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Imaging Pain in Arthritis: Advances in Structural and Functional Neuroimaging

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Abstract Arthritis is a heterogeneous disease characterized by joint stiffness, swelling, and pain. Although primarily considered a peripheral joint disease, the severity of pain reported by arthritis patients does not always reflect the extent of joint pathology detectable by conventional means. Using structural and functional brain imaging techniques, a growing number of evolving neuroimaging methods are providing insight into these observed discrepancies at different time-scales. Of these methods, functional magnetic resonance imaging is exploited for short-term evoked pain examination and treatment evaluation; 'resting-state' approaches provide insight into fluctuations in pain; perfusion imaging captures elements of ongoing clinical pain; and morphological brain assessment provides evidence for long-term structural changes in the brain associated with chronic pain. Further insight into arthritic pain processing at the brain-systems level could in the future be provided by combined neuroimaging approaches, specifically investigating the interactions between functional and structural alterations.

Keywords Arthritic pain · Clinical pain · Experimental pain · Chronic pain · Rheumatoid arthritis · Osteoarthritis · Chronic low back pain · Fibromyalgia · Functional neuroimaging · Functional magnetic resonance imaging · Structural neuroimaging · Structural plasticity · Resting-state · Functional connectivity · Painful fluctuations · Positron emission tomography · Arterial spin labeling · Default mode network · Voxel-based morphometry · Treatment evaluation

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Introduction

Derived from the Greek words for joint (*arthro-*) and inflammation (*-itis*), arthritis is a collective term that describes joint disorders that commonly involve inflammation, stiffness, pain and swelling of one or more joints. There are over 100 types of arthritis of which the most prevalent are osteoarthritis (OA), a degenerative (mechanical) disorder, and rheumatoid arthritis (RA), a systemic inflammatory disease. While arthritic pain can be typically characterized as a dull ache widespread within the joint, RA patients often suffer from prolonged morning stiffness, whereas osteoarthritic joint pain would classically worsen with usage over the course of the day.

Although arthritis is considered primarily a peripheral joint disease, a number of observations suggest the contribution of additional processes outside of the joint in arthritic pain processing. Firstly, there is no clear correlation between radiographically determined OA and the extent of pain [1]. Secondly, the extent of joint pathology does not always correspond to the level of pain experienced by the patient [2, 3]. Thirdly, surgical replacement of the painful joint does not always alleviate pain [4], and placebo surgery can reduce pain

in some patients [5]. Finally, abnormal sensory processing has been reported in OA patients; with high incidences of referred pain [2], central sensitization [6], and heightened responses to standardized peripheral painful stimuli that is driven by changes in the central nervous system [7]. There is, thus, ample evidence suggesting that arthritic pain processing is more complex than a linear transmission of sensory information from the joint to the brain.

Thanks to significant recent advances in functional and structural neuroimaging techniques [8], the discrepancies between peripheral joint pathology and self-reporting of pain in arthritis are now being addressed [3]. In this review, we will outline the key functional and structural neuroimaging studies that have contributed towards improved understanding of the pain experienced by arthritis patients. The majority of studies have been undertaken in patients with OA, primarily knee OA and chronic back pain (CBP), and in patients with fibromyalgia syndrome (FMS), which is seen as a rheumatological condition.

This review will first summarize the main findings from pain neuroimaging studies in healthy volunteers in order to examine generic pain processing concepts. The subsequent analysis of patient studies is organized on the basis of the time-scales over which different imaging techniques are sensitive to alterations in brain function or structure. The relevance of various functional (short- and medium-term) and structural (long-term) pain-related changes in arthritis is discussed.

Short-term evoked pain related responses are demonstrated by blood oxygenation level dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) studies [9, 10•, 11•, 12, 13•]. We consider medium-term functional changes as alterations in the 'state' of the brain depending on background and fluctuating pain, and these arguably reflect more clinically relevant endogenous pain. This brain state can be examined by a range of functional neuroimaging modalities including electroencephalography (EEG) [14, 15]; BOLD 'resting-state' MRI (or measures of 'functional connectivity') [16, 17•]; and perfusion imaging methods including positron emission tomography (PET) [18, 19] and arterial spin labeling (ASL)-MRI [20•, 21•, 22•].

