Imaging Pain of Fibromyalgia

Dane B. Cook, PhD, Aaron J. Stegner, PhD, and Michael J. McLoughlin, BS

Corresponding author
Dane B. Cook, PhD
William S. Middleton Memorial Veterans Hospital, Madison, WI 53706; Department of Kinesiology, University of Wisconsin, Madison, WI 53706, USA.
E-mail: dcook@education.wisc.edu

Current Pain and Headache Reports 2007, **11:**190–200
Current Medicine Group LLC ISSN 1531-3433

Brain imaging studies have provided objective evidence of abnormal central regulation of pain in fibromyalgia (FM). Resting brain blood flow studies have reported mixed findings for several brain regions, whereas decreased thalamic blood flow has been noted by several investigators. Studies examining the function of the nociceptive system in FM have reported augmented brain responses to both painful and non-painful stimuli that may be influenced by psychologic dispositions such as depressed mood and catastrophizing. Treatment approaches are beginning to demonstrate the potential for brain imaging to improve our understanding of pain-alleviating mechanisms. Data from other chronic conditions suggest that idiopathic pain may be maintained by similar central abnormalities as in FM, whereas chronic pain conditions with a known nociceptive source may not be. Future neuroimaging research in FM is clearly warranted and should continue to improve our understanding of factors involved in pain maintenance and symptom exacerbation.

Introduction

Functional neuroimaging methods such as single photon CT (SPECT), positron emission tomography (PET), and functional MRI (fMRI) are now at the forefront of understanding the psychobiological mechanisms underlying acute and chronic pain, including ill understood conditions such as fibromyalgia (FM). Studies of abnormal pain perception, exaggerated central responses to pain, sensory and affective contributions to pain, endogenous pain control, and treatment effects on neural activity are beginning to elucidate potential mechanisms of chronic pain maintenance and hold promise for novel treatment approaches (Table 1).

FM is a severe chronic pain condition characterized by diffuse and widespread musculoskeletal pain, fatigue, sleep disturbance, and general joint stiffness. It is defined by pain lasting for at least 3 months, occurring in all four quadrants of the body (including axial skeletal sites), and by the presence of at least 11 of 18 tender points upon digital palpation [1]. The cause of FM is unknown, and the overall health of the patient tends to deteriorate over time [2]. Although the etiology of FM as a clinical disorder is still a mystery, there is mounting evidence that FM pain is produced and maintained by central nervous system dysregulation of nociceptive and pain processes. Central dysregulation or central sensitization may represent a cause or consequence of chronic pain, but the lack of prospective research limits the study of FM to determining potential mechanisms of symptom maintenance and exacerbation. Functional neuroimaging methods provide a window into the brain and should prove useful as tools for understanding the psychobiological complexities of chronically maintained pain conditions.

Evidence for Central Dysregulation of Pain Processing in FM

Psychophysical examination of responses to experimental pain stimuli has provided strong support for abnormal nociceptive processing in FM. Several different techniques have offered convergent evidence that increased pain sensitivity to experimental pain stimuli in FM is the result of augmented nociceptive processing, and this may play a role in the maintenance of FM pain. Compared to controls, FM patients have lower pain thresholds and report higher pain ratings in response to experimental pain stimuli including pressure, heat, cold, and electricity [3]. The heightened sensitivity occurs at both tender and non-tender sites and appears to reflect the generalized nature of pain that is characteristic of FM [4,5].

More sophisticated experimental techniques have been used to determine the extent and potential location along the neural axis of abnormal nociceptive processing. These experiments aimed at examining the function of the nociceptive system have shown that FM subjects exhibit the following:

1. A dysregulation of diffuse noxious inhibitory controls, suggesting a failure of the central nervous system to modulate afferent sensory information [6];

2. Augmented wind-up and delayed after-sensations to repetitive pain stimuli, suggestive of increased sensitivity of wide dynamic range and nociceptive specific neurons within the dorsal horn of the spinal cord [7];
3. An absence of an exercise-induced analgesic response accompanied by hyperalgesia to painful stimuli and worsening of symptoms after physical exertion [8–10].

In addition, FM patients exhibit significantly increased substance P levels [11] and low cerebrospinal fluid levels of 5-hydroxyindole acetic acid, 3-methoxy-4-hydroxyphenethylene glycol, and homovanillic acid, the metabolites of serotonin, norepinephrine, and dopamine, respectively [12–14]. These biochemicals have established roles in pain processing, and abnormal spinal cord levels suggest that there may be increased nociceptive transmission combined with decreased descending central regulation of sensory information in FM.

In summary, the results from these studies characterize FM pain sensitivity as a dysfunctional endogenous pain control system. However, an accepted limitation for most of the previous research examining nociceptive processes in FM has been the reliance on self-report measures of pain. Although extremely useful and necessary, the inherent biases that accompany such techniques cannot be overlooked. Objective evidence of abnormal central regulation in FM is needed to give a better understanding of the pathophysiologic processes that underlie FM pain, as well as provide physiologic support for the patient's self-reported symptoms. Brain imaging methods such as SPECT, PET, and fMRI have emerged as powerful tools for understanding the complexity of the nociceptive system in humans. These techniques supply the means to objectively measure central nervous system responses at rest and in response to nociceptive stimuli, and can be used to test potential mechanisms of pain exacerbation in chronic pain conditions such as FM.

