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.

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-319-99822-0_2) contains supplementary material, which is available to authorized users.

M. Caulo (✉) · A. Ferretti
Department of Neuroscience, Imaging and Clinical Sciences, University "G. d'Annunzio" of Chieti, Chieti, Italy

ITAB - Institute of Advanced Biomedical Technologies, University "G. d'Annunzio" of Chieti, Chieti, Italy
e-mail: caulo@unich.it

V. Maruotti
ITAB - Institute of Advanced Biomedical Technologies, University "G. d'Annunzio" of Chieti, Chieti, Italy

Neurology Department, IRCCS Neuromed, Pozzilli, Isernia, Italy

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

M. A. Cova, F. Stacul (eds.), *Pain Imaging*, https://doi.org/10.1007/978-3-319-99822-0_2

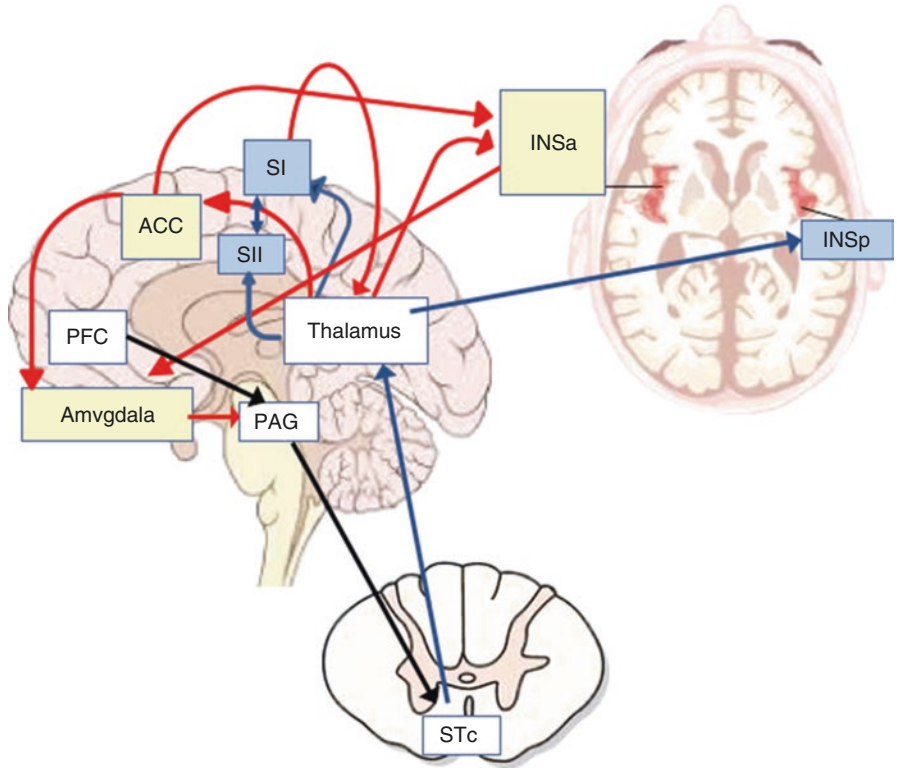

Fig. 2.1 Schematic representation of the pain matrix. Nociceptive inputs enter the spinal dorsal horn and ascend through the contralateral spinothalamic tract (STc) to the thalamus. The medial pathway (yellow square and red arrows) projects from the medial thalamus to the anterior cingulate cortex (ACC), 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].

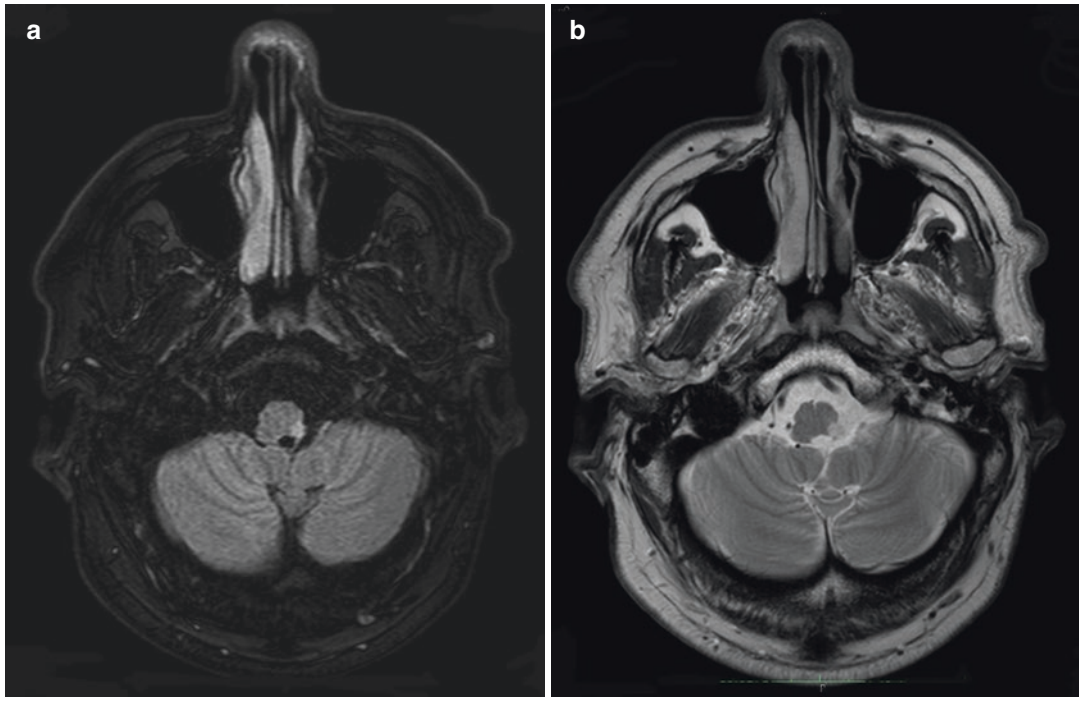

Fig. 2.2 Wallenberg syndrome: axial FLAIR (**a**) and T2 (**b**) MR images showing a hyperintense ischemic lesion in the left posterolateral medulla oblongata

