Pain Imaging

A Clinical-Radiological Approach to Pain Diagnosis

Maria Assunta Cova
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To Gabrio

Foreword

Writing a radiological book dedicated to a symptom, rather than to an organ or a disease process, is quite unusual. It is, however, a much needed new way to present radiology. As a matter of fact, patients come to the Radiology Department complaining of symptoms and signs and with a request for imaging in order to identify their origin. I do really believe that the better the radiologist understands his/her patient's complaints, the better he/she is able to choose the correct imaging modalities to evaluate them and to provide a correct interpretation of their findings. The editors of this volume have prepared a radiological textbook that takes into consideration the patient's symptoms first: in this case, the book is dedicated to the symptom of pain.

Our discipline has a central role in healthcare: all diagnoses and decisions on patients' management are mostly based on the results of imaging, and image-guided procedures allow minimally invasive therapies in many cases. However, the radiologist is almost unknown to the patient, and many people do not even know that we are physicians.

It is quite important to learn how to work through this "clinical-radiological approach." On one side, it makes us able to provide a better service to our patients; on the other, it teaches how to get closer to patients, to understand better their symptoms, and to link them to our results. This underlines our role as physicians and, I am sure, makes it perceived by our patients too.

Clinical chapters are written by clinicians, and this reinforces the "clinical-radiological approach" of the book by providing information on what clinicians want from our examinations. I am sure this volume will prove useful not only to radiologists but also to emergency medicine physicians and to colleagues of other specialties who want to understand which are the best tests to use to identify the causes of pain in different areas of the body and what are the results they can expect from them.

M. A. Cova and F. Stacul have to be thanked for guiding the preparation of this book through a novel way and for helping the authors of the different chapters in following it. I am sure this is the starting point of a new teaching method in radiology.

January 2019

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Preface

Pain can be a major clinical challenge. Its correct assessment is often related to a careful analysis of the patient history, to an accurate physical examination, to the evaluation of laboratory data, and to an appropriate referral to diagnostic imaging.

This book addresses pain imaging aspects in both neuro and body, thus updating the international literature scenario on the topic. Actually, books on pain imaging published so far provided a partial approach to this issue, considering specific fields only. The book aims to provide a comprehensive clinical-radiological approach, and it underlines the need of a close cooperation among clinicians and radiologists. It offers differential diagnoses for a number of painful syndromes, as many of them can mimic one other, and it aims to help in the diagnostic management of these patients, suggesting the most appropriate diagnostic algorithm.

The book is structured into sections for each anatomical macro-area (the brain, spine, thorax, abdomen, and pelvis), and dedicated chapters cover the topics from both a clinical and radiological point of view.

Following introductive chapters considering mechanisms of pain and the brain imaging of pain, the neurological section approaches headache, trigeminal neuralgia, and spine pain. As to the thorax, both vascular and nonvascular causes of pain are addressed. A number of disease possibly responsible of abdominal pain are considered, including biliary colic and cholecystitis, pancreatitis, renal colic, pyelonephritis, bowel obstruction, bowel perforation, inflammatory bowel disease, and vascular disease. Finally, some diseases causing pelvic pain are addressed, namely, uterine disease, ovarian disease, endometriosis, and testicular disease.

The chapters offer a state-of-the-art approach to clinical challenging situations and provide up-to-date knowledge on the present contribution of imaging techniques, thanks to the newest technological developments.

The book provides electronic supplementary material including radiological images that allow a comprehensive evaluation of some cases that were included in the chapters. This approach allows the reader to consider a full set of images, thus getting an overall view of the anatomical involvement by the disease overcoming the limit of evaluating just a single selected image.

We strongly hope the book could be a valuable tool for radiologists, neuroradiologists, neurologists, clinicians, and surgeons, working in general hospitals and teaching hospitals, from residents to consultants.

Trieste, Italy

Maria Assunta Cova
Fulvio Stacul

Contents

Mechanisms of Pain

1

Paolo Manganotti and Stefano Tamburin

Neuropathic pain (NP) afflicts 6–8% of the general population and has a severe burden on quality of life, sleep, and mood and a heavy impact in terms of disability [1]. Although its prevalence overlaps to that of very common pathologies, such as diabetes mellitus and bronchial asthma, NP still represents a difficult condition to diagnose and treat, both for the general practitioner and for the specialist in neurology, pain therapy, or physical and rehabilitation medicine.

NP is defined as "pain that arises as a direct consequence of a lesion or disease involving the somatosensory system" [2]. This definition allows a clear distinction with nociceptive pain, which is caused by an actually or potentially dangerous stimulus for a tissue or organ, in the presence of a normal functioning of the somatosensory system.

The site of the injury or disease also allows to classify the NP in either peripheral or central (Table 1.1).

Table 1.1 Some common neuropathic pain conditions according to the site of damage of the somatosensory system

Peripheral nervous system—mononeuropathy
Post-traumatic mononeuropathy
Entrapment mononeuropathy (e.g., carpal tunnel syndrome)
Postsurgical mononeuropathy
Trigeminal neuralgia
Cervical and lumbosacral radiculopathy
Diabetic painful monoradiculopathy and mononeuropathy
Postherpetic neuralgia
Peripheral nervous system—multineuropathy
Brachial and lumbosacral plexopathy
Vasculitic multineuropathy
Peripheral nervous system—polyneuropathy
Diabetic symmetrical and small fiber polyneuropathy
Metabolic neuropathy
Immune-mediated polyneuropathy
Chemotherapy-induced polyneuropathy
HIV-related polyneuropathy
Central nervous system—spinal cord lesions
Traumatic lesions of the spinal cord
Inflammatory myelopathy
Spondylotic myelopathy
Central nervous system—brain
Central post-stroke pain
Central nervous system—multiple sites of lesions
Multiple sclerosis-related neuropathic pain

Based on the evidence from animal models and the clinical conditions of NP, the pathophysiological mechanisms of NP are traditionally classified into peripheral and central ones (Table 1.2).

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Table 1.2 Some pathophysiological mechanisms of neuropathic pain according to the site of the nervous system

Site of the nervous system		Mechanism
Peripheral nervous system	Peripheral nerve Dorsal root ganglion	Release of pain-related inflammatory mediators Upregulation of transient potential receptors Increased activity or increased expression in voltage-gated sodium and potassium channels Hyperexcitability of neuronal soma Increased synthesis of proinflammatory cytokines Infiltration of activated macrophages
Central nervous system	Dorsal horn neuron (spinal cord) Descending systems (brainstem) Brain	Increased release of glutamate and substance P Increased expression of voltage-gated sodium and calcium channels Loss of γ-aminobutyric acidergic neurons Functional reorganization of nociceptive neurons Hyperactivation of *N*-methyl-D-aspartate or glutamate metabotropic receptors Microglial activation Loss of function in inhibitory opioidergic, serotoninergic, and noradrenergic pathways Functional reorganization in the somatosensory thalamic and cortical nociceptive neurons

1.1 Peripheral Mechanisms

The alterations affecting the peripheral nerve involve the unmyelinated C and small-caliber myelinated Aδ nociceptive fibers, but some studies also suggest the involvement of large-caliber myelinated fibers, which do not carry the nociceptive information.

