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Neuroimaging the pain network – Implications for treatment

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A B S T R A C T

In this chapter, we provide an overview of neuroimaging studies in chronic pain. We start with an introduction about the phenomenology of pain. In the following section, the application of functional and structural imaging techniques is shown in selected chronic pain syndromes (chronic back pain, fibromyalgia syndrome (FMS), phantom limb pain, and complex regional pain syndrome (CRPS)), and commonalities and peculiarities of imaging correlates across different types of chronic pain are discussed. We conclude this chapter with implications for treatments, with focus on behavioral interventions, sensory and motor trainings, and mirror and motor imagery trainings.

Phenomenology of pain

Pain is a multidimensional experience described in terms of its three dimensions: “sensory-discriminative” (sense of the intensity, location, quality, and duration of pain), “affective-motivational” (unpleasantness and the urge to escape the unpleasantness), and “cognitive-evaluative” (cognitions such as distraction, appraisal, and cultural values). This suggests that pain is not only determined by the nociceptive input, the stimulus intensity, and unpleasantness alone and that cognitions can affect both the sensory and the affective-motivational dimensions [1]. This model corresponds with the neuroanatomical distinction between the lateral and the medial pain system [2]. The terminology of the pain system is deduced from the localization of the involved nuclei of the thalamus. The lateral system of the thalamus projects to the primary and secondary

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somatosensory cortex (SI and SII) discussed to represent the sensory-discriminative component of pain. The affective-motivational component is discussed to be represented by the medial thalamic system, which projects to limbic (e.g., anterior cingulate cortex, ACC) and frontal structures [3]. However, the distinction of brain regions according to the medial and lateral branches of the spinothalamic tract fails for some regions known to be important for the processing of painful experimental stimuli such as the insula [3]. The insula is connected to the limbic system, which has projections to the ACC [4]. The results from brain imaging studies suggest that instead of an isolated brain region being involved in pain, it is rather a network of several interconnected brain areas. These brain regions comprise somatosensory (SI, SII, and insula), limbic (insula and ACC), and associative (prefrontal cortex (PFC)) structures receiving parallel inputs from multiple nociceptive pathways [2]. However, different chronic pain syndromes seem to be characterized by unique functional and structural brain signatures [3,5]. Some authors have stressed that chronic pain is characterized by decreased sensory processing and enhanced emotional/cognitive processing of pain [2,6,7]. It should be noted that nociception and pain are related but not the same. Nociception is the transduction of nociceptive information from the periphery to the central nervous system. Pain is a perceptual phenomenon integrating and modulating several neuronal, psychological, and cultural processes and requires a conscious organism. However, nociceptive input into the brain does not necessarily lead to pain, and pain is not necessarily accompanied by nociception [8,9]. For instance, approximately 50 kg of weight is applied on 1 cm^2 of skin, when experienced ballerinas dance with point shoes for several hours. Nevertheless, professional ballerinas are capable of dissociating nociception from perceiving pain [7].

Acute, sub-acute and chronic pain

Normally, acute pain can be treated and is limited to one site of the body. The function of acute pain is to warn of imminent danger and should encourage resting behavior of the affected body part. The *International Association for the Study of Pain* (IASP)-definition of pain is either based on duration of pain or as "*pain that extends beyond the expected period of healing*" [10]. According to the tautological timeframe definitions of pain, chronic pain is defined as pain lasting longer than 3 or 6 months (in some definitions, even 12 months). It has lost its warning functions and attends with psychosocial changes. Normally, there is not only one triggering or maintaining cause but chronic pain is rather multicausal emphasizing the psychosocial model for the treatment of chronic pain [11]. Sub-acute pain lasts from 1 to 3–6 months. However, it should be noted that the timeframe definitions of pain rely upon arbitrary intervals of time from onset. Moreover, it is often unclear how the "expected period of healing" can be defined (e.g., when considering rheumatoid arthritis or trigeminal neuralgia) [8]. To address the complex phenomenon of chronic pain, Flor and Turk [8] suggested a two-dimensional model for conceptualizing acute and chronic pain including a time dimension and a physical pathology dimension. In this model, cases with a short duration or high physical pathology would be viewed as acute pain, whereas cases with low physical pain and long duration would be viewed as chronic pain.

Neuroimaging of pain in chronic pain syndromes: comparing healthy vs. chronic pain populations

As pain is processed in a network of several brain areas, it is of interest how a chronic pain condition such as chronic back pain, FMS, phantom limb pain, or CRPS influences this network during the processing of painful experimental stimuli. Pain researchers invest hopes in neuroimaging to reveal more sensitive measures that complement subjective self-reports on pain [12]. However, the use of neuroimaging, especially for diagnosis at an individual level, is thus far at the beginning. Normally, publications report group results and comparisons with a healthy control group. Recent applications of machine learning algorithms seem to be promising in delineating prognostic and diagnostic functional and structural imaging markers in pain [13,14]. However, there is lack of studies on applying machine learning algorithms in clinically relevant pain states [13].