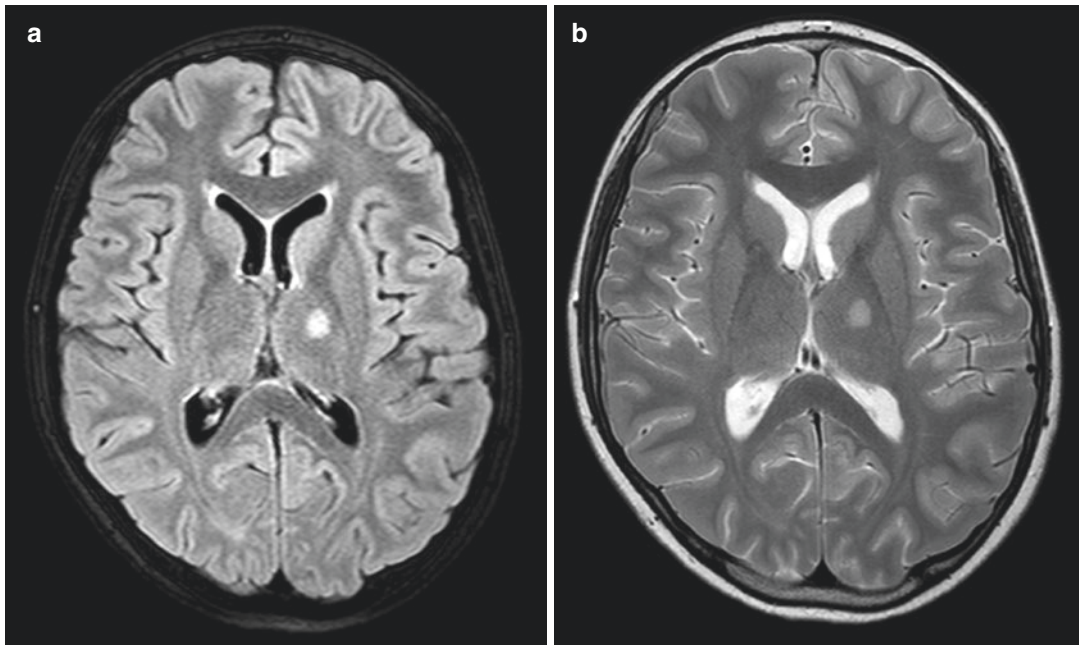

Fig. 2.3 Thalamic stroke: axial FLAIR (**a**) and T2 (**b**) MR images showing a hyperintense ischemic lesion in the left lateral thalamus

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).

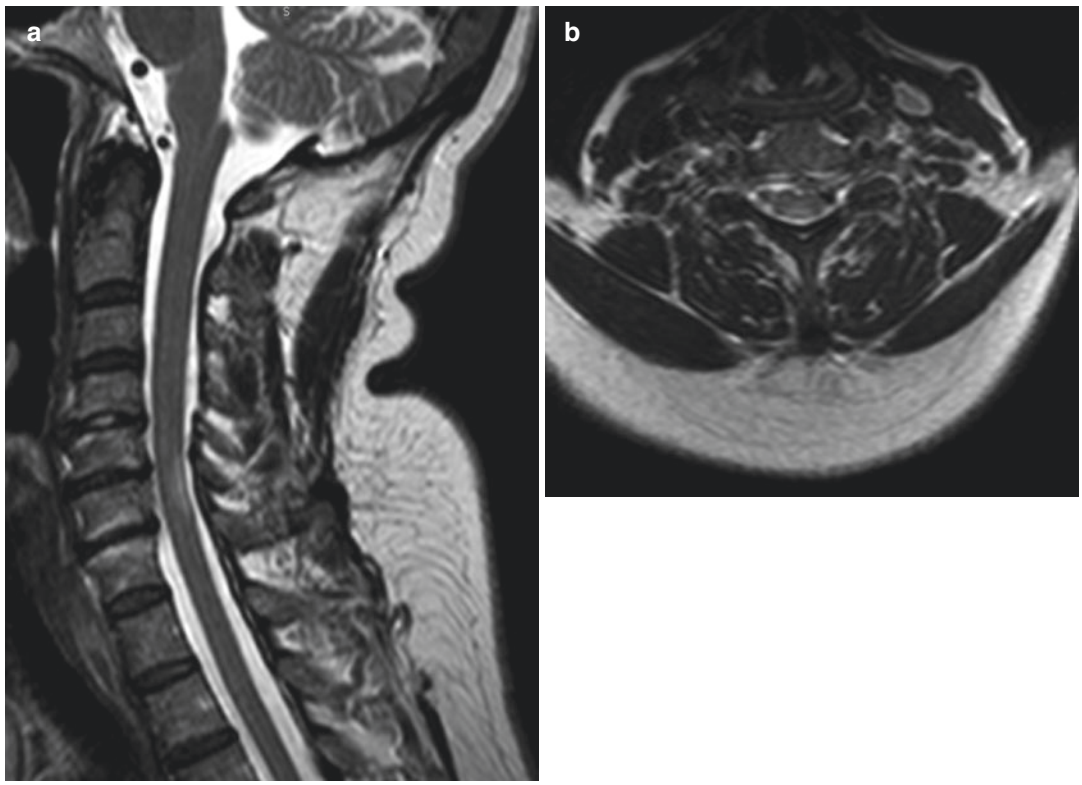

Fig. 2.4 Cervical spinal cord lesion in a patient with multiple sclerosis. Sagittal (**a**) and axial (**b**) T2 MR images showing a hyperintense demyelinating lesion in the posterior columns

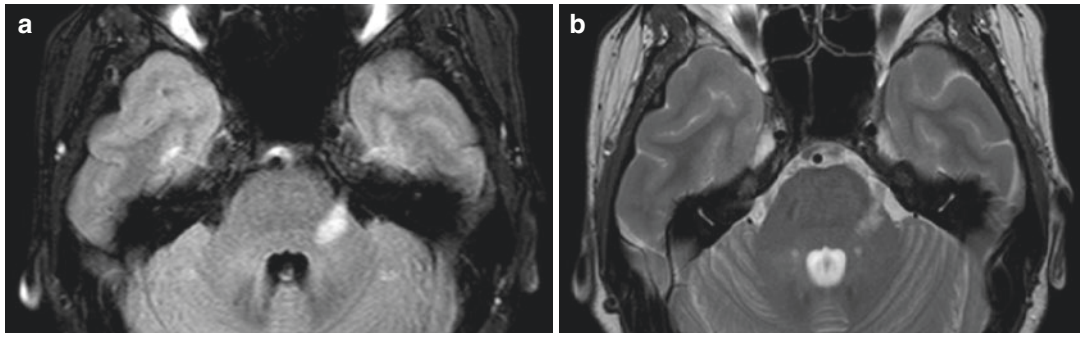

Fig. 2.5 Trigeminal neuralgia in a patient with multiple sclerosis. Axial FLAIR (**a**) and T2 (**b**) MR images showing a demyelinating lesion in the left lateral pons near the root entry zone