Different type of nerves and receptors can carry pain sensation. For example, the epidermal mechanoreceptors for touch are composed of Meissner corpuscles, Merkel cells, and free nerve endings. In the dermis, there are Ruffini endings and Pacinian corpuscles in a glabrous (or hairless) skin, whereas there is a complex combination of mechanoreceptors and their associated nerves and hair follicle receptors in a hairy skin [3]. The low-threshold mechanoreceptors (LTMR) were found to be the major activators of Aβ and C fibers, and LTMR around hair follicles were posited to activate C fibers. These mechanoreceptors are selectively connected to the nerves. Meissner corpuscles connect to Aα and β fibers for stroking, Merkel cells connect to Aα and β fibers for pressure, and Ruffini corpuscles connect to Aα and β fibers during skin stretching. The primary sensory afferents innervating the human skin are connected to the nerves as follows: discriminative touch nociceptors for pain are connected to Aβ fibers, nociceptors for pain connect to Aδ fibers, and polymodal nociceptors for pain, emotional touch, and itch connect to C fibers [4]. Pacinian corpuscles and a part of the lanceolate endings surrounding hair roots sometimes show rapidly adapting firing responses. From this, we posit that to achieve a long-lasting effect, vibration may be the most potent type of stimulation. These mechanoreceptors have various types of mechanosensitive (TRP) channels: TRPV1–TRPV4, TRPA1, TRPM8, and TRPCs in keratinocytes. Many signaling chemicals have been proposed including NGF, bradykinin, 5-HT, ATP, H+, glutamate, somatostatin, and GABA. Among them, only ATP and H+ are known to be associated with TRP channel activation. In the dorsal root ganglion (DRG) and dorsal horn (DH), essential modification of the pain signal may occur through interactions among astrocytes, microglia, and presynaptic and postsynaptic neurons. Peripheral nerve fibers show alterations of voltage-dependent sodium and potassium channels and an abnormal expression of receptors of the transient receptor potential family. Similar alterations have been documented in the dorsal root ganglia, the site cell bodies of the first-order sensory neurons, which give rise to peripheral nerve fibers. Following a painful stimulus, if sufficient numbers of a particular

type, or types, of nociceptor are activated, an afferent volley will be produced. The afferent volley travels along the peripheral nociceptor and enters the spinal cord via the dorsal horn [5]. The whole of these alterations leads to a hyperexcitability of the peripheral nerve and the dorsal root ganglion, which can be responsible for both spontaneous and evoked pain to either Tinel maneuvers or root stretching (i.e., Lasegue and Wassermann maneuvers).

1.2 Spinal Mechanisms

Beyond the peripheral nociceptor and dorsal horn, depending on the type of nociceptor activated, pain-related information ascends in the contralateral spinothalamic tract (STT), but there are also direct connections to the medulla and brainstem via the spino-reticular (SRT) and spino-mesencephalic (SMT) tracts and to the hypothalamus via the spino-hypothalamic tract (SHT). Outside of the thalamus, there are spinal projections to the ventrolateral medulla, parabrachial nucleus, periaqueductal gray (PAG), and brainstem reticular formation. Of particular interest is the role of these structures in both inhibiting and facilitating nociceptive transmission and subsequent pain perception [6].

Numerous animal models have documented abnormalities in second-order nociceptive neurons, which are found in the dorsal horn of the spinal cord. These alterations include changes in the calcium channels and neurotransmitters and neuromediators. These changes, together, shift the spinal excitability balance toward excitation rather than inhibition and result in a set of phenomena that characterize the so-called spinal sensitization [7, 8].

Changes in neuroplastic receptive fields at spinal level may be responsible for phenomena such as the extraterritorial expansion of pain and sensory symptoms, for example, in patients with simple carpal tunnel syndrome [7].

A reduction in the strength of opioidergic, serotoninergic, and noradrenergic pain control descending systems, which are located in the brainstem and project to the dorsal horn of the spinal cord, has been documented in animal models of chronic NP [1].

The drugs that are currently available for the treatment of NP aim to correct the alterations listed above, which occur mainly at the neuronal level. For example, some antiepileptic drugs (e.g., phenytoin, carbamazepine) can reduce the hyperexcitability of the peripheral nerve by blocking the voltage-dependent sodium channels. The drugs that are active on the α2δ subunit of calcium channels (i.e., gabapentin, pregabalin) can reduce spinal sensitization. Opioids and serotonin-noradrenaline reuptake inhibitor antidepressants (i.e., duloxetine, venlafaxine) may potentiate pain control descending inhibitory systems. Tricyclics (e.g., amitriptyline) may control NP through multiple mechanisms. Meta-analyses and guidelines document that these classes of drugs are effective in reducing NP, although in a limited number of patients [2] and with an unfavorable side effect profile in a consistent number of cases.

1.3 Central Mechanisms and Pain Matrix

Neuroimaging studies have revolutioned the understanding of the involvement of the cortex in pain sensation. Not only is the pain primarily being represented in the primary somatosensory cortex (S1), but large distributed brain networks were found to be active during painful stimulation [9–12]. The cortical and subcortical brain regions found to be commonly activated from these early studies by nociceptive stimulation included anterior cingulate cortex, insula, frontal cortices, S1, second somatosensory cortex (S2), and amygdala and are often referred to as the "pain matrix" [13].

Because pain signals are important for survival, it is as important to regulate pain signaling in the central nervous system. The brainstem has a tonic regulatory influence from the spinal cord dorsal root level (Table 1.2). There are also strong suggestions that the analgesic system is heavily related to the endogenous opioid systems. The brainstem integrates information from

autonomic, homeostatic, affective, and limbic brain centers and can participate to the descending control of pain [14]. The relationship between reported pain intensity and the peripheral stimulus that evokes it depends on many factors such as the level of arousal, anxiety, depression, attention, and expectation or anticipation. These factors are in the process of being characterized on the physiological and pharmacological levels by means of functional imaging. These "psychological" factors are in turn regulated by overt and covert information as well as more general contextual cues that establish the significance of the stimulus and help determine an appropriate response to it. Simple manipulations with attention alter the subjective pain experience as well as the corresponding pattern of activation during painful stimulation [15]. Functional and connectivity analyses in neuroimaging suggest that the increased activity within prefrontal and cingulate cortices during distraction decreases pain perception via the descending pain modulatory system, presumably via anti-nociceptive pathways [16].

