Review

Chronic pain may change the structure of the brain

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Abstract

Recently, local morphologic alterations of the brain in areas ascribable to the transmission of pain were detected in patients suffering from phantom pain, chronic back pain, irritable bowel syndrome, fibromyalgia and two types of frequent headaches. These alterations were different for each pain syndrome, but overlapped in the cingulate cortex, the orbitofrontal cortex, the insula and dorsal pons. These regions function as multi-integrative structures during the experience and the anticipation of pain. As it seems that chronic pain patients have a common "brain signature" in areas known to be involved in pain regulation, the question arises whether these changes are the cause or the consequence of chronic pain. The author suggests that the gray matter change observed in chronic pain patients are the consequence of frequent nociceptive input and should thus be reversible when pain is adequately treated.© 2008 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

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1. Introduction

In the past decade of pain research, a network of pain-transmitting areas within the CNS has been established, based on both animal studies [75] and findings from functional imaging studies in humans [58]. Consequently, the neurobiology of pain is increasingly understood as an integration of activity in distinct neuronal structures. Evidence of altered local brain chemistry and functional reorganization in chronic back pain patients supports the idea that chronic pain could be understood not only as an altered functional state, but also as a consequence of central plasticity [20]. Recent neurobiological findings suggest cortical reorganization on a functional level [33]. For example, amputation of a limb is very often accompanied by phantom pain. In these patients, the deafferentation leads to cortical reorganization where the representational fields of adjacent areas move into the representation zone of the deafferented limb [25,61]. This “functional reorganization” was not only detected in patients suffering from phantom limb pain [23], but also in chronic back pain patients [21]. Regarding chronic back pain, increased cortical activity and a shift of the cortical representation of the back, which was interpreted as an expansion of the back’s representation into the neighboring foot and leg area [21], was found. In patients suffering from chronic regional pain syndrome (CRPS Typ I), a shrinkage of the representational field of the affected arm was found and the extent of shrinkage correlated highly with the intensity of pain and the magnitude of mechanical hyperalgesia [48,59]. It is noteworthy, that the functional changes in CRPS [49] and in phantom pain [22] were dynamic, i.e. cortical reorganization reversed coincidently with clinical improvement. Currently, chronic pain states are attributed to abnormal nociceptive/antinociceptive function on different levels of the neuroaxis [75] with a normal brain structure. However, any significant challenge that requires a specific function,
including learning a specific task, has the potential to alter brain structure [55]. Given that the initiation of chronicification of pain involves nociceptive input, one would expect that neuroplasticity would probably occur in modulatory areas of nociception – namely, the antinociceptive system.

Two fundamental questions arise:

- Is there any evidence that humans suffering from chronic pain show altered brain morphology in structures related to the perception and behavioral response to pain, such as the thalamus, insulae, sensorimotor and cingulate cortices and the antinociceptive descending pathways?
- Is this alteration the cause or the consequence of chronicification?

2. Plasticity in chronic pain

Plasticity is a term used to refer to changes that occur in the established nervous system. The last decade has unraveled some of the mysteries of chronic pain and has clearly demonstrated that neuroplasticity at several levels of the nervous system is related to the propagation of pain long after the original cause is gone, depriving pain of its functional role and becoming the disease itself. Neuroplastic changes relating to function, chemical profile, or structure during the process of pain chronicification have been described for both, the peripheral (receptor and ion-channel reorganization, neurotransmitter changes) and cerebral nervous systems (functional changes of representational fields) including the spinal cord (sensitization and disinhibition) as well as the dynamic interaction of all these levels with the immune system and higher cognitive functions. Fig. 1 summarizes the different levels of plasticity in chronic pain known so far. However, this meta-analysis will focus on the most recent studies using structural brain imaging in chronic pain patients and will not cover the other neuronal systems that have already been considered in excellent reviews [25,40,50,70,80].