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

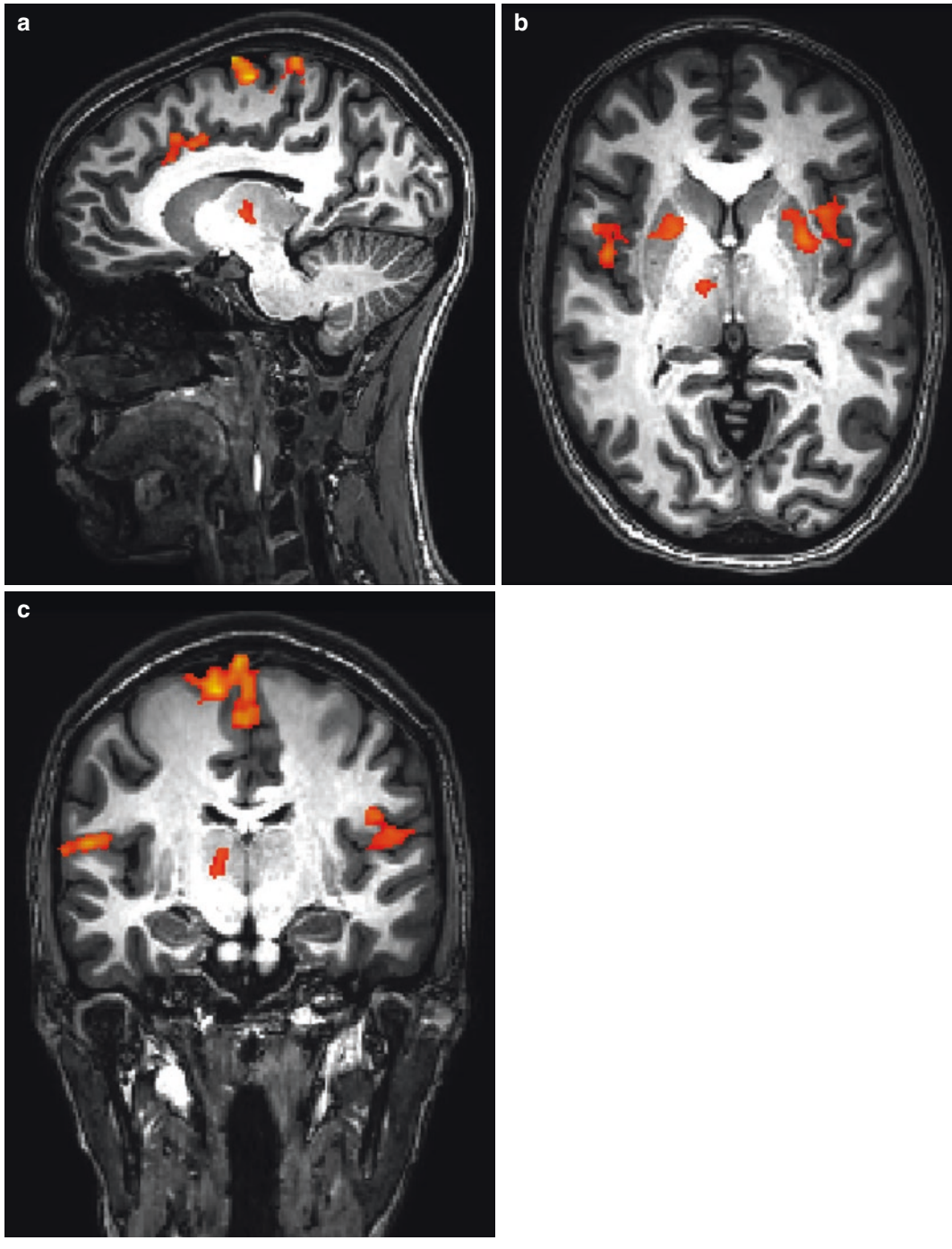

Fig. 2.6 BOLD fMRI activations during painful electrical stimulation of the left ankle. (**a**) Sagittal view: SI, anterior cingulate and thalamus activations. (**b**) Axial view: putamen, bilateral insula, and left thalamus activations. (**c**) Coronal view: left SI, bilateral SII, and left thalamus 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