Potential of Functional Neuroimaging Methods to Understand Pathophysiology of Pain in FM

Functional neuroimaging of pain in healthy men and women

Studies using experimental pain stimuli (eg, noxious heat, noxious pressure, noxious chemicals, and electricity) and using PET and fMRI techniques have identified many of the brain areas involved in processing nociceptive signals in healthy people. The areas most consistently implicated in pain processing are the primary and secondary somatosensory cortices, dorsolateral and medial prefrontal cortices (DLPFC and MPFC), inferior parietal cortex (IPC), anterior cingulate cortex (ACC), supplemental motor cortex, insula, lentiform nucleus, thalamus, and cerebellum [15,16]. The distributed network of pain-related areas is supportive of the multidimensional nature of the pain experience. Moreover, improvements in behavioral research designs give more specific information regarding the cognitive, sensory, and emotional processes that are intrinsic components of pain perception. Consequently, brain areas including the primary and secondary somatosensory cortices, the posterior cingulate cortex, and lateral thalamus have been implicated in the sensory-discriminative aspects of pain, whereas regions including the DLPFC, ACC, and insular cortices, caudate, and the midbrain periaqueductal gray (PAG) have been identified as important regions for affective, cognitive, and motivational aspects of the pain experience [15]. Thus, the host of identified regions is not unique to pain perception alone, but is certainly involved in a complex parallel system that is widely distributed and designed to identify, modulate, and cope with nociceptive information. Given the proper research design, functional brain imaging methods are capable of identifying networks within a system that may be dysfunctional in FM.

Functional neuroimaging in FM

Resting studies

Initial efforts to examine the role of central nervous system dysregulation in FM relied on PET and SPECT imaging technologies. These studies compared baseline or resting measures of brain activity (ie, regional cerebral blood flow [rCBF] or cerebral metabolism) between FM patients and healthy controls [17–23]. Investigators using rCBF as their primary dependent measure have uniformly reported differences in regard to this variable between patients and controls during resting scans. However, there is a lack of consensus on which brain regions exhibit the reported differences as well as whether differences are due to hyper- or hypoperfusion. Multiple investigations have detailed differences in cerebral blood flow between FM patients and controls for the thalamus [17,20,21], caudate nucleus [18,21], pontine tegmentum [17,20], and various frontal [17,19,21,22], parietal [17,18], and temporal cortical regions [17,22]. It is not entirely surprising that so many diverse regions have been indicated in these studies because different researchers have chosen to focus on different regions of the brain. Conversely, the dissimilarity of results within a particular region is less easy to explain. For example, Mountz et al. [21], Kwiatek et al. [20], and Gur et al. [18] all elected to perform region-of-interest analyses for rCBF in the caudate nuclei as part of their comparisons of FM patients to controls. The design of each protocol was very similar (ie, resting SPECT scans of female patients and controls, blood flow expressed relative to the cerebellum), but their results were incongruous. Mountz et al. [21] reported hypoperfusion of the heads of the caudate nuclei in FM patients relative to controls, Gur et al. [18] found hyperperfusion of the caudate nuclei for patients, and Kwiatek et al. [20] saw no difference between patients and controls in regard to

Table 1. Functional neuroimaging studies in FM patients

Study, year	Imaging	Patients	Rest or stimulation type	Major brain areas	Interpretation
Johansson et al. [19], 1995	Xenon CT	FM	Rest	FM decreased rCBF in DLPFC, compared with healthy controls	Decreased rCBF supportive of central dysfunction in FM
Mountz et al. [21], 1995	SPECT	FM	Rest	FM decreased rCBF thalamus, right and left heads caudate nucleus, compared with healthy controls	Decreased rCBF supportive of central dysfunction in FM
Kwiatek et al. [20], 2000	SPECT	FM	Rest	FM decreased rCBF right thalamus and pontine tegmentum, compared with healthy controls	Decreased rCBF supportive of central dysfunction in FM
Gracely et al. [24], 2002	fMRI	FM	Thumbnail pressure	FM increased BOLD frontal, sensory, temporal, limbic, and motor regions, compared with healthy controls	First study to demonstrate augmented nociceptive processing in FM
Gur et al. [18], 2002	SPECT	FM	Rest	FM increased rCBF caudate and decreased pons, parietal, and gyrus rectalis, compared with healthy controls	Significant differences in both rCBF and serum cytokines
Wik et al. [22], 2003	PET	FM	Rest	FM increased rCBF retrosplenial cortex, decreased frontotemporal, tempo-parietal-occipital regions, compared with healthy controls	Increased rCBF retrosplenial cortical activity suggests attention toward subnoxious somatosensory signaling and may be supportive of secondary hyperalgesia in FM
Adigüzel et al. [29•], 2004	SPECT	FM	Treatment (TCA)	FM increased rCBF thalamus, basal ganglia, and decreased temporo-occipital regions	3-month amitriptyline improved tender point count and clinical pain scores, with associated rCBF changes
Cook et al. [25•], 2004	fMRI	FM	Thermal	FM increased BOLD frontal, sensory, temporal, limbic, and motor regions in response to non-painful and painful stimuli, compared with healthy controls	Further support showing augmented sensory processing in FM
Giesecke et al. [28•], 2004	fMRI	CLBP/FM	Thumbnail pressure	FM and CLBP increased BOLD frontal, sensory, temporal, limbic, and motor regions, compared with healthy controls	Idiopathic CLBP maintained by the same central abnormalities as FM
Gracely et al. [26•], 2004	fMRI	FM	Thumbnail pressure	Positive relationships between BOLD responses and catastrophizing in FM across regions involved in attention, anticipation, and emotional pain responses	Pain catastrophizing predicts central responses to pain in FM, independent of depressive symptoms
Giesecke et al. [27], 2005	fMRI	FM	Thumbnail pressure	Depressive symptoms correlated with BOLD in amygdala, insula; clinical pain correlated with BOLD in insula, ACC, PFC, and sensory testing results	Anterior insula may integrate sensory and emotional information in FM

ACC—anterior cingulate cortex; BOLD—blood oxygen level–dependent; CLBP—chronic low back pain; DLPFC—dorsolateral prefrontal cortex; FM—fibromyalgia; fMRI—functional MRI; PET—positron emission tomography; rCBF—regional cerebral blood flow; SPECT—single photon emission CT; TCA—tricyclic antidepressant.