Finally, long-term structural changes, detected by morphological tissue analysis, provide evidence for neural plasticity in response to chronic pain [23•, 24•]. A summary of the features, strengths and weaknesses of the imaging methods described in this review is provided in Table 1.

Pain Neuroimaging

Over the last 20 years, the involvement of various brain areas in pain processing has been extensively studied using a range of rapidly developing functional and structural neuroimaging techniques. The novelty afforded by these methods is their objectivity, in the strict sense that they do not rely on self-reporting of pain experience, and their ability to capture brain activity non-invasively in humans.

Stemming from early neuroimaging studies, the concept of the 'pain matrix' refers broadly to the extensive network of cortical (anterior cingulate cortex, ACC; primary somatosensory cortex, S1; secondary somatosensory cortex, S2; prefrontal cortex, PFC, and insula cortex) and subcortical (thalamus, amygdala and brainstem) brain regions involved in pain processing. It suggests that there is a unique cerebral signature for pain perception that can be unequivocally defined [25], a notion that is now regarded by many as an over-simplification. Instead, it appears that the network of brain areas correlating with pain is dynamic [8, 19, 26, 27•, 28•] and is dependent on variables such as the pain stimulus [9, 11•, 12, 19] (Fig. 1), type of patient [29•], and imaging method. Additionally, a similar brain network can be activated by the anticipation of pain [30], and is also involved in processing the saliency of (non-painful) sensory events [27•, 28•].

Neuroimaging research has also improved our understanding of how cognition (e.g., attention), mood, context, and pharmacological agents can modulate pain perception specifically activating the frontal lobe, ACC, insula, amygdala, hypothalamus and brainstem [8]. Although studies that examine these variables in patients with arthritis [9, 13•] are limited, these factors are important to consider because of the high prevalence of depression [32, 33] and catastrophizing [34] reported in arthritis patients.

The majority of pain neuroimaging studies to date have focused on healthy volunteers with acute experimental stimuli. Whilst these studies form much of the basis of what is known about pain processing in humans at the brain-systems level, an extensive meta-analysis of pain neuroimaging studies has illustrated that the network of brain areas involved in processing acute pain in healthy volunteers, is at least partially distinct from the network that processes clinically-relevant chronic pain in patients [35].

The frequency of brain areas activated in normal volunteers during experimental pain was: ACC (81 %); S1 (79 %); S2 (81 %); insula (100 %); thalamus (81 %); and PFC (70 %) [26]. In patients with clinical pain conditions, however, the high frequencies shifted from the sensory-discriminatory brain areas to the affective-cognitive-evaluative regions: ACC (45 %); S1 (28 %); S2 (20 %); insula (58 %); thalamus (59 %) and PFC (81 %) [26].

Several groups have now illustrated that arthritic pain also engages different neural pathways from standardized experimental stimuli [9, 11•, 19]. These findings highlight the need to study pain, and, in particular, clinically relevant endogenous pain, in the patients themselves, rather than relying on healthy volunteer studies.

Table 1 Summary of the features, strengths and weaknesses of the functional and structural brain imaging methods described in this review. Positron emission tomography (PET), electroencephalography (EEG), magnetic resonance spectroscopy (MRS), magnetic resonance imaging (MRI), arterial spin labeling (ASL), cerebral blood flow (CBF)