Chronic back pain

Back pain with different amounts of pain intensity and triggered by different causes affects between 27% and 40% of the people. To observe these potential neuroplastic changes in the SI representation of the back in patients with chronic lower back pain, nonpainful and painful electrical intracutaneous stimulation was used [15]. Magnetoencephalography (MEG) recordings revealed a 25 mm medial shift of an equivalent current dipole source at approximately 70 ms after stimulus onset. The extent of this shift was positively correlated with chronicity. Furthermore, within the early time window (100 ms), the root mean square amplitude of the somatosensory evoked field (SEF) was significantly higher in patients with chronic low back pain than in the healthy controls when painful back stimulation was used. In another study, enhanced perceptual sensitization and enhanced processing of the sensory-discriminative aspect of pain, as expressed in the N80 component of the electroencephalography (EEG), were reported [16]. Using functional magnetic resonance imaging (fMRI), Giesecke et al. [17] reported that comparable levels of subjectively reported painful pressure stimulation to the left thumbnail resulted in activation patterns that were similar in patients with chronic low back pain and healthy controls, whereas similar objective pressure intensities resulted in greater effects in patients in regions specific for pain processing. Although similar regions of brain activation were found for similar painful pressure stimulation, patients with chronic low back pain showed a significantly reduced BOLD-signal in the periaqueductal gray (PAG) and significantly increased BOLD-responses in SI and SII and the lateral orbitofrontal cortex, supporting the hypothesis of a dysfunctional inhibitory system controlled by the PAG [18]. Similar results were found by stimulating 5 cm left to the fourth-to-fifth lumbar spinal interspace, with patients showing augmented activation for subjectively identical stimuli compared to healthy controls specifically at the right insula, SMA, and the PCC [19]. In resting-state fMRI-analysis, five meaningful resting-state networks were isolated, of which only the default mode network (DMN) exhibited deviations from healthy controls [20]. The authors reported a decreased connectivity of medial PFC to the posterior constituents of the DMN and increased connectivity to the insula in proportion to the intensity of pain. Similar results were found by Tagliazucchi et al. [21] demonstrating that chronic pain disrupts normal activity in the DMN even when the brain is in the resting state.

It remains unclear whether the described functional changes are caused by structural changes or cause structural alterations. Apkarian et al. [22] reported 5–11% less neocortical gray matter (GM) volume in subjects with chronic back pain than that in control subjects. The magnitude of this decrease is equivalent to the GM-volume lost in 10–20 years of normal aging. The decreased volume was related to pain duration, indicating a 1.3 cm^3 loss of GM for every year of chronic pain. GM density was reduced in bilateral dorsolateral PFC and right thalamus. The reduction of GM in the dorsolateral PFC could be replicated in other studies. Fritz et al. [23] found decreased GM volume in the ventrolateral and dorsolateral PFC, both the ventral and dorsal medial PFC and the anterior insula. Pain intensity showed a weak negative correlation with GM volume in the left dorsolateral and ventrolateral PFC, and ACC [23]. Ivo et al. [24] showed decreased GM density in the dorsolateral PFC, the thalamus, and the MCC. Schmidt-Wilcke et al. [25] found a significant decrease of GM in the brainstem and the SI. Correlation analysis of pain unpleasantness and intensity on the day of scanning revealed a strong negative correlation (i.e., a decrease in GM with increasing unpleasantness/increasing intensity of pain) in these areas. Additionally, a significant increase in GM bilaterally in the basal ganglia and the left thalamus was found.

Fibromyalgia syndrome (FMS)

Fibromyalgia syndrome (FMS) is characterized by chronic widespread pain and tenderness at specific sites [26]. FMS is a chronic pain disorder with symptoms at the joint muscles and tendons on all four quadrants of the body. The pain particularly increases under load. Additional symptoms include a general weakness, impaired concentration, cognitive dysfunction, sleep disturbance, chronic fatigue, and a reduced mental and physical capacity. Physical, mental, and emotional load needs unnatural long recovery phases. In the population, the prevalence of FMS is between 0.6% and 4%, of them, 85–90% are women. While the etiology of FMS remains unclear, the generalized hyperalgesia, widespread pain,

and spontaneous pain in FMS cannot be explained by changes in peripheral tissues like muscle. To summarize, FMS is a chronic pain condition with a sensitized pain perception but is not recognized or explained medically. The question arises whether patients with FMS process experimental pain are different from healthy controls.

Gibson et al. [27] showed that patients with FMS displayed a significant increase in the peak-to-peak amplitude of the cerebral potential in a time window 207 and 370 ms poststimulus evoked by painful CO_2 laser stimulation. De Tommaso [28] reported an increased amplitude of the vertex laser-evoked potential going along with an increased subjectively perceived laser pain intensity. Furthermore, patients with FMS had less habituation of perceived pain intensity and less habituation-induced reduction of vertex laser-evoked potentials than controls. Similar results were found by Lorenz et al. [29] and Lorenz [30]. Compared to matched controls, patients with FMS exhibited significantly lower heat pain thresholds and had higher amplitudes of the laser-evoked potential components N170 and P390 [29]. The observation of amplitude enlargement of the N170 suggests enhanced nociceptive activation and neuronal synchronization in SII by radiant heat. The P390 enhancement in patients with FMS might indicate greater attention to or cognitive appraisal of painful stimuli. In another study, lower pain thresholds after electrical stimulation and a higher N80 amplitude of the EEG, both indicative of enhanced sensory processing, were reported [31].