Table 1. Functional neuroimaging studies in FM patients *(continued)*

Study, year	Imaging	Patients	Rest or stimulation type	Major brain areas	Interpretation
Guedj et al. [17], 2006	SPECT	FM	Rest	FM increased rCBF somatosensory, decreased frontal, cingulate, temporal, cerebellum, thalamus, pontine tegmentum, and putamen, compared with healthy controls	Hypoperfusion in affective regions and hyperperfusion in sensory regions suggest altered central processing in FM
Usui et al. [31•], 2006	SPECT	FM	Treatment (electroconvulsive)	FM increased rCBF thalamus with treatment	Electroconvulsive therapy improved clinical pain scores and tender point count, which coincided with increased thalamic rCBF

ACC—anterior cingulate cortex; BOLD—blood oxygen level–dependent; CLBP—chronic low back pain; DLPFC—dorsolateral prefrontal cortex; FM—fibromyalgia; fMRI—functional MRI; PET—positron emission tomography; rCBF—regional cerebral blood flow; SPECT—single photon emission CT; TCA—tricyclic antidepressant.

blood flow for this region. A more consistent pattern is observed for the thalamus. Mountz et al. [21] and Guedj et al. [17] both reported decreased rCBF for patients bilaterally in the thalamus, whereas Kwiatek et al. [20] reported decreased rCBF in the right thalamus. Despite the lack of complete agreement, it bears repeating that all of the aforementioned studies, regardless of the particular region of interest analyses, indicated some differences in resting cerebral blood flow between individuals suffering from FM and healthy controls. The known heterogeneity of the FM patient population is one potential explanation for some of the inconsistent findings. Future research comparing subgroups of FM patients perhaps on variables such as comorbid illnesses (eg, depression, chronic fatigue syndrome), illness duration and severity (new-onset patients vs longer-term patients), or illness onset (sudden vs gradual) may help clarify the usefulness of resting brain blood flow in understanding pain in FM.

Brain responses to pain

In order to test the function of the nociceptive system in FM, investigators have begun to determine the neural responses to experimental pain stimuli. In the first study to use this approach, Gracely et al. [24] reported that fMRI brain responses to experimental pressure pain, set at either similar stimulus levels or similar subjective pain levels, were augmented in FM patients compared with controls. Regions of augmentation included the primary and secondary somatosensory cortices, inferior parietal lobe, ACC, anterior insula, superior temporal gyrus, and cerebellum. An absence of thalamic activity in the FM group, but not in controls, during painful pressure was also observed. These data supplied the first objective evidence that physiologic processing of pain is altered in FM and demonstrated that augmented responses occurred over multiple networks involved in somatosensory integration, motor control, and cognitive-affective appraisal.

Work conducted in our laboratory extended upon these findings and demonstrated that, compared with healthy controls, FM patients exhibited augmented fMRI responses to non-painful and painful heat stimuli [25•]. Greater responses to both painful and non-painful stimuli were further objective support of augmented physiologic processing of sensory information in FM. The brain regions that showed the greatest differences between FM and controls were the anterior insula, pre-motor, PFC, and ACC. Furthermore, by using both a temperature equivalent stimulus (47° C for all participants) and a perceptually equivalent stimulus (temperature rated as strong pain "5" by both groups) that was of an absolute greater intensity for the controls (48.5° C vs 47° C), we were able to clearly demonstrate augmented central processing of pain in FM. The greatest difference between FM patients and controls occurred in the anterior insula cortex. We also observed an absence of thalamic activity in FM during the non-painful warm condition. Finally, during the last non-painful warm condition we observed PAG activity for the control group, but not the FM group, suggesting that the delivery of multiple painful stimuli failed to excite descending pain inhibitory processes in the FM group, whereas the pain regulatory system of the control subjects was actively attempting to inhibit further nociceptive input. Our laboratory is currently pursuing these initial observations and closely examining PAG activity and other pain modulation networks in FM.

Recently, studies have begun to more specifically determine the influence of other relevant variables on pain sensitivity and brain responses to pain in FM patients. Gracely et al. [26•] reported that pain catastrophizing was related to multiple brain regions involved in the anticipation, attention, and motivational aspects of pain. After statistically controlling for depressive symptoms, pain catastrophizing was positively related to brain activity within the claustrum, cerebellum, DLPFC, MPFC, parietal cortex, ACC, and lentiform nuclei. Patients characterized as high catastrophizers were found to exhibit a greater magnitude of activity in the ipsilateral secondary somatosensory cortex and unique activity in the contralateral ACC and bilateral lentiform. Thus catastrophizing, with its influence on somatosensory and cognitive-emotional aspects of pain processing, can have widespread effects on how pain is perceived and coped with in FM. Work from the same group [27] demonstrated that self-reports of depressed mood in FM patients were significantly related to neural responses to slightly intense painful stimuli in the amygdala and contralateral anterior insular cortex. Depressed mood was not significantly related to sensory regions of the brain. Moreover, FM patients diagnosed with major depressive disorder exhibited greater activity within these same regions (amygdala and insula), compared with FM patients without depression or with healthy controls. The patients' clinical reports of pain were found to be associated with two unique brain regions, the PFC and the ACC, and one common region, the anterior insula. These results suggest that depression in FM can impact the affective-motivational aspects of pain, while being independent of the sensory-discriminative aspects. Furthermore, the anterior insula, which is significantly associated with both depression and pain symptoms, may serve an important integrating role for sensory and emotional information and appears to be particularly important for pain processing in FM [25•,28•].