3. Structural brain imaging

In the past, studies of brain morphology completely depended on autopsy material. This situation changed with the advent of modern in vivo imaging methods, in particular, magnetic resonance (MR) imaging. All quantitative MR-based methods are subsumed under the heading of MR morphometry of the brain and are based on the idea of using a common coordinate system or atlas. Normally, three-dimensional, high-resolution, T1-weighted MRI images acquired with conventional 1.5 T MR scanners and 1 mm³ voxels provide sufficient detail and contrast [5] whereas scanners with higher field strength (3 T, 7 T) allow for higher spatial resolution. Images from several subjects can be grouped together and analyzed by mapping them onto a standardized coordinate space. Voxel-based morphometry (VBM) is the most commonly applied technique. It is relatively simple to use, has moderate demands on computational resources and is available in common software packages like FSL [28,71] or SPM [27] (Table 1).

As a non-invasive procedure, MR morphometry is the ideal tool for finding the morphological substrates of diseases, deepening our understanding of the relationship between brain structure and function, and even to monitor therapeutic interventions. It has to be said that most studies focus on cohort or cross-sectional studies, leading to the question of cause and consequence. Important contributions to the exact causes of structural changes will come from studies that look at the time parameters of these changes and include independent factors (i.e. electrophysiology or genetics). Moreover, the exact cause of lesion- and training-related morphological changes in the adult brain is still not known. A decrease in the brain gray matter, such as has been described in chronic pain patients, does not necessarily mean neuronal destruction. Potential correlates of the observed morphometric changes include a simple change in cell size, shrinkage or atrophy of neurons or glia, as well as changes in the intra-cortical axonal architecture (synaptic loss) [54]. The analysis of the cortical
surface complements these voxel-based methods. For these approaches, the cortical surface is extracted from brain scans and further computations are applied then to calculate parameters such as cortical thickness [19] or complexity [73]. More recently, this has also allowed the local three-dimensional computation of the gyrification index as a measure of the degree of folding of a given cortical area [47]. An advantage over VBM and DBM is the improved reduction of inter-subject variability in cortical folding patterns [4]. However, the extraction of the cortical surface imposes high demands on computational resources and crucially depends on the quality of surface extraction, which sometimes requires additional manual correction or interaction.

Notwithstanding these limitations, with the development of novel computational techniques during the last few years and increasing image resolution, the era of MRI-based morphometry has begun to expand. Recent findings and further methodological developments should lead to scientific breakthroughs that will change how we think of the brain. Following is a summary of the most recent of these developments with regard to chronic pain.

4. Chronic back pain

In many countries, chronic back pain is one of the most frequent pain disorders in the general population. 70–85% of all people have experienced back pain at some point in their lifetime [2]. Nevertheless, the mechanisms of chronification are the subject of intense research and debate. The pioneering work by Apkarian et al. using sophisticated morphometric analysis methods in 17 patients suffering from chronic back pain demonstrated brain atrophy and suggested that the pathophysiology of chronic pain includes thalamo-cortical processes [3]. Specifically, this study found a decrease in gray matter in the dorsolateral prefrontal cortices (DLPFC) bilaterally and a decrease in gray matter in the right thalamus. The authors suggested that neurodegeneration – rather than tissue shrinkage – without a substantial impact on neuronal properties may be the cause of this finding. This study was in part replicated by Schmidt-Wilcke et al., who investigated 18 patients with matched healthy controls and also found a decrease in gray matter in the DLPFC. However, this study also found an increase in thalamic gray matter and an additional decrease in the dorsolateral pons and the somatosensory cortex [67]. Interestingly, the correlation analyses suggested that the gray matter decrease in the brainstem does not correlate with pain duration, but rather with pain intensity and pain unpleasantness experienced at the time of scanning, thus possibly accounting for the degree of impaired antinociception at that time. The differences between the studies by Apkarian et al. and Schmidt-Wilcke et al. are not easy to interpret.
One explanation is the relatively small sample sizes used in these studies, so that negative findings have little meaning. However, Schmidt-Wilcke et al. only included patients without radiating pain, including radiculopathy, whereas Apkarian studied a mixture of patients with and without neurological manifestations as well as patients with pain outside of his region (for example, in the upper back). In summary, chronic back pain is accompanied by specific morphological alterations in structures known to play a crucial role in antinociception, which may correlate to the intensity and unpleasantness of pain.