In an fMRI study, Gracely et al. [32] reported that only similar objective pressure intensities resulted in greater effects in patients with FMS in regions specific for pain processing, whereas comparable levels of subjectively reported painful pressure stimulation resulted in activation patterns that were similar in patients with FMS and healthy controls (Fig. 1). This applied to regions involved in the

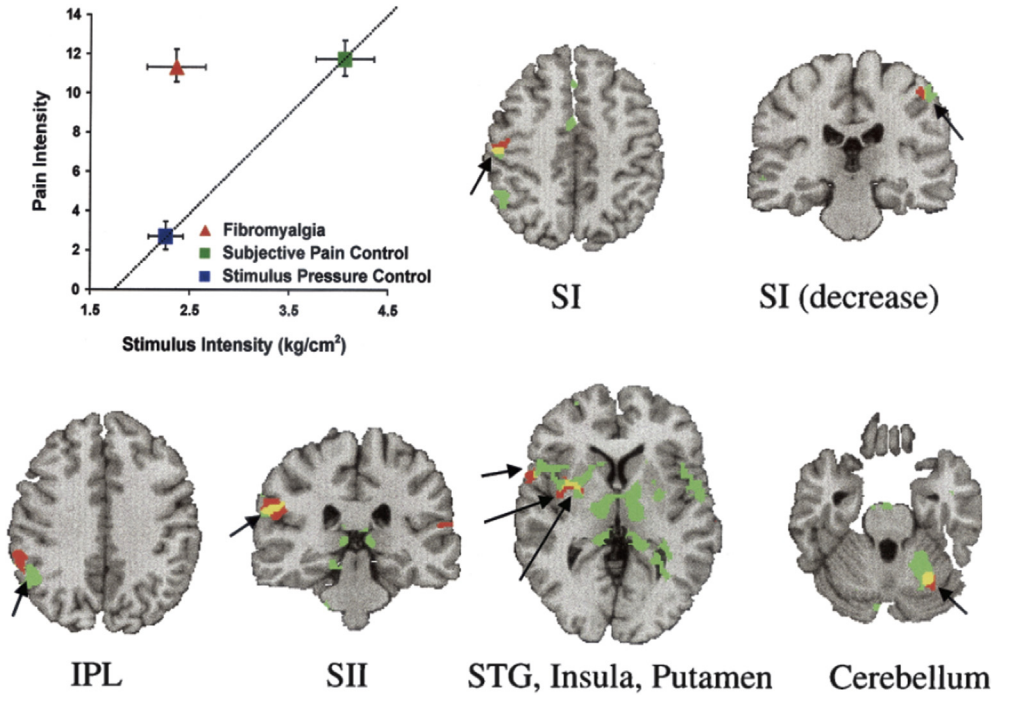

Fig. 1. Upper left: In the stimulus pressure-controlled condition (blue), the healthy controls rate the objective same-stimulation intensity as less intense compared to the patients with fibromyalgia (red). To obtain a similar pain intensity (subjective pain control, green) higher objective stimulation intensities are need in healthy controls. An MRI anatomic standard brain image displays common regions of activation in patients with fibromyalgia (red) and in the subjective pain control condition (green). Overlapping activations are shown in yellow. Similar pain intensities, produced by significantly less pressure in patients, resulted in overlapping or adjacent activations. For objective same-stimulation intensities, with higher pain ratings in fibromyalgia, healthy controls show decreased brain activations compared to the patients (not displayed here). Figure reprinted (with permission) from Gracely et al. [32].

sensory-discriminative component of pain such as SI and SII as well as to those involved in the affective-motivational component such as insula and ACC and could be replicated by Pujol et al. [33] using fMRI and by Maestu et al. [34] using MEG. Cook et al. [35] could replicate these results with heat stimuli and found differences between groups, especially in the contralateral insula. By using an incision as an acute pain stimulus, it was shown that patients with FMS showed different brain activation responses from those of controls not only during painful stimulation but also during the anticipation of painful stimuli [36]. The authors conclude that central mechanisms of pain processing in the medial pain system alter cognitive/affective factors even during the anticipation of pain and may play an important role in pain processing in FMS. There is also evidence that the endogenous pain inhibitory system is changed in patients with FMS. Studies examining the descending modulation of pain could show the importance of the rostral (r)ACC in pain inhibition [37–40]. Jensen et al. [41] reported that patients with FMS display significantly lower activation in the rACC than healthy subjects in response to unpredictable pressure pain stimulation [41] and that they have less functional connectivity between the rACC and hippocampi, amygdala, brainstem, and the rostral ventral medulla [42]. These findings support the hypothesis that FMS is characterized by cortical augmentation of pain processing. Resting-state data showed that patients with FMS had greater connectivity between the DMN and the insula. Furthermore, greater intensity of spontaneous pain at the time of measurement correlated with greater intrinsic connectivity between the insula and the DMN [43]. In another study, patients with FMS showed decreased connectivity between thalamus and premotor areas, between the right insula and SI, and between supramarginal and PFC [44]. The authors suggest that abnormal connectivity patterns between pain-related regions and the remaining brain during rest reflect an impaired central mechanism of pain modulation in FMS. Weaker coupling between pain regions and prefrontal and sensorimotor areas might indicate a less efficient system level control of pain circuits. In a recent study [45], state changes in resting brain connectivity following experimental pressure were investigated. The authors report that acute pressure pain stimulation increased the connectivity between the insula, the ACC, and the hippocampus compared to the measurement before the stimulation. Additionally, the authors found an increased thalamic connectivity to the precuneus/posterior cingulated cortex, which is part of the DMN in patients but not in controls. This connectivity was correlated with changes in clinical pain. The changes in resting-state brain activity following a noxious stimulus suggest that acute painful stimulation may contribute to the alteration of the neural signature of chronic pain.

