Brain imaging in fibromyalgia syndrome

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ABSTRACT

Fibromyalgia (FM) is a chronic musculoskeletal pain syndrome which is characterised by clinical pain as well as widespread hyperalgesia/allodynia to mechanical, thermal, electrical, and chemical stimuli. Lack of consistent tissue abnormalities in FM patients has more and more shifted the focus away from peripheral factors and towards central nervous system abnormalities including central sensitisation as well as aberrant pain facilitation and inhibition. Besides quantitative sensory testing, functional brain imaging has been increasingly utilised to characterise the abnormal pain processing of FM patients. Whereas initial work in FM patients identified abnormally increased pain-related brain activity within the thalamus, insula, anterior cingulate, S1, and prefrontal cortex (so-called "pain matrix"), more recent research focused on altered "connectivity" between multiple interconnected brain networks in these patients. Additionally, magnetic resonance spectroscopy studies demonstrated high concentration of the excitatory neurotransmitter glutamate in FM patients in pain-related brain areas which correlated not only with experimental but also with clinical pain ratings. Overall, functional brain imaging studies have provided compelling evidence for abnormal pain processing in FM, including brain activity that correlated with patients' augmented pain sensitivity (hyperalgesia/allodynia), temporal summation of pain, and prolonged pain aftersensations. Future imaging work needs to focus on identifying the neural correlates of FM patients' abnormal endogenous pain modulation which will likely not only shed more light on this important pain regulatory mechanism but may also provide useful information for future treatments of FM symptoms.

Fibromyalgia

Fibromyalgia (FM) is a musculoskeletal disorder characterised by chronic widespread pain and tenderness (hyperalgesia/allodynia). FM symptoms comprise pain, fatigue, tenderness, sleep disturbance, decreased physical functioning, and psychological/cognitive dysfunction including memory problems, diminished mental clarity, mood disturbances, and lack of well-being (1-3). In general, FM patients show signs of mechanical (primary hyperalgesia) and heat hyperalgesia (secondary hyperalgesia). These sensory abnormalities are widespread and not limited to so-called tender points (4). The widespread distribution of pain in FM without consistent evidence for peripheral tissue abnormalities strongly suggests the involvement of central nervous system mechanisms that facilitate peripheral (nociceptive input) and central pain processing (emotions, expectations, catastrophising, etc.). Such central mechanisms may involve spinal or supraspinal modulation of peripheral impulse input, including dysfunctional pain facilitation and inhibition that increase pain sensitivity at the periphery. Central pain mechanisms most often simultaneously involve the spinal cord and brain which can be indirectly assessed through functional imaging.

Measuring brain activity

Over the last 25 years, brain imaging methods such as single photon computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) have greatly enhanced our understanding of the perception and modulation of the pain experience (5). These procedures indirectly evaluate neural activity from a) cerebral blood flow changes or glucose metabolism, b) measure brain metabolites with magnetic resonance spectroscopy techniques, and c) document the amount of receptor binding by specific ligands. These techniques can be used to study the brain mechanisms involved in generating and maintaining chronic pain, including FM pain. SPECT and PET require injections of radioactive tracers into the vascular system before brain scanning, whereas fMRI captures changes in oxygenated haemoglobin concentration associated with brain activity. Despite its dependence on radioactive tracers, SPECT and PET have several advantages when compared with fMRI, including direct measurements of blood flow. Disadvantages of PET and SPECT scanning include exposure to ionising radiation and cost. The total dose of radiation from these procedures can be significant and is usually around 5–7 mSiverts.

