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Review

Central mechanisms of experimental and chronic neuropathic pain: Findings from functional imaging studies

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Abstract. Over the last few years remarkable efforts have been made using functional imaging studies to unravel brain processing of pain and decipher underlying neuronal mechanisms. Cerebral processing in experimental pain models, especially those provoking hyperalgesia, and its pharmacological modulation will form the first part of this review. In a second part we will address central mechanisms of clinical neuropathic pain. Up to now, there are at least six main mechanisms involved in the chronification of neuropathic pain: (i) activity increase in areas of the pain neuromatrix, (ii) recruitment of additional cortical areas beyond the classical pain neuromatrix, (iii) cortical reorganization and maladaptive neuroplasticity, (iv) alterations in neurochemistry (v) structural brain changes and (vi) disruption of the brain default mode network. In a third part of this review we discuss mechanisms of endogenous pain modulation.

Keywords. CNS, neuroplasticity, MRI, fMRI, MEG, PET, neuropathic pain, hyperalgesia, allodynia, surrogate model.

Brain imaging: a short description of the methods

Functional imaging techniques have revolutionized our experimental approaches to assess brain function. Before the era of non-invasive mapping techniques of human brain activity, neuroscientists had to mainly rely on lesion studies and conclusions by analogy derived from invasive (e.g. electrophysiological recordings) studies in non-humans. For example, one of the most famous patients in cognitive neuroscience is "Monsieur Tan", who was nick-named so by Paul Broca because this patient was only able to say "tan … tan … tan". When the patient died, Broca performed an autopsy on the brain and found a lesion in the left inferior frontal cortex. These findings localized a brain area dedicated to language processing and can be regarded as the birth of modern cognitive neuroscience [1].

Today we have three different main techniques for functional brain imaging: positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG). These techniques markedly differ in their invasiveness and technical properties, i.e. temporal and spatial resolution. It is important to note that fMRI and PET do not assess the activity of neurons directly, rather they measure a downstream effect of neuronal activity (i.e. metabolic and vascular changes). Both PET and fMRI exploit the phenomenon that energy consumption increases in activated brain regions. This leads to an increased regional cerebral blood flow (so-called neurovascular coupling).

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Basically, *PET* uses radioactive tracers (often ^{15}O) injected into the bloodstream. The tracer passes the blood-brain barrier and its concentration increases in activated brain regions [2]. During the decay, the tracer emits a positron which – following fusion with one electron – emits 2 γ-quants (photons). These photon pairs are detected using circular detectors and their origin is computed. Accordingly, depending on the tracer, regional blood flow or consumption of oxygen or glucose can be assessed. The spatial resolution of PET is $>$ 4 mm and the temporal resolution several seconds to minutes.

fMRI uses gradient echo sequences sensitive to the amount of desoxyhemoglobin in the blood [3, 4]. When neurons consume oxygen they convert oxyhemoglobin to desoxyhemoglobin, which has strong paramagnetic properties and introduces distortions in the local magnetic field. These distortions can be measured and indicate the local ratio between oxyhemoglobin and desoxyhemoglobin. This technique has been termed BOLD-imaging (blood oxygenation level dependent) [5]. The spatial resolution of fMRI is better than PET (~ 2–4 mm), the temporal resolution is several seconds (2–4 s) [6], depending on the elicited neurovascular response.

In contrast, *MEG* provides an excellent temporal (ms) and spatial resolution (2–3 mm) [7, 8]. However, this technique is mainly limited to investigating regions at the brain's surface. The basic idea is that electrical currents of neurons produce a magnetic field which can be measured at the skull. However, this field is very weak as compared to the ambient magnetic field and superconducting devices (SQUIDS) are needed to measure the magnetic field induced by neuronal activity.

The central pain matrix

In the last decade remarkable efforts have been undertaken to uncover the cortical processing of the human pain experience by non-invasive functional brain imaging techniques, such as PET, fMRI and MEG. The human pain experience is a complex sensation that is of paramount importance to maintain the body integrity and survival of human beings. It is a multidimensional phenomenon with sensory-discriminative, affective-motivational, motor and autonomic components [9]. Functional imaging techniques provided evidence for an involvement of the thalamus, primary somatosensory cortex (S1), secondary somatosensory cortex (S2), insula, forebrain and anterior cingulated cortex (ACC); for review see [9–12]. Primary nociceptive areas in all are often termed the pain neuromatrix [13]. There is accumulating evidence that these areas process different aspects of pain [14–16]. Evidence suggests that nociceptive input into primary and secondary somatosensory cortices at least partially underlies the perception of sensory-discriminative features of pain (lateral pain system). In contrast, ACC and parts of the insula have been implicated in the affective-motivational processing of pain (medial pain system) [9, 17–19]. Prefrontal cortical areas may be related to cognitive variables, such as memory or stimulus evaluation [10]. In particular, the sensory-discriminative component includes stimulus localization, intensity and quality discrimination. In contrast, the affective-motivational component predominantly comprises emotional reactions and stimulus related selective attention [9]. Figure 1 depicts a schema illustrating the pain neuromatrix with its lateral and medial parts.

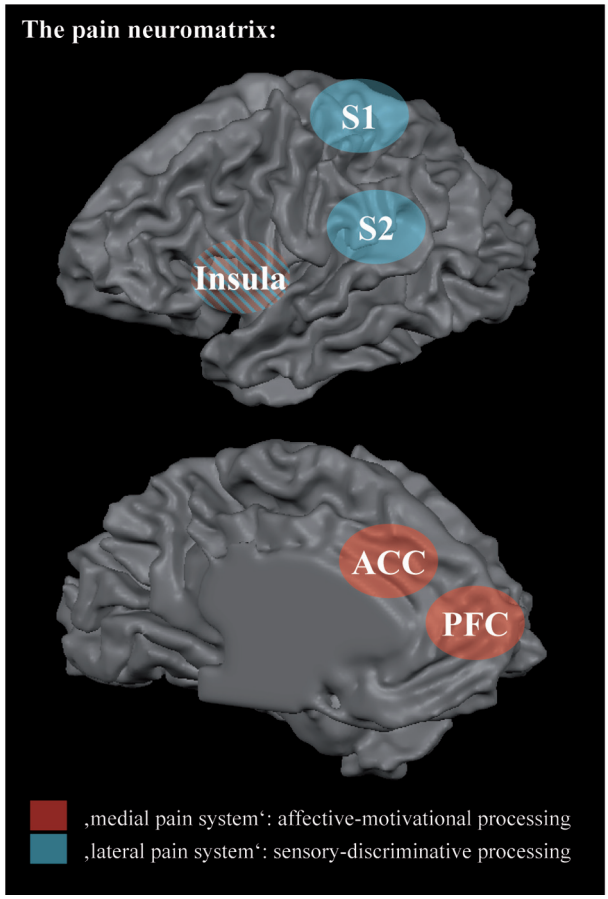

Figure 1. This schematic illustration shows the pain neuromatrix on a reconstructed left hemisphere from lateral (top) and from mesial (bottom). Areas of the lateral pain system that process the sensory-discriminative component of pain are coded in blue, areas of the medial pain system that process the affective-motivational component of pain are coded in red. The insula is anatomically and functionally positioned between these two systems.