The complex mechanism of pain at spinal and central system based on sensitization and modulation can explain in most occasions the limited efficacy of current NP treatments. The first, and probably the most important reason, is that many of the evidence in favor of the mechanisms described above come from animal models of NP, where the main outcome is usually the reduction of pain evoked by mechanical or thermal stimuli [17]. Indeed, this type of outcome cannot capture the complexity and multidimensional features of pain in humans, whereby the main complaint is spontaneous pain [17]. The second reason is that the treatment of pain should aim to reduce the negative effects of pain on mood, sleep and quality of life, features that are difficult to explore in animal models. The third reason is that current models do not allow to understand the complex mechanisms that take place in patients with NP in several brain areas, which include thalamic and cortical areas that cannot be explored in animal models [18, 19] and have been just studied by neuroimaging in humans.

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Brain Imaging of Pain

2

Massimo Caulo, Valerio Maruotti, and Antonio Ferretti

2.1 Introduction

Pain is not just a warning symptom informing our body of actual or potential damage to the tissue, but it is an unpleasant sensation with sensory, emotional, and cognitive dimensions occurring after nervous system lesions. Neuroimaging techniques provide a tool for understanding the mechanisms involved in perception and modulation of the pain experience. Brain functional magnetic resonance imaging shows that multiple pain conditions are associated with changes within large-scale distributed networks involved in sensory, motor, autonomic, cognitive, and emotional functions. The importance of the brain for pain perception derives from patients with cerebral lesions. Traditionally pain has been conceptualized as the neural substrate that passively reflects peripheral changes following injury. Today it is clear that the conscious perception of a sensory stimulus cannot be completed in sensory areas, but rather there is an extensive, interconnected network of cortical and subcortical areas. The group of brain structures jointly activated by painful stimuli is commonly called "the pain matrix." Generally, the ascending pain processes divide signals into localization and emotional/motivation centers (Fig. 2.1). The brain regions involved in processing pain depend on the type of pain experienced (acute and chronic pain) and on the different pathologies.

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2.2 Structural and Functional Neuroimaging Techniques

2.2.1 Magnetic Resonance Imaging (MRI)

MRI uses a strong static magnetic field and radiofrequency (RF) waves to create multiplanar cross-sectional images. The main parameters on which the image contrast is based are T1 and T2. T1 (the longitudinal relaxation time) is a measure of how long atomic nuclei take to realign longitudinally with the main magnetic field, after they have been knocked over by an RF pulse. T2 (the transverse relaxation time) is a measure of how long a group

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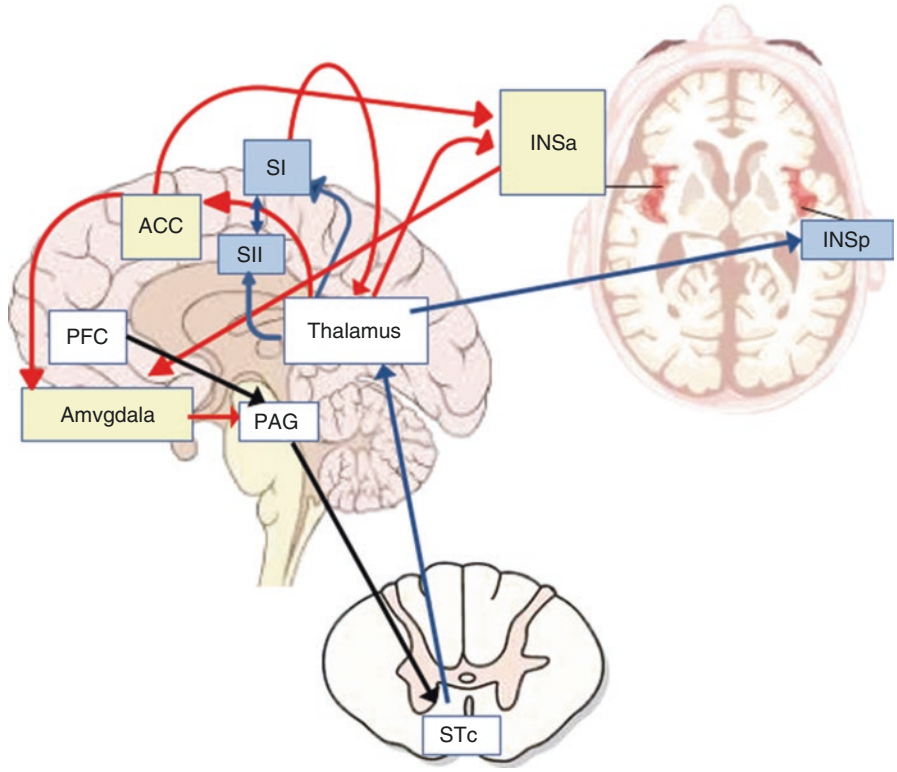

Fig. 2.1 Schematic representation of the pain matrix. Nociceptive inputs enter the spinal dorsal horn and ascend through the contralateral spinothalamic tract (STc) to the thalamus. The medial pathway (yellow square and red arrows) projects from the medial thalamus to the anterior cingulate cortex (ACC), anterior insular cortex (INSa), and amygdala; the medial pathway processes the affective-motivational component of pain. The lateral pathway (light blue square and blue arrows) projects from the lateral thalamus to the primary and secondary somatosensory cortices (SI and SII) and posterior insular cortex (INSp); the lateral pathway processes the corporal specificity of bodily pain. Inhibitory projections (black arrows) descend from the prefrontal cortex (PFC), via the periaqueductal gray matter (PAG), to the spinal cord

of atomic nuclei that have been knocked over by an RF pulse take to become maximally disordered in the transverse plane. Different tissues have different T1 and T2. Images with T2 weighting are most commonly used when looking for pathology, while T1-weighted images are more commonly used to highlight anatomy [1].

2.2.2 Functional Magnetic Resonance Imaging (fMRI)

Beyond the study of normal and pathological brain anatomy, MRI has been used during the last 20 years to investigate brain functions with a technique generally defined as functional MRI (fMRI). Since its introduction [2] fMRI has become an indispensable tool in neuroscience research and in clinical neurological and neurosurgical practice. fMRI is classically performed using the blood-oxygen-level-dependent contrast (BOLDc) technique. The functional contrast is based on deoxyhemoglobin which acts as an endogenous contrast medium. Deoxyhemoglobin is a paramagnetic molecule, thus creating magnetic field distortions within and around the blood vessels that affect T2*- and T2-weighted images. fMRI is based on the hemodynamic response triggered by an increase of neuronal activity related to a given stimulus or task. Briefly, an increased neuronal activity triggers a local vasodilation (the neurovascular coupling mechanism), altering cerebral blood flow (CBF) and cerebral blood volume (CBV). These physiological responses are needed to

support the increased oxygen metabolism of activated neuronal pools. These hemodynamic and metabolic changes alter the local deoxyhemoglobin content, producing a slight alteration in the MR signal [3]. fMRI is usually performed using T2*-weighted echo-planar imaging sequences that are the most sensitive to the BOLD effect, allowing to map regional brain activation robustly and with good spatial resolution. The BOLD technique can also be used to study the brain at rest by mapping temporally synchronous, spatially distributed, spontaneous signal fluctuations and generating measures of functional connectivity [4].