There is conflicting evidence for the hypothesis that there is a general hypervigilance in FMS. Tiemann et al. [46] found no hypervigilance measured as an abnormal increase of attention to external stimuli in patients with FMS; Carrillo-de-la-Peña et al. [47] reported no differences in sensory gating of the P50 component, as indicated by P50 suppression rates to the second identical stimuli; and Lorenz et al. [30] found no hyper-reactivity in auditory-evoked potentials. On the contrary, McDermid et al. [48] reported decreased pain tolerance, pain threshold, and noise tolerance in patients with FMS compared to those in rheumatoid arthritis and healthy controls and that both patient groups preferred lower levels of external stimulation. Carrillo-de-la-Peña et al. [49] reported shorter N1 and P2 latencies and increased N1–P2 amplitudes in relation to loud tones, suggesting that defects in an inhibitory system protecting against overstimulation may be a crucial factor in the pathophysiology of FMS. In another study with 30 patients with FMS, 70% of the patients had a decreased noise tolerance [50].

It remains unclear whether the described functional changes are caused by structural changes or cause structural changes. In a VBM study, patients with FMS had a significant decreased volume and a 3.3 times increased age-related loss of the gray substance compared to those in healthy controls [51]. Additionally, the duration of the chronic pain correlates with loss of GM, although one year of FMS is equivalent to 9.5 years of normal aging. Another study reported decreased GM volumes in the thalamus and also increased volumes in the cerebellum and the striatum [52]. Voxel-based morphometry structural covariance network analysis showed more connections within the cerebellum in FMS and more connections in the frontal lobe in HC [53]. Spectral partitioning identified dense cerebellar connections to medial prefrontal/orbitofrontal cortex, medial temporal lobe, and right inferior parietal lobule in FMS. The GM volume of these regions was associated with severity of depressive symptoms. The number of fibers in these regions, measured by probabilistic diffusion tensor imaging (DTI) white matter (WM) connectivity analyses, was associated with greater evoked pain hyperalgesia and clinical

pain interference [53]. Reduced fractional anisotropy (FA) was reported in the bilateral thalamus, the thalamocortical tracts, and bilateral in the insula [54]. Additionally, reduced GM volumes were reported in pain processing areas going along with an increased FA. Sundgren et al. [55] reported a reduced FA in the right thalamus.

Phantom limb pain

The amputation or deafferentation of a limb or another body part is commonly followed by a global feeling that the missing limb is still present (phantom limb awareness), as well as specific sensory and kinesthetic sensations (phantom sensations) [56]. These nonpainful phantom sensations may include a specific position, shape, or movement of the phantom; feelings of cold or warmth, tingling, itching, or electric sensations; and other paresthesias [57] and are reported by almost all amputees. Phantom limb pain, or phantom pain, belongs to a group of neuropathic pain syndromes characterized by pain in the amputated limb or pain that follows partial or complete deafferentation. Residual limb (or stump) pain and nonpainful residual limb phenomena are sensations in the still-present body part adjacent to the amputation or deafferentation line. Pain in the body part that is no longer present occurs in 60–80% of all amputees [58,59]. Phantom pain or phantom sensations were reported after upper limb [e.g. Ref. [60]], lower limb [61–63], breast [64,65], tooth [66,67], internal organs [68], and penis [69,70] amputations. The influence of peripheral, spinal, and central changes on phantom pain was reported previously [for review, see Refs. [71,72]. Psychological factors do not seem to contribute to the causation but may instead affect the course and the severity of the pain [73,74]. In persons with amputations, it has been shown that the region of SI that formerly received input from the now amputated limb reorganizes and receives input from neighboring regions [60,75–77] (Fig. 2). These changes are mirrored in MI [78–82]. Interestingly, reorganizational changes were found only in amputees with phantom limb pain after amputation but not in amputees without pain [60]. This suggests that pain may contribute to the changes observed and that the persisting pain might also be a consequence of the plastic changes that occur. In several studies carried out on human upper-extremity amputee patients, displacement of the lip representation in the MI and SI was positively correlated with the intensity of phantom limb pain and was not present in pain-free amputee patients or healthy control subjects [e.g., [60,80]]. In addition, in patients with phantom limb pain but not in the pain-free amputee patients, imagined movement of the phantom hand was shown to activate the neighboring face area [81]. This co-activation probably occurs due to the high overlap of the hand, arm, and mouth representations.

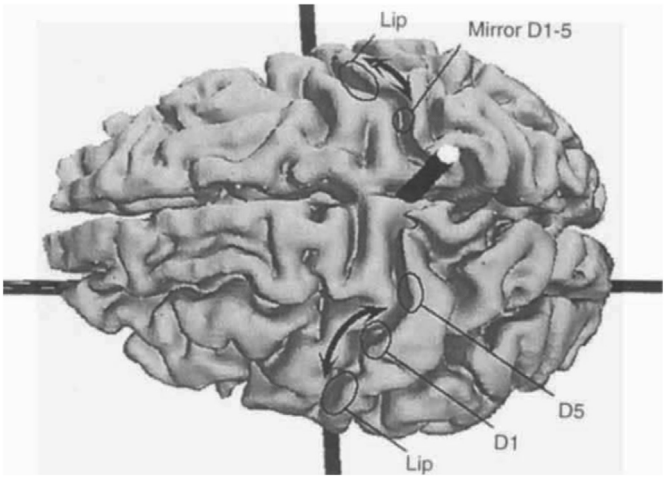

Fig. 2. Location of the left and right lip areas, the thumb and little finger of the intact hand, as well as the mirrored positions of the thumb and little finger to the side of the amputation in amputees with phantom limb pain superimposed schematically on a magnetic resonance image. At the side of amputation, the lip area has shifted into the former hand area. This shift is called cortical reorganization and is correlated with the amount of phantom limb pain. Figure reprinted (with permission) from Flor et al. [60].

