PERSPECTIVE

Central plasticity resulting from chronic low back pain in degenerative disorders of the spine

Degenerative disorders of the spine are the most common cause of chronic low back pain (cLBP); in Western Europe alone, billions of euros are spent each year on both conservative and surgical treatments for cLBP. And though only 5% of all patients with low back pain suffer from lumbar disc herniation (LDH), more than 30% of the overall annual cost of treating cLBP goes to this one agonizing and disabling pain disorder. Previous findings have shown that intervertebral disc herniation can occur in people who are asymptomatic (Jensen et al., 1994). However, much effort has been expended to identify prognostic variables based on the classification of the magnetic resonance imaging (MRI) of the spine. Unfortunately, no factor has yet been revealed that reliably distinguishes between patients who should be treated conservatively and those who would instead benefit from surgery. In fact, only a weak correlation has been observed between the size of the prolapsed disc and the presence of clinical symptoms (Benson et al., 2010). Since it is the brain that ultimately interprets pain, the neuroscientific community has in recent years increased its focus on studying pain-induced cerebral alterations. And indeed, the adult human brain has an astonishing capacity for the morphological alterations that follow the learning and adaptation processes necessary to a changed environment (Draganski et al., 2004). Until recently, chronic pain was thought to be associated with abnormal nociceptive function but an unchanged brain structure. Now, however, a large body of new evidence supports the idea that chronic pain not only signals an altered functional state but is also a consequence of central plasticity (May, 2011). While acute pain is associated with structural changes appearing mainly in the somatosensory system, predominantly the thalamus, chronic pain is believed to be more complex. Since the pioneering work of Apkarian and colleagues (2004), who were the first to observe cortical alterations in chronic pain, more than 50 studies investigating patients suffering from headache, migraine, phantom pain, fibromyalgia, and trigeminal and low back pain documented structural brain alterations that had occurred in the different chronic pain states. A striking characteristic of these observed structural alterations is that the changes are not distributed randomly (Smallwood et al., 2013). Thus, structural alterations of the brain were found frequently in the dorsolateral prefrontal cortices, basal ganglia and hippocampus. However, the precise locations of the regions that are affected by structural reorganization do slightly differ among the various studies. This lack of consistency is difficult to explain, but may be due to the different neuropathological mechanisms of the processes that ultimately lead to pain chronification. But it is still not at all clear why some people develop chronic pain syndromes and why others do not. It has been hypothesized that patients with long lasting pain have lost the ability to habituate themselves to pain due to increased cortical activity and/or a shift of the cortical representation, which is interpreted as either an expansion or a shrinkage of the representational field of the affected part of the body (May, 2011). The ensuing heightened sensitivity for pain is a result of central plasticity in the nociceptive pathways of the brain. This central sensitization, a form of (maladaptive) central synaptic plasticity, is a main pathophysiological cause for the development of chronic pain. Once chronic pain is generated, the increased sensitivity typically persists for a long time, even though the underlying cause of the pain is disappeared. Therefore, chronic pain is maladaptive in the sense that the pain neither protects nor support healing and repair. The underlying central malfunctions have been considered as a disease on its own right (Costigan et al., 2009).

Using voxel-based morphometry (Ashburner and Friston, 2000), we recently observed several cortical and subcortical regions with altered gray matter volume (GMV) in patients suffering from lumbar disc herniation, including a decrease in the right caudate nucleus, the orbitofrontal cortex, and the cerebellum (Luchtmann et al., 2014). In contrast, we found increased GMV in the dorsal anterior cingulate cortex (dACC) and the precuneal area, as seen in the **Figure 1**. The regions illustrated there are believed to be crucially involved in the pain perception and processing that form the concept of the *pain matrix*. As we had expected, we found no morphological alterations resulting from LDH-induced chronic back pain in the primary somatosensory cortex. Some authors explain that absence of GMV changes with the theory of cognitive maladaptation to acute pain. They speculate that significant noxious input is no longer present and that it is the brain that mostly drives the experience of constant pain. In a recent quantitative meta-analysis, Smallwood et al. (2013) investigated structural brain anomalies in different chronic pain syndromes. Several clusters were identified where GMV was altered in chronic pain patients but not in healthy controls. The only regions in the brains of the chronic pain patients found to have increased in GMV were the hippocampus and the parahippocampal gyrus. Interestingly, we observed that these specific regions showed decreased gray matter volume after microsurgical lumbar discectomy in patients with lumbar disc herniation, indicating that pain-induced maladaptive structural reorganization of the brain is potentially reversible after successful treatment (Luchtmann et al., 2015). The hippocampus itself is critically involved in anxiety, learning, and memory, and it is essential in contextual conditioning

