Chapter 32
Evaluation of Pain with Functional Neuroimaging

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Abstract Pain is generally caused by peripheral events, and patients and medical professionals therefore tend to focus locally on those parts of the body where patients complain of pain. However, pain modulation occurs in patients who suffer pain not only due to localized factors but also due to various causes such as repeating memories of pain, environmental/social problems, and the mental/psychological state of the patient.

According to the International Association for the Study of Pain, pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage," and indeed, these types of incidents that are encountered clinically indicate that pain is a subjective experience of the brain. In recent years, functional neuroimaging techniques have frequently been applied to depict pain and its attendant sensory and emotional experiences as an image or to quantify these factors from the perspective that pain is perceived in the brain.

We conducted a review of the current state of functional neuroimaging in the brain and spinal cord based on recent research findings.

Keywords Brain • Functional neuroimaging • Spinal cord

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32.1 Introduction

Pain is generally caused by peripheral stimulation, and patients and medical professionals therefore tend to focus locally on those parts of the body where patients complain of pain, such as the "leg," "hip," and "neck." However, pain modulation occurs in patients who suffer pain not only due to local factors, but also due to various causes such as repeating memories of pain, environmental/social problems, and the mental/psychological state of the patient. As this modulation becomes stronger or weaker, the severity of the primary pain and the accompanying discomfort can vary greatly.

According to the International Association for the Study of Pain, pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage," and indeed, these types of incidents that are encountered clinically indicate that pain is a subjective experience of the brain. Traditionally, questionnaires such as the visual analogue scale (VAS), numeric rating scale (NRS), and McGill Pain Questionnaire have been used to assess pain. However, in recent years, functional neuroimaging techniques (Table 32.1) such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT) have frequently been applied to depict pain and its attendant sensory and emotional experiences as an image or to quantify these factors from the perspective that pain is perceived in the brain. We introduce herein the endeavors using these methods to evaluate pain involving the musculoskeletal system, focusing primarily on research progress to date.

32.2 Transmission of Pain Signals at the Spinal Cord Level and Efforts to Visualize This Phenomenon

Pain impulses traveling to the spinal cord from the periphery via primary afferent fibers are transmitted to spinothalamic tract cells, which are a type of cell in the spinal dorsal horn, and subsequently transmitted as pain signals to the brain via the

Table 32.1 Types of functional Imaging Technologies

	Target	Spatial resolution (mm)	Temporal resolution (S)
EEG/MEG	Neuronal current	10	0.001
fMRI	Regional changes in blood flow	4–5	1–10
PET	Oxygen consumption, glucose metabolism etc.	5–10	30–1,000
SPECT	Changes in blood flow change	10	60–1,000
NIRS (near-infrared spectroscopy)	Changes in blood flow change	8–	0.01–

ventrolateral pathway on the opposite side. In contrast to the brain, which ultimately experiences pain through various modulations, the spinal cord receives fewer of these modulations and tends to directly reflect nerve response to outside stimulation. For this reason, a method of inserting an electrode directly into the dorsal horn of the spinal cord to record neural activities of spinothalamic tract cells has been widely applied in animal studies, and this particular method has been used to elucidate mechanisms of pain exacerbation such as spinal cord sensitization and to evaluate drug treatments. However, direct insertion of a needle into the spinal cord can be difficult in humans, so studies using fMRI and PET have been progressing as an alternative.