Treatment

The influence of treatment on functional neural responses in FM is an exciting and emerging field of investigation. Recent studies have used functional neuroimaging methods in creative ways to determine the influence of pharmacologic [29•,30] and electroconvulsive [31•] therapies on brain responses and symptoms associated with chronic pain. Adigüzel et al. [29•] determined the impact of 3 months of amitriptyline therapy on pain symptoms

and self-reported level of depression in association with changes in cerebral blood flow in 14 female FM patients. Participants were scanned at rest before treatment and again after 3 months of daily amitriptyline therapy (10 mg/day for first 10 days; 25 mg/day thereafter). Pain symptoms were quantified by a visual analog scale (VAS) and tender point count pre- and post-treatment. Self-reported depression was measured with the Beck Depression Inventory (BDI). Statistically significant decreases in VAS ratings and tender point counts after amitriptyline treatment coincided with significant increases in hemithalamic and basal ganglia blood flow. Decreases in rCBF were also noted in bilateral temporal, left temporo-occipital, and right occipital lobes at follow-up. For the group, BDI scores at baseline did not suggest significant depression and did not change after therapy. Although the changes in FM symptomology were considered to be of clinical significance, the investigators found no significant correlations between changes in pain symptom indicators and SPECT results.

Usui et al. [31•] completed a methodologically similar investigation designed to explore changes in cerebral blood flow and pain symptoms in nondepressed FM patients as a result of electroconvulsive therapy. Fifteen FM patients submitted to two resting SPECT scans. The first scan was conducted immediately before the commencement of electroconvulsive therapy, and the second scan took place 3 days after the completion of the treatment course. Improvements in pain symptoms after therapy were indicated by significant decreases in VAS ratings and tender point counts. Concomitant increases in rCBF were reported bilaterally in the thalamus. Parallel to the results of Adigüzel et al. [29•], BDI scores were not altered with treatment. Pain symptoms of FM, as measured by VAS, were still significantly reduced from baseline 3 months after the completion of electroconvulsive therapy. The authors concluded that electroconvulsive therapy had a significant impact on FM pain symptoms and that this reported symptom relief was associated with an increase in thalamic blood flow. The results of these investigations are exciting not only in regard to the successful use of two different therapeutic modalities to ease FM symptoms, but also in light of their demonstration of the usefulness of imaging technology to examine functional changes in the brain with treatment. Follow-up investigations are encouraged.

Functional Neuroimaging in Other Chronic Pain Conditions

An important aspect of studying FM is determining whether resting brain activity or abnormal brain responses to painful stimuli are unique to FM or are a general consequence of experiencing chronic pain. Functional neuroimaging studies have been conducted on several chronic pain conditions such as chronic low back pain (CLBP), neuropathic pain (NP), irritable bowel syndrome (IBS), rheumatoid arthritis (RA), cancer, and atypical face pain (AFP; Table 2). These studies demonstrate the resting and functional aspects of the brain in chronic pain patients and offer some interesting insights for FM research. For example, decreased rCBF in the thalamus has been observed in chronic pain conditions such as NP [32–34] and cancer pain [35]. Furthermore, thalamic stimulation has been shown to relieve chronic pain [36,37], and increases in thalamic blood flow have been observed after successful pain alleviation with a lidocaine nerve block in NP [32]. These results suggest that low rCBF in the thalamus is a general consequence of experiencing chronic pain and may represent an inability of the system to compensate for the constant barrage of incoming nociceptive signals.

Experimental pain stimulation studies have revealed both similarities and differences in the way that pain is processed in select chronic conditions. Patients with IBS exhibit augmented pain responses similar to FM. In response to visceral stimulation, IBS patients generally exhibit significantly greater responses in PFC, ACC, and amygdala and lower activity in the PAG, compared with healthy controls [38–40]. In addition, fMRI studies in IBS suggest abnormal endogenous pain control mechanisms in this patient group [41,42], similar to those suggested by behavioral studies in FM. It will be important to pursue similar methodologic approaches for future neuroimaging studies in FM.

Functional neuroimaging studies of patients with chronic pain from known peripheral origins such as RA and ulcerative colitis (UC; ie, inflammation) show that these patients exhibit characteristically different brain responses to experimental pain than those seen in FM patients. RA patients were found to have reduced cortical and subcortical responses to experimental stimuli, compared with controls and patients with AFP [43]. Furthermore, IBS patients showed greater responses to rectal distention in the amygdala, hypothalamus, ACC, and MPFC, whereas controls and UC patients had significantly more robust activation of the lateral prefrontal areas and the PAG [40]. These findings suggest that there may be important differences between chronic pain resulting from known peripheral abnormalities (ie, RA and UC) and pain conditions thought to be maintained by central nervous system abnormalities in sensory processing (ie, AFP and IBS).

