belonging to DMN; connectivity differences were not correlated with clinical indices such as duration of disease, etc. (Zhou *et al.* 2019).

A resting state fMRI study of emotive traits in 108 patients with chronic back pain found four emotive trait factors that appear to emerge in this population: a "Pain trait", a "Character trait" (extraversion, conscientiousness, openness), an "Aware trait" (awareness capacities and abilities to regulate emotions) and an "Emote trait" (low neuroticism, low sensitivity to loss, high optimism, strong attentional control in presence of emotion, high aptitude for mindfulness) (Vachon-Presseau *et al.* 2019). The "Pain trait" was associated with almost all aspects of clinical pain quality and the "Emote trait" was inversely related only to the negative affect aspect of chronic pain. Using fMRI, the investigators were able to predict "Pain trait" scores from correlations between the DMN, sensorimotor, cingulate, salience and ventral attention regions. "Emote trait" scores could be predicted from correlations between the DMN, visual, sensorimotor, salience and frontoparietal regions. Self-reported income was also significantly associated with pain characteristics and with connectivity patterns.

A resting state fMRI study of 20 right-handed chronic neck pain patients, that compared to 20 age- and sex-matched controls, found connectivity between right dorsolateral prefrontal cortex and right precuneus and right anterior insular cortex were significantly associated with kinesiophobia (Ihara *et al.* 2019).

An 8-day, longitudinal study of experimentally induced pain in 19 patients with chronic low back pain, 21 patients with depression and 21 healthy controls found that patients with chronic low back pain show increased activation in the thalamus,

amygdala, midcingulate cortex and sensorimotor regions (Rodriguez-Raecke *et al.* 2014). Depression patients without chronic back pain showed less activation in midbrain and brainstem areas.

A cross-sectional study of 12 chronic back pain patients, aged 29 to 67, demonstrated increased functional connectivity between three out of the four DMN sites and bilateral insula as well as middle frontal gyrus (Tagliazucchi *et al.* 2010).

A cross-sectional study of 50 patients with chronic low back pain of at least six months duration were compared to 44 healthy controls. Results showed that chronic pain patients have decreased functional connectivity between the DMN and mFC/ Rostral Anterior Cingulate Cortex (rACC), with increased functional connectivity between the mFC/rACC and sensorimotor network (TuJung *et al.* 2019). Duration of pain, but not pain intensity, was associated with abnormal functional connectivity.

A cross-sectional study compared 18 chronic back patients, 19 complex regional pain syndrome patients, and 14 osteoarthritis patients to 36 healthy controls. In all chronic pain groups, they found decreased connectivity of mPFC to posterior constituents of the DMN, with increased connectivity to the insular cortex, to be in proportion to intensity of pain (Baliki *et al.* 2014).

A cross-sectional resting-state fMRI study of 15 chronic back pain patients compared to 15 healthy controls found increased high-frequency blood oxygen level-dependent (BOLD) oscillations within the mPFC and parts of the DMN (posterior cingulate cortex, lateral parietal). The mPFC exhibited increased correlation with the Anterior Cingulate Cortex (ACC), with the right insular cortex, and with the secondary somatosensory cortex (Baliki *et al.* 2011). The increased BOLD oscillations in the mPFC were correlated with spontaneous pain ratings.

A longitudinal resting state MRI study of 20 patients with chronic low back pain before and after four weeks of acupuncture treatment compared to 10 age- and gender-matched healthy controls without treatment showed that, at baseline, chronic low back pain patients demonstrated less connectivity within the DMN (dorsolateral PFC, mPFC, anterior cingulate gyrus and precuneus). Four weeks of acupuncture normalized this connectivity. The normalization of connectivity was associated with clinical reduction of pain as measured by Visual Analog Scale (VAS) (Li *et al.* 2014).

A cross-sectional, resting state fMRI study of 28 chronic neck and shoulder pain, compared to 25 age- and sex-matched healthy controls, demonstrated abnormal low-frequency fluctuations and abnormal functional connectivity in the posterior cerebellum, middle orbitofrontal gyrus, medial superior frontal gyrus, middle temporal gyrus, precuneus, cingulate gyrus, middle occipital gyrus, middle frontal gyrus, pre- and post-central gyrus and superior parietal gyrus. The low frequency fluctuation within the medial superior frontal gyrus correlated with pain score, as measured by VAS (Yue & Du 2020).