However, research by Makin et al. suggests that PLP might rather be driven by the disrupting of inter-regional functional connectivity than by changes in the local cortical representation [83]. They could show that multiple factors contribute to PLP, including a preserved structural representations of the area of the amputated hand [84]. However, maladaptive reorganization and persistent representation of the limb are not necessarily mutually exclusive and may depend on the task used to measure cortical changes. For example, in a computational model of phantom limb pain Boström et al. [85] showed that both the amount of reorganization during tactile stimulation (used by [60]) and the level of cortical activity during phantom movements (used by [83]) were enhanced in a scenario with strong phantom pain as compared to a scenario with weak phantom pain (for a further discussion see also [86]). Thus, we suggest that depending on the experimental context or method chosen one might find evidence for either cortical reorganization or preservation of the amputated limb representation. We believe that both, cortical reorganization and preservation might not be contradictory but rather complementary. Studies assessing brain activation of experimental pain in amputees are still missing. Resting-state functional connectivity values between the missing hand cortex and the sensorimotor network were reduced in amputees, and connectivity was weaker in individuals amputated for longer periods. Lower levels of functional coupling between the missing hand cortex and the sensorimotor network were also associated with emerged coupling of this cortex with the DMN [87].

There are only few studies reporting structural changes. Draganski et al. [88] reported a decrease in GM of the posterolateral thalamus contralateral to the side of the amputation. The thalamic GM differences were positively correlated with the time span after the amputation but not with the frequency or magnitude of coexisting phantom pain. Phantom limb pain was unrelated to thalamic structural variations but was positively correlated to a decrease in brain areas related to the processing of pain. In a voxelwise DTI analysis of the body of the corpus callosum, Simoẽs et al. [63] found reduced FA values bilaterally in pain-free amputees compared with controls.

Complex regional pain syndrome (CRPS)

As in phantom limb pain, similar observations have been made in patients with complex regional pain syndrome (CRPS). An external impact (e.g., trauma, operation, or inflammation) leads to dystrophia or degeneration and atrophy of tissue. Symptoms of CRPS are circulatory disorders, edemata, alterations of the skin, pain, and restrictions of functions. Frequently, CRPS follows a distal radius fracture (7–37% of all cases). Accordingly, CRPS is more often on the upper than on the lower extremity. Changes in the somatosensory system were assessed in these patients too. Here, the representation of the affected hand tended to be smaller than that of the unaffected hand, and the individual digit representations had moved closer together [89–92]. The extent of the pathological changes in the cortical representations correlated with the intensity of pain or motor dysfunction [92–94] but was additionally related to a degradation of sensibility in the affected hand. It was, however, unrelated to a loss of motor function [94]. It is thus far not known how an expansion of adjacent representations and a shrinking of adjacent representations as observed in phantom limb pain and CRPS, respectively, can both be associated with pain. Similar to chronic back pain in resting-state fMRI analyses, five meaningful resting-state networks were isolated, of which only the DMN exhibited deviations from healthy controls [20]. Again, a decreased connectivity of medial PFC to the posterior constituents of the DMN and increased connectivity to the insula in proportion to the intensity of pain were reported. In another study, significantly greater reductions in functional DMN connectivity were found in patients with CRPS than in controls [95]. The functional connectivity maps of SI/MI and intraparietal sulcus (IPS) in patients revealed greater and more diffuse connectivity with other brain regions, mainly with the cingulate cortex, precuneus, thalamus, and PFC. In contrast, controls showed greater intraregional connectivity within SI/MI and IPS.

Barad et al. [96] reported a decreased GM volume in several pain-affect regions including the dorsal insula, left orbitofrontal cortex, and several aspects of the cingulate cortex. Greater GM volume was seen in the bilateral dorsal putamen and right hypothalamus. Pain duration was associated with decreased GM in the left dorsolateral PFC. Pain intensity was positively correlated with volume in the left posterior hippocampus and left amygdala and negatively correlated with the bilateral dorsolateral PFC. Lee et al. [97] found thinner right dorsolateral PFC and left ventromedial PFC in patients with CRPS than in healthy

controls. There were no correlations between cortical thickness and depression, although the Beck Depression Inventory and the Beck Anxiety Inventory showed significant difference between the groups. WM changes measured by decreased FA were found in the left cingulum-callosal bundle [98].