BOLD fMRI has enough temporal resolution (around 1 s) to allow the study of acute pain with paradigms alternating short periods of pain followed by short periods that are pain-free, causing a hemodynamic response in the activated brain regions. However these paradigms are not well suited to study chronic or sustained pain since these conditions cannot be easily switched on and off [5]. Furthermore, due to its complex nature, the BOLD signal is not able to offer quantitative physiological measurements referred to a particular brain condition. In these and similar applications, fMRI based on arterial spin labeling (ASL) can be more appropriate.

ASL [6] provides a direct measure of cerebral blood flow using magnetically labeled water in the blood to act as an endogenous diffusible tracer. The blood water is magnetically labeled in the main cerebral feeding arteries with radiofrequency pulses that invert the direction of nuclei magnetic moment. When the bolus of magnetically inverted blood reaches the different brain regions, it will affect the MRI signal according to the local CBF. ASL is able to measure both absolute levels of CBF and perfusion changes triggered by neuronal activity [7–9]. Despite a lower sensitivity and temporal resolution with respect to BOLD, these features make ASL fMRI an ideal technique to study brain functioning when control and stimulus conditions cannot be rapidly alternated. In addition, compared with BOLD, ASL offers increased spatial specificity to neuronal activity due to the capillary/tissue origin of the signal [10]. fMRI ASL techniques have consequently been used to assess the central processing of pain in patients with migraine [11] and chronic pain [12].

2.2.3 PET

Positron emission tomography (PET) can measure changes in hemodynamic, metabolic, or chemical events at receptor and neurotransmitter reuptake sites or neurotransmitter precursor uptake in living tissues.

Although PET is an invasive technique requiring the injection of a radioactive tracer (e.g., $H_2{}^{15}O$ or ^{18}F-FDG) and suffers from low spatial and temporal resolution with respect to fMRI, it can quantify regional CBF, oxygen uptake, and glucose metabolism in physiological units. Thus, PET can be used to indirectly and directly measure different aspects of the neuronal response to painful stimuli. PET is also unique in its ability to evaluate the neurochemical components of central pain processing by using tracers which directly measure events within the central opioid and dopaminergic systems [13].

2.2.4 MEG

Magnetoencephalography (MEG) is an electrophysiological technique that has higher temporal resolution than fMRI and PET, but lacks good spatial resolution.

MEG detects the tiny magnetic field generated by postsynaptic ionic currents of synchronically active pyramidal cortical neurons, oriented in palisade. These postsynaptic potentials reflect the integrative information processing of signals coming from the thalamus, brainstem, and other cortical areas. The magnetic currents are detected by arrays of superconducting quantum interference devices (SQUIDs) in a magnetically shielded room. Heavy magnetical shielding is necessary to attenuate external magnetic fields, since neuromagnetic fields are very weak. These technical requirements make the MEG device relatively expensive [14]. MEG studies are often used to evaluate separate temporal components of the cerebral pain response, for instance, in relation to expectation [15, 16] or the processing of first and second pain due to the varying conduction times by A and C fibers [17].

2.2.5 NIRS

Near-infrared spectroscopy (NIRS) is a noninvasive, relatively inexpensive portable optical imaging technique based on the principle that diffusion and absorption of light in the near-infrared (NIR) range (700–1000 nm) is sensitive to blood oxygenation. This light is able to pass through the skin, soft tissue, and skull with relative ease and can penetrate brain tissue to a depth of up to 8 cm in infants and 5 cm in adults. It measures the hemodynamic response to neural activity based on the different absorption properties of biological chromophores. The hemodynamic signal obtained with the NIRS technique is based on the absorption of NIRS light depending on the oxygenation state of hemoglobin circulating through the tissues. NIRS quantifies levels of oxygenated and deoxygenated hemoglobin in brain tissue and allows for calculation of absolute changes in blood flow and cerebral blood volume [18]. Functional NIRS research is rapidly expanding across a wide range of areas. This technique can be usefully applied to assess cerebral hemodynamic changes associated with pain in infants and in non-collaborative patients [19].

2.3 Structural Neuroimaging of Pain

Neuropathic pain can arise as a direct consequence of a lesion or disease affecting the somatosensory system at central and peripheral level.

2.3.1 Central Post Stroke Pain

Central pain results from a primary lesion or dysfunction of the central nervous system in different pathologies: stroke, multiple sclerosis, spinal cord injury, syringomyelia, vascular malformations, infections, and traumatic brain injury.

Déjerine and Roussy described initially patients with severe, persistent, paroxysmal, and often intolerable pains on the hemiplegic side related to lesions of the thalamus and parts of the posterior limb of the internal capsule [20].

Central post stroke pain (CPSP) can develop after both hemorrhagic and ischemic lesions in sensory pathway of the central nervous system [21]. The onset is usually within the first few months, but it can occur some years later, and it is often gradual coinciding with improvements in sensory loss [22]. Abnormalities in either thermal (particularly cold) or pain (e.g., pinprick) sensation are found in more than 90% of patients, whereas sensory loss in other modalities (such as touch and vibration) is less frequent [23]. Pain can be localized within the entire area of sensory abnormalities or within a fraction of this area [24]. Non-sensory findings depend on the localization and severity of the cerebrovascular lesion. Pain is characterized by an intense spontaneous or evoked pain, typically constant and often made worse by touch, movement, emotions, and temperature changes. It is often described as constant burning or aching, with paresthesia and intolerable intermittent stabbing. Allodynia and hyperalgesia are usually present [25].

The stroke can be anywhere along the somatosensory system from the cortex to spinal cord, although lateral medullary (Wallenberg syndrome) and thalamic infarctions have the highest incidence. Wallenberg syndrome is the most frequent ischemic stroke in posterior circulation (Fig. 2.2). It is most often secondary to intracranial vertebral artery or posterior inferior cerebellar artery (PICA) occlusion due to atherothrombosis, embolism, and sometimes to spontaneous dissection of the vertebral arteries. A complete Wallenberg syndrome is not common. Facial pain is homolateral to lesion. Different combinations of the following homolateral (ataxia, vertigo, diplopia, nystagmus, Horner's syndrome, hiccups, hoarseness, dysphonia, dysphagia, dysarthria, decreased gag reflex) and contralateral deficits (loss of pain and temperature sensation over the side of body) may all be found. The thalamus plays an important role in the underlying mechanisms of central pain, and CPSP is common after lesions affecting the thalamus. The thalamus may be involved by ischemic and hemorrhagic stroke, in particular in hypertension (Fig. 2.3). Ischemic stroke is most often secondary to intracranial occlusion due to atherothrombosis of the posterior cerebral artery. In thalamic lesions pain is located in the contralateral hemibody. The side of lesion is not a consistent predictor of pain [26]. Lesions can be located in the posterolateral, ventral posterior lateral, and medial nuclei [27].