Because imaging modalities such as SPECT and PET are limited as cross-sectional time-specific measures and fMRI studies represent relative changes from an unknown baseline, comparisons of brain responses across studies are problematic. Therefore, directly contrasting FM patients with other chronic pain conditions is important. Chang et al. [44] used PET to directly compare the neural responses during either rectal distention or pressure pain in IBS patients and IBS patients with comorbid FM (IBS + FM). Differences between the patient groups were limited to one region in the middle ACC. Specifically, patients with IBS + FM had greater neural responses in this region to

Table 2. Functional neuroimaging studies in other chronic pain conditions

Study, year	Imaging	Patients	Rest or stimulation type	Major findings	Interpretation
Hsieh et al. [32], 1995	PET	NP	Rest/regional nerve block	Decreased rCBF anterior insula, posterior parietal, lateral PFC, right posterior ACC, posterior cingulate, and cerebellar vermis and increased rCBF contralateral thalamus during pain alleviation	Relief of NP alters rCBF in multiple pain-relevant brain regions
Jones and Derbyshire [43], 1997	PET	RA	Thermal	RA decreased rCBF, DLPFC, and ACC, compared with AFP and healthy controls	Suggests that RA patients develop adaptive responses to pain that differ from those of AFP patients
Davis et al. [36], 2000	PET	NP	Treatment (thalamic stimulation)	Increased rCBF, ACC, globus pallidus	Thalamic stimulation provides pain relief in some cases and alters pain-relevant brain responses
Naliboff et al. [38], 2001	PET	IBS	Rectal distention	Increased rCBF right PFC, ACC, posterior cingulate, decreased rCBF perigenual, temporal, and brain stem, compared with healthy controls	IBS patients exhibit augmented neural activity in response to both anticipated and delivered rectal stimuli, suggestive of altered central brain processing
Berman et al. [45], 2002	PET	IBS	Treatment ($5HT_3$ antagonist)	Decreased rCBF MPFC, hypothalamus, infragenual cingulate, and amygdala; increased rCBF lateral PFC, anterior insula in response to treatment	Alosetron can decrease unpleasantness of painful stimuli and affects brain areas with a role in descending pain regulation
Chang et al. [44], 2003	PET	IBS/IBS + FM	Rectal distention/ arm pressure	IBS increased rCBF ACC to visceral stimulation; IBS + FM increased rCBF ACC to somatic stimulation	Accounting for comorbid illness in chronic pain can reveal interesting differences in pain processing
Verne et al. [39], 2003	fMRI	IBS	Rectal distention/hot water foot immersion	IBS increased BOLD ACC, thalamus, somatosensory, insula, and PFC, compared with healthy controls	Augmented neural responses to both visceral and cutaneous pain suggest pain in IBS can be maintained by central mechanisms
Wilder-Smith et al. [42], 2004	fMRI	IBS	Rectal distention with and without ice water foot immersion	IBS altered BOLD frontal, sensory, temporal, and limbic regions, compared with healthy controls	Suggests dysfunction of DNIC in IBS
deCharms et al. [47•], 2005	rtfMRI	Chronic pain	Treatment (direct feedback)	Patients actively controlled rostral ACC BOLD activity	rtfMRI feedback has potential for treatment of chronic pain
Mayer et al. [40], 2005	PET	IBS/UC	Rectal distention	IBS increased rCBF ACC, amygdala, MPFC and decreased rCBF lateral PFC, PAG, compared with healthy controls and UC	Suggests that failure of antinociceptive mechanisms is important in the maintenance of IBS

ACC—anterior cingulate cortex; AFP—atypical facial pain; BOLD—blood oxygen level–dependent; DLPFC—dorsolateral prefrontal cortex; DNIC—diffuse noxious inhibitory controls; FM—fibromyalgia; fMRI—functional MRI; IBS—irritable bowel syndrome; MPFC—medial prefrontal cortex; NP—neuropathic pain; PAG—periaqueductal gray; PET—positron emission tomography; RA—rheumatoid arthritis; rCBF—regional cerebral blood flow; rtfMRI—real-time functional MRI; TCA—tricyclic antidepressant; UC—ulcerative colitis.

Table 2. Functional neuroimaging studies in other chronic pain conditions *(continued)*

Study, year	Imaging	Patients	Rest or stimulation type	Major findings	Interpretation
Morgan et al. [46], 2005	fMRI	IBS	Treatment (TCA)	Decreased BOLD ACC, posterior parietal cortex post-treatment	4 weeks of amitriptyline decreased brain activity within pain-relevant areas during rectal distention and concurrent auditory stress
Song et al. [41], 2006	fMRI	IBS	Rectal distention with and without ice water foot immersion	IBS altered BOLD in multiple brain regions involved in anticipation, attention, emotion, and interoceptive processing	Suggests dysfunction of DNIC in IBS

ACC—anterior cingulate cortex; AFP—atypical facial pain; BOLD—blood oxygen level–dependent; DLPFC—dorsolateral prefrontal cortex; DNIC—diffuse noxious inhibitory controls; FM—fibromyalgia; fMRI—functional MRI; IBS—irritable bowel syndrome; MPFC—medial prefrontal cortex; NP—neuropathic pain; PAG—periaqueductal gray; PET—positron emission tomography; RA—rheumatoid arthritis; rCBF—regional cerebral blood flow; rtfMRI—real-time functional MRI; TCA—tricyclic antidepressant; UC—ulcerative colitis.

pressure pain, whereas those with IBS alone displayed greater responses to rectal distension.