	Nature of signal	Spatial resolution	Temporal sensitivity	Advantages	Disadvantages
PET	CBF	A few millimetres	'Brain state' over a few minutes	Can also be used for other measurements such as cerebral metabolism and specific ligand and drug binding for mapping receptors	Relies on a radioactive tracer, limiting repeated application.
EEG	Stimulus evoked response	Millimetres to centimetres	Evoked responses over a few milliseconds	Low cost, portable, widely available, sensitive to pharmacological effects; reflective of ensemble neural activity	Relies on an external 'artificial' stimulus that may not reflect real arthritic pain, deep sources hard to localize accurately
EEG	Endogenous cortical oscillations	Millimetres to centimetres	'Brain state' typically examined over minutes	Low cost, portable, widely available, sensitive to pharmacological effects; reflective of ensemble neural activity	Deep sources hard to localize accurately, functional significance of oscillations often not well understood
MRS	NMR signal indicating concentration of chemical species	Centimetres	'Brain state' typically examined over minutes	Millimolar concentrations of metabolites and neurotransmitters can be measured	Sensitivity is not high and the specificity of chemical signals to pain or a disease state may not be well established
Structural MRI	Chemical and microstructural properties of the brain tissue	Millimetres	Weeks to years	Exquisite structural information Multiple forms of image contrast, e.g. diffusion, T1, T2, volumetric quantification. Good for longitudinal assessment of disease	Requires an MRI system (costly)
Functional MRI	Stimulus evoked haemodynamic response	A few millimetres	Evoked responses over a few seconds	Good spatial resolution, option to modulate, in detail, cognitive processes associated with pain	Relies on an external 'artificial' stimulus that may not reflect real arthritic pain, an indirect measure of neural activity
Functional MRI	Resting-state fluctuations yielding a haemodynamic response	A few millimetres	'Brain state' over a few minutes	Focuses on the brain as a system of networks, does not require an explicit or artificial task or pain stimulus	An indirect measure of neural activity, interpretation of this kind of data are still developing
MRI ASL	CBF	A few millimetres	'Brain state' over a few minutes	Does not require an explicit or artificial task or pain stimulus, can represent ongoing clinical pain according to early studies	An indirect measure of neural activity

Short-Term Functional Responses

Evoked Pain Blood Oxygenation Level Dependent (BOLD) fMRI Studies

The BOLD fMRI signal in pain-focused studies depends on *contrast* between rapidly repeating painful and non-painful events. By correlating the activity of different brain regions to a pre-defined pain stimulus presentation pattern, the brain areas involved in processing the painful stimulus can be inferred. The type of response that is captured using this technique is therefore short-term, the optimal stimulus duration being in the order of seconds. Due to the difficulties associated with turning clinically relevant pain (including arthritic pain) 'on' and 'off', evoked pain BOLD fMRI studies predominantly rely on comparing the responses of patients and healthy controls to experimentally-induced pain [10•, 15, 18, 31], or comparing patient responses between various pain stimuli [9, 11•, 12]. Although these studies may not highlight aspects of the daily pain experience, they have contributed towards a better understanding of the evoked pain pathways in arthritis patients.

BOLD fMRI, combined with sensory testing, has shed light on the abnormal sensory processing experienced by arthritis patients [10•]. In particular, the periaqueductal grey (PAG) of the brainstem has been revealed as a candidate mediator of central sensitization in response to painful punctate stimuli administered at areas of referred pain in hip OA patients [10•].

BOLD fMRI has also been used to distinguish the brain areas involved in processing mechanically evoked pressure pain stimuli and spontaneous pain in knee OA patients [11•].

Evoked pain activated brain regions are those that are commonly associated with processing of acute painful stimuli in healthy volunteers. Spontaneous knee pain, however, is mapped to activity in the prefrontal-limbic areas [11•], which are involved in processing other types of chronic pain [26]. Focusing on the role of the ACC in knee OA, independent component analysis has identified two distinct activity patterns associated with sustained attention versus evoked finger pressure pain [31].

Frontal and limbic activation have also been observed in RA patients using BOLD fMRI [9]. Compared to heat pain stimulus responses, provoked joint pain processing was related to medial PFC (mPFC) and limbic activation [9]. Furthermore, the activation correlated with the tender-to-swollen joint ratio and depression [9]. This suggests a relationship between depression and pain severity in RA, potentially mediated by the brain areas involved in affective and self-referential processing [9].

With increasing knowledge of the networks involved in pain processing, attempts have been made to identify BOLD signal patterns associated with specific chronic pain conditions. In particular, FMS-unique activation patterns have been reported in response to thumb nail compression [36•] and forearm incision [37•]. In contrast, an attenuated response to pain in the rostral ACC has been identified, suggesting that FMS pain may be a result of impaired endogenous pain inhibition [36•].