Implications for treatment

Behavioral interventions

The assumption that chronic pain is largely influenced by learning and memory processes suggests that treatment should focus on the alteration of these memory traces. Behavioral and cognitive methods or their combination are particularly well suited for this purpose because they can specifically modulate alterations in brain function or brain chemistry present in a specific pain condition, whereas pharmacological treatments act in a more unspecific manner. The operant behavioral training specifically aims at high levels of pain behaviors. The goals of this training are as follows: (1) to decrease pain behaviors in an effort to extinguish pain; (2) to increase activity levels and healthy behaviors related to work, leisure time, and family; medication reduction and management; and (3) to change the behavior of significant others [99]. The overall goal is to reduce disability by reducing pain and increasing healthy behaviors. To avoid negative reinforcement, learning medication is switched from a pain contingent to a fixed time schedule, where medication is given at certain times of the day. The enhancement of activity and the reduction of inactivity and invalidity will be targeted with similar principles. Studies have shown the effectiveness of this training in patients with FMS as well as other pain syndromes such as chronic back pain [100,101], and it is particularly effective in reducing pain behaviors. After an operant behavioral treatment in FMS, a shift from an emotional motivational processing of experimental pain to a more sensory discriminative processing was reported [102]. Of particular interest was the activation in the insula, which shifted bilaterally from a more anterior site before treatment to a more posterior location after treatment. The pre- to post-treatment reduction in both interference related to pain and pain severity were significantly associated with bilateral activation in pain-evoked activity in the posterior insula, the ipsilateral caudate nucleus/striatum, the contralateral lenticular nucleus, the left thalamus, and the primary somatosensory cortex contralateral to the stimulated side [102].

The cognitive-behavioral model of chronic pain emphasizes the role of cognitive, affective, and behavioral factors in the development and maintenance of chronic pain [103]. The cognitive-behavioral training modifies pain-eliciting and -maintaining behaviors, cognitions, and emotions to reduce feelings of helplessness and lack of control with the aim of establishing a sense of control over pain. Therefore, patients are taught several techniques to deal with pain episodes, such as cognitive restructuring, pain coping strategies, and relaxation and imagery techniques. Cognitive-behavioral pain management has been shown to be a very effective treatment of chronic pain [104]. Whereas operant treatment reduces particularly pain behaviors and pain intensity, cognitive-behavioral therapy has a special effect on the affective and cognitive aspects of pain [101]. It was suggested that a cognitive-behavioral treatment changes the brain's processing of pain through an altered cerebral loop between pain signals, emotions, and cognitions, which leads to an increased access to executive regions for reappraisal of pain [105]. High catastrophizing thoughts, which were correlated with an increased resting state functional connectivity between the primary somatosensory cortex and the anterior insula, could be reduced by cognitive-behavioral therapy and accompany a reduced resting-state connectivity between these regions [106]. As extinction is more difficult than acquisition, principles of extinction training need to be considered [107]. For an overview of randomized controlled trials using operant- or cognitive-behavioral treatments, see Ref. [108], and for a discussion of the potential psychobiological mechanisms, see Ref. [109].

Sensory and motor training

As described above, phantom limb pain and CRPS are associated with increased peripheral input into the brain and an overlap of topographic neighboring brain regions. From this, we can conclude that

changes in the brain as well as an altered peripheral input can influence the brain maps and the perception of pain. Possible methods are stimulation, motor-, mirror-, or imagery-trainings.

In amputees with phantom pain, several stimulation-related procedures were found to be effective. Intense input into the cortical amputation zone by the use of a myoelectric prosthesis or other prosthetic devices like a Sauerbruch prosthesis, for example, was found to reduce both cortical reorganization and phantom limb pain [110,111]. By wearing a Sauerbruch prosthesis, the use of the amputation stump is increased and could produce a countervailing use-dependent, afferent-increase [110]. A myoelectric prosthesis directly controls the prosthesis through electromyography signals of the stump, thereby increasing the efferent input into the stump [111]. The negative correlation between prosthesis use and phantom limb pain became non-significant when the effect of cortical reorganization was removed by partial correlation. This is interpreted that the phantom limb pain reduction is mediated by cortical reorganization [111]. In a longitudinal study, Dietrich et al. [112] showed that a sensory feedback prosthesis effectively reduces phantom limb pain, modulated by visual and sensory feedback to the brain through the prosthesis, combining efferent input into the stump with afferent-increase into the brain. The results of these studies suggest that muscular training and stimulation of the stump combined with visual feedback from the prosthesis might have a beneficial effect on maladaptive cortical reorganization and phantom limb pain. This is also in accordance with animal experiments, which showed that the cortical representation of the stimulated body region expands through input from behaviorally relevant tactile stimulation [113,114].

In patients in whom the use of prosthesis is not possible, sensory discrimination training might be beneficial. In one study, electrodes were closely spaced over the amputation stump in a region where stimulation excites the nerve that supplies the amputated portion of the arm. Patients then had to discriminate the frequency and location of the stimulation in an extended training period that lasted for 90 min/day over a 2-week period. Substantial improvements to both two-point discrimination and phantom limb pain were demonstrated in the trained patients. These improvements were accompanied by changes in cortical reorganization, which indicates a normalization of the shifted mouth representation [115]. An asynchronous stimulation of the stump and lip area also yielded a significant reduction in phantom limb pain suggesting that the separation of overlapping cortical networks involved in pain may be important [116]. Recently, we could show that such a training is also working with tactile stimuli using cotton swabs, which could easily be applied by the partner of the patient [117].