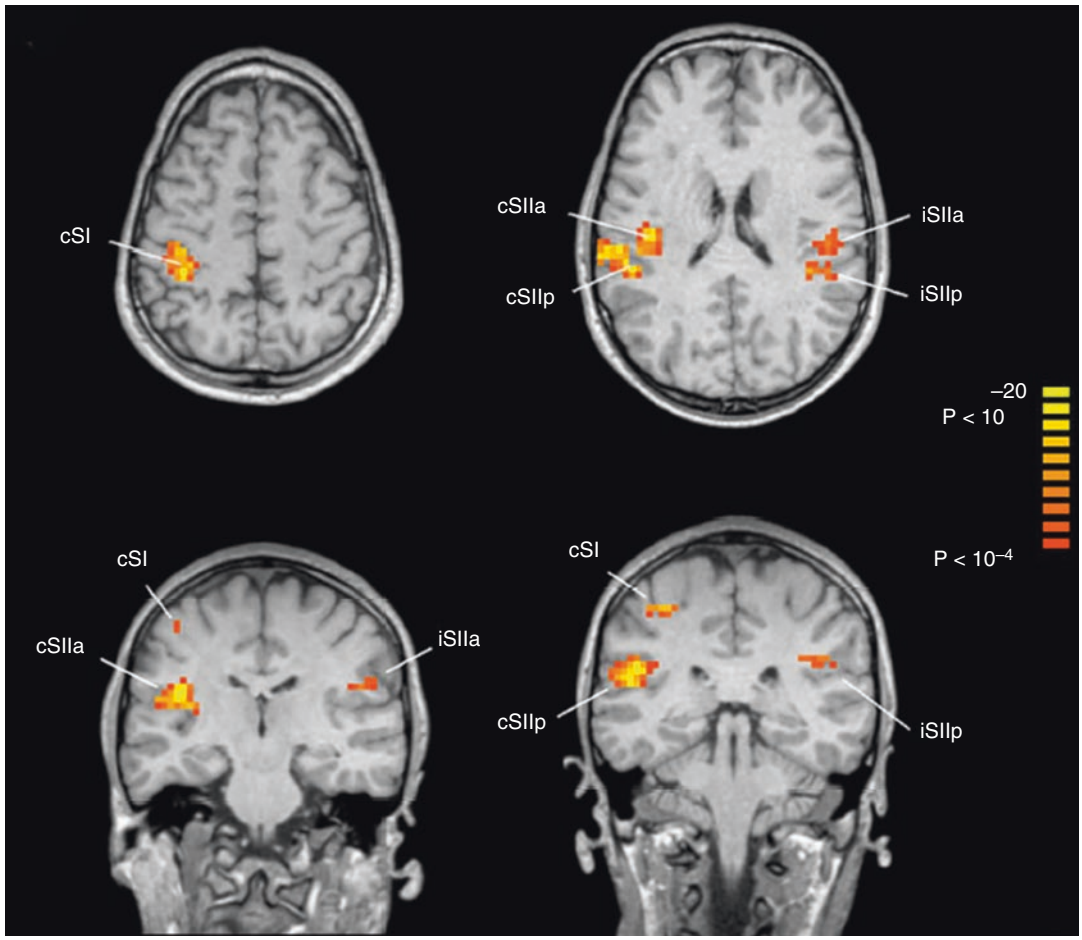

Fig. 2.7 Activated areas in the somatosensory cortex during painful electrical stimulation of the right median nerve, obtained from a group of healthy individuals. The activations are superimposed onto structural images of an individual brain using the neurological convention, i.e., right is right, left 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].

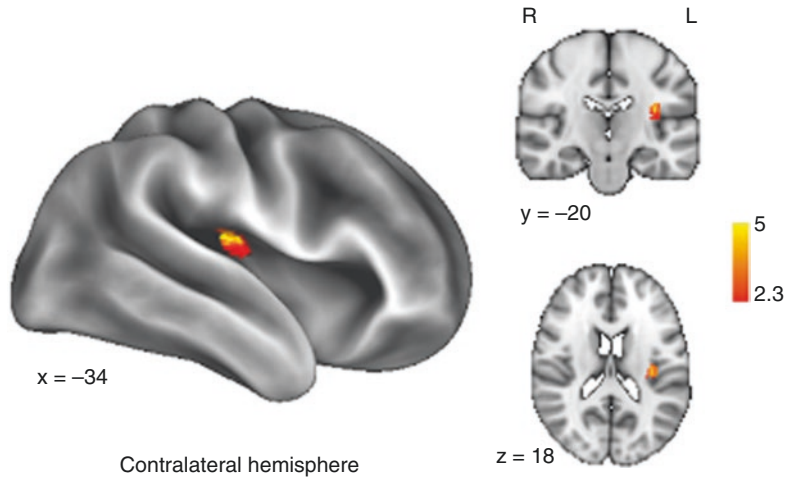

Fig. 2.8 Perfusion MRI study with ASL technique (pCASL sequence) after capsaicin application in the anteromedial aspect of the lower right leg. Note the increased CBF in the dorsal insula of the left hemisphere. Modified from Segerdahl et al. [43] with permission

2.4.1 Pain Network and Connectivity

Painful stimuli induce a robust activation directly proportional to the intensity of the stimulus into the pain matrix. Connectivity in the pain matrix revealed synchronous activity in the bilateral SI cortex, mid-cingulate cortex, posterior insula, and bilateral SII, but not in ACC, one of the brain regions most consistently associated with affective dimension of pain. Similar results were obtained placing a seed in SII. When ACC and anterior insula are used as the seed regions for connectivity analysis, significant synchronous activity is observed in several brain regions including bilateral ACC, mid-cingulate cortex, bilateral anterior and middle insula, thalamus, caudate, orbital PFC, LPFC, and cerebellum, but not in SI or SII. These data confirm a functional segregation of lateral and medial pain system, supporting different functions [52, 53].

In addition, painful stimulation induces a simultaneous decrease in activation in several brain regions, including some of the "core structures" of the default mode network (DMN) [54]. The DMN maintains its typical temporal properties during painful stimulation although an increase of connectivity was found between the left prefrontal cortex and posterior cingulate cortex-precuneus and a decrease in the lateral parietal cortex [55] (Fig. 2.9).

Functional connectivity analyses indicate that the activity of areas displaying pain-evoked changes in the same direction is highly correlated, though there are no significant correlations between brain activations and deactivations indicating that activations and deactivations might underlie different aspects of the pain experience [52].

2.4.2 Pain in Infants

Most of the tools that have been developed for assessing pain perception in infants encompass either behavioral (brow bulge, eye squeeze, nasolabial furrow, qualities of infant cry, flexion of fingers and toes) or physiological (heart rate, arterial oxygen saturation, and blood pressure) responses or combine both into a composite measure. Behavioral responses, particularly facial actions, are the most sensitive and specific pain indicators in infants. NIRS response to painful stimuli found a significant increase over the somatosensory cortex in oxyhemoglobin, total hemoglobin, and deoxyhemoglobin. Biobehavioral pain scores found a significant correlation with NIRS response. Also the areas of BOLD response to painful stimulation are similar in infants and adults, with amygdala and the orbitofrontal cortex not activated in infants. The cortical response depends on the age, the gestational age, and awake/sleep states of the infants. It is directly associated with postnatal age and inversely correlated with gestational age. Less robust cortical responses are also observed in neonates asleep versus awake [56].