So far, numerous functional imaging studies were primarily undertaken in healthy subjects during experimentally induced pain. Additionally, an increasing number of investigations focused also on the neural correlates of neuropathic pain syndromes. Therefore, cerebral nociceptive processing in experimental pain models of neuropathic pain and its pharmacological modulation will form the first part of this review. In a second part we will address the central mechanisms of clinical neuropathic pain. Finally, mechanisms of endogenous pain modulation will be discussed.

Functional imaging studies of experimental pain models

Basically, clinical neuropathic pain syndromes are markedly heterogeneous and, therefore, surrogate models of neuropathic pain provide a unique opportunity to scrutinize single symptoms isolated under controlled conditions in healthy volunteers with neuroimaging methods. However, it has to be emphasized that these models provide no complete substitute for clinical neuropathic pain syndromes, as they do not totally mimic clinical neuropathic pain with its whole complexity.

Basically, surrogate pain models in healthy subjects have been used to examine cerebral processing of different forms of hyperalgesia and allodynia. In the following section we will focus on studies investigating capsaicin-induced hyperalgesia, UV-B-induced thermal and mechanical hyperalgesia, menthol-induced cold allodynia and hyperalgesia induced by intramuscular injection of hypertonic saline.

Capsaicin-induced allodynia and hyperalgesia. Capsaicin, the burning compound in chilli pepper, binds to the TRPV1 receptor on peripheral terminals of nociceptive neurons. Receptor occupancy triggers cation influx, action potential firing, and the consequent burning sensation [20]. Furthermore, the compound induces peripheral sensitization due to excitability changes of the nociceptor. Ongoing nocicptor discharge, especially from the subgroup of so-called silent nociceptors consecutively results in central sensitization [21]. One initial PET-study by Iadarola and colleagues investigated brain processing of capsaicin-induced dynamic mechanical hyperalgesia at the left forearm in 13 volunteers [22]. The following conditions were assessed: rest, brushing of normal skin, intradermal injection of capsaicin, waning of capsaicin pain and allodynia (starting when the capsaicin-induced pain had disappeared). Capsaicin pain induced activation of S1, ACC, insula, putamen, thalamus and cerebellum. The prefrontal cortex (PFC) and S2 showed no significant activation. Light brushing mainly activated S1, S2, insula, ACC and PFC. The experimental allodynia activated a network that partially overlapped with areas activated by both capsaicin and light brush alone. The most significant responses were in PFC, S2 and insula. However, unlike capsaicin-induced pain, allodynia was characterized by bilateral activation of inferior prefrontal cortices, suggesting that prefrontal responses to pain may be context dependent.

Baron and colleagues investigated cerebral activation patterns underlying capsaicin-induced pin-prick hyperalgesia using fMRI in nine subjects [23]. Capsaicin was injected at the dominant forearm to induce secondary mechanical hyperalgesia. Activation patterns during non-painful mechanical stimulation and hyperalgesic stimulation were compared to isolate the specific pain-related component of mechanical hyperalgesia from the tactile component. As expected, nonpainful mechanical stimulation induced activity in contralateral S1 and bilateral S2. In contrast, during hyperalgesia significantly higher activation was found in the contralateral PFC, i.e. the middle and inferior frontal gyrus. No change was detected in S1, S2, and the anterior cingulate cortex. In this study, prefrontal activation was interpreted as a consequence of attention, cognitive evaluation, and planning of motor behaviour in response to pain.

Lorenz and colleagues studied thermal allodynia in a PET study following topical capsaicin application in 14 subjects [24]. Processing of thermal allodynia was compared with heat pain of equal intensity. This was based on the hypothesis that heat allodynia may be functionally and neuroanatomically distinct from normal heat pain. As intended by the study design, perceived intensities of heat pain and heat allodynia did indeed not differ. However, one interesting psychophysical finding was that heat allodynia provoked significantly higher scores of pain unpleasantness compared to normal heat pain. PET scans obtained during painful heating of normal skin were subtracted from scans during equally intense but normally innocuous heating of capsaicin-treated skin. This comparison revealed the specific activation of a medial thalamic pathway to the frontal lobe during heat allodynia. There was no major difference in S1 and S2 between both conditions. These results imply that different central pathways mediate the intensity and certain qualitative aspects of pain. It was concluded by the authors that, in making this differentiation, the brain may recognize unique physiological features of different painful conditions, thus permitting adaptive responses to different pain states.

Intradermal injection of capsaicin produces a very intense burning pain consistently accompanied by mechanical allodynia [25, 26]. However, in order to dissociate allodynia from the ongoing pain, functional imaging can only be performed with a delay. Unfortunately, not only the ongoing pain, but also the area of allodynia significantly decreases in this waning phase [25, 26]. Thus, the intensity of pain evoked during allodynia is usually very low. In contrast, the heat/capsaicin model has the great methodological advantage of on-demand rekindling of allodynia without concomitant ongoing capsaicin pain, also allowing pharmacological cross-over designs [27]. Moreover, the provoked allodynic areas are comparably large. Maihöfner and colleagues investigated cortical activations associated with dynamic-mechanical allodynia in the heat/capsaicin model using fMRI [28]. Large and stable areas of brush-evoked allodynia were induced in 11 healthy subjects by topical capsaicin (2.5 %, 30 min) application following local heating (45 °C for 5 min), thus combining both physical and chemical sensitization. During the fMRI experiments, allodynia was rekindled by local heat application (40 °C for 5 min) immediately before the allodynia testing. Brushing the untreated forearm (control condition) led to activation of the contralateral S1, contralateral PA, bilateral S2 and contralateral insula. Brushing the allodynic skin was painful and the cortical responses partially overlapped those induced by the nonpainful brush stimulation. Additionally, the contralateral inferior frontal cortex and the ipsilateral insula were activated. Direct comparison between nonpainful brushing and brush-evoked allodynia revealed significant increases in BOLD signals in contralateral S1, PA, IFC and bilateral S2/insula during allodynia. This study highlighted the importance of a cortical network comprising S1, PA, S2/insula and inferior frontal cortex (IFC) in the processing of dynamic-mechanical allodynia in the human brain. Furthermore, it demonstrated that the combined heat/capsaicin model can be used successfully in the exploration of brain processes underlying stimulus-evoked pain.