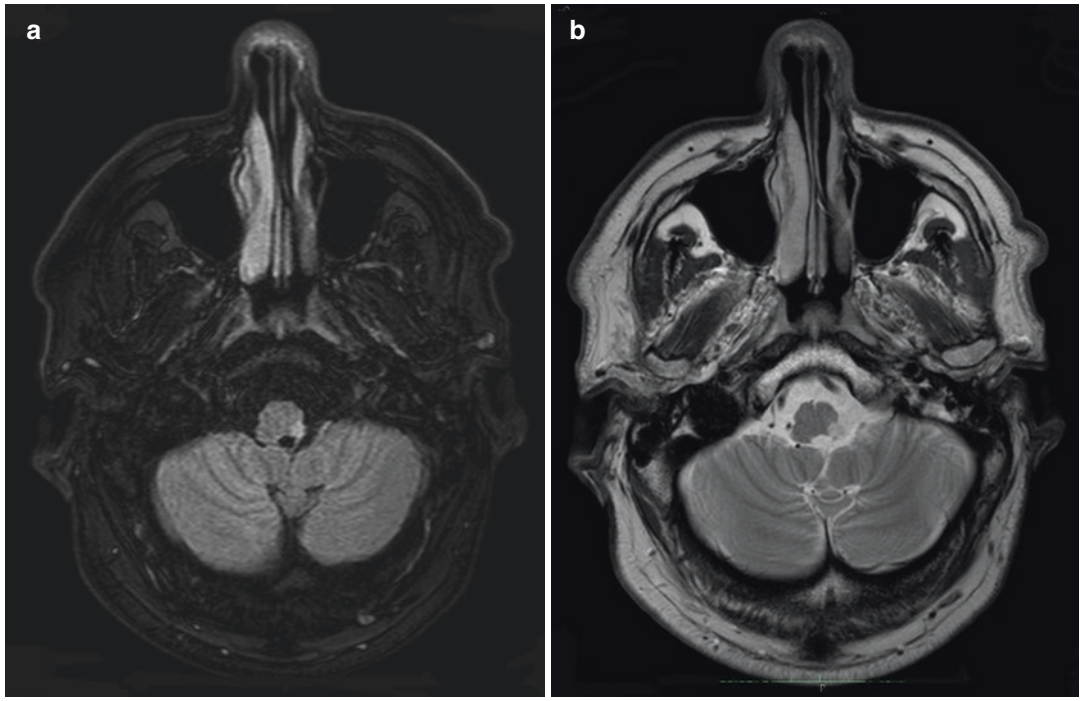

Fig. 2.2 Wallenberg syndrome: axial FLAIR (**a**) and T2 (**b**) MR images showing a hyperintense ischemic lesion in the left posterolateral medulla oblongata

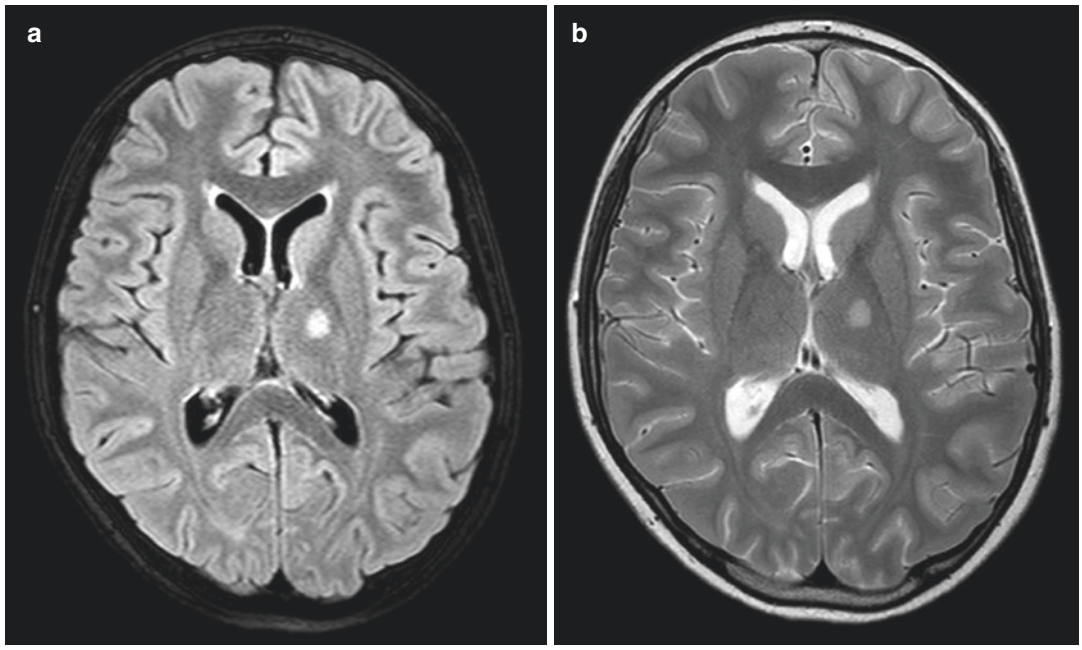

Fig. 2.3 Thalamic stroke: axial FLAIR (**a**) and T2 (**b**) MR images showing a hyperintense ischemic lesion in the left lateral thalamus

In addition to Wallenberg syndrome, trigeminal nuclei can be involved in hypertensive hemorrhage, cavernous angiomas, arteriovenous malformations (AVMs), or trauma (Duret's hemorrhage) [28]. The most common cause is hypertension in middle-aged elderly patients and cavernous angiomas in young.

2.3.2 Multiple Sclerosis

Multiple sclerosis (MS) is an unpredictable autoimmune and neurodegenerative disease of the central nervous system characterized by demyelination and axonal loss. It is a heterogeneous disease with a variety of sign and symptoms depending on the site of lesions that leads to motor, sensory, and cognitive impairment [29].

Chronic pain is one of the most frequent MS-associated symptoms that dramatically reduces the quality of life. Pain in multiple sclerosis (MS) has a variable prevalence of 20–90%. Patients usually have more disability at expanded disability severity score (EDSS), depression, and anxiety. Imaging studies showed that lesions are most commonly reported in the brainstem and less commonly in the spinal cord [30].

MS patients can suffer from nociceptive pain (such as pain resulting from musculoskeletal problems), neuropathic pain, or a mixed nociceptive/neuropathic pain (e.g., tonic painful spasms or spasticity). The most common MS-associated chronic neuropathic pain conditions are dysesthetic pain in the lower extremities, paroxysmal pain, (Lhermitte's phenomenon and trigeminal neuralgia), migraine, and tension-type headache.