The relevance of these findings to arthritis patients is in the potential for distinguishing between different types of chronic musculoskeletal pain, for example, between FMS and RA pain on the basis of condition-specific neural pain signatures [37•, 38]. Such multivariate pattern analysis has been used to decode subjective pain ratings in healthy volunteers [39•], and a similar approach has been proposed for morphological structure classification [29•] (Fig. 1).

The bulk of BOLD fMRI work in arthritis has focused on comparing pain responses between patients and healthy volunteers to experimentally induced pain. It is not clear, however, how well the findings from experimentally induced pain research can be generalized to explain clinical pain conditions [40]. The reliance of BOLD fMRI signal on *contrast* (between 'on' and 'off' states), with exogenous *short duration* and *repeated* stimuli effectively precludes it from capturing clinical pain that cannot be easily manipulated within an experimental session. The BOLD signal is also somewhat delayed, and while differences in BOLD

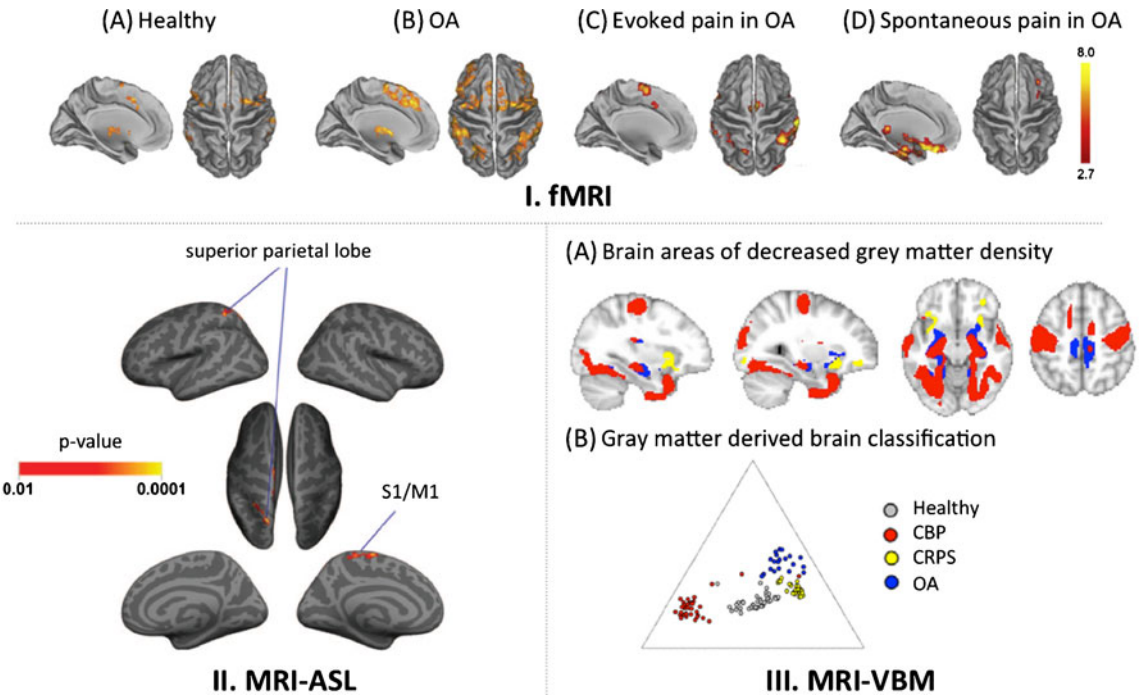

Fig. 1 **I**. fMRI reveals group averaged brain activity relating to pain. Brain activity for pressure-evoked pain in (A) healthy subjects and (B) OA patients. Brain activity in OA patients for (C) pressure-evoked pain after correcting for spontaneous knee OA pain, and (D) spontaneous knee OA pain after correcting for pressure-evoked pain. [*Modified from* [11•]*, with permission*]. **II**. MRI-ASL illustrates brain regions of significant rCBF changes associated with clinical manoeuvres performed in CBP patients versus healthy controls [*Modified from* [21•]*, with permission*]. **III**. MRI-VBM assesses morphological gray matter changes. (A) Distinct cortical patterns of regional gray matter density decreases in three patient groups, compared to healthy controls. (B) Classification of patients and healthy controls on the basis of barcode representations of gray matter density. [*Modified from* [29•]*, with permission*]. fMRI – functional magnetic resonance Imaging; ASL – arterial spin labelling; VBM – voxel-based morphometry; rCBF – regional cerebral blood flow; OA – osteoarthritis; CBP – chronic back pain; CRPS – complex regional pain syndrome; S1 – primary somatosensory cortex; M1 – primary motor cortex

response patterns can be delineated, it is not always clear whether these represent activation or deactivation within the delineated brain regions. This highlights the need for neuroimaging methods that capture endogenous clinical pain, including associated cognitive and emotional processing, rather than relying on short-term responses to evoked stimuli.