Hyperalgesia can be differentiated into primary and secondary hyperalgesia. The former results from sensitization of peripheral nociceptive structures, the latter involves sensitization processes within the CNS. Hypersensitivity towards heat stimuli, i.e. thermal hyperalgesia, is a key feature of primary hyperalgesia, whereas secondary hyperalgesia is characterized by hypersensitivity towards mechanical (e.g. pin-prick) stimulation. Using fMRI, Maihöfner and Handwerker investigated if brain activation patterns associated with primary and secondary hyperalgesia might differ [29]. Thermal and pin-prick hyperalgesia were induced on the left forearm in 12 healthy subjects by topical capsaicin (2.5 %, 30 min) application. Equal pain intensities of both hyperalgesia types were induced during fMRI experiments, based on previous quantitative sensory testing. Simultaneously, subjects had to rate the unpleasantness of stimulus-related pain. Pin-prick hyperalgesia (i.e. subtraction of brain activations during pin-prick stimulation before and after capsaicin exposure) led to activation of S1 and S2, PA, insula and superior frontal cortex (SFC) and IFC. Brain areas activated during thermal hyperalgesia (i.e. subtraction of brain activation during thermal stimulation before and after capsaicin exposure) were S1 and S2, insula, PA, ACC, SFC, medial frontal cortex (MFC) and IFC. When compared to pin-prick hyperalgesia, thermal hyperalgesia led to an increased activation of bilateral anterior insular cortices, MFC, ACC (Brodmann area 24' and 32') and contralateral SFC and IFC, despite equal pain intensities (Fig. 2). Interestingly, stronger activation of ACC, contralateral MFC and anterior insula significantly correlated to higher ratings of the stimulus-related unpleasantness. These results imply that thermal and mechanical hyperalgesia indeed produce substantially different brain activation patterns. This is linked to different psychophysical and perceptual properties.

Recent studies also investigated brainstem structures involved in the modulation of sensitization processes such as the reticular formation and the rostral ventromedial medulla (RVM). To characterise the supraspinal contributions to central sensitisation in humans, Zambreanu and collegues used fMRI and studied brain responses to punctate mechanical stimulation in an area of capsaicin-induced secondary hyperalgesia on the right lower leg in 12 healthy volunteers [30]. Activation maps obtained during punctate stimulation of the secondary hyperalgesia area and those recorded during control punctate stimulation were compared. Areas showing significantly increased activation during hyperalgesia were contralateral brainstem, cerebellum, bilateral thalamus, contralateral S1 and S2, bilateral posterior insula, ACC, right MFC and right PA. Brainstem activation was localised to two distinct areas of the midbrain reticular formation. These regions were consistent with the putative location of nucleus cuneiformis (NCF) and rostral superior colliculi/periaqueductal gray (SC/PAG). As the PAG and the NCF are major sources of input to the RVM, it was concluded that structures in the mesencephalic reticular formation (i.e. NCF and PAG), may be involved in central sensitisation in humans.

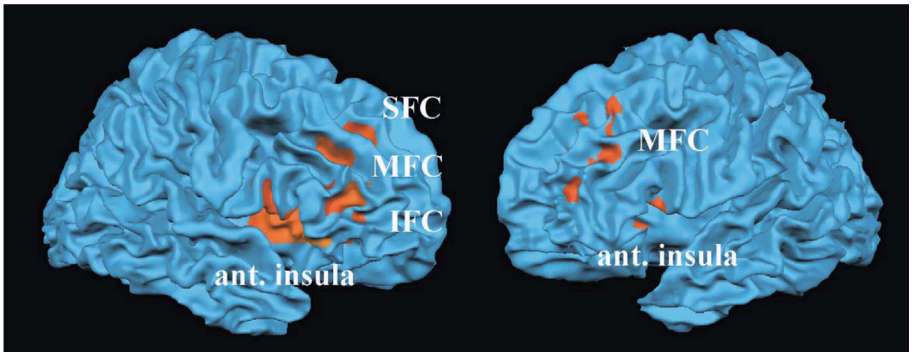

Figure 2. This Figure shows stronger activations in contralateral SFC, IFC and of bilateral ACC, MFC and anterior insular cortices during (primary) thermal hyperalgesia compared to (secondary) pin-prick hyperalgesia, despite equal pain intensity between both conditions. When the individual differences of pain unpleasantness ratings were introduced between both hyperalgesia conditions as covariates, it was found that these ratings significantly correlate with activations of the contralateral anterior insular cortex, bilateral ACC, and the contralateral MFC. That is, the higher the unpleasantness differences between thermal and mechanical hyperalgesia, the higher the activation of these cortices. Modified from [29]. The right hemisphere is depicted on the left side and the left hemisphere is depicted on the right side.

UV-B model. To compare brain activations of different submodalities of hyperalgesia, Seifert and colleagues [31] induced both heat and mechanical hyperalgesia, using the UV-burn model [32, 33] in healthy volunteers. An advantage of the UV-B model is that the induced hyperalgesia is stable over many hours, broadly follows intensity of the erythema and does not extend beyond the irradiated area, so that at least by the use of small radiated areas the resulting hyperalgesia is highly localized to the area of inflammation [34], although greater radiated areas are reported to induce relevant secondary hyperalgesia [35]. The resulting areas of mechanical and heat hyperalgesia allow a comparison of the brain processing of both conditions directly and at balanced intensities. Heat and mechanical hyperalgesia were induced in this study on the right forearm by UV-B application in 14 healthy subjects. Four test conditions (non-sensitized heat and non-sensitized mechanical pain, sensitized heat and sensitized mechanical pain) were perceptually matched and a 2 x 2 factorial analysis was performed. Areas with main effect of sensitization were insula, ACC, PFC, PA, thalamus and basal ganglia. A main effect of modality with more activation during heat hyperalgesia was found in S1, ACC, prefrontal cortices and PA, and with more activation during mechanical hyperalgesia in S2, posterior insula and contralateral IFC. An interaction of sensitization and modality was found bilaterally in IFC. Areas with similar effects of sensitization in both stimulus modalities were ACC, bilateral anterior insula and bilateral IFC. Thus, it could be concluded that different types of hyperalgesia in a human surrogate model of evoked pain produce different brain activation patterns. This was partly due to a differential processing of thermal and mechanical pain and an interaction of sensitization and modality in the caudal portion of the IFC. Furthermore, a common "sensitization network" consisting of ACC, bilateral anterior insula and parts of the IFC was demonstrated in this study.