2.4.3 Chronic Pain

Painful conditions that usually end without treatment or that respond to simple analgesic measures may also become intractable and develop into a long-lasting condition: chronic pain. Chronic pain (CP) is considered as a condition affecting normal brain function and causing cognitive impairment, depression, sleeping disturbances, and decision-making abnormalities. Altered cortical dynamics have been demonstrated using functional magnetic resonance imaging in patients with CP [57]. A prominent difference between acute and chronic pain consists in the major activation, in the latter, of brain regions involved in cognitive and/or emotional pain processing. Evidence of frontal-limbic dysfunction comes also from PET studies suggesting abnormal opioidergic transmission within frontal-limbic regions in patients with CP [41]. CP disrupts the dynamics of the default mode network. Various types of CP (chronic back pain complex, regional pain syndrome, knee osteoarthritis, diabetic neuropathy, fibromyalgia) are associated with MR functional connectivity changes within the DMN [52]. The most common reorganization consists in an increased asso-

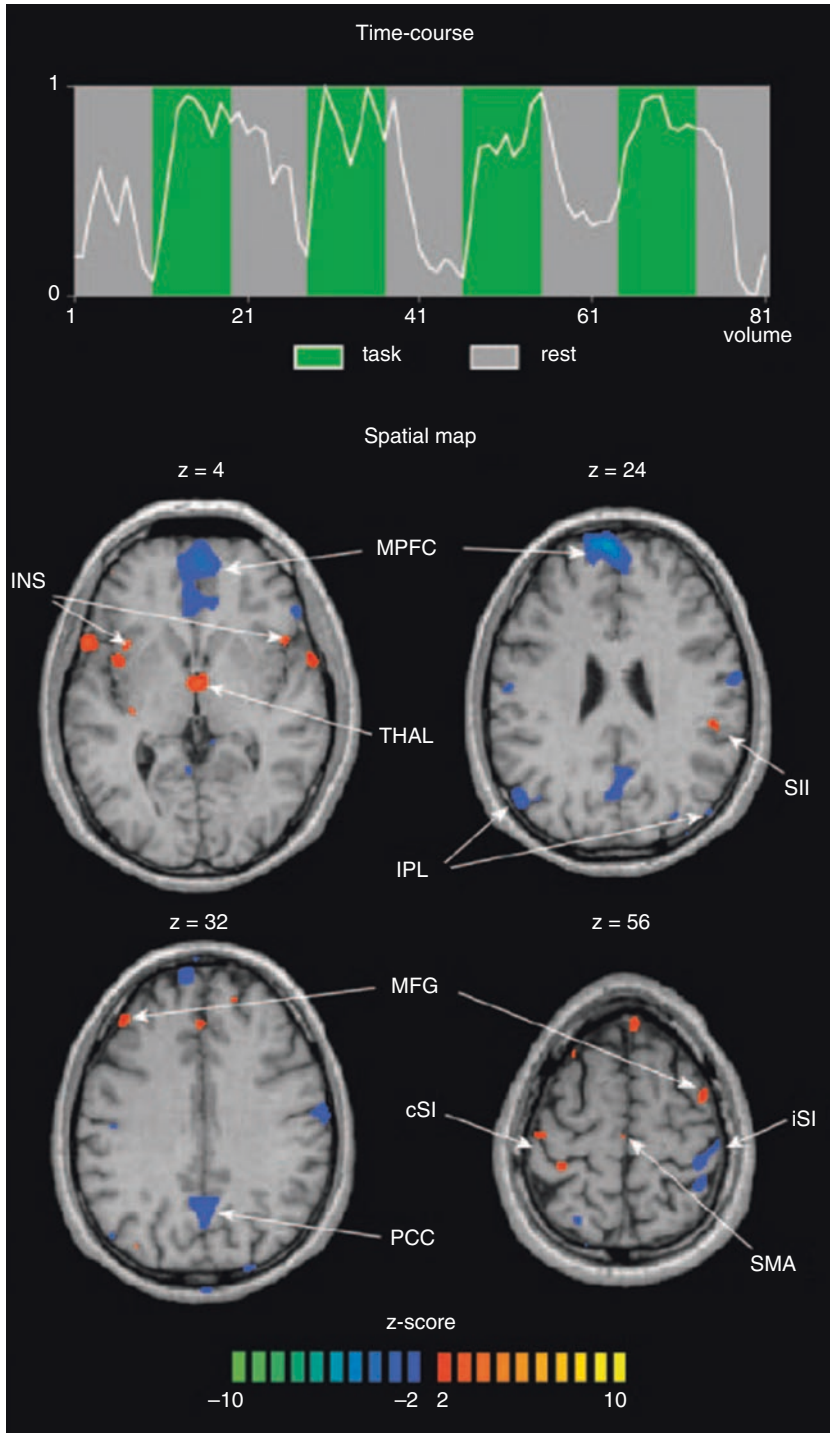

Fig. 2.9 Modulation of the DMN during painful electrical stimulation of the right median nerve. DMN was separated from a single-subject functional MR imaging data set at independent component analysis. Brain areas of the DMN are colored in yellow-orange or azure in case of a positive or negative correlation with the task. *cSI* contralateral primary somatosensory area, *INS* insula, *IPL* inferior parietal lobule, *iSI* ipsilateral primary somatosensory area, *MFG* middle frontal gyrus, *MPFC* medial prefrontal cortex, *PCC* posterior cingulate cortex-precuneus, *SII* secondary somatosensory area, *SMA* supplementary motor area, *THAL* thalamus. Images are displayed using the neurological convention, i.e., right is right, left is left. Reproduced from Mantini et al. [55] with permission

ciation of the medial prefrontal cortex (MPFC) with the insula and dissociation from the posterior components of the DMN (precuneus). The precuneus is involved in autobiographical and episodic memory retrieval and mentalizing. It is primarily involved in elaborating and integrating information rather than directly processing stimuli [52]. The functional correlation of insular regions with portions of the MPFC correlates with the intensity and the extent of pain and decreases after successful treatment of pain [58].

The decreased MPFC connectivity with the precuneus is directly related to the increased connectivity with the insular cortex, suggesting that chronic pain might modulate higher cognitive processes by altering normative functions of the DMN.

The extent of this reorganization is a function of the intensity of the chronic pain and the duration, with functional changes occurring after more than a decade living with chronic pain. In addition an increase of functional connectivity between the PFC and nucleus accumbens predicts pain persistence, suggesting that the frontal-striatal connection is involved in the transition from acute to chronic pain.

Prolonged pain can lead to neuroplastic changes at the cortical level, which induce central sensitization [46].