32.2.1 Spinal fMRI Studies in Healthy Subjects

Although research to evaluate spinal cord function has only just scratched the surface, our group has been proceeding with the analysis of spinal cord activity induced by a mechanical pain stimulation device, using the blood oxygen level-dependent (BOLD) method. Functional tasks to elicit spinal cord activity are conducted using our original plastic mechanical pain stimulation device. Functional MRI using echo planar imaging (EPI) was conducted on healthy subjects administered painful stimuli, BOLD signal changes were recorded with a 3-T MRI scanner, and analysis was undertaken using statistical parametric mapping (SPM) (www.fil.ion.ucl.ac.uk/spm/). Since large mechanical movements occur in the cervical vertebrae due to breathing and swallowing, we created and utilized a cervical collar to suppress these movements during imaging. As a result, we were able to visualize the inner spinal cord area that was activated in response to the nociceptive stimuli applied in the study (Fig. 32.1). However, variations in activation were seen between subjects. Before clinical application can be achieved, the function of a spinal cord that has flattened and shrunk in size due to spinal cord compression will need to be assessed in the future. We therefore believe that further technical improvements in the method are essential [1].

32.2.2 Spinal PET Imaging in Patients with Neuropathic Pain in the Spinal Cord

PET and SPECT are imaging modalities that detect gamma-ray distributions emitted from drugs administered to the body, allowing the creation of tomographic images. PET is a method in which radioisotopes that emit positrons are injected into the body to produce gamma-rays that arise during pair annihilation between positron and electrons in the body and is performed with a sensor set up to enclose the body. Uchida et al. investigated glucose metabolism in the cervical spinal cord using fusion

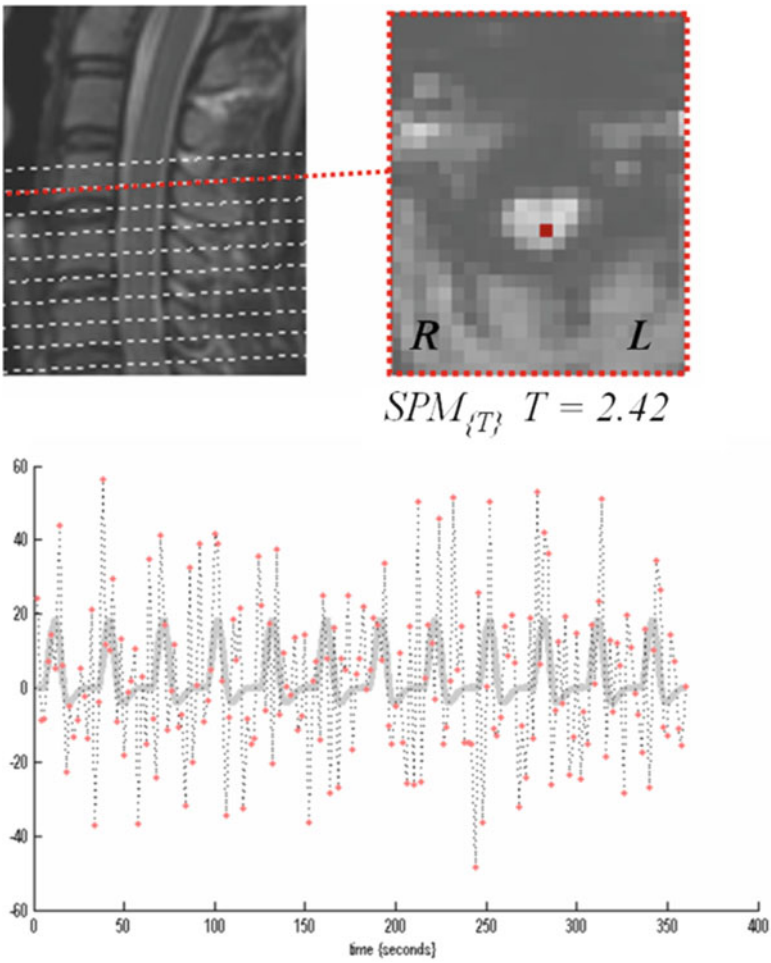

Fig. 32.1 Time-dependent changes in BOLD signal and site of spinal cord activity

images of 3-T MRI and 18 fludeoxyglucose (FDG)-PET in patients with compressive cervical myelopathy [2]. We applied this PET technology to assess whether functional changes in the spinal cord occur in patients with neuropathic pain in the spinal cord. We observed sites of FDG uptake in the spinal cord and were able to obtain an image that suggests enhanced neural activity due to pain. However, some aspects of the results, such as resolution, remain to be optimized in the future (Fig. 32.2).