Menthol-induced cold allodynia. Menthol is an agonist on TRPM8 ion channels expressed on cold-activated primary afferent neurons. Selective activation of afferent fibres expressing this ion channel induces a sensation of coldness, pain and cold allodynia [36, 37]. Cold allodynia is a characteristic, but enigmatic feature of neuropathic pain. Seifert and Maihöfner [38] used fMRI and investigated brain activations underlying menthol induced cold allodynia. 12 healthy volunteers were investigated using a block-design fMRI approach. Firstly, brain activity was measured during application of innocuous cold stimuli (at 5 °C above cold pain threshold) and noxious cold stimuli (at 5 °C below cold pain threshold) to normal skin of the forearm. The stimuli were adjusted to the individual cold pain threshold. Secondly, cold allodynia was induced by topical menthol and cortical activations were measured during previously innocuous cold stimulation, which was then perceived as painful. Sensory and affective components of allodynic and cold pain were equal in the McGill pain questionnaire. All tested conditions (innocuous cold, noxious cold and cold allodynia) led to significant activation of bilateral insular cortices, bilateral frontal cortices and the anterior cingulate cortex. When noxious cold and innocuous cold were compared, noxious cold contributed significantly more to activation of the posterior insula and innocuous cold contributed more to activation of ipsilateral anterior insular cortex. However, comparing cold allodynia and equally intense cold pain conditions,

significantly increased activation in bilateral dorsolateral prefrontal cortices (DLPFC) and the brainstem (ipsilateral parabrachial nucleus) were found during cold allodynia. Furthermore, in contrast maps, cold allodynia contributed significantly more to activation of the bilateral anterior insula, whereas the contribution to activation of the contralateral posterior insula was equal. These results suggest that cold allodynia activates a network similar to that of normal cold pain but additionally recruits bilateral DLPFC and the midbrain/dorsolateral pons, implying that these brain areas are involved in central nociceptive sensitisation processes.

Hypertonic saline injection. Kupers and colleagues investigated brain activations underlying experimental jaw-muscle pain and its interference by simultaneous mechanical stimuli provoking hyperalgesia [39]. Ten healthy subjects participated in this PET study. Jaw-muscle pain was induced by bolus injections of 5 % hypertonic saline into the right masseter muscle and von Frey filaments were used for elicitation of mechanical hyperalgesia. Jaw-muscle pain was mainly associated with significantly increased activation of bilateral dorsal-posterior insula, ACC and prefrontal cortices, right PA, brainstem and cerebellum. No changes occurred in S1 and S2. Using an interaction analysis, the authors showed that mechanical hyperalgesia was associated with activation in the subgenual cingulate and the ventroposteromedial and dorsomedial thalamus. These results agree with animal data showing that hyperalgesia is associated with sensitization processes in the thalamus [40]. Furthermore, this study implied that the cerebral processing of jaw-muscle pain may differ from the processing of cutaneous pain.

Functional imaging of pharmacological interventions

Recently, functional imaging has also been used to understand effects of analgesic and anthihyperalgesic drugs in the human brain. Two studies will be presented investigating effects of gabapentin and cyclooxygenase inhibition in experimental pain models [41, 42]. Iannetti and colleagues investigated effects of gabapentin on capsaicin-induced mechanical hyperalgesia using fMRI [41]. Independent of the presence of central sensitization, gabapentin reduced activations in bilateral operculoinsular cortices. Furthermore, only during central sensitization did gabapentin reduce the activation of brain stem structures and suppress stimulus-induced deactivations. No main effects were seen on positive BOLD responses. These findings indicated that gabapentin has a measurable antinociceptive effect and a stronger antihyperalgesic effect most evident in the brain areas undergoing deactivation. The authors concluded that gabapentin may be more effective in modulating nociceptive transmission when central sensitization is present. To investigate pharmacological modulation of brain areas, Maihöfner and colleagues examined potential differential fMRI correlates of analgesic and antihyperalgesic effects of two intravenous cyclooxygenase (COX) inhibitors, i.e. parecoxib and acetylsalicylic acid (ASA) by using the UV-B model [42]. In contrast to other surrogate models the UV-B model has the advantage of an extended time frame in which hyperalgesia can be investigated [32, 35]. Previous psychophysical studies have demonstrated antihyperalgesic and analgesic effects of non-steroidal anti-inflammatory drugs (NSAIDs) in this model [33, 43]. Fourteen healthy volunteers participated in this double-blind, randomized and placebo-controlled crossover study. Mechanical hyperalgesia was tested at the site of a UV-B irradiation and acute mechanical pain was tested at a site distant from the irradiated skin. These measurements were conducted before and after intravenous infusion of saline (placebo), parecoxib or ASA. Acute mechanical pain and mechanical hyperalgesia led to widespread activation of brain areas known to comprise the human pain matrix. Analgesic effects were found in S1 and S2 cortices, PA, insula, ACC and prefrontal cortices. These brain areas were also modulated under antihyperalgesic conditions. However, a greater drug-induced modulation of mainly PA and inferior frontal cortex was observed during mechanical hyperalgesia. In contrast, during acute mechanical pain a greater modulation of mainly bilateral S2 was detected. Therefore, the results of this study suggested a differential modulation of brain areas under either analgesia or antihyperalgesia.

In summary, central imaging in experimental human pain models improves our understanding of central processing of pain and hyperalgesia. Existing results with pharmacological interventions indicate that central imaging also generates objective data to test compounds for their analgesic and antihyperalgesic effects.

Functional imaging of neuropathic pain

Functional imaging has drastically changed our view of chronic pain in recent years. Mechanisms of pain chronification are increasingly better understood. A relevant part of these mechanisms is located in the brain. Conservative estimates assume a prevalence of neuropathic pain of 2–4 % in western countries [44]. This prevalence increases with age. Neuropathic pain