Giesecke et al. [28•] directly compared patients suffering from idiopathic CLBP (ie, no identifiable abnormality) with patients with FM and with controls. Compared with controls, patients with CLBP were characterized by levels of hyperalgesia and augmented brain responses similar to those in patients with FM. Specifically, when an equal pressure stimulus of 2 kg (rated as moderately painful by CLBP and FM patients and as faint pain by controls) was applied to the thumbnails of the participants, both the CLBP and FM patients demonstrated neural activity in the contralateral primary and secondary somatosensory cortices, ipsilateral secondary somatosensory cortex, IPC, and the cerebellum. The only neural activity detected within the control group at this pressure was the contralateral secondary somatosensory cortex. When equally painful pressure (slightly intense pain) was applied to all three groups, similar neural activity was noted in the primary somatosensory, secondary somatosensory, inferior parietal, insular, and anterior cingulate cortices and the cerebellum. Thus, CLBP patients displayed both hyperalgesic responses to pressure pain stimuli applied to the thumb, indicative of generalized pain sensitivity, and augmented neural responses to pain compared with controls. These findings demonstrate central pain amplification in a condition with regional pain and suggest that idiopathic CLBP is maintained by similar central phenomena as FM. An interesting and unique area of activity in the anterior insula was noted in the FM group, suggestive of a more robust affective response to experimental pain stimuli for FM patients versus both chronic pain patients and healthy controls. The results of these studies highlight the importance of comparing different chronic pain conditions to FM. Moreover, studies of augmented nociceptive processing in chronic pain can benefit from careful selection of pain stimulus modality.

Functional neuroimaging methods have been useful for evaluating potential mechanisms of treatment for other chronic pain conditions such as NP [32,36] and IBS [45,46]. As mentioned earlier, NP patients exhibit lower thalamic blood flow that can be restored with pain alleviation [32]. For IBS patients, 3 weeks of treatment with a $5HT_3$ receptor antagonist (alosetron) decreased the unpleasantness of rectal distention and was associated with decreased neural responses in the MPFC, hypothalamus, infragenual cingulate, and amygdala, compared with baseline and placebo control [45]. Increased activity to distention was found in the lateral PFC and anterior insula, suggesting that treatment also influenced brain regions implicated in descending inhibition of pain [45]. Four weeks of tricyclic antidepressant therapy (amitriptyline) in IBS patients was associated with lower activation of the ACC and left posterior parietal cortex, compared with baseline and placebo control, although only during concurrent auditory stress [46].

A recent study suggests that self-control of brain activity in chronic pain patients can provide pain relief. Thus, fMRI also may be used as a tool for treatment of chronic pain. deCharms et al. [47•] used real-time fMRI (rtfMRI) and applied it as the treatment modality. Twelve chronic pain patients underwent training using rtfMRI to actively control a region involved in the pain modulatory network, the rostral ACC. Patients were trained to either decrease or increase activity within this region by direct feedback from the rostral ACC or by autonomic biofeedback. After training, chronic pain patients receiving ACC feedback reported significant decreases in their pain symptoms, whereas the autonomic biofeedback control group showed no significant changes.

Conclusions

This review, although not comprehensive, highlights the use of functional neuroimaging methods in FM and attempts to demonstrate the potential utility of these methods toward understanding and treating this poorly understood clinical syndrome. Neuroimaging studies in FM give objective support to the large body of behavioral research suggesting that FM pain is maintained by abnormal central pain regulation. Although not entirely uniform, certain commonalities in the results do exist. For the resting brain, decreased blood flow in regions such as the thalamus has been replicated and has been found to occur in other chronic pain conditions. Pain-alleviating treatments also result in increases in or restoration of thalamic blood flow. For experimental pain stimuli, the distribution of augmented responses suggests that central dysregulation of pain processing affects several networks involved in sensory, affective, and cognitive aspects of the pain experience. Furthermore, these augmented responses do not appear to be unique to FM but occur in other poorly understood conditions, such as IBS, idiopathic CLBP, and AFP. Regions that deserve particular attention in FM appear to be the thalamus, anterior insula, and PAG. Thalamic and PAG activity is consistently observed in healthy controls during pain stimulation protocols and is notably absent in FM. Several reports have highlighted robust anterior insula activity in FM compared with both healthy controls and other chronic pain conditions (eg, idiopathic CLBP). The paucity of functional neuroimaging data and the degree of individual variability in brain responses, both within and between studies, limit recommendations involving the utility of brain imaging in the clinical setting. One promising application of neuroimaging in FM, which may eventually translate to the clinical setting, is the potential to monitor brain responses throughout the course of treatment. Although the current number of studies is admittedly small, the future of functional neuroimaging in FM appears bright. We can expect that advances in imaging technology, behavioral research

designs, and ultimately, our understanding of risk factors associated with the development of FM will lead to prospective neuroimaging studies that reveal neural mechanisms of pain maintenance and possibly even disease progression.