Previous findings from functional neuroimaging of the spinal cord suggest that both fMRI and PET will be able to be applied to humans in the future as methods to evaluate pain. However, further investigations are necessary before these approaches can be used in clinical cases such as cervical myelopathy.

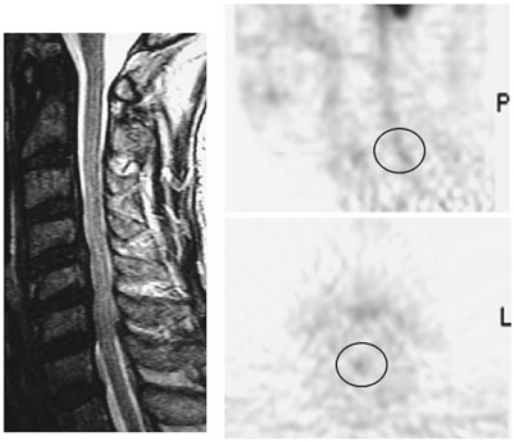

Fig. 32.2 Cervical spinal FDG PET (left cervical radiculopathy, 60's years, male). In collaboration with the Department of Orthopedic Surgery at the University of Fukui

32.3 Functional Brain Imaging and Musculoskeletal Pain

Previous studies of functional brain imaging in healthy subjects have revealed that the pain signals that ascend through the spinal cord are primarily projected to the region of cerebral cortex called the "pain matrix," an area related to pain. This region includes the first and second somatosensory areas (S1 and S2), insular cortex, anterior cingulate gyrus, and medial prefrontal cortex via the thalamus. However, in clinical settings where patients with chronic pain require pain evaluation, plastic changes and sensitization of the nervous system may be induced, and a transmission pathway may not necessarily be experienced in a similar manner to that in healthy subjects with acute pain. Here, we show functional neuroimaging findings from previous studies of chronic musculoskeletal pain, focusing on the latest research outcomes.

32.3.1 Brain Activity in the Thalamus and Acute and Chronic Pain

The thalamus is said to be the center of senses and is where pain transmission from the aforementioned spinothalamic tract terminates. The thalamus has therefore been a major focus in pain research for many years, and many detailed analyses have been conducted.

In studies that have investigated neural activity in the thalamus using PET or SPECT, neural activity in the thalamus is known to be enhanced in acute pain pathology. However, several reports on chronic pain have indicated a decrease in

thalamic activity on the side contralateral to where the transmission of stimulation primarily occurs in pain conditions [3, 4]. Such decreases in contralateral thalamic activity are also known to be exacerbated with longer disease staging, and this is thought to imply plastic changes in the central nervous system [5]. Several causes have been postulated for such changes: (1) persistent and chronic pain activates the inhibitory system to suppress thalamic function; (2) the cortical sensory area has fallen into a persistently and easily excitable state due to chronic input from the thalamus, and even small pain signal inputs from the thalamus equate to the recognition of pain; or (3) enhancement of blood flow is not required because synaptic transmission at the thalamus has become extremely efficient. However, several reports on chronic pain have indicated enhancement of thalamic activity on the contralateral side, so further mechanistic clarification is necessary.

32.3.2 Evaluation of Induced Pain in the Brain Using fMRI

Functional MRI offers not only good spatial resolution but also moderate temporal resolution and is appropriate for the evaluation of brain activity when and where pain is inflicted.