5. Phantom pain

At least in primates, plasticity in the adult brain can occur rapidly as a consequence of peripheral lesions and sensory deprivation [61]. Cortical reorganization on a functional level, as revealed by neuromagnetic and neuromagnetic source imaging as well as functional MRI and PET, has been found to correlate with a massive expansion of adjacent cortical representational areas following limb deafferentation in monkeys and humans [13,23,46,76,77]. Functional reorganization following amputation has been described in the primary somatosensory cortex, which was suggested to correlate with painful, but not with non-painful phantom sensations [17,23,34]. For non-painful phantom sensations, the suggested candidate structures for plasticity changes are the thalamus, posterior parietal and prefrontal cortices as well as the secondary motor cortex [13]. These findings led to the concept of “maladaptive plasticity” challenging the assumption of an obligatory beneficial effect of functional plasticity in terms of adaptation and recovery of function after lesion of the nervous system with loss of afferent input.

However, only a few studies have examined structural alterations in the primate brain following limb amputation (for review see [38]). Several postmortem studies claim to have identified the anatomical correlates as a consequence of a loss of afferent input. Considering the results of two recent histopathological studies on primates after limb deafferentation, there are different possible anatomical locations in the adult human brain where structural changes could occur. It was demonstrated that long-standing limb amputation can cause structural reorganization of the brainstem, thalamic nuclei or the somatosensory cortex [26,39].

To test the hypothesis, whether the loss ofafferent input can structurally alter the adult human brain, we applied voxel-based morphometry (VBM) on structural MRI scans of 28 unilateral amputees and 28 corresponding age- and sex-matched controls [15]. This study demonstrated a specific gray matter reduction in the postero-lateral thalamus in patients with a traumatic upper/lower limb amputation compared to healthy volunteers. A positive correlation between these structural variations and time since amputation [15] supports the assumption that these alterations may occur as a consequence of chronic absence of behaviorally relevant information. Interestingly, phantom limb pain as a covariate failed to show thalamic differences and demonstrated subtle structural alterations, i.e. a decrease in gray matter in brain areas involved in pain processing and modulation, such as the anterior and posterior cingu-late cortices as well as the SMA and dorsal mid-brain. These data support the concept of “maladaptive plasticity” and accordingly may reflect some of the cortical somatosensory “pain memory”, whose subjective features have been described by Katz and Melzack [41].

6. Chronic head pain

Chronic daily headache (CDH), defined as headache occurring on 15 or more days per month [78], is a frequent disorder. The most frequent subtypes are chronic tension type headache (CTTH) and medication overuse headache (MOH) [37]. Whereas CTTH is still difficult to treat, MOH shows distinct improvement after medication withdrawal. Given that patients with cluster headache [53] or migraine [65] have subtly different brain structures, the question arises whether the distinct subtypes of CDH may also be distinguishable on a morphometric level. Using VBM in 40 CDH patients (20 chronic tension type headache patients and 20 medication overuse headache patients according to the International Headache Society criteria [37]) and comparing them with healthy controls, only CTTH patients showed a significant decrease in gray matter in the dorsal rostral and ventral pons, the perigenual ACC (BA 24), mid-ACC (BA 24/31) and right PCC (BA 23), the anterior and posterior insula bilaterally, the right posterior temporal lobe, the orbito-frontal cortex and parahippocampus bilaterally and the right cerebellum [68]. This decrease in gray matter correlated positively with increasing headache duration in years, i.e. patients with longer history had less gray matter in these regions. The fact, that this change in gray matter in CTTH patients mainly involves structures involved in pain processing could reflect either the cause or the consequence of chronic head pain. At the moment, these data suggest that while CTTH and MOH may share some common features, i.e. frequent head pain, the underlying pathogenesis differs significantly, as inferred from the different clinical patterns of pain characterization and responses to treatment.