A cross-sectional, resting state fMRI study of 40 chronic back pain patients, 40 knee osteoarthritis patients, 12 subacute back pain patients and 75 healthy controls showed that patients with chronic pain exhibited a similar disruption of degree rank order in functional networks with a relatively equal magnitude (approximately 20% reduction), regardless of the etiology of pain. The extent of degree rank order disruption correlated with extent of clinical pain (Mansour *et al.* 2016).

A cross-sectional study of 30 chronic back pain patients, half of whom responded to placebo treatment in a prior clinical trial, and half of whom did not respond, showed that the extent of functional connectivity between left mPFC and bilateral insula can predict clinical placebo response (Hashmi *et al.* 2012).

A cross-sectional, resting state fMRI study of 90 patients with chronic low back pain (between 20 and 50 years old), compared to 74 controls, found increased connectivity between the primary visual network and somatosensory motor network in chronic low back pain patients. This association was inversely related to duration of pain. Changes in the primary visual system were able to classify participants as pain vs. non-pain controls with approximately 79% accuracy (Shen *et al.* 2019).

A cross-sectional, resting state fMRI study of 25 chronic neck and shoulder pain patients with an average age of 48 found significantly increased regional homogeneity in the bilateral middle frontal gyrus, and decreased regional homogeneity in left insula, superior frontal gyrus, middle cingulate gyrus, supplementary motor area, right postcentral gyrus, and superior parietal lobule (Yu *et al.* 2017).

A longitudinal resting state fMRI study comparing 40 subacute back pain patients to 28 chronic back pain patients and 30 healthy controls found that patients with chronic pain display a smaller nucleus accumbens volume at baseline. Regarding functional connectivity measured by low-frequency (0.01 to 0.027 Hz) oscillations at rest, a loss of power spectral density in the nucleus accumbens was observed only after the onset of the chronic pain phase (Makary *et al.* 2020).

A 4-week, randomized trial of acupuncture vs. sham acupuncture in 50 patients with chronic back pain found that pre-treatment functional connectivity can predict responses to both real and sham acupuncture treatments. Results from acupuncture treatment found that stronger pre-treatment mPFC functional connectivity with the insula, putamen, and caudate as well as weaker functional connectivity with the angular gyrus were predictive of treatment response. Functional connectivity between mPFC and the dorsal ACC, the superior parietal lobule, and the paracentral lobe were predictive of sham treatment response indicating a different underlying mechanism (Tu *et al.* 2019).

A cross-sectional, resting state fMRI study of 10 patients with failed back surgery syndrome, and preliminary positive response to spinal cord stimulation trial prior to permanent implant, comparing to 12 age-matched controls, showed decreased functional connectivity between the striatum network and six other brain networks. The extent of connectivity loss between the striatum network and the other networks was inversely associated with pain symptoms. This study also found decreased functional connectivity between PAG and amygdala, with increased functional connectivity PAG and sensorimotor cortex as well as DMN (i.e., cingulate gyrus) (Pahapill *et al.* 2020).

A cross-sectional, resting state fMRI study investigating small-world network alterations in 20 patients with low back pain, compared to 17 age- and gender-matched controls, found that pain patients displayed longer path lengths, lower clustering coefficients, lower global efficiency, lower local efficiency, and with decreased functional connectivity in the anterior/ middle/ posterior cingulate cortex, inferior frontal gyrus, middle temporal gyrus, occipital gyrus, post/ precentral gyrus, supplementary motor area, thalamus, fusiform, caudate and cerebellum (Liu *et al.* 2018).

A cross-sectional, resting state fMRI study of 18 chronic back pain patients, meeting Quebec I or II Classification Criteria, compared to 18 age, sex and race-matched controls, found decreased connectivity within the right primary somatosensory and motor areas (S1 and M1) (Kong *et al.* 2013). Chronic pain patients also had greater connectivity in left fusiform gyrus, occipital gyrus, right posterior cingulate cortex and inferior parietal gyrus. Functional connectivity changes within left insula, left precuneus, left amygdala and right fusiform gyrus correlated with pain intensity (Kong *et al.* 2013).