Functional Responses Indicating 'Brain State'

More appropriate markers of clinical pain, including arthritic pain, are functional medium-term responses that can potentially depict the background 'state' of the brain, rather than requiring explicit pain modulation or contrast. These responses can be identified by 'resting-state' BOLD fMRI, EEG methods, and perfusion imaging, which may be related to painful fluctuations, sleep-wake interactions and background pain, respectively.

'Resting-State' BOLD fMRI Studies

Resting-state BOLD fMRI, which records resting-state fluctuations over time, can be used to identify the correlates of the default mode network (DMN), a network of brain regions that is active 'at rest' and is involved in self-referential orientation and monitoring [41]. In some cases of chronic pain, the resting-state can be 'painful'. As such, resting-state BOLD fMRI can provide a suitable framework for identifying the 'natural state' of chronic pain and DMN dynamics, at least averaged over the period of an experimental session.

The advantage of resting-state BOLD fMRI, over brain activity correlated with experimentally painful stimuli, is that it inherently captures spontaneous fluctuations that may be related to pain. To our knowledge, the only studies that have examined spontaneous pain using resting-state BOLD fMRI have been in patients with CBP [16, 17•] and FMS [42•, 43•].

Initially demonstrated using a non-painful visual attention task, CBP patients reveal pronounced alterations in functional connectivity between brain regions of the DMN, implying a disruption in cognitive processing [16]. In a pain-related study, CBP patients revealed increased high-frequency BOLD oscillations specifically in the mPFC and regions of the DMN associated with spontaneous pain [17•]. This result reasonably suggests that pain is a consequence of aberrant DMN functional connectivity, which is supported by evidence from neuropathic pain [44] and in patients with FMS [42•]. In FMS, pain-related compromised functional connectivity was localized to the pain inhibitory network [43•], thus endorsing the evoked pain findings from the same group [36•].

A variety of BOLD resting-state studies have therefore suggested that the cognitive impairments observed in chronic pain patients could be rooted in disturbed DMN dynamics. The underlying idea is that chronic pain is maladaptive and influences brain function and behavior by altering the flow and integration of information across brain regions [16].

It is, however, not clear whether alterations in DMN are causation or correlation in relation to pain and cognition. Studying the DMN inherently taps into the attention-related and self-referential resources of the brain, thereby potentially clouding the interpretation of aberrant DMN dynamics with respect to chronic pain. Nonetheless, further studies are required to establish whether painful fluctuations in arthritis are associated with abnormal resting-state functional connectivity.

EEG Studies

An alternative method for examining brain 'state' is via EEG, which permits the recording of electrical activity derived from synchronized neural activity over a network of neurons. It can be used to study sleep-wake interactions by identifying characteristic frequency oscillations associated with various stages of sleep. For example, abnormal α-EEG activity during sleep has been identified in patients with RA [14, 45]. This finding may be important in explaining the associations between sleep disturbances, morning stiffness and pain in RA patients [14, 45]. Combined with repetitive painful stimulation (intranasal stimulation with gaseous CO_2), EEG has also demonstrated increased cortical responses to the first of a series of painful stimuli in RA patients. This suggests that abnormal pain processing occurs in RA patients [15], as well as in OA patients [6, 10•].

PET (Perfusion) Studies

A third approach for obtaining information about the brain 'state' is perfusion imaging, which generates quantitative regional cerebral blood flow (rCBF) maps of the brain. Such methods, including PET and ASL-MRI, are suitable for capturing the background or on-going components of the clinical pain experienced by patients.