Blood oxygen level dependent (Bold) measures of blood flow

During MRI radio-frequency pulses are used to activate protons in tissues and the resulting radio signals emitted from such activated protons provide the basis for contrast maps with high temporal and spatial resolution. Most methods of fMRI rely on measuring regional cerebral blood flow (rCBF) changes associated with brain activity which are closely correlated to the magnitude and duration of neuronal activity. Overall the time course of rCBF is indicative of metabolic demand and thus brain function. Unlike SPECT and PET, fMRI relies on measuring blood oxygen level depended (BOLD) changes in the brain which are correlated to rCBF. The different magnetic properties of de-oxygenated compared to oxygenated haemoglobin can be readily assessed in a magnetic brain scanner. During neuronal activity the regional concentration of oxygenated haemoglobin rapidly changes, resulting in alterations of fMRI signals associated with that brain region. In scanners of high magnetic field strength low intensity BOLD signals can be detected originating from capillaries which are in close vicinity to active neurons (6). While at magnetic field strength of 1.5 tesla (T) most BOLD signals will arise from larger blood vessels like arterioles and venules, at 7 T about 70% will originate from capillaries (7, 8). With today's scanners BOLD images can be acquired with relatively good spatial and temporal resolution with voxel sizes of several mm^3. Recent technical advances, such as high magnetic field strength and multichannel radio-frequency reception, have increased spatial resolution to even smaller voxel size (9).

Arterial Spin Labelling (ASL)

Like BOLD, ASL measures rCBF by using magnetised blood. In contrast to BOLD, most ASL methods tag blood with radio frequency 180-degree inversion pulses (10, 11). Subsequently, the contrast between tagged and untagged images is used to quantify rCBF. This approach can provide a three-dimensional map of basal rCBF of the brain. An additional advantage of ASL is that it provides a better image of brain parenchyma compared to the BOLD method which is more centered on the draining veins. It also lacks BOLD's susceptibility to imaging artifacts specifically at tissue-air interfaces including the nose, sinuses, and roof of the mouth. Thus ASL can provide excellent functional images of brain regions that are difficult to evaluate with BOLD, specifically the orbitofrontal cortex (12). Because of its good signal to noise characteristics, ASL is more stable over time than BOLD, permitting repeat measures during long-duration observations.

Similar to PET and SPECT, ASL is able to provide robust estimates of basal and activity dependent rCBF (13). Importantly, because it does not require radioactive tracers it can be used for long-term studies of patients. However, ASL is limited by low sensitivity particularly for the relatively small rCBF changes observed in pain imaging, typically of the order of 5% (14). Several advances in MRI technology, however, including increased magnetic field strengths and the use of highly sensitive receiver coils have significantly improved ASL sensitivity (15).

Pain-related brain activation

Pain is a sensory and emotional experience that almost always depends on nociceptive input from the periphery which may undergo modulation at every level of the neuroaxis, including both facilitation and inhibition. Furthermore, peripheral input can be strongly modulated by external and internal factors (16-19). Some of the internal factors include negative emotions such as depression or anxiety which can increase the perceived pain intensity (20) and augment pain-related brain activation (21), attention (22, 23), anticipation (24) and pain memories (25).

It is well known from brain imaging studies in healthy volunteers that acute pain evokes a response in several brain regions including thalamus, primary and secondary somatosensory cortices, insula, anterior cingulate cortex, and prefrontal cortex. These brain areas have been found consistently activated by various painful stimuli in most imaging studies (26). Other less frequently observed pain-related brain activation includes the posterior parietal cortex, brainstem, basal ganglia, amygdala, and cerebellum (27). All these areas, however, can also become activated by non-painful sensory stimuli, including touch and warmth. Thus pain-related brain activity does not seem to rely on a specific "pain matrix", but rather on extensive, interconnected networks of cortical and subcortical structures involved in the central processing of pain.

Brain activation during acute and chronic pain

Although brain activity observed in acute pain appears to be similar to chronic pain (28) small but significant differences seem to exist. The results of a meta-analysis suggest that some of the brain regions most frequently activated during acute pain are less often involved in chronic pain processing (27). The most frequently reported brain area activated during chronic pain is the prefrontal cortex (27) which is not only involved in descending pain modulation (29, 30) but also plays an important role in cognition and processing of negative emotions (31) (32). Furthermore, activation of the medial prefrontal cortex seems to be correlated with the intensity of chronic back pain (33). In contrast the thalamus appears to become deactivated during chronic pain (34-

37). Importantly, these changes appear to be reversible after successful therapy of chronic pain conditions (34).