Acknowledgment

This material is based upon work supported in part by Office of Research and Development, Clinical Science R & D Service, Department of Veterans Affairs.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Wolfe F, Smythe HA, Yunus MB, et al.: **The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee.** *Arthritis Rheum* 1990, **33:**160–172.
2. Wolfe F, Anderson J, Harkness D, et al.: **Health status and disease severity in fibromyalgia: results of a six-center longitudinal study.** *Arthritis Rheum* 1997, **40:**1571–1579.
3. Staud R: **Biology and therapy of fibromyalgia: pain in fibromyalgia syndrome.** *Arthritis Res Ther* 2006, **8:**208.
4. Geisser ME, Gracely RH, Giesecke T, et al.: **The association between experimental and clinical pain measures among persons with fibromyalgia and chronic fatigue syndrome.** *Eur J Pain* 2007, **11:**202–207.
5. Staud R: **Predictors of clinical pain intensity in patients with fibromyalgia syndrome.** *Curr Pain Headache Rep* 2005, **9:**316–321.
6. Kosek E, Hansson P: **Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects.** *Pain* 1997, **70:**41–51.
7. Staud R, Price DD, Robinson ME, et al.: **Maintenance of windup of second pain requires less frequent stimulation in fibromyalgia patients compared to normal controls.** *Pain* 2004, **110:**689–696.
8. Cook DB, Nagelkirk PR, Poluri A, et al.: **The influence of aerobic fitness and fibromyalgia on cardiorespiratory and perceptual responses to exercise in patients with chronic fatigue syndrome.** *Arthritis Rheum* 2006, **54:**3351–3362.
9. Mengshoel AM, Vollestad NK, Forre O: **Pain and fatigue induced by exercise in fibromyalgia patients and sedentary healthy subjects.** *Clin Exp Rheumatol* 1995, **13:**477–482.
10. Vierck CJ Jr, Staud R, Price DD, et al.: **The effect of maximal exercise on temporal summation of second pain (windup) in patients with fibromyalgia syndrome.** *J Pain* 2001, **2:**334–344.
11. Sprott H, Bradley LA, Oh SJ, et al.: **Immunohistochemical and molecular studies of serotonin, substance P, galanin, pituitary adenylyl cyclase-activating polypeptide, and secretoneurin in fibromyalgic muscle tissue.** *Arthritis Rheum* 1998, **41:**1689–1694.
12. Juhl JH: **Fibromyalgia and the serotonin pathway.** *Altern Med Rev* 1998, **3:**367–375.
13. Russell IJ, Michalek JE, Vipraio GA, et al.: **Platelet 3H-imipramine uptake receptor density and serum serotonin levels in patients with fibromyalgia/fibrositis syndrome.** *J Rheumatol* 1992, **19:**104–109.
14. Schwarz MJ, Spath M, Muller-Bardorff H, et al.: **Relationship of substance P, 5-hydroxyindole acetic acid and tryptophan in serum of fibromyalgia patients.** *Neurosci Lett* 1999, **259:**196–198.
15. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK: **Human brain mechanisms of pain perception and regulation in health and disease.** *Eur J Pain* 2005, **9:**463–484.
16. Peyron R, Laurent B, Garcia-Larrea L: **Functional imaging of brain responses to pain. A review and meta-analysis (2000).** *Neurophysiol Clin* 2000, **30:**263–288.
17. Guedj E, Taieb D, Cammilleri S, et al.: **(99m)tc-ECD brain perfusion SPECT in hyperalgesic fibromyalgia.** *Eur J Nucl Med Mol Imaging* 2006, **34:**130–134
18. Gur A, Karakoc M, Erdogan S, et al.: **Regional cerebral blood flow and cytokines in young females with fibromyalgia.** *Clin Exp Rheumatol* 2002, **20:**753–760.
19. Johansson G, Risberg J, Rosenhall U, et al.: **Cerebral dysfunction in fibromyalgia: evidence from regional cerebral blood flow measurements, otoneurological tests and cerebrospinal fluid analysis.** *Acta Psychiatr Scand* 1995, **91:**86–94.
20. Kwiatek R, Barnden L, Tedman R, et al.: **Regional cerebral blood flow in fibromyalgia: single-photon-emission computed tomography evidence of reduction in the pontine tegmentum and thalami.** *Arthritis Rheum* 2000, **43:**2823–2833.
21. Mountz JM, Bradley LA, Modell JG, et al.: **Fibromyalgia in women. Abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels.** *Arthritis Rheum* 1995, **38:**926–938.
22. Wik G, Fischer H, Bragee B, et al.: **Retrosplenial cortical activation in the fibromyalgia syndrome.** *Neuroreport* 2003, **14:**619–621.
23. Yunus MB, Young CS, Saeed SA, et al.: **Positron emission tomography in patients with fibromyalgia syndrome and healthy controls.** *Arthritis Rheum* 2004, **51:**513–518.
24. Gracely RH, Petzke F, Wolf JM, Clauw DJ: **Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia.** *Arthritis Rheum* 2002, **46:**1333–1343.
25.• Cook DB, Lange G, Ciccone DS, et al.: **Functional imaging of pain in patients with primary fibromyalgia.** *J Rheumatol* 2004, **31:**364–378.

This study extended upon the study by Gracely et al. [24] by demonstrating augmented brain responses in FM to both painful and non-painful heat stimuli and in response to both relative and absolute pain stimuli. This research provides evidence that FM patients may exhibit altered central nervous system processing for both sensory and nociceptive signals.

26.• Gracely RH, Geisser ME, Giesecke T, et al.: **Pain catastrophizing and neural responses to pain among persons with fibromyalgia.** *Brain* 2004, **127:**835–843.

This study highlights the influence of psychologic dispositions on functional neuroimaging responses by showing significant relationships between self-reports of pain catastrophizing and brain responses to pain in regions such as the DLPFC and ACC. The study also demonstrates the value of fMRI for the study of pain in FM, particularly with regard to the sensory and affective aspects of the pain experience.