PET, using radioactive isotopes, is the traditional method used to measure alterations in rCBF as an index of changes in neuronal activity. In one of the first neuroimaging studies to be performed in arthritis patients, PET revealed reduced ACC and PFC responses to heat pain in RA patients versus healthy volunteers [18]. Compared to the increased cingulate responses observed in a similar study of patients with atypical face pain [46], these reductions in rCBF suggest a distinct network response associated with inflammatory pain in RA.

PET has also been used to compare experimental pain and arthritic pain processing in patients with knee OA [19]. Although both pain conditions activated areas traditionally associated with pain [8, 26], arthritic pain was associated with increased activity in the cingulate cortex, thalamus, and amygdala; areas involved in the processing of fear and emotions. This suggests that osteoarthritic pain processing includes a significant emotive-affective component, which confirms previous findings identified using BOLD fMRI [11•].

Arterial Spin Labeling MRI (Perfusion) Studies

A relatively new neuroimaging method, ASL, is capable of measuring rCBF using MRI technology by magnetically labeling water in the blood, which subsequently acts as an endogenous diffusible tracer. The advantage of ASL compared to PET is that there is no need for injectable tracers.

ASL is suitable for studying clinical pain [47], for example in arthritis [19], because it is sensitive to on-going pain-related responses over the course of minutes or longer. The application of ASL to phasic pain was first demonstrated in healthy volunteers, by revealing distinct rCBF time-course increases in response to acute and tonic muscular pain [48•].

The first study to reveal rCBF increases associated with on-going pain in a clinical setting was a well-designed cross-over trial in patients requiring bilateral tooth removal [20•]. More recently, ASL has revealed that worsening of on-going CBP is associated with rCBF increases in areas associated with experimental pain (S1, S2, PFC, insular cortex) and other areas seen less frequently in pain studies (superior parietal lobe and part of the dorsal attention network) [21•] (Fig. 1). ASL has also been used, in a simple block design, to highlight pain-related responses associated with baseline neuropathic pain and periods of cooling relief [49•].

The sole application of ASL to arthritic pain to date has demonstrated rCBF increases in pain- and emotion-related processing areas (including S1, S2, insula cortex, cingulate cortex, thalamus, amygdala, and hippocampus) associated with on-going pain in thumb OA [22•]. These rCBF increases imply a degree of neuroplasticity associated with the painful arthritic state [22•]. Further ASL examination of on-going pain in arthritis is warranted in order to determine whether this plasticity is consistent between various osteoarthritic joints and different types of arthritis.

Long-Term Structural Brain Changes

The studies discussed so far in this review have focused on short- and medium-term pain-related responses in the brain. Although some variability is observed, arthritic pain processing appears to consistently recruit frontal [11•, 19, 22•] and limbic areas [11•, 19, 22•] that are involved in affective-emotional-evaluative processing (Fig. 1).

Questions that arise from these findings are whether there are long-term structural changes that reflect the functional responses observed, and to what extent such changes may be reversible. These issues can be addressed by structural and neurochemical inspection, namely MRI voxel based morphometry (VBM) and magnetic resonance spectroscopy (MRS), respectively.

Although pain processing has a genetic component, neural processing is modified by experience. The brain is a dynamic and plastic structure, with evidence for morphological brain changes taking place in fewer than 20 days [50].

While different regions appear to be implicated in different chronic musculoskeletal pain states [51–55], there appears to be consistent atrophy in the cingulate, insula, and frontal regions across CBP and FMS [56], with some evidence for a link between pain duration [51] and severity [53] to the extent of cortical atrophy.

The first study to identify structural brain changes in inflammatory arthritis used manual segmentation to demonstrate that patients with long-standing RA were vulnerable to cerebral vasculitis and cerebellar atrophy [57]. In contrast, a recent morphometric brain analysis identified structural changes in subcortical grey matter, specifically the basal ganglia, in RA patients versus healthy volunteers [58•]. Structural plasticity has also been illustrated in patients with painful hip OA, revealing atrophy of the left thalamus [24•] and dorsolateral PFC, cingulate cortex, amygdala, and brainstem [23•] compared to healthy volunteers. Furthermore, a barcode system comprising within-subject co-variation of grey matter density has been used to classify CBP and knee OA [17•], resembling attempts at functionally decoding different types of pain [37•, 39•].