Brain networks

Spontaneous, non-task oriented brain activity appears to be a non-random event (38). Moreover, this ongoing activity reflects the organisation of a number of highly coherent functional networks which have been named "resting-state networks"(RSN) or "default-mode networks (DMN) (39, 40). Interestingly, these networks have been found to be negatively correlated with regions that increase their activity during attention tasks (41, 42). While demonstrating only limited anatomical connectivity, RSNs can be identified by an imaging strategy known as "functional connectivity MRI" (fcMRI). In fcMRI, correlations of BOLD fluctuations for brain regions of interest are used to determine the degree of connectivity. It is important to emphasise, however, that neuronal interconnections can be established at both the structural (anatomic) and functional level and that fcMRI is unable to distinguish between these two forms of connectivity. The two most widely used techniques for performing fcMRI are seed-based correlations and independent component analysis (ICA). In the seed-based technique signals are extracted from a specific region of interest, and maps are created by computing the correlation between the extracted signals and all other brain voxels (43). In contrast, ICA considers all voxels at once and uses mathematical algorithms to separate datasets into distinct systems or networks that are correlated in their spontaneous fluctuations but are also maximally independent, usually in the spatial domain (44). Regardless of technique, regions with similar functional properties, including the left and right motor cortices, consistently exhibit similar BOLD fluctuations even in the absence of movement (45). Similar findings have been reported in multiple other networks including attention (46), visual (47), auditory (47), language (47, 48), corticothalamic systems (49), and the frontal opercular network (50).

RSN comprise functional networks observed across a range of cognitive, emotional, motor, and perceptual tasks (46, 51). They are robust across individuals and time (52), can affect task-evoked activity (43), correlate with behavioral measures (53), and are distinct from underlying neuronal dynamics (54). Such observations have contributed to the assumption that RSN represent an intrinsic property of functional brain organisation (43). RSN correlation patterns across various networks have been shown to predict task-response properties of brain regions (55). Depending on the approach used, it is estimated that only 20%–40% of the brain's energy consumption is used for functions other than communication among neurons and glia. The additional energy requirements associated with momentary tasks may be in the order of 0.5% to 1.0% of the total energy demand (56). This cost-based analysis alone implies that intrinsic activity may be at least as important as evoked activity for overall brain function. Overall, most of the intrinsic brain activity seems to be devoted to maintaining a dynamic network (57-61).

Functional brain imaging studies in FM

Single-Photon Emission Computed Tomography (SPECT)

The earliest functional brain imaging studies in patients with FM were reported in the 1990s. Using SPECT these studies demonstrated decreased rCBF in the thalamus and in the caudate nuclei of FM patients compared to normal controls (NC) (62-64). These findings were relevant because thalamus and caudate nucleus receive nociceptive input from afferent pain pathways, including both nociceptive-specific and wide-dynamic-range neurons (65). One FM study, however, utilising MRI and SPECT, could only partially replicate these results (66). Although region of interest (ROI) analysis detected statistically significant reductions in rCBF in the right thalamus as well as the inferior pontine tegmentum of FM patients this study did not find reduced rCBF in the caudate nucleus. Subsequently, it was shown that reductions of rCBF in the thalamus were not specific for FM but could also be observed in patients with other chronic pain conditions including peripheral neuropathy (67) breast cancer pain (68), and other chronic pain conditions (69). Similarly, decreased rCBF levels in the caudate nucleus have also been reported in patients with pain after spinal cord injury (70), and in restless leg syndrome (71). Importantly, however, hypoperfusion of the thalamus and caudate nuclei normalised in some FM patients whose symptoms responded to ketamine injections (72).

Because of technical limitations (poor temporal and spatial resolution) only a small number of SPECT brain imaging studies have been undertaken in FM patients.

Functional Magnetic Resonance Imaging (fMRI) Studies in FM

Because SPECT and PET studies require the injection of radioactive tracers and have limited temporal and spatial resolution, they have been mostly applied to precise measurement of rCBF. Functional magnetic resonance imaging (fMRI) which does not have these shortcomings has become the most widely used method to assess brain activity in patients with chronic pain, including FM.