Similar results were found in patients with CRPS where active discrimination between tactile stimuli led to an improvement in pain intensity and two-point discrimination compared to passive stimulation alone [118]. When patients watch the reflected image of their unaffected limb during training, the effect of tactile discrimination training is enhanced [119]. Tactile spatial acuity also improved when a Hebbian stimulation protocol of tactile coactivation [120] was used. The question arises whether active stimulation is necessary or whether passive stimulation is sufficient. In rats, it could be shown that associative (Hebbian) pairing of passive tactile stimulation leads to a selective enlargement of the areas of cortical neurons representing the stimulated skin fields and of the corresponding receptive fields [121]. In humans, paired tactile stimulation goes along with an improved spatial discrimination performance [121,122] matched by alterations of primary somatosensory cortex [123], indicating that fast plastic processes based on co-activation patterns act at a cortical and perceptual levels. It is possible that in healthy controls, passive stimulation without a task is sufficient for changes at the perceptual and cortical levels, whereas patients who are less able to discriminate stimuli [118,120] may need active stimulation for improvement in discrimination ability (and pain intensity). These training effects can be enhanced by the use of pharmacological agents. For example, two-point discrimination after a coactivation protocol was doubled by amphetamine and was blocked by a N-methyl-D-aspartate-receptor blocker [124], or by lorazepam, a GABAA receptor agonist [125]. However, these pharmacological modulation effects are not easily translated into clinical practice. In stroke patients, amphetamine showed mixed results [126].

Mirror and motor imagery training

Ramachandran et al. [127] suggested that the use of a mirror might reverse the reorganizational changes observed in patients with phantom limb pain, and they provided anecdotal evidence that

viewing movements of one's intact hand in a mirror, which provides the impression of viewing the amputated hand, led to better movement of and less pain in the phantom limb. In lower limb amputees, Brodie [128] reported a significantly greater number of movements in the phantom when a mirror box was used. Hunter et al. [56] showed that a single trial mirror box intervention led to a more vivid awareness of the phantom and a new or enhanced ability to move the phantom. In contrast to a mirror box with executed movement, Brodie et al. [129] reported that movements in front of a mirror as well as movements without a mirror attenuated phantom limb pain and phantom sensation. Contrary to these findings, which were based on a single trial, 4 weeks of mirror training led to significantly more decrease in phantom limb pain than training with a covered mirror or using mental visualization in lower limb amputees [130], suggesting that phantom pain can be altered by visual feedback. The visual system has a perceptual dominance in inter-sensory conflicts. The reason is the better spatial solution provided by vision than other senses (including touch) [118,131,132]. We observed in an fMRI session that amputees with phantom limb pain were unable to activate the sensorimotor cortex opposite to the amputated limb when the intact hand was moved in front of a mirror (appearing as movement of the phantom). A similar lack of activation was, however, also present with executed movements of the intact hand and with imagery of the phantom hand [133]. Moreover, phantom limb pain was inversely correlated with activation on the hemisphere contralateral to the amputation, suggesting that mirror training may not be special [134]. In a 4-week mirror training program in patients with chronic phantom limb pain treatment, effects were predicted by a telescopic distortion of the phantom, with those patients who experienced a telescope profiting less from treatment. fMRI data analyses revealed a relationship between change in pain after mirror training and a reversal of dysfunctional cortical reorganization in primary somatosensory [135].

Other reports on imagined phantom movements in amputees [81,136–139] showed activation in primary sensorimotor cortex representing the amputated limb in the pain-free amputees and the healthy controls but not in the patients with phantom limb pain [133] and were supported by results from transcranial magnetic stimulation (TMS), which showed that perceived phantom hand movement could be triggered by stimulation over the motor cortex in an area that represented the now amputated limb [140]. Both Giraux and Sirigu [141] and MacIver and colleagues [142] showed that imagery alone also affects the cortical map representing the amputated limb and relieves phantom limb pain in contrast to the findings reported by Chan and colleagues [130] who did not find changes in phantom pain related to imagery but did not assess cortical changes. These studies suggest that several types of modification of input into the affected brain region may alter pain sensation. For a review on the effects of mirrored and imagined movements, see Ref. [143].

Moseley used a tripartite program to treat patients with CRPS [144,145]. This program consisted of a hand laterality recognition task (a pictured hand was to be recognized as left or right), imagined movements of the affected hand, and mirror therapy (patients were asked to adopt the hand posture of both hands shown on a picture in a mirror box while watching the reflection of the unaffected hand). After a 2-week treatment, pain scores were found to be significantly reduced. This results were replicated in patients with CRPS and phantom limb pain [146]. In addition, McCabe and colleagues [147] found a reduction in pain ratings during and after mirrored visual feedback of movement of the unaffected limb in patients with CRPS. Gieteling and colleagues [148] asked patients with CRPS with dystonic postures of the right upper extremity to execute or imagine movements during an fMRI measurement. Compared with controls, imaginary movement of the affected hand in patients showed reduced activation in the ipsilateral premotor and adjacent PFC, and in a cluster comprising the frontal operculum, the anterior part of the insular cortex and the superior temporal gyrus. On the contralateral side, reduced activation was seen in the inferior parietal and adjacent primary sensory cortex. There were no differences between patients and controls when they executed movements or when they imagined moving their unaffected hand. Watching an enlarged view of the limb during movement significantly increased the pain and swelling evoked by movements while shrinking the view of the limb decreased pain and swelling [149]. These observations were interpreted as being due to a top-down effect of body image on the integration of incoming sensory information [149]. Transcranial motor cortex stimulation (TMS) contralateral to the CRPS-affected side has also been found to reduce pain intensities in CRPS [150].