Lhermitte's phenomenon, defined as a transient short-lasting sensation related to neck flexion in the back of the neck, the spine, and into the legs and arms, has a prevalence from 9 to 41%. It is frequently associated with posterior columns lesions of the cervical spinal cord (Fig. 2.4).

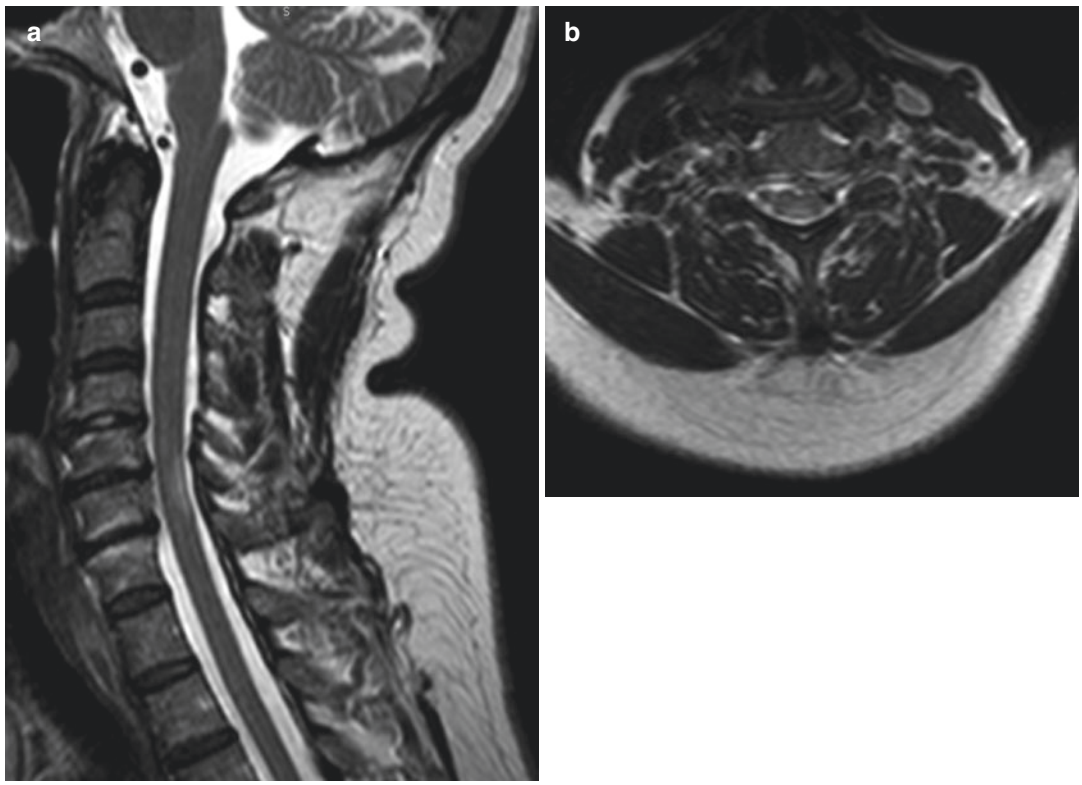

Fig. 2.4 Cervical spinal cord lesion in a patient with multiple sclerosis. Sagittal (**a**) and axial (**b**) T2 MR images showing a hyperintense demyelinating lesion in the posterior columns

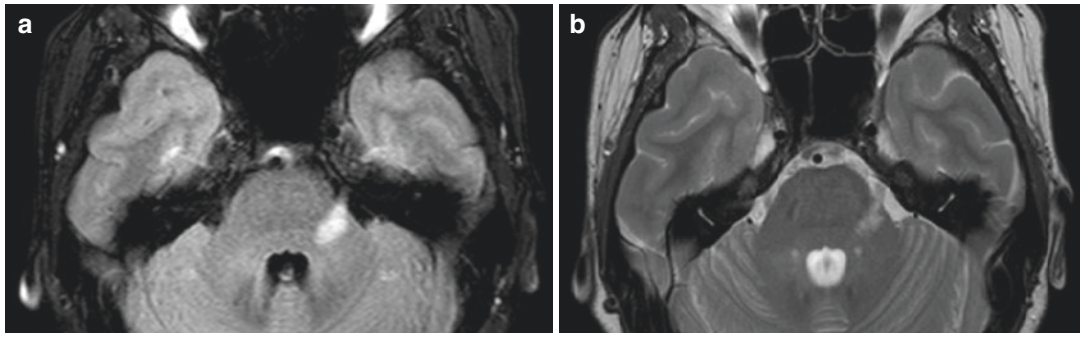

Fig. 2.5 Trigeminal neuralgia in a patient with multiple sclerosis. Axial FLAIR (**a**) and T2 (**b**) MR images showing a demyelinating lesion in the left lateral pons near the root entry zone

Hyperexcitability resulting by miscommunication between the lesioned nerves is considered as the main pathophysiological mechanism.

The pathophysiology of trigeminal neuralgia (TN) in MS patients involves CNS demyelination along the fifth cranial nerve at "entry zone" or at the main sensory nucleus. If a patient under the age of 50 presents face pain, MS is the most common etiology. In MS patients, the facial neuropathic pain syndrome is similar to classic TN. While classic TN is caused by neurovascular compression of the fifth cranial nerve (CN V), MS-related lesions correlate with MRI lesions in the trigeminal nucleus, nerve, and brainstem. Conventional MRI, better high-resolution MRI at 3 T, demonstrates demyelination in the trigeminal root entry zone and intrapontine tracts (Fig. 2.5) that could extend in either direction to the trans-cisternal part of the nerve and to both ascending and descending trigeminal nuclei [31].

2.4 Functional Neuroimaging of Pain

The first half of the twentieth century was dominated by the idea that pain integration in the central nervous system was limited to subcortical structures, not extending beyond the thalamus.

Further studies suggested that the pain experience reflected interacting sensory, affective, and cognitive dimensions that could influence each other and implied that it could only be conceived as a conscious sensation.

The first human brain imaging studies of pain using PET and SPECT indicated that multiple cortical and subcortical regions are activated by noxious stimuli in normal subjects [13]. Since then many other functional hemodynamic and neurophysiologic studies (PET, MEG fMRI, ASL) confirmed that pain activates several brain regions. The group of brain structures jointly activated by painful stimuli is commonly described as "the pain matrix." The pain matrix includes the thalamus, basal ganglia, anterior cingulate cortex (ACC), insula, amygdala, primary and secondary somatosensory cortices (S1 and S2), prefrontal cortex (PFC), and the periaqueductal gray (PAG) [32] (Fig. 2.6).