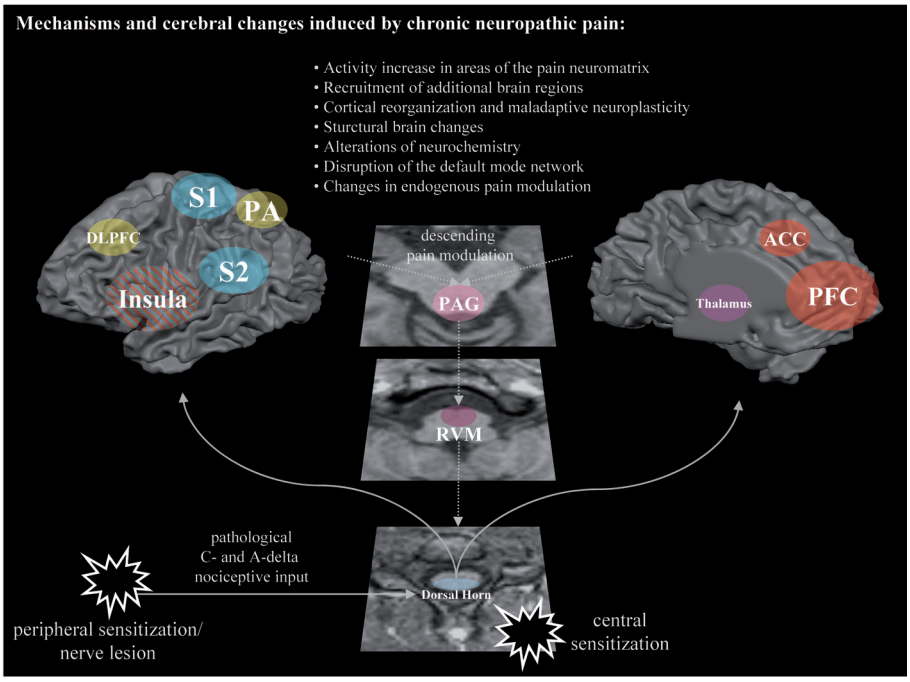

Figure 3. This schematic illustration shows the main mechanisms that are involved in the chronification of neuropathic pain. The size of the labels codes for the incidence of reported activation of areas of the pain neuromatrix in studies that investigated cerebral activation in neuropathic pain. The areas attributed to the lateral pain system are coded in blue, areas attributed to the medial pain system are coded in red. Areas that are additionally recruited in patients in neuropathic pain are coded in yellow. Brainstem structures (peraqueductal grey; PAG, rostroventral medulla; RVM) are involved in endogenous pain modulation. The brainstem is axially sliced at the midbrain-level (top) and at the level of the medulla oblongata (middle). The axial slice at the bottom is at the spinal level.

results in a significant decrease in quality of life and functioning in everyday life [45]. Neuropathic pain is defined as pain initiated or caused by a primary lesion or dysfunction of the nervous system [46]. During the last years numerous research groups have tried to decipher cerebral activations during neuopathic pain and structural cerebral changes by use of neuroimaging methods. There are at least six main mechanisms which seem to be crucially involved in the chronification of neuropathic pain: (i) activity increase in areas of the pain neuromatrix, (ii) recruitment of cortical areas beyond the classical pain neuromatrix, (iii) cortical reorganization and maladaptive neuroplasticity, (iv) alterations in neurochemistry, (v) structural brain changes and (vi) disruption of the brain default mode network. These mechanisms will be presented in detail in the following text and are schematically illustrated in Figure 3.

Activity increase in areas of the pain neuromatrix. Cerebral activations during neuropathic pain compared to nociceptive pain can be classified in two fundamental phenomena: (i) activity increase in primary nociceptive areas, i.e. classical areas of the pain neuromatrix, and (ii) recruitment of cortical areas beyond the classical pain neuromatrix. When cerebral processing of neuropathic pain is investigated, the heterogeneity of symptoms has to be taken into account, as different pathophysiological mechanisms underlie these symptoms. Classification of symptoms and imaging studies involves differentiation between (a) spontaneous pain (ongoing or paroxysmal) and (b) evoked pain such as (i) dynamic mechanical allodynia, (ii) mechanical hyperalgesia, (iii) thermal allodynia and (iv) thermal hyperalgesia. Spontaneous neuropathic pain is often generated in the peripheral nervous system by ectopic discharges of damaged primary afferents [47] with consecutive sensitization of dorsal horn neurons. Furthermore, it may result from disinhibition phenomena within the central nervous system [48, 49]. Cerebral correlates of spontaneous pain were mainly explored in PET studies. In contrast to fMRI, PET allows measurement of the basal brain activity in patients compared to healthy control subjects; therefore, application of fMRI is problematic due to the lack of a stable baseline. PET enables the continuous measurement of regional cerebral blood flow (rCBF) and appropriate comparisons can reveal activated or deactivated brain regions. In patients with spontaneous pain due to mononeuropathy and post-traumatic neuropathic pain, PET studies consistently revealed a reduced rCBF in the contralateral thalamus [50, 51]. Increased rCBF was detected in insula, ACC, parietal association cortex and PFC, but not in S1 and S2 [50]. As an explanation for the thalamic rCBF decrease, an inhibition of excessive nociceptive input or a decoupling of CBF from neuronal activity has been discussed [51, 52]. Baliki and colleagues explored brain activity during different phases of spontaneous pain in patients with chronic back pain using an elaborated fMRI design with percept-related regressors. They found an increased activity in the PFC and ACC during phases of high spontaneous pain. However, in

phases of increasing pain an activation of the classical pain neuromatrix was detected. These findings suggest that the subjective spontaneous pain associated with chronic back pain involves distinct spatiotemporal neuronal mechanisms differing from those observed during acute experimental pain [53].

Beside spontaneous pain, evoked pain is a cardinal symptom of neuropathic pain. Thus, the understanding of underlying mechanisms is of particular scientific interest. Basically, hyperalgesia can be divided in primary hyperalgesia (in damaged tissue) and secondary hyperalgesia (in the surrounding tissue). Primary hyperalgesia exists for different submodalities (e.g. heat, cold and mechanical stimuli) and is induced by sensitization of nociceptors. However, secondary hyperalgesia results from sensitization at the spinal or supraspinal level following barrage from nociceptors. Sensitization of dorsal horn neurons is predominantly generated by C-fibre input, particularly from the group of the so-called silent nociceptors [21, 54, 55]. Alternatively, hyperalgesia (mainly towards cold stimuli) can be generated by lesion-induced disinhibition and disintegration phenomena at all levels of the neuraxis [47, 56]. A different mechanism underlies the phenomenon of dynamic mechanical allodynia, where A-beta fibre input normally projecting to the tactile system gains a pathological connection to the nociceptive system.

Cerebral processing of stimulus-evoked pain has been explored in patients with neuropathic pain due to lesions of the peripheral or central nervous system and in patients with CRPS [9, 10, 52, 57]. During dynamic mechanical allodynia, activations were predominantly detected in the lateral pain system, whereas ACC was not consistently activated. In detail, dynamic mechanical allodynia was investigated as a symptom of: (i) peripheral neuropathic pain [58–61], (ii) central neuropathic pain [62, 63], (iii) CRPS [64], and (iv) a heterogenous population of patients with peripheral and central neuropathic pain [65]. In the studies of Petrovic and Witting PET was used, in the others fMRI. A common finding in three of these studies [59, 62, 63] was the lack of ACC activation, whereas the lateral pain system (S1, S2), insula, parietal and frontal cortices showed increased activation. This cerebral pattern contrasts those observed during acute experimental pain or pin-prick hyperalgesia. The reason for lack of ACC activation in these studies is not entirely clear. Possible mechanisms include a differential cerebral processing of dynamic-mechanical allodynia due to pathologically connected A-beta fiber input and resulting aberrant activity in ascending systems, or an insufficient sensitivity in these studies due to unstable baseline activity [52]. Support for the latter possibility comes from a further four studies demonstrating robust cingulate gyrus activity during dynamic mechanic allodynia [60, 61, 64, 65].

Another symptom examined in patients is pin-prick hyperalgesia. Maihöfner and colleagues analyzed cerebral activations in 12 patients with CRPS [66]. Increased activations were detected in all areas of the pain neuromatrix and regions associated with motor or cognitive processing, i.e. PFC and motor cortices. Thus, the cerebral activation pattern during pin-prick hyperalgesia seems to differ from that during dynamic mechanical allodynia. However, a direct comparison is definitely necessary.