32.3.2.1 Brain Activity when Pain Stimulation Is Inflicted (Comparison Between Healthy Subjects and Patients with Neuropathic Pain)

With the objective of investigating brain activity in patients with allodynia who experience pain from stimuli that would not normally provoke pain, Ikemoto et al. captured the brain activity of such patients using fMRI following mechanical stimulation (non-nociceptive stimulation) that would not normally provoke pain at the site in which they experience pain and compared these results to when healthy subjects were provoked with mechanical nociceptive and non-nociceptive stimulation [6]. Results indicated that when healthy subjects were provoked with mechanical nociceptive stimulation, enhancement of activity in the thalamus, somatosensory areas (S1 and S2), cingulate gyrus, and cerebellum was detected. On the other hand, even though stronger pain was observed in patients on the VAS compared to healthy subjects, activity in the thalamus, which is the center for pain from the periphery, was not detected. Activities are now known to arise in S1, S2, cingulate gyrus (primarily anterior cingulate gyrus), as well as the motor cortex and supplementary motor cortex (Fig. 32.3) [7]. Peyron et al. [8] conducted a study of brain activity upon inflicting mechanical stimulation that would not normally provoke pain on the affected side as well as the unaffected side in patients with allodynia and reported results similar to those reported by Ikemoto et al.

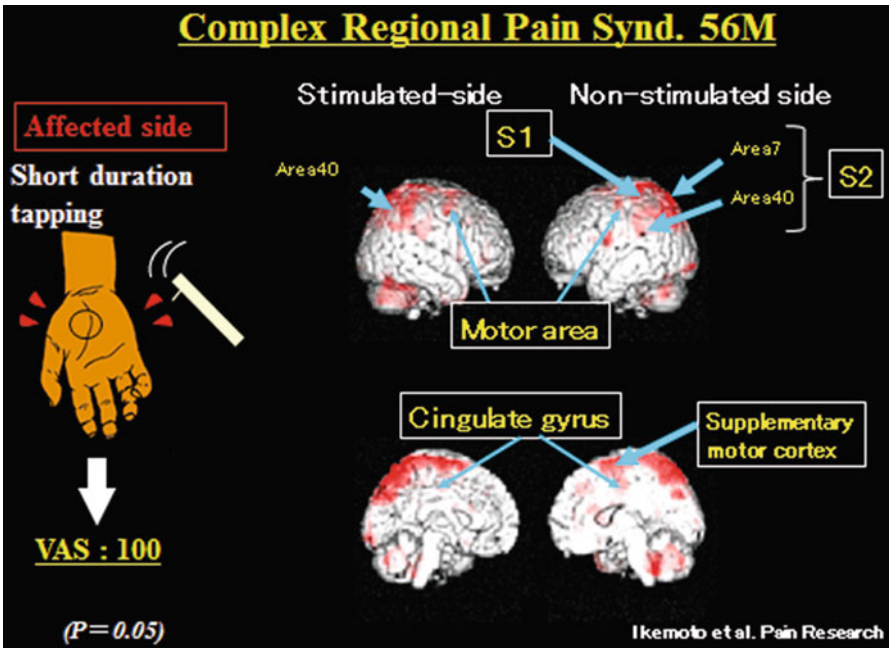

Fig. 32.3 In CRPS patient, even though stronger pain was observed on the VAS , activity in the thalamus, which is the center for pain from the periphery, was not detected. Activities are now known to arise in S1, S2, cingulate gyrus (primarily anterior cingulate gyrus), as well as the motor cortex and supplementary motor cortex

32.3.2.2 Brain Activity Sites During Reproduction of Joint Pain and Low Back Pain Induced by External Stimulation

Even in chronic pain that is generally considered to represent a repetition of acute pain in conditions such as osteoarthritis of the knee, pain while walking and localized tenderness are observed. Since pain is confined in these patients, attempts have been made to stimulate the tender sites with a special device. As a result, fMRI revealed that patients with osteoarthritis of the knee exhibit significant neural activity in areas of the pain matrix such as bilateral thalami, S2, insula, supplementary motor cortex, and anterior cingulate gyrus, as well as pain when pressure stimulation is applied to tender sites [9].