7. Migraine

Functional imaging of headache has demonstrated that neuronal activation patterns in primary headache syndromes fall into two groups: areas known to be gen-
erally involved in pain processing, such as the cingulate, insular cortex and thalamus, and areas activated specifically in primary headache such as the hypothalamus in cluster headache attacks [53] and the brainstem in acute migraine [1,52]. These regions are not thought to be involved in the response to pain stimuli, but seem to play a permissive, possibly even a causative role, which supports the idea of an underlying neurovascular rather than purely vascular mechanism. Regarding surface-based methods, a very recent study described structural abnormalities in the network of motion-processing areas which could account for the cortical hyperexcitability observed in migraineurs [32]. The same group showed in the same group of patients that migraineurs may have a thicker somatosensory cortex (S1) than the control group [8]. Both findings are highly interesting and demonstrate the future potential impact of these methods on our pathophysiological concepts of pain and headache.

Regarding voxel-based morphometric analysis (VBM) of structural T1-weighted MRI scans, cluster headache patients show a colocalization of morphometric alterations and functional activation [53]. A pioneering study by Matharu et al. did not find any significant morphometric changes in gray or white matter in patients suffering from episodic migraine [51], whereas patients with chronic tension type headache showed a decrease in brain gray matter in several pain-transmitting structures [68].

Three recent studies question the findings by Matharu et al. The first one was published by Rocca et al., who investigated 16 migraine patients and reported reduced gray matter density in the anterior cingulate cortex, anterior insulæ and temporal lobes [65]. They also described increased density of the PAG and of the dorsolateral pons in migraine patients [65]. The second study investigated 35 patients suffering from migraine and compared them to 31 healthy controls with no headache history. The third study investigated 27 migraine patients and compared them to 27 healthy controls [74]. Using MRI and voxel-based morphometry (VBM), both studies reported a significant decrease in gray matter in areas ascribable to the transmission of pain (cingulate cortex), but not in areas specific for migraine, such as the brainstem [66]. One possibility for this discrepancy is the fact that the Matharu study, the Valfre study as well as the Schmidt-Wilcke study used a 1.5 T scanner, whereas the Italian group used a higher field strength (3 T), which may be an advantage in detecting subtle differences in cohort studies. However, the migraine cohort of the Italian group was rather small (16 patients) and comprised only patients with T2-visible brain lesions, a finding which is not part of the IHS criteria and moreover, rather unusual in migraine patients. As migraine has a strong genetic component, the ideal inclusion criteria for future studies to render groups as homogeneous as possible could be based on genotype (cohort study) or response to treatment (longitudinal study including controls).

Although the main finding by Rocca et al. is very similar to our findings (decrease of gray matter in pain-transmitting structures), our interpretation of the results is different. Rocca et al. suggested that gray matter changes may be the consequence of repeated brain insult or damage during migraine attacks [65]. According to their interpretation, the topographical distributions of gray matter changes would be the consequence of cortical regions having varying susceptibilities. This mechanism was discussed to be facilitated by a “retrograde degeneration of axons passing through T2-visible lesions of the white matter,” which was an inclusion criterion in the above-mentioned study. However, a striking feature of both studies is the fact that the gray matter changes were not randomly distributed, but concerned defined and functionally highly specific brain areas – namely, involvement in supraspinal nociceptive processing. It is indeed remarkable that the alterations (i.e. decrease in gray matter) seen in the anterior cingulate cortex in migraine patients are similar to a decrease in this region in chronic back pain [67] and chronic phantom pain [15]. As most changes correlate to pain duration, it seems plausible to argue that the alteration of this region is a consequence, rather than a cause, of frequent nociceptive input. It is not known why migraine usually remits with age. It is a very interesting question for future studies whether the morphological changes reverse, when migraine and hence the disproportionate amount of nociceptive stimulation stops.