Thermal hyperalgesia was the focus of two fMRI studies investigating clinical pain syndromes: cold hyperalgesia has been scrutinized in patients with syringomyelia where cerebral activations were found in insula, ACC, PFC parietal association cortex and SMA [63]. The authors compared activations during cold allodynia with those during dynamic tactile allodynia and found that different sub-types of allodynia were associated with distinct patterns of brain activity, not necessarily corresponding to the pain neuromatrix involved in acute physiological pain. The PFC was the only area consistently activated by both types of pathologically evoked pain, suggesting that alteration of high-level pain modulatory mechanisms might play a major role in allodynia due to central lesions [63]. Becerra and colleagues recruited patients with trigeminal neuropathy for their study and applied cold, mechanical and heat stimuli [61]. Conjointly increased activations were detected in PFC and basal ganglia during cold and mechanical stimulation of the affected as compared to the unaffected side and during heat and mechanical stimulation in the insula.

Recruitment of additional cortical areas beyond the pain neuromatrix. It has to be emphasized that cerebral activations observed during neuropathic pain are not simply an isolated left shift of the stimulus response curve in areas of the pain neuromatrix [52]. Additional cortical areas are recruited during dynamic mechanical allodynia and different forms of hyperalgesia. This individual pain signature markedly exceeds the classical pain neuromatrix and is influenced by underlying type of pathological pain, attention, affect and mood [67]. Those areas include the dorsolateral frontal cortex [24, 29, 63], as well as a bunch of brainstem nuclei embedded in pain modulatory systems [67]. Moreover, areas of the parietal association cortex are found to be significantly more activated in various studies. A function in attentional processes and the integration of sensory processes is discussed [68].

Table 1. Table 1 provides a short overview of functional imaging studies investigating surrogate models of neuropathic pain.

Study	Experimental model	Type of stimulus evoked pain investigated	Key brain areas activated during hyperalgesic or allodynic condition
[23]	intradermal capsaicin injection	pin-prick hyperalgesia	PFC
[22]	intradermal capsaicin injection	dynamic mechanical allodynia	PFC
[39]	intramuscular hypertonic saline	mechanical hyperalgesia	ACC, thalamus
[24]	intradermal capsaicin injection	heat allodynia	PFC, ACC, thalamus, anterior Insula
[28]	topical capsaicin/ heat	dynamic mechanical allodynia	PFC, insula, S1, S2
[29]	topical capsaicin	heat and pin-prick- hyperalgesia	PFC, insula, S1, S2, PA
[38]	topical menthol	cold hyperalgesia	PFC, brainstem
[31]	UV-B radiation	heat- and mechanical hyperalgesia	PFC, ACC, insula
[30]	topical capsaicin/ heat	pin-prick hyperalgesia	PFC, ACC, insula, S1, S2, PA, PCC, thalamus, PAG, NCF

Table 2. Table 2 provides a short overview of functional imaging studies investigating clinical neuropathic pain.

Study	Type of neuropathic pain	Type of spontaneous or stimulus evoked pain investigated	Key brain areas activated during spontaneous pain or hyperalgesic or allodynic condition
[53]	chronic back pain	spontaneous pain	PFC, ACC
[61]	trigeminal neuropathy	heat-, cold- and dynamic mechanical allodynia	PFC, ACC, insula, thalamus, IPL
[63]	syringomyelia	cold- and dynamic tactile allodynia	PFC
[51]	post traumatic neuropathic pain	spontaneous pain	thalamic decrease
[50]	painful mononeuropathy	spontaneous pain	thalamic decrease, PFC, ACC, insula, PA
[66]	CRPS	pin-prick hyperalgesia	PFC, ACC, insula, S1, S2, PA
[64]	CRPS	dynamic mechanical allodynia	ACC, insula, S1, S2, PA
[58]	peripheral nerve lesion	dynamic mechanical allodynia	ACC, insula, S1, S2, thalamus, brainstem
[62]	ischemic brainstem lesion	cold- and dynamic mechanical allodynia	PFC, insula, S1, S2, IPL, thalamus
[65]	peripheral and central nervous system lesions	cold- and dynamic mechanical allodynia	ACC, insula, S1, S2
[60]	peripheral nerve lesion	dynamic mechanical allodynia	ACC, insula, S2, basal ganglia
[59]	peripheral nerve lesion	dynamic mechanical allodynia	PFC, insula

Tables 1 and 2 summarize the key findings of the presented functional imaging studies investigating hyperalgesia and allodynia in surrogate models (Table 1) and neuropathic pain patients (Table 2). More studies in the surrogate models group reported a PFC activity increase in the evoked pain condition compared to the clinical pain group (8 of 9 versus 5 of 9). However, ACC activity increase was more often reported in the clinical pain group during evoked pain (6 of 9 versus 4 of 9).

Cortical reorganization and maladaptive neuroplasticity Phantom pain. Phantom pain occurs after extremity amputations. It belongs to the complex group of phantom phenomena which often develop after amputations. Other phantom phenomena are feeling the presence of the previously amputated extremity, paresthesias inside the phantom or the feeling of phantom movements. Pain in the non existing body part develops in between 50 to 80 % of all amputees [69]. Underlying mechanisms within the peripheral nervous system include pathological sympathico-afferent coupling and ectopic discharges within the stump neuroma [69, 70]. Furthermore, the presence of referred sensations (e.g. tactile sensations allocated to the amputated arm upon stimulation of the face, [71]) gave reason to investigate the somatotopic arrangement of S1 in amputated patients. As demonstrated with MEG the mouth area of S1 was found to be shifted into that of the former hand

[72–74]. Interestingly, the extent of this shift was highly correlated with the intensity of phantom limb pain [72, 73]. It has been hypothesized that ongoing nociceptive input before amputation leads to neuroplastic changes and to organization of a pain memory, with nociceptive input from neighboured regions into the deafferented area after amputation, resulting in phantom pain [69, 70]. This thesis is supported by a study of Nikolajsen and colleagues showing that the presence of pre-amputation pain is positively correlated with the presence of phantom limb pain three months after amputation [75]. However, these neuroplastic changes are not irreversible. Cortical reorganization can be reduced by behaviourally relevant sensory discrimination training in the stump area [76]. Furthermore, reorganization of somatotopic maps in phantom limb pain is also present in the primary motor cortex (M1), where – identical to the changes in S1 – the mouth area shifts into that of the former hand [77]. Accordingly, Lotze and colleagues presented evidence that the use of a myoelectric prosthesis is accompanied by reduction of phantom pain and cortical reorganization.