The long-term structural consequences of arthritic pain require further examination, including application of MR diffusion tensor imaging (DTI), which has enabled visualization of microstructural changes in FMS patients that were not detectable using MR-VBM [55]. To explore the neurochemical mechanisms underlying the structural responses, MRS could determine whether arthritis is accompanied by the abnormal neurotransmitter levels identified in other chronic pain conditions [59, 60].

Grey matter loss in chronic pain patients occurs predominantly in regions related to pain and pain-related processing [56]. The potential impact of this cortical loss, however, may be more widespread: patients with FMS have compromised non-verbal working memory [61]; and CBP patients are impaired on attention and mental flexibility tasks [62]. It appears that in addition to chronic pain, patients suffer from

neurocognitive deficits that correlate with local morphological brain alterations.

It is important to note that it is, however, not clear whether the observed structural changes are pain-specific, or whether they are an indirect consequence of an additional variable related to pain (e.g. life-style changes in response to chronic pain) or accelerated aging [52].

To provide insight into this discussion, there is evidence that the observed changes in grey matter volume are reversible when pain is adequately treated [56]. This suggests that the atrophy observed in chronic pain conditions is the consequence rather than cause of chronic pain. VBM analysis in hip OA patients before and after hip replacement surgery has illustrated this point in arthritis patients; cerebral atrophy can be reversed by replacement of the painful joint [23•, 24•]. These changes were observed in the dorsolateral PFC, cingulate cortex, amygdala, and brainstem at four months post-surgery [23•]; and in the thalamus at nine months post-surgery [24•].

Table 2 Summary of pain neuroimaging studies involving arthritis patients

Study	Patient group	Neuroimaging technique	Pain stimulus	Main findings
Moldofsky et al. (1983) [45]	RA	EEG	–	Abnormal α-EEG activity during sleep in RA patients
Bekkelund et al. (1995) [57]	RA	Structural MRI	–	Long-standing RA patients reveal brain atrophy
Jones et al. (1997) [18]	RA	$C^{15}O_2$-PET	Heat pain	Reduced PFC and ACC responses in RA patients
Drewes et al. (1998) [14]	RA	EEG	–	Increase in α-EEG activity during sleep in RA patients
Hummel at al. (2000) [15]	RA	EEG	Painful intranasal CO_2 pain	Abnormal pain processing in RA patients
Baliki et al. (2005) [65]	Psoriatic arthritis	Functional MRI	Pressure pain to hand joint and knee caps; COX-2i therapy	Neural correlates of pain attenuation 1 h after COX-2i treatment identified as S2 and insula
Buffington et al. (2005) [31]	Knee OA	Functional MRI (BOLD)	Finger pressure pain	ACC activity is spatially distinct during pain-related and attention-related tasks
Kulkarni et al. (2007) [19]	Knee OA	^{18}F-FDG-PET	Heat pain and clinical pain	Arthritic pain is processed by areas involved in emotive processing
Wartolowska et al. (2007) [12]	RA	Functional MRI	Joint compressive pain and heat pain; anti-TNF-α therapy	Central modulation effects of anti-TNF-α treatment observed at 2-4 weeks
Schweinhardt et al. (2008) [9]	RA	Functional MRI	Provoked joint (hand) pain and heat pain	Medial PFC activation associated with provoked clinical pain and depression
Gwilym et al. (2009) [10•]	Hip OA	Functional MRI	Punctate pain	Brainstem as potential mediator of central sensitisation
Rodriguez-Raecke et al. (2010) [23•]	Hip OA	Structural MRI (VBM)	–	Reversible atrophy in cortical and subcortical areas at 4 months after hip replacement
Gwilym et al. (2010) [24•]	Hip OA	Structural MRI (VBM)	–	Hip OA patients reveal thalamic atrophy, which is reversed after hip replacement (9 months)
Baliki et al. (2011) [65]	Knee OA	Structural MRI (VBM)	–	Condition-specific brain morphological signatures (barcodes) for chronic pain
Parks et al. (2011) [11•]	Knee OA	Functional MRI	Mechanical (knee) pain and spontaneous pain; COX-2i therapy	Targets of COX-2i therapy in OA patients are the prefrontal-limbic brain
Hess et al. (2011) [13•]	RA	Functional MRI	Joint (hand) compression; anti-TNF-α therapy	TNF-alpha neutralization occurs at level of brain (within 24 h) before it acts at the joint
Howard et al. (2012) [22•]	Thumb OA	ASL-MRI	–	RCBF increases in pain and affect processing areas
Wartolowska et al. (2012) [58•]	RA	Structural MRI (VBM)	–	Grey matter atrophy in basal ganglia of RA patients