2.4.4 Phantom Limb Pain (PLP)

Arm amputation often can be followed by pain sensation in the missing limb (PLP). It occurs in up to 80% of amputees and may be exacerbated by many physical (e.g., temperature changes) and psychological (e.g., stress) factors. It is usually described as stabbing, throbbing, burning, or cramping and commonly starts in the first week after amputation. The duration of PLP is unpredictable, resolving in months or persisting for years.

The cause of phantom pain experience has commonly been attributed to maladaptive plasticity of the primary sensorimotor cortex contralateral to the amputation. The representations of body parts adjacent to the missing limb expand and invade the deprived cortex leading to phantom limb pain. The degree of cortical reorganization appears to be directly related to the degree of phantom pain, and imaging studies have correlated greater extent of somatosensory cortex changes with more intense phantom limb experience. A greater phantom pain is associated with more local activity and more structural integrity within the phantom cortex and with disrupted interregional functional connectivity of the primary sensorimotor cortex of the other body parts [59].

References

1. Atlas SW. Magnetic resonance imaging of the brain and spine. Philadelphia: Wolters Kluwer Health; 2008. p. 1923. [cited 2018 Feb 26]. https://books.google.it/books?hl=it&lr=&id=Mu7MmTXkPeAC&oi=fnd&pg=PA2&dq=Atlas+SW+et+al+magnetic+Resonance+Imaging+of+the+brain+and+spine&ots=r0IH3g6Olm&sig=IXU6TlWiEAXchZFdJGb3IPEQZ3s#v=onepage&q=Atlas&f=false.
2. Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, et al. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci U S A. 1992;89(13):5951–5. [cited 2018 Feb 26]. http://www.ncbi.nlm.nih.gov/pubmed/1631079.
3. Buxton RB, Uludağ K, Dubowitz DJ, Liu TT. Modeling the hemodynamic response to brain activation. NeuroImage. 2004;23:S220–33. [cited 2018 Feb 26]. http://www.ncbi.nlm.nih.gov/pubmed/15501093.
4. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007;8(9):700–11. [cited 2018 Apr 9]. http://www.nature.com/articles/nrn2201.
5. Peyron R, Laurent B, García-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiol Clin. 2000;30(5):263–88. [cited 2018 Feb 26]. http://www.ncbi.nlm.nih.gov/pubmed/11126640.
6. Detre JA, Leigh JS, Williams DS, Koretsky AP. Perfusion imaging. Magn Reson Med. 1992;23(1):37–45. [cited 2018 Apr 8]. http://www.ncbi.nlm.nih.gov/pubmed/1734182.
7. Alsop DC, Detre JA, Golay X, Günther M, Hendrikse J, Hernandez-Garcia L, et al. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: a consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. Magn Reson Med. 2015;73(1):102–16. [cited 2018 Apr 8]. http://www.ncbi.nlm.nih.gov/pubmed/24715426.