Brain activity during a painful stimulus

Mechanical stimulation

Several fMRI studies used painful mechanical stimuli at non-painful body sites to investigate FM pain mechanisms (73, 74). Pain-free subjects were used as NC. Because of the well-known hyperalgesia of FM subjects, the stimuli for patients and NC were adjusted to achieve equal perceptual stimulus intensities. This normalisation procedure resulted in significantly lower pressure stimuli given to FM subjects compared to NC. Group comparison demonstrated that similarly intense pressure pain evoked comparable brain activity in several regions implicated in pain processing. Such stimulus associated brain activity was observed in the primary and secondary somatosensory cortex, temporal gyrus, inferior parietal cortex, putamen, cerebellum, and anterior insula. In contrast similarly intense pressure stimuli resulted in significantly greater brain activation for FM participants in most pain-related brain areas compared to NC. In addition, the time course of brain activation during mechanical stimuli demonstrated prolonged activation of the insula in patients with FM but not in NC. The greater perceived pain intensity of fixed pressure stimuli in FM subjects is consistent with centrally augmented pain processing in this chronic pain condition. Furthermore, the levels of brain activity in these studies highly correlated with subjects' verbal reports of pain magnitude.

Heat stimulation

The results of the above studies have been corroborated by several follow-up FM studies using contact heat instead of pressure stimuli (75, 76). In these studies heat stimulus intensities were also adjusted to each subject's pain sensitivity resulting in similar experimental pain ratings. One study used only single heat stimuli during fMRI (75), whereas another study applied repetitive heat stimuli to the extremities at a frequency of 0.3 Hz in order to achieve perceptual "windup" (76). In both studies the corresponding brain activation patterns between FM patients and NC were not statistically different showing that brain processing of painful experimental stimuli is not abnormal in FM. Overall, these results seem to indicate that the hyperalgesia/allodynia of FM patients is not primarily associated with abnormal brain mechanisms but may be mostly related to sensitisation of spinal cord neurons.

Tonic stimulation

Whereas most previous studies explored the effects of phasic pain stimuli, a recent study applied tonic pain to FM subjects during fMRI (77). Tonic pain is clinically more relevant for the study of chronic pain syndromes like FM. An fMRI-block design was used to compare brain activity of FM patients and NC immediately after incision of the right forearm skin and muscles (7 mm deep). Additionally, the temporal profile of brain activity before, during, and after the incision was recorded in all subjects. Significant differences in activation of the right frontal gyrus, right mid-cingulate cortex and ACC, supplemental motor areas, and the thalamus were detected between both groups. Importantly, there were distinct group differences in BOLD-signals changes over the time course of tonic pain with FM patients demonstrating more prolonged brain activation compared to NC.

Brain imaging of temporal summation of pain

Abnormalities of temporal pain summation mechanisms have been described in FM using psychophysical methods (78-80). In particular, temporal summation of ‘‘second pain” (TSSP), termed ‘‘windup” appears to be a clinically relevant mechanism for central sensitisation and chronic pain (81). TSSP is considered to be the result of C-fibre-evoked responses of dorsal horn neurons and is dependent on stimulus frequency ($\geq$0.33 Hz) and intensity. In several fMRI studies, the brain responses associated with TSSP of NC and FM patients were identified during repeated heat-pulses to the glabrous surface of the foot (76, 82). TSSP was associated with activation in several brain areas known to receive input from ascending spinal pathways and sites involved in pain-related somatic sensation, cognition, and affect. When the magnitude of TSSP was adjusted to each individual's pain sensitivity, no group differences in pain-related brain activity were apparent on functional MRI images. Both the magnitude and time course of TSSP-related brain activity were similar in NC and FM patients. However, FM patients required lower stimulus intensities for TSSP, indicating that their TSSP mechanisms necessitate less primary afferent input compared to NC, but are not qualitatively different. Brain regions showing TSSP-related activity included those involved at all levels of somatosensory afferent processing (post-Thal, mid-Thal, S1, S2, mid- and post-Ins), pain-related cognition (dorsal ACC, inferior frontal gyrus, medial frontal gyrus) and affect (rostral ACC and ACC area 24). Furthermore, the temporal summation of BOLD responses observed in this study remained well above baseline levels for more than 40 seconds after termination of the heat stimulus trains consistent with prolonged pain aftersensations. Such pain aftersensations are characteristic of central sensitisation and have been confirmed by dorsal horn neuronal recordings (83).