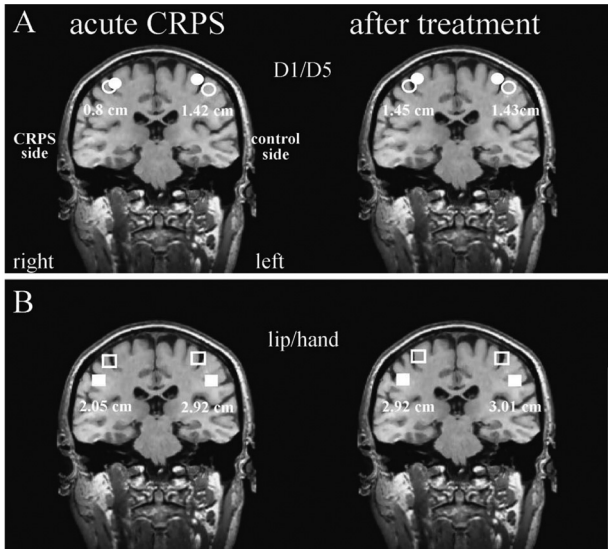

Figure 4. This figure depicts cortical reorganization and maladaptive plasticity in patients with complex-regional pain syndrome (CRPS). A: The distance between D1 and D5 in the contralateral somatosensory cortex is decreased in CRPS. B: After sufficient treatment of the CRPS these changes were reversed. Coronary slices are shown. Modified from [81].

Complex-regional pain syndrome. Complex regional pain syndromes (CRPS) develop after trauma and are defined by the occurrence of pain accompanied by sensory, motor and autonomic changes beyond the territory of a single peripheral nerve or radix [78]. In addition to facilitated neurogenic inflammation and pathological sympatho-afferent coupling, there is accumulating evidence that central nervous system changes may be involved in the pathogenesis of CRPS [79]. Regarding the somatosensory system, there is evidence for a substantial reorganization of the somatotopic map within the primary somatosensory cortex of CRPS patients [79–84]. Using functional imaging techniques, a significant shrinkage of the cortical hand representation contralateral to the CRPS affected painful arm was found [79, 81, 83]. In addition, the hand position was shifted towards the mouth. Predictors for this cortical reorganization were spontaneous CRPS pain and the extent of mechanical hyperalgesia. Interestingly, when treatment is efficacious and CRPS pain reduced, this S1 cortical reorganization in CRPS can be reversed [81, 83]. These findings are illustrated in Figure 4.

Cortical reorganization may be able to explain some of the often puzzling clinical signs of CRPS, e.g. the spatial distribution of sensory disturbances in a glove or stocking like distribution, the occurrence of tactile induced referred sensations [82] and hemisensory deficits. Furthermore, there is accumulating evidence that the central motor system shows significant alterations in CRPS. About 70% of patients with CRPS have weakness of all muscles of the affected region, difficulties in the performance of complex movement patterns, and a decrease of active range of motion [84, 85]. About half of patients have a postural or action tremor that represents increased amplitude of physiological tremor. Other symptoms include movement disorders such as dystonia and myoclonus. Finally, a neglect-like syndrome may lead to the disuse of the limb [84, 86]. Electrophysiological studies using magnetoencephalography (MEG) or transcranial magnetic stimulation (TMS) revealed a deficiency of inhibitory mechanisms and an increased excitability at the level of the contralateral primary motor cortex in CRPS patients [80, 87, 88]. Interestingly, abnormalities of inhibitory mechanisms were also be observed in the ipsilateral motor cortex of CRPS patients [87, 89], which might be paralleled by a slight motor impairment of the contralateral unaffected side [90], and point to a widespread impairment of central motor processing in CRPS. Maihöfner et al. used fMRI and investigated cortical activations during tapping movements of the CRPS-affected hand [84]. During finger tapping of the affected extremity, CRPS patients showed a significant reorganization of central motor circuits, with an increased activation of primary motor and supplementary motor cortices (SMA). Furthermore, the ipsilateral motor cortex showed a markedly increased activation. When the individual amount of motor impairment was introduced as regressor in the fMRI analysis, it was demonstrated that activations of the posterior parietal cortices, SMA

and primary motor cortex were correlated with the extent of motor dysfunction. In summary, the results of this study suggest that substantial adaptive changes within the central nervous system may contribute to motor symptoms in CRPS. Therefore, understanding neuroplastic changes in CRPS strategies interfering with maladaptive plasticity are promising avenues for new treatment strategies in CRPS.

Carpal tunnel syndrome. Carpal tunnel syndrome (CTS) is a frequent entrapment neuropathy of the median nerve characterized by paresthesia and pain in the first three digits. Although CTS is a classical peripheral nerve lesion, it is accompanied by central nervous changes. Tecchio and colleagues used MEG to show that patients have changes in cortical hand somatotopy in strict relationship to self-referred assessment of symptoms and hand disability in daily activities, including a more extended representation of the affected hand when paresthesias prevailed. In contrast, a more restricted hand representation due to lateral shift of the little finger was observed when pain symptoms dominated [91]. When amplitudes of peripheral sensory nerve action potentials of median and ulnar nerves were compared with cortical responses, a central magnification mechanism in brain responsiveness to stimulation of median innervated fingers could be demonstrated. This result implies a central amplification factor enabling sensory perception despite compromised peripheral input due to nerve trunk dysfunction. Napadov and colleagues confirmed and extended these findings in two fMRI studies. They demonstrated more extensive and stronger contralateral sensorimotor cortical representations of the CTS-affected fingers compared to healthy adults [92]. Moreover, the contralateral somatotopic S1 representations for D2 and D3 were less separated for CTS patients. Together with a greater extent of SI representation for these CTS affected digits, the closer cortical representations can be interpreted as a blurred somatotopic arrangement for CTS affected digits. In a second study they demonstrated that CTS treatment with acupuncture leads to reversal of cortical reorganization correlating with clinical improvement [93].

Alterations in neurochemistry. Two neuroimaging methods enable the non invasive exploration of regional neurochemistry in the human brain: PET and magnetic resonance spectroscopy (MRS).

PET can detect regional cerebral blood flow (rCBF) and regional glucose metabolism. Furthermore, ligand PET provides the opportunity to measure regional allocation of different receptors. Ligand PET studies investigating clinical pain predominantly used ligands of the opioidergic system. Additionally, PET allows investigation of changes of receptor occupation with its natural ligand [94]. Basically, opioid receptors were shown to be present in all areas of the pain neuromatrix. The opioid receptor binding potential is equal in the lateral and the medial pain system [95]. Compared to healthy controls, opioid receptor ligand binding is decreased in PFC, ACC, insula, parietal association cortex and thalamus of patients with trigeminal neuropathy and post-stroke-pain [94, 96–99]. A decrease in the number of free opioid receptors has been shown for fibromyalgia within several regions known to play a role in pain modulation, including the nucleus accumbens, the amygdala, and the dorsal cingulate [100]. A proposed underlying mechanism is a down regulation of opioid receptors in these areas as well as changes in binding capacity [94].