Thus far, only little research has focused on mirror training, distorted body image, and cortical representations in chronic musculoskeletal pain. A recent study suggested the use of mirror training to treat fibromyalgia and found anecdotal evidence for reduced pain ratings [151]. In chronic back pain, a disrupted body image and decreased tactile acuity, measured by two-point discrimination, in the area of usual pain was found [152]. Patients in this study reported that they could not find the outline of their trunk in the region of chronic pain. The larger two-point discrimination threshold in patients with chronic back pain could be positively related to worse performance on voluntary lumbopelvic movements, suggesting that a tactile acuity training might support recovery of normal motor performance [153]. In another study, patients with chronic back pain participated on a left/right trunk rotation judgment task and a left/right hand judgment [154]. The patients made more mistakes and were less accurate in the trunk rotation task. No differences were found for the hand judgment task. This gives further evidence of a disrupted working body schema of the trunk in patients with chronic musculoskeletal pain. By visualizing the back in patients with chronic back pain, it could be shown that seeing the back during repeated lumbar spine movements reduces movement-evoked pain [155]. This approach works not only for movements but also for visualizing one's own back on experimental pain perception at this site. Therefore, real-time video feedback of the back during painful stimulation of the trapezius muscle was implemented. Visual feedback of the back reduced perceived pain intensity compared to feedback of the hand in both patients with chronic back pain and controls [156]. Additionally, we could show that real-time video feedback could improve habitual pain [157] and improve massage treatment [158] or manual therapy [159]. These findings suggest that multisensory modulation could enhance pain treatments as previously suggested [72,156,160] and may lead to novel intervention modes for chronic back pain based on visualization of body parts by augmented reality (AR) applications.

Even in the behavioral training described above, which focuses on the extinction of pain behaviors and the acquisition of healthy behaviors, another kind of visual feedback is used. The video feedback of patients' pain behaviors and activity trainings as well as spouse trainings is used to extinguish pain and to increase healthy behaviors [101,161] with concomitant positive brain changes [102].

Virtual reality approaches to mirror training

Use of a mirror box has some technical limitations. The intact limb has to move symmetrically with the mirrored limb. This is particularly highly unnatural for the leg. This led to the invention of virtual reality (VR) and AR mirror boxes [for review, see Ref. [162]. In the first approach, the perceived phantom arm was presented on a flat screen in 3D and controlled using a wireless data glove on the intact arm [163]. The advantage of the VR mirror box was the possibility of incongruent movements between the intact hand with the data glove and the virtual phantom hand. For example, some of the virtual/phantom fingers were frozen, and movements of the complete phantom led to more pain. The number of moved phantom fingers was thus gradually increased, and it came to a relaxation and less pain sensation in 2 of the 3 cases. A different approach used immersive virtual reality (IVR) to transpose the movements made by an amputee's remaining anatomical limb into movements of a virtual limb [164]. These authors found a reduction in phantom pain intensity in 2 of 3 cases [165,166]. The advantage of this system is that the entire body is implemented in the IVR, and thus, complex hand–eye coordination is possible. A novel variation of this method is the use of motion capture to collect data directly from a patient's stump and then transform it into goal-directed, virtual action in the VR environment [167]. In a first experimental study with 14 patients, 72% reported the ability to move the phantom and reduction in phantom limb pain. Another possibility is the use of AR home training systems. Here, several training tasks could be implemented to make the training more exciting and increase the commitment of the patients. Therefore, a head-mounted display equipped with cameras captures one hand held in front of the body, mirrors it, and displays it in real time [168–170]. These VR applications are promising and could be extended in the future. With the rubber hand illusion, it could be shown that the transfer of tactile sensations from the stump to a prosthetic limb by tricking the brain is possible [171]. This is an important contribution to the field of neuroprosthetics where a major goal is to develop artificial limbs that feel like a real part of the body. Another possibility is a flexible multielectrode implantation for multimovement prosthesis control and sensory feedback.

The multielectrodes were implanted in the median and ulnar nerves of an amputee and led to real-time control of motor output [172].

Summary

Based on neuroscientific evidence of alterations in the primary sensory and motor areas in sensory and motor disorders such as chronic pain, sensory and motor training methods have been developed. They include training of perceptual abilities, motor function, direct cortical stimulation, and behavioral approaches and have been shown to reorganize altered sensory and motor maps. The cellular mechanisms underlying these changes still need to be determined, but they involve changes in inhibitory circuits and long-term synaptic changes. In addition, treatments that combine several modalities such as imagery or mirror treatment as well as use of prostheses seem to have beneficial effects. Further, much work still needs to be carried out to demonstrate the efficacy of these plasticity-related treatment approaches, which were usually tested in small heterogeneous samples without adequate controls and without adequate follow-ups. However, they may point out new approaches to treatment of chronic disorders and rehabilitation for the future. Future research should assess additional benefits that might arise from using brain stimulation methods in conjunction with behavioral trainings, VR applications, or plasticity-modifying pharmacological interventions.

Practice points

- As chronic pain is largely influenced by learning and memory processes, treatment should focus on the alteration of these memory traces.
- Stimulation-related procedures as prosthesis training or sensory discrimination training seem to be effective for the treatment of chronic pain.
- Visual-related procedures as real-time video feedback and mirror and motor imagery training could be improved by virtual reality techniques.

Research agenda

- The cellular mechanisms underlying the changes in sensory and motor maps still need to be determined.
- Much work still needs to be conducted to demonstrate the efficacy of these plasticity-related treatment approaches in larger samples with adequate control groups and follow-ups.
- Future research should assess additional benefits that might arise from using brain stimulation methods in conjunction with behavioral trainings, virtual reality applications, or plasticity-modifying pharmacological interventions.

Conflicts of interest

The authors do not have any conflicts of interest, neither financial nor otherwise related directly or indirectly to this article.

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