Effects of depression on brain activity

FM patient have an increased lifetime prevalence of clinical depression (84, 85) and the majority of FM patients complain of depressed mood (86). Thus the effects of depression on brain responses to evoked pain are highly relevant for patients with FM. In a study of FM patients with and without major depressive disorder (MDD), fMRI scans during painful mechanical stimulation was performed (87). The Center for Epidemiologic Studies Depression Scale (CES-D) was used for assessment of depression. There was no correlation in FM subjects between depression and either pressure pain sensitivity or brain activity in sensory discriminative regions associated with pain processing. However, in depressed FM subjects CES-D scores significantly predicted pressure pain-related activity in the contralateral anterior insula and bilateral amygdala. These findings suggest that depression modulates pressure pain-related activity in brain areas involved in processing affective components of the pain experience.

Effects of catastrophising on brain activity

Catastrophising refers to a set of negative emotional and cognitive processes that have been implicated in the processing of pain in many chronic pain disorders including FM (88). Catastrophising comprises magnification of pain-related symptoms, rumination about pain, feelings of helplessness, and pessimism about pain-related outcomes. High levels of catastrophising are associated with increased pain intensity and emotional disturbance among individuals with FM (89-92).

In chronic pain patients, including FM, experimental pain-related brain activity appears to be associated with catastrophising (93). Using mechanical stimuli, significant correlations of experimental pain with catastrophising were detected in brain regions related to the anticipation, attention, emotion, and motor responses to pain (93). Similar results have been obtained in patients with irritable bowel syndrome (94). The pain augmenting effects of catastrophising appear to be mediated through several different cognitive mechanisms, and cognitive behavioural therapy (CBT) may provide an effective approach to treat patient with chronic pain syndrome. Alternatively, early CBT may prevent the transition from acute to chronic pain in many FM patients.

Brain activity related to dysfunctional pain inhibition in FM

Dysfunctional endogenous pain modulation during painful experimental stimulation has been consistently reported in FM patients (95-97) and is thought to reflect abnormal descending inhibition of clinical pain. Similar finding have also been demonstrated in localised chronic pain syndromes, including chronic low back pain (98) and osteoarthritis (99). In one fMRI study FM and NC subjects received sensitivity adjusted mechanical painful and non-painful stimuli in randomised order (100). Sensitivity adjusted mechanical stimuli resulted in comparable brain activity of sensory-discriminative and affective areas in FM patients and NC. FM patients, however, had significantly lower activity in the pulvinar nucleus of the left thalamus and bilateral rostral anterior cingulate cortices (rACC), regions known for its involvement in pain modulation (5).Although not specifically tested, the study authors explain this de-activation as the result of impaired descending pain inhibitory mechanism in FM. Because the study was not specifically designed to evaluate pain modulation in FM subjects, future research will be necessary to assess brain activity related to this important endogenous pain mechanism.

Supporting information for dysfunctional endogenous pain modulation in chronic pain patients comes from an fMRI study of IBS patients (101). IBS shares many similarities with FM and both have previously demonstrated abnormal endogenous pain modulation (96, 102). Twelve IBS patients and 12 matched NC received painful rectal balloon distensions during brain fMRI while simultaneously undergoing conditioned pain modulation (CPM) (101). During CPM ice water immersion of the foot was used as conditioning stimulus. The CPM condition significantly decreased rectal pain scores in NC but not in IBS patients. fMRI of IBS patients showed significantly greater activation of the anterior insula, S2 and putamen during rectal stimulation alone compared to rectal stimuli plus CPM. During CPM greater activation was seen bilaterally in the superior temporal gyrus of NC compared to IBS patients. Overall, IBS patients showed dysfunctional endogenous pain inhibition associated with aberrant activation of brain areas involved in pain processing and integration.