Proton magnetic resonance spectroscopy enables quantitative measurement of defined metabolites in distinct brain regions. Fukui and colleagues studied N-acetylapartate (NAA), a marker of neuronal integrity, in neuropathic pain syndromes (CRPS, postherpetic neuralgia, chronic low back pain) [101]. A reduced NAA concentration was found in the contralateral compared to the ipsilateral thalamus and to healthy controls. The authors interpreted this finding as reduced neuronal activity or neuronal degeneration in the contralateral thalamus in these patients. Another study investigating chronic low back pain patients found reduced NAA and glucose concentration in the dorsolateral PFC (DLPFC) [102]. Furthermore, a case report of a patient with severe CRPS described reduced NAA in the DLPFC, too [103]. Pattany and colleagues explored neurochemistry changes in patients with chronic neuropathic pain after spinal cord injury [104]. The authors found reduced NAA in the contralateral thalamus. Interestingly, the concentrations of NAA correlated negatively with the pain intensity. These MR-spectroscopic analyses demonstrate that longer persistent pain states are not only accompanied by functional changes but also with substantial chemical abnormalities within the CNS.

Structural brain changes. Subtle structural changes of the brain can be measured *in vivo* with voxel based morphometry (VBM). Draganski and colleagues reported a decrease in contralateral thalamic grey matter in patients with unilateral limb amputation [105]. The thalamic grey matter differences were positively correlated with the time span after the amputation but did not correlate with the presence or the intensity of phantom pain. However, a decrease of

grey matter in PFC, cingulate gyrus, SMA and dorsal midbrain was positively correlated with pain intensity. In patients with chronic low back pain a decrease in grey matter was measured at the global brain level and regional in the bilateral PFC and the right thalamus [106]. Thereby, the grey matter decrease at the brain level positively correlated with disease duration and was regionally pronounced in the DLPFC in a subgroup of patients with neuropathic pain. A study by Kuchinad and colleagues in individuals with fibromyalgia found a reduction of total grey matter amount and a decreased grey matter density in pain relevant regions like PFC, cingulate gyrus and anterior insula [107]. However, other studies failed to exactly reproduce these initial findings in chronic low back pain and fibromyalgia. They found structural changes in other brain regions, such as a striatal grey matter increase in fibromyalgia or a decrease of grey matter in brainstem and the somatosensory cortex and an increase in grey matter bilaterally in the basal ganglia and the left thalamus in low back pain [108, 109]. These divergent results of VBM studies in chronic pain syndromes clearly demonstrate the need for future studies with a higher number of cases and advanced methodology.

Disruption of the default mode network. In a very recent study, Baliki and colleagues propose that long-term pain alters functional connectivity of cortical regions known to be active at rest, i.e. components of the so-called default mode network [110]. This default mode network is characterized by balanced positive and negative correlations between activities in key brain regions, e.g. PCC, cuneus and prefrontal cortices [111]. In several disorders, this balance seems to be disrupted. Using well-validated fMRI paradigms to study the default mode network, Baliki and colleagues investigated whether the impairments of chronic pain patients could be rooted in disturbed default mode network dynamics. Studying a group of chronic back pain patients and healthy controls while executing a visual attention task, the authors discovered that chronic back pain patients, despite performing the task as equally well as controls, displayed reduced deactivation in several key default mode network regions. These findings demonstrate that chronic pain has a widespread impact on overall brain function, and suggest that disruptions of the default mode network may underlie the cognitive and behavioural impairments accompanying chronic pain [110].

Functional imaging of endogenous pain modulation

Central pain modulating systems may inhibit or facilitate nociceptive input. The periaqueductal grey (PAG) of the midbrain and the rostroventral medulla (RVM) are important nuclei of descending pain modulation. PAG and RVM receive input from prefrontal and cingulate cortices, anterior insula, amygdala and hypothalamus [67]. This enables differential processing of nociceptive information during distinct affective or cognitive processes. PAG and RVM project as the common final pathway of cerebral pain modulation to dorsal horn neurons, where they act inhibiting or facilitating [112, 113]. In particular, descending facilitation seems to play an important role in chronic pain states [113]. The mechanisms involved in attentional, cognitive and emotional processes that influence cerebral nociceptive processing were illuminated by recent neuroimaging studies, for a detailed review see [67, 114]. Bantick and colleagues investigated the effect of distraction on pain processing [115]. When subjects were distracted during painful stimulation, pain intensity was significantly reduced and brain areas associated with the affective division of the ACC and orbitofrontal regions showed increased activation. In contrast, many areas of the pain matrix (i.e. thalamus, insula, cognitive division of the ACC) displayed reduced activation, supporting the behavioural results of reduced pain perception. In another study of the same group, an increase in PAG activity during a distraction task was detected, and the total increase in activation was predictive of changes in perceived intensity [116]. The authors concluded that this provides direct evidence supporting the notion that the periaqueductal gray is a site for higher cortical control of pain modulation in humans. These two studies were extended by Valet and colleagues, who used a connectivity analysis and were able to show that ACC and PFC operate top-down regulation on PAG and posterior thalamus during distraction from nociceptive input [117].

The placebo effect is an outstanding example of cognitive modulation of nociceptive input. Placebo cognition and opioid analgesia share a common neuronal network with increased activity in the ACC [118]. Placebo effects are mediated by regional activation of μ-opioid receptors in both higher-order and sub-cortical brain regions, which included the ACC, the DLPFC, the insular cortex and the nucleus accumbens [119]. Wager and colleagues examined whether placebos alter sensory pain transmission, pain affect, or simply produce compliance with the suggestions of investigators [120]. They found that placebo analgesia is related to decreased brain activity

in pain-sensitive brain regions, including the thalamus, insula, and anterior cingulate cortex. Furthermore, it is associated with increased activity during anticipation of pain in the PFC, providing evidence that placebos alter the experience of pain. These studies provide evidence for increased PAG activity during placebo correlating with the activity in the PFC. Bingel and colleagues have shown increased functional connectivity during placebo cognition between ACC and PAG and bilateral amygdala [121].

Also emotional processes play an important role in chronic pain syndromes. Especially pain anticipation, which is accompanied by fear, increases subjective pain intensity and, as demonstrated in healthy volunteers, activity in ACC [122], PFC and insula [123–125] and hippocampus [126]. Unfortunately, functional imaging studies investigating pain modulation by attentional, cognitive or emotional processes in clinical pain states are not yet available. Basic mechanisms of pain modulation may be comparable in healthy volunteers and patients. However, there is accumulating data that activity of endogenous pain modulatory systems may be defective in neuropathic pain contributing to chronification [127]. Therefore, future imaging studies are needed to address this exciting topic.

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