8. Fibromyalgia and irritable bowel syndrome

Primary fibromyalgia is a common yet poorly understood syndrome characterized by diffuse chronic pain accompanied by other somatic symptoms, including poor sleep, fatigue, and stiffness. The study of chronic pain has yielded new insights into the pathophysiology of fibromyalgia and related chronic pain disorders, suggesting that fibromyalgia may be associated with a central nervous system dysfunction [12,31]. A very recent work by Kuchinad and coworkers examined, using morphometric methods, the brains of 10 female fibromyalgia patients and 10 healthy controls. Despite the relatively low numbers, they found a reduction in regional gray matter in the left parahippocampal gyrus, bilateral mid/posterior cingulate gyrus, left insula and medial frontal cortex [43]. Just like in most other studies investigating gray matter differences between chronic pain patients and healthy controls, no areas with a significant increase in gray matter were found. Another study found a decrease in orbitofrontal structures as well as a striatal gray matter increase in patients suffering from fibromyalgia [69]. A very recent study investigated patients with irritable bowel syndrome (IBS) using
VBM and surface-based methods [9]. Using a cortical thickness analysis (CTA) algorithm, implemented in BrainVoyager QX, the authors describe a significant cortical thinning in the patients with IBS which was localized to the right ACC and the anterior insula bilaterally. Moreover, the authors found, using VBM, reduced gray matter in the rostral ACC (BA32) and the anterior/medial thalamus in the IBS group relative to healthy controls. These findings show a remarkable overlap with the above-mentioned findings in other chronic pain syndromes, suggesting a common basis. Notably, these findings also relate to functional changes found in fMRI studies in those patients [45].

9. Do chronic pain patients have a common brain signature?

All eight morphometric studies in chronic pain together suggest that the concept of central structural plasticity is important for an understanding of chronic pain. As neither pain-related inactivity [15], nor pain medication [3,43,68] explains this finding, the in vivo demonstration of a loss of brain gray matter in patients suffering from chronic pain compared to age- and sex-matched healthy controls could represent the heavily discussed neuroanatomical substrate for pain memory. All studies but one showed structural alterations in specific brain areas referred to as the pain matrix. These alterations were different for the different pain syndromes, but, in terms of functional systems, overlapped to an astounding extent (Fig. 2). Irrespective of the location, nature or course of the different pain syndromes, the most common finding is a decrease of gray matter in the cingulate cortex, the orbitofrontal cortex, the insula and the dorsal pons, suggesting a common basis. It is, however, crucial to stress that this phenomenon, which coincides with the chronification of pain does not act in isolation. It influences and is influenced by nociceptive and spinal events. The plasticity and dynamic interaction among nociceptors [80], neurotransmitters [42], glial, neuronal and endothelial cells [30], receptive fields [72] and the immune system [50] as well as higher cognitive functions [24,35] needs to be considered. They comprise a complex collection of many discrete, but interacting, systems [56]. However, although the complexity of pain perception involves many levels of the neuraxis, cortical plasticity is certainly not restricted to functional changes.

The data indicating that the cingulate cortex is affected in chronic pain raise some speculation on the anterior cingulate integrative structures during the experience and the anticipation of pain [58,62]. The anterior cingulate cortex, including the perigenual part, is of particular interest, since it plays a deterministic role in pain modulation and analgesia. The analgesic/modulating effect is mediated through the interaction with other structures, such as the orbitofrontal cortex, the amygdala and the PAG [81]. All of these structures also showed alteration in some of the studies mentioned here. The collective evidence for the rACC as a crucial site for endogenous pain control has been observed in the context of pain modulation by attention, anticipation of pain and placebo analgesia [6,18,57,60,63,64] (for a review see [44] and also studies of neurostimulation for pain relief [10]).

The brainstem is another anatomical site which is linked to antinoception. In humans, stimulation of the brainstem is suggested to be effective in intractable pain states [16,36] and in functional imaging studies an activation in the mesencephalon following the application of pain stimuli has been frequently described [11,58]. Recently, evidence has been provided that iron levels in the PAG might be abnormally high in migraine patients [79], correlating with disease burden.