In addition, low back pain due to external stimulation has been reproduced, and the associated brain activity has been examined. Kobayashi et al. [10] reproduced low back pain by applying pressure stimuli to the lumbar area in patients with chronic low back pain and reported the brain activity during such reproduction. In patients with low back pain, significant brain activity was observed in the prefrontal cortex, supplementary motor cortex, premotor cortex, thalamus, insula, and posterior cingulate gyrus compared to healthy subjects. This cerebral network associated

with low back pain is termed the "LBP matrix." Neural activities in the prefrontal cortex, which are known to be deeply associated with cognitive function, and in the posterior cingulate gyrus where unpleasant emotions are known to be reflected when chronic pain patients experience pain have been clarified to occur in a different area than the "pain matrix," which is a pain-related region that is observed in acute pain experienced by healthy subjects.

32.3.2.3 Cranial Nerve Activity and Virtual Pain Stimulation Induced by Image Presentation

In patients with neuropathic pain, thalamic activity had not been detected even when patients experienced strong pain with pain stimulation. Similarly to the findings of PET and SPECT studies, plastic changes to the nerves in the brain are considered to be a possible cause of this phenomenon. In addition, this indicated that even when thalamic activity is decreased, pain is thought to be provoked in patients with neuropathic pain.

A virtual experiment on pain was therefore conducted by having subjects view videos [11]. Patients with neuropathic pain who suffer allodynia were shown a video where a palm was being touched by a brush and subsequently demonstrated that, compared to healthy subjects, activity in the prefrontal cortex and anterior cingulate gyrus was enhanced. The anterior cingulate gyrus had previously been shown to be activated in healthy subjects when they watched "a painful image" [12] (Fig. 32.4), so the video of a brush touching the palm may have unconsciously induced a "painful" emotion in patients with neuropathic pain. In addition, the possibility was suggested that some kind of obstacle to the integration of cognitive and emotional aspects of pain is caused in the medial prefrontal area.

It was postulated that similar results may ensue when patients with low back pain experience virtual pain in the brain as to when patients with neuropathic pain receive similar treatment. Brain activity was therefore investigated when an image of "a man carrying luggage in a half-crouching position" was shown to patients [6]. The group of patients who had previously experienced low back pain showed significant brain activity in regions such as the supplementary motor cortex, premotor cortex, visual association cortex, thalamus, insula, posterior cingulate gyrus, fusiform gyrus, hippocampus, and posterior parietal lobe compared to those who had not previously experienced low back pain. Furthermore, the visual information of "a man carrying luggage in a half-crouching position" induced all subjects in the low back pain group to complain of unpleasantness, and some even complained of pain. In contrast, in the non-low back pain group, no one complained of pain or unpleasantness. Supplementary motor cortex, premotor cortex, thalamus, insula, and posterior cingulate gyrus are all common to the "LBP matrix," which is activated when pain is actually inflicted. As a result, patients who have previously experienced low back pain, even without actual nociceptive stimulation, were suggested to experience unpleasant emotions that can be described as virtual low back pain from visual information (Fig. 32.5).