27. Giesecke T, Gracely RH, Williams DA, et al.: **The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort.** *Arthritis Rheum* 2005, **52:**1577–1584.
28.• Giesecke T, Gracely RH, Grant MA, et al.: **Evidence of augmented central pain processing in idiopathic chronic low back pain.** *Arthritis Rheum* 2004, **50:**613–623.

This study shows that FM may not be completely unique from other idiopathic chronic pain conditions by demonstrating augmented brain responses to pain in CLBP patients. However, augmented responses in regions such as the anterior insula may be able to discriminate FM from other chronic pain conditions. This study points out the importance of chronic pain control groups in FM research.

29.• Adigüzel O, Kaptanoglu E, Turgut B, Nacitarhan V: **The possible effect of clinical recovery on regional cerebral blood flow deficits in fibromyalgia: a prospective study with semiquantitative SPECT.** *South Med J* 2004, **97:**651–655.

This study demonstrates the utility of neuroimaging to objectively quantify physiologic changes associated with FM symptom relief as a result of therapy. Participants exhibited an increase in thalamic blood flow, coinciding with a decrease in reported pain symptoms, following a pharmacologic treatment.

30. Koeppe C, Schneider C, Thieme K, et al.: **The influence of the 5-HT3 receptor antagonist tropisetron on pain in fibromyalgia: a functional magnetic resonance imaging pilot study.** *Scand J Rheumatol Suppl* 2004, **119:**24–27.

31.• Usui C, Doi N, Nishioka M, et al.: **Electroconvulsive therapy improves severe pain associated with fibromyalgia.** *Pain* 2006, **121:**276–280.

This study provides further evidence of changes in cerebral blood flow corresponding with decreases in reported FM pain symptoms after successful treatment. Congruent to the findings of Adigüzel et al. [29•], participants exhibited an increase in thalamic blood flow after completing a course of electroconvulsive therapy.

32. Hsieh JC, Belfrage M, Stone-Elander S, et al.: **Central representation of chronic ongoing neuropathic pain studied by positron emission tomography.** *Pain* 1995, **63:**225–236.

33. Iadarola MJ, Max MB, Berman KF, et al.: **Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain.** *Pain* 1995, **63:**55–64.

34. Wu CT, Fan YM, Sun CM, et al.: **Correlation between changes in regional cerebral blood flow and pain relief in complex regional pain syndrome type 1.** *Clin Nucl Med* 2006, **31:**317–320.

35. Di Piero V, Jones AK, Iannotti F, et al.: **Chronic pain: a PET study of the central effects of percutaneous high cervical cordotomy.** *Pain* 1991, **46:**9–12.

36. Davis KD, Taub E, Duffner F, et al.: **Activation of the anterior cingulate cortex by thalamic stimulation in patients with chronic pain: a positron emission tomography study.** *J Neurosurg* 2000, **92:**64–69.

37. Duncan GH, Kupers RC, Marchand S, et al.: **Stimulation of human thalamus for pain relief: possible modulatory circuits revealed by positron emission tomography.** *J Neurophysiol* 1998, **80:**3326–3330.

38. Naliboff BD, Derbyshire SW, Munakata J, et al.: **Cerebral activation in patients with irritable bowel syndrome and control subjects during rectosigmoid stimulation.** *Psychosom Med* 2001, **63:**365–375.

39. Verne GN, Himes NC, Robinson ME, et al.: **Central representation of visceral and cutaneous hypersensitivity in the irritable bowel syndrome.** *Pain* 2003, **103:**99–110.

40. Mayer EA, Berman S, Suyenobu B, et al.: **Differences in brain responses to visceral pain between patients with irritable bowel syndrome and ulcerative colitis.** *Pain* 2005, **115:**398–409.

41. Song GH, Venkatraman V, Ho KY, et al.: **Cortical effects of anticipation and endogenous modulation of visceral pain assessed by functional brain MRI in irritable bowel syndrome patients and healthy controls.** *Pain* 2006, **126:**79–90.

42. Wilder-Smith CH, Schindler D, Lovblad K, et al.: **Brain functional magnetic resonance imaging of rectal pain and activation of endogenous inhibitory mechanisms in irritable bowel syndrome patient subgroups and healthy controls.** *Gut* 2004, **53:**1595–1601.

43. Jones AK, Derbyshire SW: **Reduced cortical responses to noxious heat in patients with rheumatoid arthritis.** *Ann Rheum Dis* 1997, **56:**601–607.

44. Chang L, Berman S, Mayer EA, et al.: **Brain responses to visceral and somatic stimuli in patients with irritable bowel syndrome with and without fibromyalgia.** *Am J Gastroenterol* 2003, **98:**1354–1361.

45. Berman SM, Chang L, Suyenobu B, et al.: **Condition-specific deactivation of brain regions by 5-HT3 receptor antagonist alosetron.** *Gastroenterology* 2002, **123:**969–977.

46. Morgan V, Pickens D, Gautam S, et al.: **Amitriptyline reduces rectal pain related activation of the anterior cingulate cortex in patients with irritable bowel syndrome.** *Gut* 2005, **54:**601–607.

47.• deCharms RC, Maeda F, Glover GH, et al.: **Control over brain activation and pain learned by using real-time functional MRI.** *Proc Natl Acad Sci U S A* 2005, **102:**18626–18631.

This study highlights the potential of functional neuroimaging technology for both understanding and treating chronic pain conditions.