A cross-sectional, resting state fMRI study comparing 39 chronic headache patients with 49 chronic low back pain patients and 88 controls found strong inter-regional correlations between the left multisensory association area and right S1 cortex as well as between the left posterior cingulate cortex and right V1 cortex in both headache and low back pain groups. Two cortical region pairs of interest showed increased connectivity in back pain vs. controls (left multisensory association area with left posterior cingulate cortex, left premotor cortex with left posterior cingulate cortex); another two cortical region pairs of interest showed increased connectivity in controls vs. back pain patients (left premotor cortex with right V1 cortex, right multisensory association area with right V1 cortex); and two cortical region pairs of interest (left premotor cortex with right V1 cortex, right V2 cortex with right V1 cortex) showed decreased connectivity in chronic pain vs. controls. Interestingly, both chronic pain and headache groups showed similar cortical thickness changes but displayed different functional connectivity (Yang *et al.* 2017).

Risk of Bias Within & Across Studies

Overall, across studies, 20% (5) percent of studies included handedness data. Most included data on clinical co-morbidities such as anxiety or depression. No studies accounted for neurodevelopmental factors such as Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), or Learning Disorder (LD). 19 studies were cross-sectional and 5 studies were longitudinal. No major biases were noted in randomization, allocation concealment, blinding, incomplete outcome data or selective reporting.

Discussion

This systematic review of resting state fMRI studies of patients with chronic musculoskeletal low back or neck pain identified 69 unique articles published in the English language since October 2000. Almost all studies demonstrated aberrant functional connectivity in pain patients when compared to healthy controls. Connectivity is typically aberrant in regions related to DMN, salience network and sensorimotor network. Aberrant connectivity is also conspicuous among/ between other regions such as primary visual network, brainstem regions (nucleus accumbens, PAG), as well as the striatal network that governs emotion, motivation and reward. Notably, most studies failed to take into account critical factors that influence functional connectivity, including neurodevelopmental factors (handedness, LD, ASD, ADHD, early life trauma). Most studies also failed to account for co-morbid emotional and personality traits that are known to influence pain. No studies included objective measurement of the adrenergic system, which may mediate functional connectivity re-organization in chronic pain (Ignatowski *et al.* 1999). Few studies accounted for medications. The majority of studies were cross-sectional studies.

One important limitation of this review was the exclusion of other chronic pain populations such as migraine, fibromyalgia, somatic symptom disorder, spinal cord injury and neuropathic pain. Task-based and resting state fMRI studies have demonstrated similar changes in salience and attentional networks in patients regardless of the underlying pain disorder (Zhang *et al.* 2019). Without including studies about chronic pain patients with other etiologies, we cannot make conclusions about central changes that may be common to more than one chronic pain disorder. The exclusion of task-based studies was another potential limitation to the generalizability of the findings. Also, findings from studies using non-fMRI measures of functional connectivity such as Position Emission Tomography (PET), electroencephalogram (EEG), single-photon emission computerized tomography (SPECT) scan, and other methods were not integrated into these findings.

Strengths of this review include focusing the study on chronic musculoskeletal pain, focusing only on resting state studies, and also following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews. Limiting the review to resting state studies was important in order to minimize the consequences of errors in reproducibility of fMRI data (Liu *et al.* 2018). However, inclusion of findings from non-back pain chronic pain populations, such as those from fibromyalgia, irritable bowel syndrome (IBS) and migraine could further inform a central framework that spans chronic pain disorders.

This review reveals several clinical co-morbid factors that have not been taken adequately into the current literature on chronic pain and functional connectivity. Specifically, most studies of chronic pain do not account for neurodevelopmental factors, such as handedness, the presence of early life trauma or the presence of developmental co-morbidities such as ADHD, LD, or Autism Spectrum Disorder. This is a critical opportunity to further discovery going forward. In fact, neurodevelopmental disorders and early life trauma are more likely to be associated with alterations in structural and functional connectivity patterns (Hunt *et al.* 2019). For example, a resting state fMRI study of 58 patients with IBS compared to 110 healthy controls showed that a) compared to healthy controls, patients with IBS show connectivity differences in the salience, left fronto-parietal and DMN; and b) early adverse life events are associated with altered connectivity in salience network (Seretny *et al.* 2019).