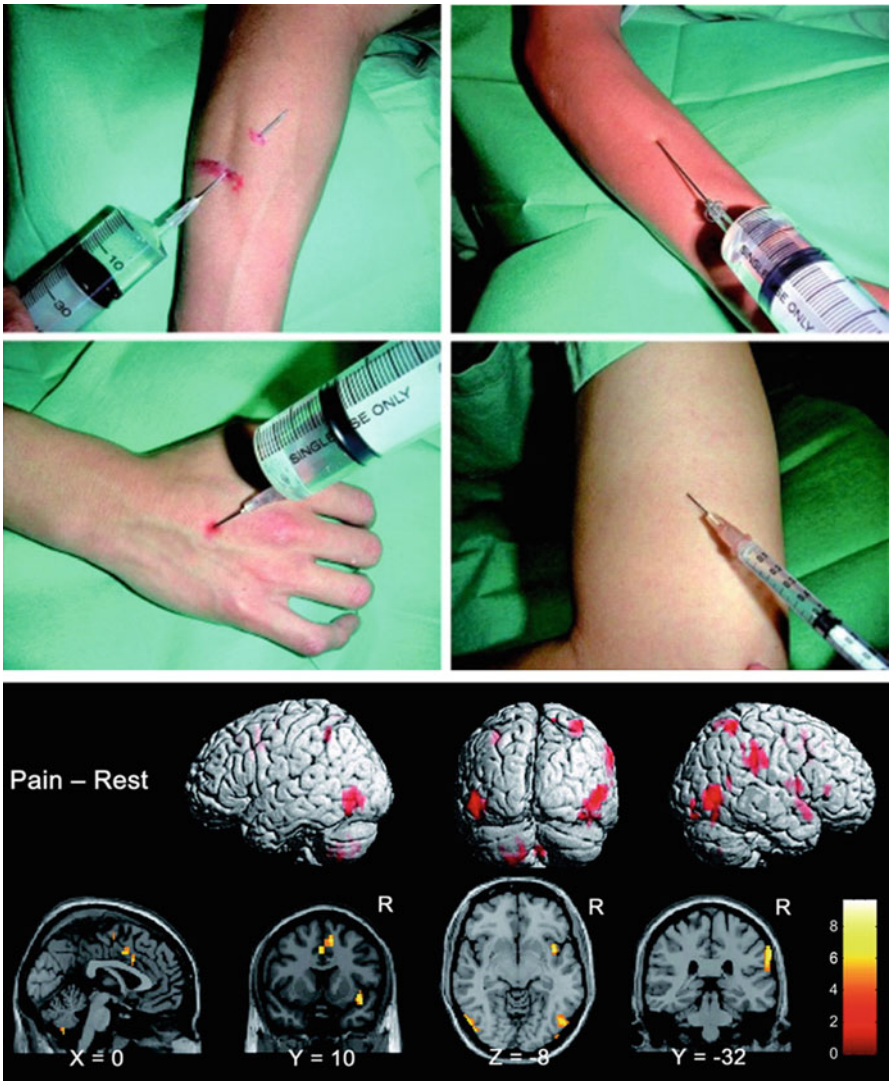

Fig. 32.4 Ogino et al. [12]

32.3.3 Evaluation of Resting Brain Activity (Default Mode Network)

Previous studies of the evaluation of brain function related to pain were structured based on the principle of determining sites at which brain activity develops on external stimulus. Our studies that we have described thus far have also focused on the pain matrix activity of sites such as the thalamus and cingulate gyrus.

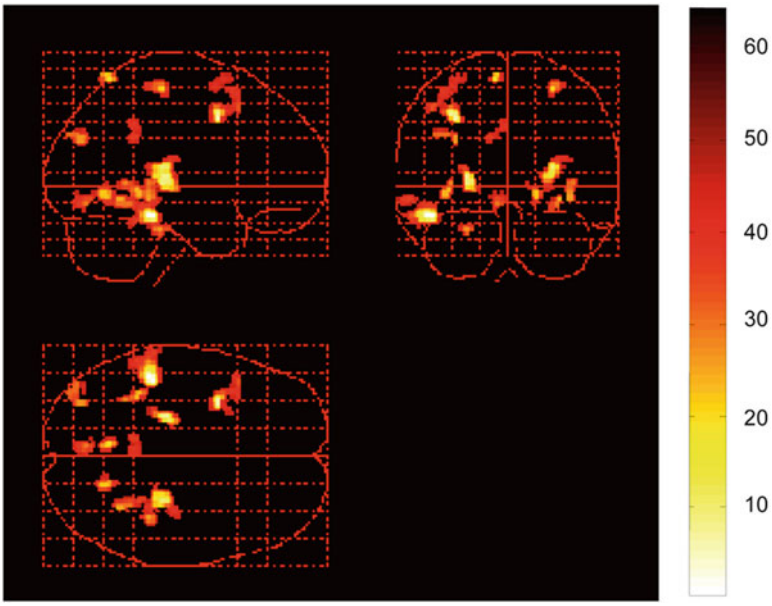

Fig. 32.5 Areas of cortical activation in the LBP group compared with the non-LBP group in response to virtual LBP stimuli (task-control condition) detected by fMRI ($p < 0.0005$, Z score > 3.4, uncorrected threshold)