A division of function between the lateral and medial components of the human pain processing system of the brain was yet proposed several decades ago [33]. The lateral pain system is formed by the lateral thalamic nuclei, the primary and secondary somatosensory cortices (SI and SII, respectively), and posterior insula [34]. Activation of these areas is thought to support the corporal specificity of bodily pain and transmits information about the intensity, location, and duration of noxious stimuli. The medial pain system is formed by medial thalamic nuclei, anterior cingulate cortex (ACC), amygdala, and anterior insula and participates in affective and attentional concomitants of pain sensation or perceiving pain as an unpleasant experience [32].

Also the descending pain modulation system includes the PFC and ACC and exerts its

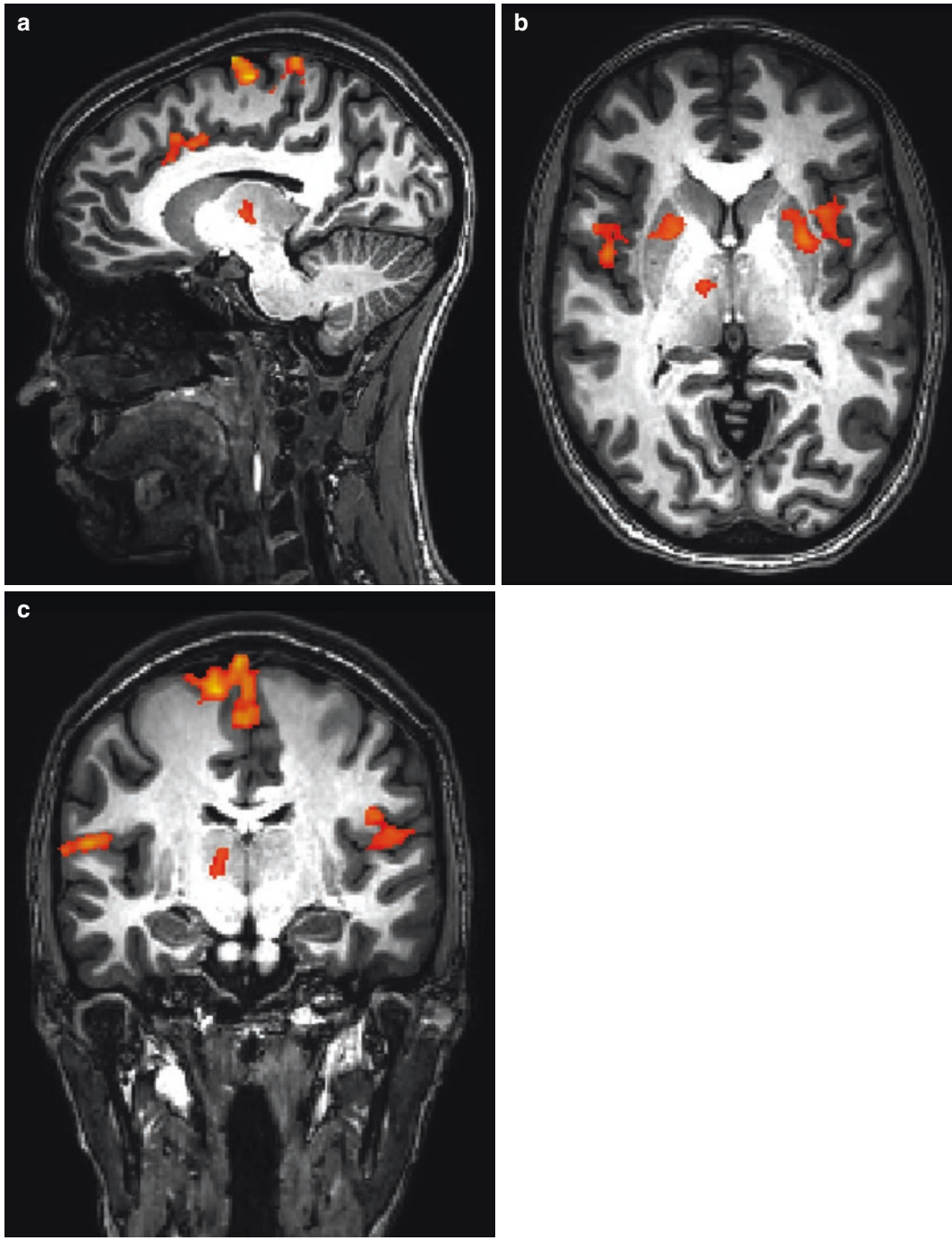

Fig. 2.6 BOLD fMRI activations during painful electrical stimulation of the left ankle. (**a**) Sagittal view: SI, anterior cingulate and thalamus activations. (**b**) Axial view: putamen, bilateral insula, and left thalamus activations. (**c**) Coronal view: left SI, bilateral SII, and left thalamus activations. Images are displayed using the neurological convention, i.e., right is right, left is left. (Courtesy of Piero Chiacchiaretta PhD, University of Chieti, Italy)

influence on the periaqueductal gray matter and thalamus [35].

SI is located posteriorly to the central sulcus, across the surface of the postcentral gyrus and seems to have the same somatotopy in the processing of nonpainful and painful somatosensory stimuli [36]. SII is hidden in the upper bank of the lateral sulcus in the parietal operculum. It has a functional segregation of the subregions involved in the processing of nonpainful and painful somatosensory stimuli [16]. Indeed, the posterior but not the anterior SII increases its activation as a function of the stimulus intensity from nonpainful to painful levels [37] (Fig. 2.7).

No clear somatotopic organization has been reported for painful input, but a topographic organization of SII is reported for nonpainful somatosensory input [38].

In the somatosensory system, SI is presumed to receive the peripheral afferents involved in the encoding of spatial and sensory-discriminative aspects and to dispatch the received input to higher order cortical areas, such as contralateral SII. Contralateral SII sends transcallosal fibers to ipsilateral SII [39].