and extinction. Until recently, though, it was thought that the hippocampus was not essential in pain processing and modulation. An increasing body of evidence has confirmed, however, that the hippocampus receives afferent pain impulses and plays an important role in pain modulation. It is an intriguing fact that the impact of preoperative pain intensity on the GMV changes in the hippocampus is significantly stronger than is the impact of pain duration prior to the surgery. The reverse constellation was found around the region of the basal ganglia. While Smallwood et al. (2013) observed in their meta-analyses that the largest, most significant decrease in GM volume of chronic pain patients was in a region that includes the putamen and the claustrum, we found the largest increase in GMV in the pallidum and putamen after successful treatment. These results are inline with the findings of several other studies investigating structural brain alterations associated with chronic pain. Seminowicz et al. (2011) likewise provided strong evidence, in their measurement of cortical thickness in patients who suffered cLBP due to spondylolisthesis, lumbar disc herniation and spinal facet arthropathy, that pain-induced changes of the brain are reversible after effective treatment. In support of the contemporary hypothesis that chronic low back pain is associated with a specific pattern of abnormal brain structure, Ung and colleagues (Ung et al., 2012) demonstrated that these changes can be classified for diagnostic purposes. With a support vector machine, they were able to distinguish, on the basis of high-resolution MRIs of the brain, between people who did in fact suffer chronic low back pain and those who did not. Their approach indicates promising progress in both our understanding of the cerebral role in cLBP and our ability to objectively classify pain syndromes.

Despite all of these remarkable findings, the results nevertheless have to be interpreted with caution. The underlying cytoarchitectonic cause of these morphological alterations is still unknown. Variable cell size, increased or decreased synaptogenesis, or an altered number of astro- and microglia might very well account for the observed structural reorganization. In addition, since almost all of the chronic pain patients studied took analgesic medications, most of which were discontinued after pain relief, the impact of these painkillers on the cortical and subcortical reorganization is not fully clear. Thus chronic opioid exposure might lead to a dose-dependent gray matter volume increase in the cingulate cortex (Younger et al., 2011). It should also be taken into account that behavioral changes resulting from the reduction or absence of chronic pain (such as engaging in physical training and making other lifestyle changes because of enhanced agility) and/or the natural course of the investigated conditions may also contribute to the gray matter volume alterations that were observed. Additionally, previous studies have shown that psychosocial variables and cognitive factors are clearly linked to the transition from acute to chronic pain disability and that these variables are associated with the continuance of pain. There is striking evidence of comorbidities (such as anxiety and depression) in chronic pain conditions that can also lead to a structural "brain signature," which indicates that these psychosocial factors increase the complexity of chronic pain disorders.

Nevertheless, we conclude from the evidence thus far that chronic low back pain and sciatica resulting from LDH can induce structural and functional alterations of the cerebral cortex that are potentially reversible after successful treatment. Additionally, the presented evidence raises the possibility that chronic neuropathic pain is similar to neurodegenerative disorders and that neuroprotective treatment could have positive impact on chronification processes (Costigan et al., 2009). Although the treatment of primary underlying cause is fundamental, understanding the pathophysiology responsible for the maladaptive central plasticity may offer additional specific therapeutic opportunities to prevent the development of chronic pain. Studying the cortical and subcortical reorganizations of the brain that result from degenerative spine disorders has the potential to enhance our understanding of the neuropathology of cLBP and sciatica and therefore may help to optimize future conservative and surgical treatment options. Particularly, the classification of specific structural alterations of the brain associated with the treatment of LDH prove useful for identifying individual predictive factors in the evaluation of whether a patient is likely to improve by non-surgical management or would instead benefit from surgery. It is interesting to speculate as to whether more advanced neuroimaging techniques and data-processing methods would enable the identification of specific patterns of altered brain functions and anatomy and thus yield additional objective diagnostic criteria that might then guide therapeutic interventions targeting the brain for effective individual management of LDH. Becoming better able to illuminate and understand more of the details underlying central pain processing in LDH, not to mention the potential economic impact of such an amplified understanding, in our view warrants future large-scale clinical studies undertaken to confirm or modify the results that we have presented here.