Meanwhile, Raichle et al. indicated while researching brain activity that, in a control state of not doing anything, there are parts of the brain that show higher activity compared to when subjects are not on psychological tasks, and this has been termed the "default network" or "resting state" [13].

Baliki et al. conducted finger exercise tasks and compared healthy subjects and patients with chronic low back pain in terms of the parts of the brain showing decreased activity and subsequently found that enhanced activity is observed at rest in the prefrontal cortex and cingulate and posterior cingulate gyrus, indicating that abnormality in the default mode network may have occurred in patients with low back pain [14] (Fig. 32.6). Patients who complain of a chronic pain often state that they "don't do anything all day and stay still because it is painful" or that their "pain is alleviated when carrying out other activities." This suggests that brain activity at rest is associated with the development and maintenance of chronic pain, and future development in this area of research is therefore anticipated.

32.3.4 Potential for Clinical Application of Brain Function Evaluation

Compared to healthy subjects, the volume of grey matter is known to be decreased in the dorsolateral prefrontal cortex, thalamus, brainstem, and SI in patients with

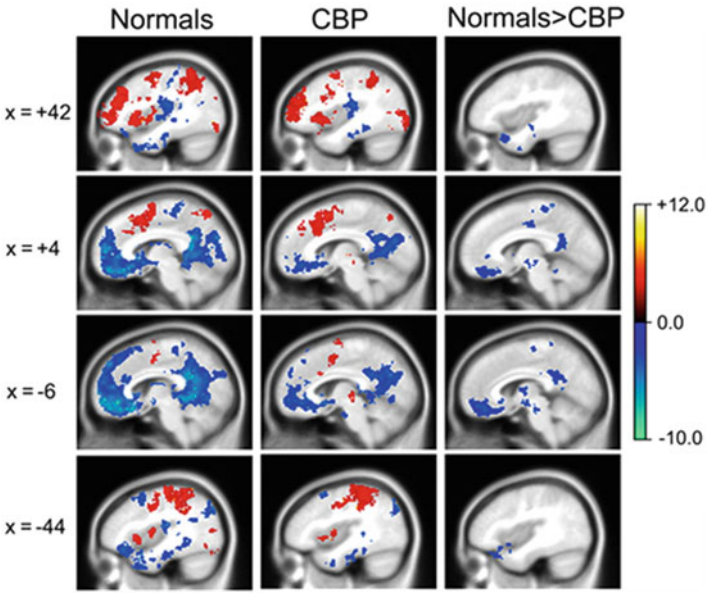

Fig. 32.6 Baliki et al. [14]

chronic low back pain [15–17]. Seminowicz et al. [18] investigated changes in the brain before and after treatment in patients with chronic low back pain and reported a significant increase in the volume of the left dorsolateral prefrontal cortex after treatment. Furthermore, increases in dorsolateral prefrontal cortex volume caused by treatment appear to be related to the severity of pain and improvement in ADL due to treatment (Fig. 32.7). In addition, a distortion in cognitive function is known to occur in patients with chronic low back pain [19–21], but brain activity while performing tasks related to cognitive function is indicated to broaden in the activated regions and conversely to become narrower in the suppressed brain regions compared to healthy subjects. These findings indicate that cognitive information processing in the brain differs between patients with chronic low back pain and healthy subjects. In a study of older patients with chronic low back pain, Buckalew et al. [22] compared brain images between those with disabling (hindered ADL, activities of daily life) low back pain and those with non-disabling (maintained ADL) low back pain. No differences in brain volume were seen between groups, but diffusion tensor analysis showed that anisotropy of the corpus callosum ampulla was decreased in the disabling group and that a correlation existed between decreased anisotropy and duration of low back pain ailment. Interestingly, even within patients with chronic low back pain who have similar durations of illness or degree of pain, brain images sometimes reflect the differences in how pain affects daily life.