8. Diekhoff S, Uludağ K, Sparing R, Tittgemeyer M, Cavuşoğlu M, von Cramon DY, et al. Functional localization in the human brain: gradient-echo, spin-echo, and arterial spin-labeling fMRI compared with neuronavigated TMS. Hum Brain Mapp. 2011;32(3):341–57. [cited 2018 Apr 8]. https://doi.org/10.1002/hbm.21024.
9. Tjandra T, Brooks JCW, Figueiredo P, Wise R, Matthews PM, Tracey I. Quantitative assessment of the reproducibility of functional activation measured with BOLD and MR perfusion imaging: implications for clinical trial design. NeuroImage. 2005;27(2):393–401. [cited 2018 Apr 8]. http://www.ncbi.nlm.nih.gov/pubmed/15921936.
10. Raoult H, Ferr J, Petr J, Bannier E, Stamm A, Barillot C, et al. Functional arterial spin labeling: optimal sequence duration for motor activation mapping in clinical practice. J Magn Reson Imaging. 2012;36(6):1435–44. [cited 2018 Apr 8]. https://doi.org/10.1002/jmri.23782.
11. Youssef AM, Ludwick A, Wilcox SL, Lebel A, Peng K, Colon E, et al. In child and adult migraineurs the somatosensory cortex stands out … again: an arterial spin labeling investigation. Hum Brain Mapp. 2017;38(8):4078–87. [cited 2018 Feb 26]. http://www.ncbi.nlm.nih.gov/pubmed/28560777.
12. Wasan AD, Loggia ML, Chen LQ, Napadow V, Kong J, Gollub RL. Neural correlates of chronic low back pain measured by arterial spin labeling. Anesthesiology. 2011;115(2):364–74. [cited 2018 Feb 26]. http://www.ncbi.nlm.nih.gov/pubmed/21720241.
13. Jones AKP, Brown WD, Friston KJ, Qi LY, Frackowiak RSJ. Cortical and subcortical localization of response to pain in man using positron emission tomography. Proc R Soc B Biol Sci. 1991;244(1309):39–44. [cited 2018 Feb 26]. http://www.ncbi.nlm.nih.gov/pubmed/1677194.
14. Babiloni C, Pizzella V, Del Gratta C, Ferretti A, Romani GL. Chapter 5 fundamentals of electroencefalography, magnetoencefalography, and functional magnetic resonance imaging. Int Rev Neurobiol. 2009;86:67–80. [cited 2018 Feb 26]. http://www.ncbi.nlm.nih.gov/pubmed/19607991.
15. Ploner M, Gross J, Timmermann L, Schnitzler A. Cortical representation of first and second pain sensation in humans. Proc Natl Acad Sci U S A. 2002;99(19):12444–8. [cited 2018 Feb 26]. http://www.ncbi.nlm.nih.gov/pubmed/12209003.
16. Torquati K, Pizzella V, Babiloni C, Del Gratta C, Della Penna S, Ferretti A, et al. Nociceptive and non-nociceptive sub-regions in the human secondary somatosensory cortex: an MEG study using fMRI constraints. NeuroImage. 2005;26(1):48–56. [cited 2018 Feb 28]. https://www.sciencedirect.com/science/article/pii/S1053811905000352.
17. Brown CA, Seymour B, Boyle Y, El-Deredy W, Jones AKP. Modulation of pain ratings by expectation and uncertainty: behavioral characteristics and anticipatory neural correlates. Pain. 2008;135(3):240–50. [cited 2018 Feb 26]. http://www.ncbi.nlm.nih.gov/pubmed/17614199.
18. Hillman EMC. Optical brain imaging in vivo: techniques and applications from animal to man. J Biomed Opt. 2007;12(5):51402. [cited 2018 Feb 26]. http://www.ncbi.nlm.nih.gov/pubmed/17994863.
19. Boas DA, Elwell CE, Ferrari M, Taga G. Twenty years of functional near-infrared spectroscopy: introduction for the special issue. NeuroImage. 2014;85:1–5. [cited 2018 Feb 26]. http://www.ncbi.nlm.nih.gov/pubmed/24321364.
20. Wilkins RH, Brody IA. The thalamic syndrome. Arch Neurol. 1969;20(5):559–62. [cited 2018 Feb 26]. http://www.ncbi.nlm.nih.gov/pubmed/5767614.
21. Weimar C, Kloke M, Schlott M, Katsarava Z, Diener H-C. Central poststroke pain in a consecutive cohort of stroke patients. Cerebrovasc Dis. 2002;14(3-4):261–3. [cited 2018 Feb 27]. http://www.ncbi.nlm.nih.gov/pubmed/12403962.
22. Andersen G, Vestergaard K, Ingeman-Nielsen M, Jensen TS. Incidence of central post-stroke pain. Pain. 1995;61(2):187–93. [cited 2018 Feb 27]. http://www.ncbi.nlm.nih.gov/pubmed/7659428.
23. Bowsher D. Central pain: clinical and physiological characteristics. J Neurol Neurosurg Psychiatry. 1996;61(1):62–9. [cited 2018 Feb 27]. http://www.ncbi.nlm.nih.gov/pubmed/8676164.
24. Vestergaard K, Nielsen J, Andersen G, Ingeman-Nielsen M, Arendt-Nielsen L, Jensen TS. Sensory abnormalities in consecutive, unselected patients with central post-stroke pain. Pain. 1995;61(2):177–86. [cited 2018 Feb 27]. http://www.ncbi.nlm.nih.gov/pubmed/7659427.
25. Leijon G, Boivie J, Johansson I. Central post-stroke pain—neurological symptoms and pain characteristics. Pain. 1989;36(1):13–25. [cited 2018 Feb 27]. http://www.ncbi.nlm.nih.gov/pubmed/2919091.
26. Bowsher D, Leijon G, Thuomas KA. Central post-stroke pain: correlation of MRI with clinical pain characteristics and sensory abnormalities. Neurology. 1998;51(5):1352–8. [cited 2018 Feb 27]. http://www.ncbi.nlm.nih.gov/pubmed/9818859.
27. Kim JS. Pure sensory stroke. Clinical-radiological correlates of 21 cases. Stroke. 1992;23(7):983–7. [cited 2018 Feb 27]. http://www.ncbi.nlm.nih.gov/pubmed/1615549.
28. Parizel PM, Makkat S, Jorens PG, Özsarlak Ö, Cras P, Van Goethem JW, et al. Brainstem hemorrhage in descending transtentorial herniation (Duret hemorrhage). Intensive Care Med. 2002;28(1):85–8. [cited 2018 Feb 27]. http://www.ncbi.nlm.nih.gov/pubmed/11819006.
29. Murphy KL, Bethea JR, Fischer R. Neuropathic pain in multiple sclerosis—current therapeutic intervention and future treatment perspectives. In: Multiple sclerosis: perspectives in treatment and pathogenesis. Brisbane: Codon Publications; 2017. [cited 2018 Mar 9]. http://www.ncbi.nlm.nih.gov/pubmed/29261265.
30. Seixas D, Foley P, Palace J, Lima D, Ramos I, Tracey I. Pain in multiple sclerosis: a systematic review of neuroimaging studies. Neuroimage Clin. 2014;5:322–31. [cited 2018 Mar 8]. http://creativecommons.org/licenses/by-nc-nd/3.0/.