Regarding clinical co-morbidities, patients with chronic pain are a heterogenous group of people who have different neural connectivity. A better accounting of clinical co-morbidities is important because the association between patterns of structural connectivity and chronic pain dissolves after taking into account salient clinical variables (Dolman *et al.* 2014). The results of fMRI studies can be completely different if patients with different underlying neurodevelopment are all grouped together. Grouping male and female patients together may also be unwarranted given the significant differences between male and female functional connectivity patterns. For example, a resting state fMRI study of 60 patients with IBS compared to 118 healthy controls, which paid special attention to gender-based differences, showed that male patients with IBS showed lower frequency oscillations in insula compared to controls, whereas female patients showed higher frequency in amygdala, hippocampus and insula, with lower frequency in sensorimotor regions, compared to controls (Hong *et al.* 2013).

Closely related to neurodevelopmental factors are emotional and/or personality traits. Personality factors such as internalizing vs. externalizing traits, and those related to resilience, which seem to influence how pain is perceived, have also been overlooked in the current literature. A significant amount of non-fMRI literature demonstrates how personality affects pain outcomes (Ong *et al.* 2010; Ozer & Benet-Martinez 2006). For example, internalizing behaviors influence the perception of sensory experiences (Boeckle *et al.* 2016).

Additionally, a lack of accounting for adrenergic measures and other stress-related factors is another opportunity to further discovery going forward. This is an important gap in the literature because task-based MRI studies show significant relationships between acute stress, pain, and functional connectivity (Vachon-Presseau *et al.* 2013). Also, most studies did not account for medication exposure, which is important considering that one month of opiate exposure can change brain function (Younger *et al.* 2011). Moreover, future studies must account more completely for socioeconomic factors. This is important because socioeconomic factors directly influence neurodevelopmental trajectories, adrenergic balance, pain disability, and response to treatment (Poleshuck & Green 2008). Finally, most functional connectivity studies are using seed regions in the brain rather than the spine. Inclusion of spinal functional MRI may be important for future work given the known findings regarding impairments in descending pain pathways in chronic pain patients (Ozer & Benet-Martinez 2006).

Several important questions are unanswerable given the current status of the literature on functional connectivity and chronic pain. One important question to consider is whether patients with similar neurodevelopmental trajectories are likely to respond distinctly to diagnostics and/or treatments, especially those treatments with influence on functional connectivity and/or functional connectivity. Separating patients who have distinct neurodevelopmental trajectories, and/or clusters of neurological/psychiatric co-morbidities, into separate groups may illuminate more specific changes that can be used to better target pain treatment. Another important research question going forward is whether measurement of the symmetry of network connectivity, rather than measurement of connectivity alone, could add value. Altered synchronization among brain resting state networks in left and right brain is associated with symptom severity (Northoff 2020).

Overall, the DMN, the salience network and the sensorimotor network show atypical activity in patients with chronic pain when compared to healthy controls. Functional connections of the primary visual network, the striatal network (e.g., nucleus accumbens), and midbrain (PAG) are also atypical in chronic pain patients. The findings from the literature on functional MRI in chronic musculoskeletal pain patients are heterogeneous, precluding any clear identification of reliable patterns that can be used as diagnostic or treatment biomarkers. Most of the literature fails to account for the co-factors that may explain this heterogeneity. Also, no studies include robust measures of

the adrenergic and other neuroendocrine systems that could represent the mechanistic link to changes in functional connectivity. Future longitudinal studies that take into account the most important factors that influence connectivity, such as handedness, early life trauma, co-morbidities (neurological, psychological and psychiatric), socioeconomic factors, personality traits (resilience, internalizing behaviors), which also account for concomitant medications, could significantly advance the current understanding of the central nervous system mechanisms of disability in different chronic pain patients.

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