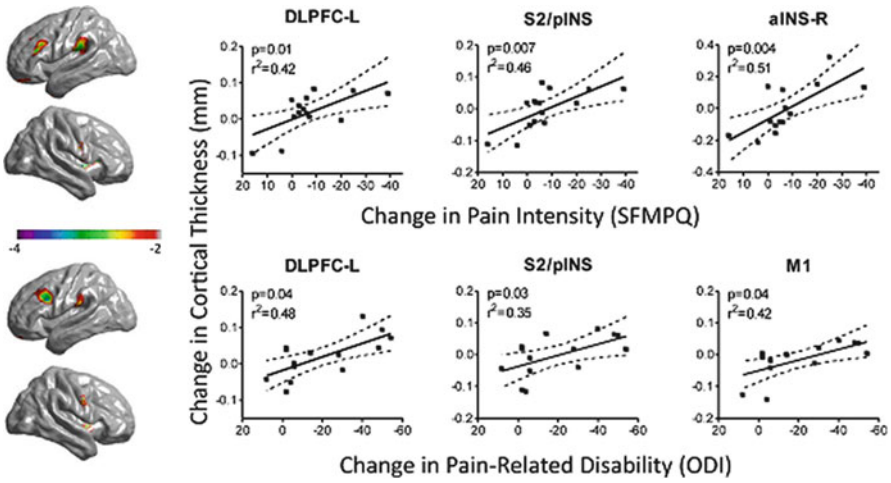

Fig. 32.7 Parts of the brain where volume change occurred in association with improved pain and ADL due to treatment (modification of [18])

32.3.5 Significance of Functional Neuroimaging as a Method to Evaluate Individual Patients with Pain

Since pain largely involves subjective elements, determining the degree of pain from the outside with standard procedures is difficult. Functional neuroimaging techniques, including fMRI, are considered to play an essential role in the evaluation of pain. Pain in the musculoskeletal system has also been revealed to be associated with activity of the "pain matrix" and it is therefore necessary to consider the changes in the central nervous system and not only the periphery where pain is inflicted. For example, comparing and studying the "pain matrix" brain activity in patients before and after intervention can lead to objective determination of the degree to which subjective and emotional pain is decreased. To conduct pain evaluation in each patient, the reproducibility and reliability of fMRI data are required for every individual patient. However, several problems (as shown below) have been encountered and clinical application has yet to be achieved. For example, in a group study, pain was found to be largely influenced by memory, awareness, and emotion, which counterbalance each other. Pain is therefore difficult to evaluate and study reproduction is problematic, as the above problems change day by day. To overcome these issues, future studies will need to determine what type of pain-related task targets which part of the brain to recognize and reflect pain and related unpleasantness and where to focus evaluations for chronic situations. In particular, pain-related tasks that adequately reflect the actual patient image have yet to be developed for pain in the musculoskeletal system, and we believe that further investigations and research in this field are essential.

32.4 Summary

We conducted a review of the current state of functional neuroimaging in the brain and spinal cord based on recent research findings. For patients with chronic pain in whom objective diagnosis is difficult, diagnosis and appropriate treatment will require elucidation of the mechanisms of pain development and maintenance in the spinal cord and brain, and establishment of imaging techniques to evaluate subjective and emotional aspects of pain in individual patients will also be indispensable.

Conflict of Interest The authors declare that they have no conflict of interest.

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