31. Mazhari A. Multiple sclerosis-related pain syndromes: an imaging update. Curr Pain Headache Rep. 2016;20(12):63. [cited 2018 Mar 9]. http://www.ncbi.nlm.nih.gov/pubmed/27864731.
32. Treede RD, Kenshalo DR, Gracely RH, Jones AK. The cortical representation of pain. Pain. 1999;79(2-3):105–11. [cited 2018 Feb 26]. http://www.ncbi.nlm.nih.gov/pubmed/10068155.
33. Melzack R. From the gate to the neuromatrix. Pain. 1999;82(Suppl 6):S121–6. [cited 2018 Feb 26]. http://www.ncbi.nlm.nih.gov/pubmed/10491980.
34. Kulkarni B, Bentley DE, Elliott R, Youell P, Watson A, Derbyshire SWG, et al. Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. Eur J Neurosci. 2005;21(11):3133–42. [cited 2018 Feb 28]. https://doi.org/10.1111/j.1460-9568.2005.04098.x.
35. Wiech K, Seymour B, Kalisch R, Enno Stephan K, Koltzenburg M, Driver J, et al. Modulation of pain processing in hyperalgesia by cognitive demand. NeuroImage. 2005;27(1):59–69. [cited 2018 Feb 28]. http://www.ncbi.nlm.nih.gov/pubmed/15978845.
36. Omori S, Isose S, Otsuru N, Nishihara M, Kuwabara S, Inui K, et al. Somatotopic representation of pain in the primary somatosensory cortex (S1) in humans. Clin Neurophysiol. 2013;124(7):1422–30. [cited 2018 Feb 28]. http://www.ncbi.nlm.nih.gov/pubmed/23415452.
37. Ferretti A, Babiloni C, Del Gratta C, Caulo M, Tartaro A, Bonomo L, et al. Functional topography of the secondary somatosensory cortex for nonpainful and painful stimuli: an fMRI study. NeuroImage. 2003;20(3):1625–38. [cited 2018 Mar 13]. https://www.sciencedirect.com/science/article/pii/S1053811903004385.
38. Ferretti A, Del Gratta C, Babiloni C, Caulo M, Arienzo D, Tartaro A, et al. Functional topography of the secondary somatosensory cortex for nonpainful and painful stimulation of median and tibial nerve: an fMRI study. NeuroImage. 2004;23(3):1217–25. [cited 2018 Feb 28]. http://www.ncbi.nlm.nih.gov/pubmed/15528121.
39. Chen TL, Babiloni C, Ferretti A, Perrucci MG, Romani GL, Rossini PM, et al. Human secondary somatosensory cortex is involved in the processing of somatosensory rare stimuli: an fMRI study. NeuroImage. 2008;40(4):1765–71. [cited 2018 Feb 27]. http://www.ncbi.nlm.nih.gov/pubmed/18329293.
40. Ploner M, Schmitz F, Freund H-J, Schnitzler A. Parallel activation of primary and secondary somatosensory cortices in human pain processing. J Neurophysiol. 1999;81(6):3100–4. [cited 2018 Feb 28]. https://doi.org/10.1152/jn.1999.81.6.3100.
41. Apkarian AV, Bushnell MC, Treede R-D, Zubieta J-K. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain. 2005;9(4):463. [cited 2018 Feb 27]. http://www.ncbi.nlm.nih.gov/pubmed/15979027.
42. Vogt BA, Berger GR, Derbyshire SWG. Structural and functional dichotomy of human midcingulate cortex. Eur J Neurosci. 2003;18(11):3134–44. [cited 2018 Feb 28]. http://www.ncbi.nlm.nih.gov/pubmed/14656310.
43. Segerdahl AR, Mezue M, Okell TW, Farrar JT, Tracey I. The dorsal posterior insula subserves a fundamental role in human pain. Nat Neurosci. 2015;18(4):499–500. [cited 2018 Feb 28]. http://www.nature.com/articles/nn.3969.
44. Mazzola L, Isnard J, Peyron R, Mauguière F. Stimulation of the human cortex and the experience of pain: Wilder Penfield's observations revisited. Brain. 2012;135(2):631–40. [cited 2018 Mar 11]. http://www.ncbi.nlm.nih.gov/pubmed/22036962.
45. Garcia-Larrea L, Perchet C, Creac'h C, Convers P, Peyron R, Laurent B, et al. Operculo-insular pain (parasylvian pain): a distinct central pain syndrome. Brain. 2010;133(9):2528–39. [cited 2018 Mar 11]. https://doi.org/10.1093/brain/awq220.
46. Morton D, Jones A, Sandhu J. Brain imaging of pain: state of the art. J Pain Res. 2016;9:613–24. [cited 2018 Feb 26]. http://www.ncbi.nlm.nih.gov/pubmed/27660488.
47. Porro CA, Baraldi P, Pagnoni G, Serafini M, Facchin P, Maieron M, et al. Does anticipation of pain affect cortical nociceptive systems? J Neurosci. 2002;22(8):3206–14. [cited 2018 Feb 28]. http://www.ncbi.nlm.nih.gov/pubmed/11943821.
48. Arntz A, de Jong P. Anxiety, attention and pain. J Psychosom Res. 1993;37(4):423–31. [cited 2018 Feb 28]. http://www.ncbi.nlm.nih.gov/pubmed/8510069.
49. Bantick SJ, Wise RG, Ploghaus A, Clare S, Smith SM, Tracey I. Imaging how attention modulates pain in humans using functional MRI. Brain. 2002;125(Pt 2):310–9. [cited 2018 Feb 28]. http://www.ncbi.nlm.nih.gov/pubmed/11844731.
50. Bingel U, Schoell E, Herken W, Büchel C, May A. Habituation to painful stimulation involves the antinociceptive system. Pain. 2007;131(1):21–30. [cited 2018 Feb 28]. http://www.ncbi.nlm.nih.gov/pubmed/17258858.
51. Iannetti GD, Mouraux A. From the neuromatrix to the pain matrix (and back). Exp Brain Res. 2010;205(1):1–12. [cited 2018 Feb 26]. https://doi.org/10.1007/s00221-010-2340-1.
52. Kong J, Loggia ML, Zyloney C, Tu P, LaViolette P, Gollub RL. Exploring the brain in pain: activations, deactivations and their relation. Pain. 2010;148(2):257–67. [cited 2018 Feb 28]. http://www.ncbi.nlm.nih.gov/pubmed/20005043.
53. Wilcox CE, Mayer AR, Teshiba TM, Ling J, Smith BW, Wilcox GL, et al. The subjective experience of pain: an FMRI study of percept-related models and functional connectivity. Pain Med. 2015;16(11):2121–33. [cited 2018 Apr 10]. http://www.ncbi.nlm.nih.gov/pubmed/25989475.
54. Perrotta A, Chiacchiaretta P, Anastasio MG, Pavone L, Grillea G, Bartolo M, et al. Temporal summation of the nociceptive withdrawal reflex involves deactivation of posterior cingulate cortex. Eur J Pain. 2017;21(2):289–301. [cited 2018 Apr 8]. http://www.ncbi.nlm.nih.gov/pubmed/27452295.
55. Mantini D, Caulo M, Ferretti A, Romani GL, Tartaro A. Noxious somatosensory stimulation affects the default mode of brain function: evidence from func-

tional MR imaging. Radiology. 2009;253(3):797–804. [cited 2018 Feb 28]. http://www.ncbi.nlm.nih.gov/pubmed/19789220.

56. Benoit B, Martin-Misener R, Newman A, Latimer M, Campbell-Yeo M. Neurophysiological assessment of acute pain in infants: a scoping review of research methods. Acta Paediatr. 2017;106(7):1053–66. [cited 2018 Mar 11]. http://www.ncbi.nlm.nih.gov/pubmed/28326623.
57. Tagliazucchi E, Balenzuela P, Fraiman D, Chialvo DR. Brain resting state is disrupted in chronic back pain patients. Neurosci Lett. 2010;485(1):26–31. [cited 2018 Feb 28]. http://www.ncbi.nlm.nih.gov/pubmed/20800649.
58. Baliki MN, Mansour AR, Baria AT, Apkarian AV. Functional reorganization of the default mode network across chronic pain conditions. PLoS One. 2014;9(9):e106133. [cited 2018 Feb 28]. https://doi.org/10.1371/journal.pone.0106133.
59. Jutzeler CR, Curt A, Kramer JLK. Relationship between chronic pain and brain reorganization after deafferentation: a systematic review of functional MRI findings. Neuroimage Clin. 2015;9:599–606. [cited 2018 Mar 10]. http://www.ncbi.nlm.nih.gov/pubmed/26740913.