The nociceptive system has a parallel structure in which SI and SII would receive in parallel painful stimuli [40]. Also pain sensory informations

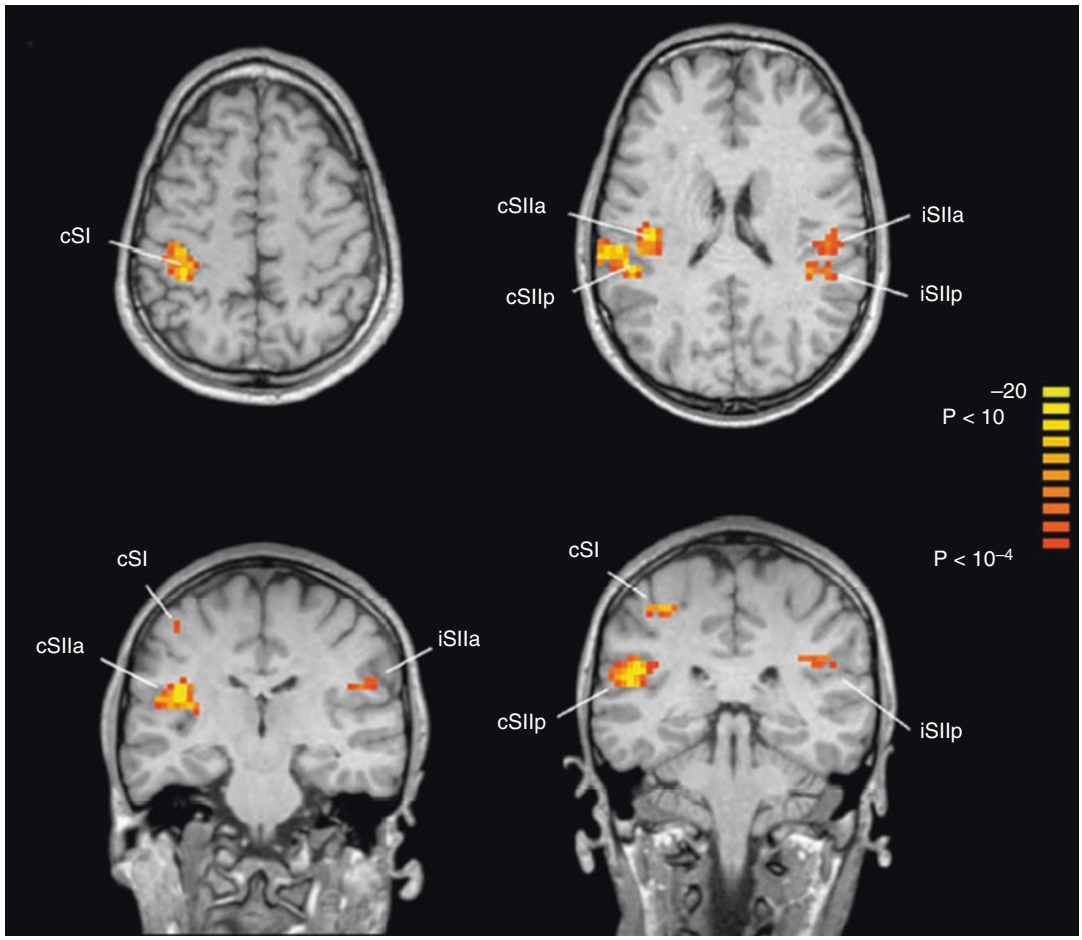

Fig. 2.7 Activated areas in the somatosensory cortex during painful electrical stimulation of the right median nerve, obtained from a group of healthy individuals. The activations are superimposed onto structural images of an individual brain using the neurological convention, i.e., right is right, left is left. Top left, contralateral SI; top right, bilateral SII anterior and posterior subregions; bottom left, anterior SII areas and contralateral SI; bottom right, posterior SII areas and contralateral SI. Reproduced from Ferretti et al. [37] with permission

are processed bilaterally by the two SII areas [41]. This parallel organization bypasses several cortico-cortical and transcallosal connections shortening the processing time of the painful stimulus. SII is consistent with the complexity of thalamic projections from several relays within a multifunctional network involved in noxious stimulus recognition, learning, and memory, autonomic reactions to noxious stimuli, affective aspects of pain-related learning, and memory [38].

ACC has a robust activation across different stimulus modalities and measurement techniques although the locus of this activation varies among studies. The perigenual or rostral ACC seems to be related to affective reactions to pain, while mid-cingulate is related to cognitive processes [42]. After cingulotomy subjects may feel pain but they are not disturbed by it. The insula shows the highest incidence of activity during painful stimulation. The activations of the posterior portion of the insula may be more related to sensory aspects of pain, while the more anterior portion is more related to emotional, cognitive, and memory characteristics of pain perception (Fig. 2.8). In addition, a somatotopic representation exists in the posterior insula for nociceptive stimuli [43]. Strong evidences suggest that the posterior operculo-insular cortex is the only known cortical region where direct stimulation can induce acute physical pain [44] and focal cortical injury to that region entails selective deficits of pain and temperature sensations while leaving other somatosensory modalities intact [45].

Emotional state is a large factor in how pain is perceived, with negative emotions enhancing pain-evoked activity in ACC and insula and pain perception [46].

In the absence of physical stimulus, expecting or anticipating pain activates SI, ACC, insula, PAG, PFC, and ventral striatum [47]. Also, attending to pain is related to stronger pain impact [48]. fMRI studies show that in attention-demanding task while experiencing pain, there is decreased activity in SII, PAG/midbrain, thalamus, and insula resulting in reduced pain perception [49]. The complexity of a task plays also a relevant role on the subjective pain rating [35].

Habituation also occurs in pain network. Repetitive applications of identical painful stimuli decrease pain ratings and decrease BOLD responses to painful stimuli in the thalamus, insula, and SII, mediated by the rACC [50].

Cortical activation has been studied related to different types of painful stimuli: cutaneous noxious cold, muscle stimulation using electric shock or hypertonic saline, capsaicin, colonic distension, rectal distension, gastric distension, esophageal distension, ischemia, cutaneous electric shock, ascorbic acid, and laser heat. These stimuli produce many similar activations in cortical and subcortical areas [51].

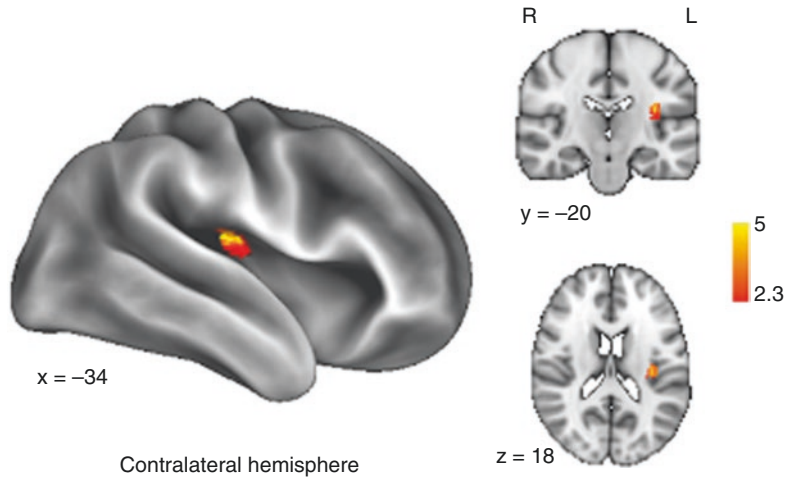

Fig. 2.8 Perfusion MRI study with ASL technique (pCASL sequence) after capsaicin application in the anteromedial aspect of the lower right leg. Note the increased CBF in the dorsal insula of the left hemisphere. Modified from Segerdahl et al. [43] with permission