The decrease of gray matter in brain regions which are highly associated with pain suppression could certainly lead to dysfunction in effective antinoception. Abnormal modulation of brain nociceptive systems, at first transient, but becoming permanent with continuing illness, could in part explain the shift from acute to
chronic pain. Very recently, and using a different methodological approach, Karen Davis et al. were able to show that patients suffering from irritable bowel syndrome (IBS) show a significant cortical thinning of the ACC, a finding which has striking similarity to the findings discussed above [9].

If it is true that chronic pain patients have a common “brain signature” in areas known to be involved in pain control, the question arises whether the central reorganization processes in chronic pain syndromes could involve a “degeneration” of specific brain areas. This question is not redundant, as a degenerative process is irreversible. Although many VBM studies demonstrate changes in gray matter, the neurobiological basis of these structural alterations on a microscopic level is not well defined [54]. VBM detects changes in gray matter concentration per voxel as well as changes in the classification of individual voxels, e.g. from white to gray matter [29] and probably a combination of both. In general, a decrease in gray matter could be due to a simple decrease in cell size, neural or glial cell apoptosis, a decrease in spine density or even changes in blood flow or interstitial fluid. Unfortunately, all available studies compared cohorts of patients and therefore no statement regarding dynamic changes can be made.

10. Central plasticity: cause or consequence?

It is not understood why only a relatively small proportion of humans develop a chronic pain syndrome, considering that pain is a universal experience. As the adult human brain may change its structure in response to environmental demands [14,55], the question arises whether in some humans a (possibly genetically) structural difference in central pain-transmitting systems may act as a diathesis for chronic pain. In the course of chronification, numerous modulatory mechanisms, such as effects at the nociceptor level, sympathetically mediated pain, the “wind-up” phenomenon, central sensitization, and changes in descending and ascending central modulatory mechanisms for the perception of pain have been postulated and altogether addressed as “neuroplasticity” [80]. The recent data referred to in this article suggest that structural changes of the brain may be added to this list. Considering chronic pain as a result of “maladaptive plasticity” argues against the assumption that functional plasticity in terms of adaptation and recovery of function after lesion to the nervous system [25] is necessarily beneficial. There are no conclusive data regarding the cause or the consequence of the different cortical and subcortical morphological changes, although the correlation of pain duration and degree of gray matter decrease in most studies suggests that the morphological changes are at least in part secondary to constant pain. It is a challenge for future studies to address this crucial question. The idea of structural maladaptive plasticity, however, serves certainly well as a good model for structural cortical/subcortical reorganization following chronic input of nociceptive information.

11. The challenge for future studies

We do not know what exactly causes the observed decrease in regional gray matter shown in all the studies. Possible explanations include a simple decrease in cell size, cell atrophy or a decrease in the intra-cortical axonal architecture (i.e. synaptic loss). Important contributions to the exact causes of the structural changes will come from studies that look at the time parameters of these changes and include independent factors (i.e. electrophysiology or genetics). The findings discussed here are not precisely consistent across all studies (for example changes in different parts of the cingulate cortex). These differences could be due to scanner effects, different preprocessing parameters or analysis of the data and finally different phenotypes or genotypes of the subjects scanned. One of the key questions is whether structural alterations in the pain matrix precede or succeed the clinical process of chronification. Thorough longitudinal studies need to address whether the morphological changes reverse when the disproportionate amount of nociceptive stimulation (i.e. following sufficient pain treatment) stops. Another crucial question is, whether, analogue to functional studies demonstrating a dynamic response to frequent nociceptive input [7] a repeated painful stimulation over several days changes the structure of the healthy human brain. It may well be, that the brain of a healthy control shows a “healthy response” such as habituation and increase of respective brain structures, whereas the brain of a chronic pain patient shows a different or even diametric response. Together, these studies could answer the question whether the above-mentioned morphometric alterations are the cause or the consequence of chronic pain. Modern neuroscience faces the challenge of unraveling the complex regulatory mechanisms underlying short- and long-term neuronal reorganization, which can follow changes in the environment throughout life.

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