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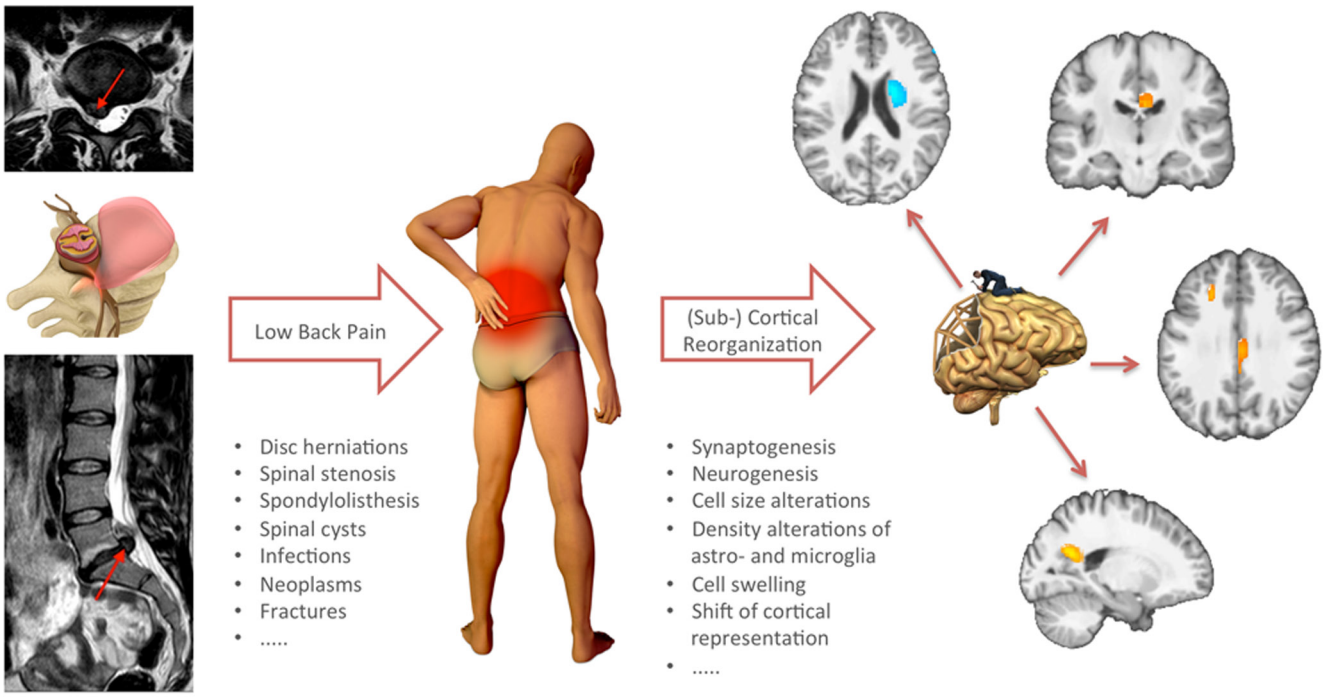

Figure 1 Chronic low back pain in degenerative disorders of the spine (*e.g.*, lumbar disc herniation) can lead to specific structural alterations of the brain.
These changes can be observed using voxel-based morphometry as increased (orange) or decreased (blue) gray matter volumes. The precise cytoarchitectonic causes of the structural alterations of the central nervous system are not fully understood yet. However, studying the cortical and subcortical changes of the brain that result from degenerative spine disorders has the potential to enhance our understanding of the neuropathology of chronic low back pain therefore may help to optimize future conservative and surgical treatment options.

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