Effects of pharmacologic therapy on pain-related brain activity

fMRI can be used to evaluate the effects of pharmacological therapy on abnormal pain mechanisms in chronic pain patients, including FM. Because most studies of FM patients have consistently provided evidence of hyperalgesia (increased pain sensitivity) and allodynia (pain related to non-painful stimuli) (79, 103), the effects of pharmacological treatments on such abnormalities have been investigated in several multicentre FM studies of the noradrenalin-serotonin reuptake inhibitor (NSRI) milnacipran (104-107). In all these trials milnacipran was found to effectively relieve the clinical symptoms of FM more than placebo. In addition, the effects of 100 mg milnacipran twice daily on pain and pain-related brain activity was tested in a European multicenter RCT of FM patients over 13-weeks (108). All subjects received sensitivity adjusted pressure stimuli to the hand during brain scanning. Milnacipran failed to significantly reduce ratings of painful pressure stimuli when compared to placebo. This result suggests ineffectiveness of milnacipran on mechanical hyperalgesia. Furthermore, FM patients treated with milnacipran demonstrated increased but not decreased activation in the caudate nucleus, anterior insula, ACC, and amygdala during pressure stimulation. Although the authors suggested that such increased activity in multiple brain areas represents a "normalising effect" of milnacipran on FM pain sensitivity, this interpretation is speculative and awaits confirmation in future trials.

Abnormal resting state networks (RSN) in FM

Functional connectivity assessments during physical inactivity have been used in fMRI studies to characterise the "resting state" of brain activity in human subjects. A number of fMRI studies in NC have defined several RSN using temporal correlations in spontaneous BOLD signal oscillations while subjects rest quietly (109). Besides functional connectivity some RSN studies have also demonstrated evidence for neural connectivity (110). Although many functional imaging studies have shown altered brain activity in FM patients, only few trials so far have investigated the degree of connectivity between multiple brain networks in patients with this disorder. In a recent study the RSN of FM patients and NC were compared using dual-regression independent components analysis (111). The connectivity of multiple brain networks and their relationship to chronic pain was evaluated including the default mode network (DMN), the executive attention network (EAN), and the medial visual network (MVN). The results of this study showed that patients with FM had greater connectivity within the DMN and right EAN, and greater connectivity between the DMN and the insular cortex, than NC. Importantly, the intensity of spontaneous pain during fMRI scanning correlated with connectivity between the insula and both the DMN and right EAN. These results showed that resting brain activity within multiple networks was not only increased in FM but also associated with spontaneous clinical pain.

Spectroscopic imaging of brain metabolites

When placed in a magnetic field, atoms absorb electromagnetic pulses at a characteristic frequency. This resonant frequency, the energy of absorption, and the intensity of the signal are proportional to the strength of the magnetic field. Magnetic resonance spectroscopy (MRS) identifies brain metabolites by their resonant frequency and provides a noninvasive technique that can be used for *in vivo* measurements of regional concentrations of glutamate, aspartate, glycine, and GABA. Concentrations of a reference metabolite (most often creatine) are commonly obtained as internal standards and used for ratio estimates of the test metabolite. The information obtained by MRS can be graphically displayed as a spectrum with different peaks corresponding to the concentrations of detected brain metabolites. Usually anatomical MRI imaging is performed to determine brain areas of interest before MRS spectra are obtained. MRS can be performed with existing MRI equipment that has been modified with additional software and hardware. Most often MRS is performed in a single voxel in an a-priori determined region of interest. Data acquisition is fast (1 to 3 minutes) but spatial resolution is rather low.