RA – rheumatoid arthritis; OA – osteoarthritic; CBP – chronic back pain; CRPS – complex regionalpain syndrome; EEG – electroencephalography; magnetic resonance imaging (MRI); PET – positron emission tomography; FDG – Fludeoxyglucose; fMRI (functional MRI); Blood oxygenation level dependent (BOLD); VBM – voxel based morphometry; ACC – anterior cingulate cortex; PFC – prefrontal cortex; TNF – tumour necrosis factor; COX-2i - cyclooxygenase-2 inhibitor; RCBF – regional cerebral blood flow

Treatment Evaluation

The studies outlined above refer to the time-scales over which different imaging techniques are sensitive functional or structural responses to arthritic pain. Functional neuroimaging, and in particular BOLD fMRI, can be used to monitor the efficacy and time-course of brain-related treatment effects in disease [11•, 12, 13•, 63, 64•, 65].

The neural correlates of pain attenuation, one hour after anti-inflammatory cyclooxygenase-2 inhibitor (COX-2i) therapy, were identified as the S2 and insula within a single patient with psoriatic arthritis [65]. In a more recent study, increased prefrontal-limbic brain activity was revealed during a time after a 2-week course of COX-2i therapy in patients with painful knee OA [11•]. Furthermore, COX-2i therapy reduced spontaneous pain and clinical characteristics of OA, which correlated with elevated blood and cerebrospinal fluid drug levels [11•]. This suggests that the targets of COX-2i in OA patients are the prefrontal-limbic brain areas [11•].

In RA patients, changes in pain-related activation have been demonstrated after (2–4 weeks) anti-tumor necrosis factor (TNF)-α therapy [12]. Providing further mechanistic insight into TNF-α neutralization, a more recent study has revealed that pain-related brain activity (S2, thalamus, and limbic areas) is blocked within 24 h of anti-TNF-α administration [13•]. Clinical and laboratory markers of inflammation, however, were not altered by anti-TNF-α at this early time-point [13•]. Importantly, this suggests that TNF-α blockage in RA modulates brain-related pain processing before the anti-inflammatory effects of TNF-α are evident in the joint [13•].

The BOLD fMRI studies discussed in this section can act as a platform for identifying central drug targets and evaluating therapeutic efficacy, with potential diagnostic and prognostic utility. Advancing functional and structural neuroimaging may thus provide economic benefit, by reasonably assisting and potentially increasing the efficiency of decision-making in the development of new drugs [64•].

Conclusion

This review has discussed the key functional and structural neuroimaging studies, summarized in Table 2, that have contributed towards an improved understanding of pain processing and therapeutic modulation in degenerative (OA) and inflammatory (RA) arthritis. Short- and medium-term pain-related responses, examined primarily by BOLD fMRI and perfusion methods, have highlighted the frontal-limbic involvement in processing endogenous arthritic pain. This implies that processing of arthritic pain is complex and confounded by emotional and cognitive elements. The consequences of these functional alterations may arguably result in long-term brain structural atrophy, and the subsequent reversal of this atrophy when the pain is alleviated. The interactions between the various functional and structural responses may be addressed more thoroughly by combined methodological approaches in the same patient cohort.

The most exciting future prospects lie in further examination of the clinical aspects of arthritic pain, in particular focusing on the background and fluctuating features of arthritic joint pain (medium-term changes), which are currently not well understood. Long-term, functional and structural neuroimaging methods could be used to evaluate and predict responses to arthritis treatment (e.g. joint replacement or drug therapy), and potentially stratify patient treatment based on imaging-based classification.

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