MRS of human subjects has been studied in a variety of chronic pain conditions including FM. In one study, ten patients with FM underwent proton MRS before and after acupuncture treatments given to reduce mechanical hyperalgesia and clinical pain (112). During this study, the anterior and posterior insula regions were separately examined using single-voxel MRS. The levels of glutamate (Glu) and other metabolites were estimated relative to levels of creatine (Cr) (*e.g.* the Glu/Cr ratio). MRS demonstrated significant correlations of Glu concentrations within the insula with pain thresholds and clinical pain ratings. Because Glu is a major excitatory neurotransmitter of pain pathways, including the insula, these associations are important for our understanding of pain processing of chronic pain patients, including FM.

Structural brain changes related to pain

Chronic pain does not only affect brain function, but also seems to result in long lasting neuroplastic changes (113). Voxel-based morphometry (VBM) and cortical thickness measurements can be used to study changes in brain structure associated with chronic pain. VBM measures differences in grey brain matter density through voxel-wise comparisons within and between groups. Some of these grey matter changes comprise atrophy of cortical and subcortical brain areas (114, 115). Grey matter atrophy has not only been described in patients with low back pain (116), but also in several other chronic pain conditions such as migraine (117, 118), chronic tension headache (115), irritable bowel syndrome (IBS) (119, 120) and FM (121-123). Several factors seem to predict cortical atrophy in chronic pain patients. In IBS patients there was a strong negative correlation between dorsolateral prefrontal cortex thickness and pain catastrophising, and a positive correlation between anterior insula thickness and pain duration (120). In patients with recent onset IBS there was cortical thinning of the insula noted, whereas long-duration IBS pain was associated with normal insula thickness. Similarly, duration of illness was a predictor of brain atrophy in FM. Patients with FM seem to experience 9.5 times more grey matter loss per year than normal individuals (121). In addition, FM patients demonstrated a 3.3 times greater age-associated decrease in grey matter volume compared with NC (121). However, not all chronic pain patients seem to develop grey matter atrophy and some chronic pain patients demonstrate increasing grey matter volumes (123, 124) or mixed results (atrophy – hypertrophy) over time (125). For example increased hypothalamic grey matter and cortical thinning in the anterior cingulate cortex was demonstrated in IBS patients compared with controls (125).

Although discrepancies in these VBM studies are puzzling and may be related to different imaging techniques, they also seem to attest to the enormous potential of the CNS for neuroplasticity. The functional consequences of grey matter atrophy in chronic pain patients are unclear at this time and may include impaired endogenous pain modulation and cognitive deficits (126-128). For example, in FM patients the performance of non-verbal working memory has been found to be positively correlated with grey matter density in the left dorsolateral prefrontal cortex, whereas performance on verbal working memory was positively correlated with grey matter density in the supplementary motor cortex (129).Furthermore, clinical pain was positively correlated with grey matter loss in the medial frontal gyrus. These findings suggest that neuro-cognitive deficits of FM patients correlate with brain atrophy in the frontal lobe and ACC, which may negatively affect both pain and cognition (129).

Summary

Functional brain imaging is providing increasing insights into pain processing of healthy individuals and chronic pain patients. Several different brain scanning methods are available which mostly vary in their spatial and temporal resolution. All functional imaging methods, except PET, indirectly measure brain activation by assessing regional cerebral blood flow. However, excellent correlations between blood flow and neuronal activation have been demonstrated. At this time fMRI is the most frequently used method for brain imaging because of its high spatial and temporal resolution. Using experimental pain several fMRI studies have demonstrated abnormal brain activation of FM patients, most frequently in the thalamus, S1, insula, ACC, and prefrontal cortex. fMRI has also been applied to brain network evaluations of FM patients showing abnormal connectivity within the default mode network and executive attention network. Direct measurement of relevant brain metabolites, including Glu, aspartate, glycin and GABA, have been non-invasively performed using MRS. Insular Glu levels significantly correlated with FM patients' clinical pain. Overall, functional brain imaging has identified multiple brain areas in chronic pain patients that are abnormally activated during pain processing. Although NC and FM patients use similar brain areas for pain processing, several important differences exist between groups.

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