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Neuroimaging of chronic pain

Tobias Schmidt-Wilcke*

Department of Neurology, Berufsgenossenschaftliche Universitätsklinik Bergmannsheil, Ruhr Universität Bochum, Bochum, Germany

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A B S T R A C T

Chronic pain is an important public health problem, and there is a need to understand the mechanisms that lead to pain chronification. From a neurobiological perspective, the mechanisms contributing to the transition from acute to subacute and chronic pain are heterogeneous and are thought to take place at various levels of the peripheral and central nervous system. In the past decade, brain imaging studies have shed light on neural correlates of pain perception and pain modulation, but they have also begun to disentangle neural mechanisms that underlie chronic pain.

This review summarizes important and recent findings in pain research using magnetic resonance tomography. Especially new developments in functional, structural and neurochemical imaging such as resting-state connectivity and γ-aminobutyric acid (GABA) spectroscopy, which have advanced our understanding of chronic pain and which can potentially be integrated in clinical practice, will be discussed.

Abbreviations: ACC, anterior cingulated cortex; ASL, arterial spin labelling; BOLD, blood oxygen level dependence; CNS, central nervous system; CPP, chronic pelvic pain; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; FA, fractional anisotropy; fc, functional connectivity; fMRI, functional magnetic resonance imaging; GABA, γ-aminobutyric acid; H-MRS, proton magnetic resonance spectroscopy; IBS, irritable bowel syndrome; MD, mean diffusivity; MTR, magnetization transfer ratios; NAA, N-acetyl-aspartate; NAc, nucleus accumbens; rCBF, regional cerebral blood flow; SI and SII, primary and secondary somatosensory cortex; SMA, supplementary motor area; SVM, support vector machine; VBM, voxel-based morphometry.

* Tel.: +49 2343023856.
E-mail address: tobias.schmidt-wilcke@bergmannsheil.de.

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Chronic pain: prevalence and concepts

Chronic pain is an important public health problem. The prevalence of chronic pain in Western, industrialized countries is estimated to be between 15% and 20% of the adult population [1–3]. As such, there is a need to better understand the mechanisms that lead to pain chronification.

From a neurobiological perspective, the mechanisms contributing to the transition from acute to subacute and chronic pain are heterogeneous and are thought to occur both within the peripheral nervous system and at various levels of the central nervous system (CNS). The role of the brain in chronic pain states remains to be fully elucidated; however, it has now been widely accepted that chronic pain cannot be thought of as an endless string of nociceptive inputs to an otherwise normally functioning brain, but that neuroplastic remodelling occurs on various levels of the nervous system ranging from synaptic plasticity to reorganization of large-scale neural networks, which can lead to the maintenance of pain, even in the absence of the original nociceptive input. With respect to the underlying pathophysiology, it is worth noting that there has been a substantial paradigm shift in thinking about the neurobiology of chronic pain. Until recently, chronic pain had been largely viewed as 'acute pain that is lasting too long', that is, that chronic pain results from an endless string of ongoing peripheral nociceptive or neuropathic inputs to an otherwise healthy/normal brain [4]; in other words, a patient experiences chronic pain because of a prolonged/repetitive nociceptive input originating from (sensitized) nociceptors (as in osteoarthritis), or irritated/damaged nerve fibres (as in demyelinating polyneuropathy, or nerve compression), which leads to a chronic stimulation of the central pain system, thus sustaining pain. However, this concept has been fundamentally challenged. There is now a general agreement that the CNS plays a prominent role in many chronic pain states due to the 'centralization' of pain. Some of the findings that strongly support this paradigm shift are outlined subsequently.

In addition to what are (or thought to be) obvious reasons for chronic pain (e.g., chronic inflammatory diseases, polyneuropathies, etc.), there are many patients for whom no adequate structural correlates for their pain can be found. This group of conditions includes chronic pain states such as chronic tension-type headache, temporomandibular disorder, irritable bowel syndrome (IBS), unspecific chronic low back pain, fibromyalgia and chronic pelvic pain (CPP) [5,6], and this represents the most common causes of chronic pain until patients reach advanced age and develop osteoarthritis.

Even in conditions where a pain generator in terms of a nociceptive source can be identified, the degree of measurable change/damage (e.g., in terms of joint narrowing in osteoarthritis) correlates only weakly with the degree of pain experienced [7,8]. Similarly, most individuals with diabetic neuropathy feel no pain, or even have decreased sensation, whereas others with the same peripheral 'lesion' suffer from severe pain or allodynia. These findings imply that cortical processing of the nociceptive input, as well as interindividual variability in antinociceptive mechanisms, plays a crucial role in the transition from nociception to conscious pain perception. Finally, in addition to pain per se, patients with chronic pain often suffer from additional symptoms, including depressive episodes, anxiety and chronic fatigue [9,10]. These co-morbidities add significantly to the degree of suffering in patients with chronic pain and are most likely caused by central mechanisms.

Brain imaging, as a tool to assess brain function, structure and chemistry, in this regard has had a great influence on our understanding of the neural correlates of pain perception and pain modulation, and it holds promise in further unravelling central mechanisms that contribute to pain chronification.

Neuroimaging in experimental pain conditions

In the past two decades, a variety of functional brain imaging techniques in human subjects, including functional magnetic resonance imaging (fMRI), positron emission tomography (PET), electroencephalography (EEG) and magnetoencephalography (MEG), as well as animal studies have shed light on the way in which the brain reacts to nociceptive stimuli (acute pain), thereby helping to establish the concept of the so-called 'pain system' [11]. The most influential technique has been fMRI due to its fairly high temporal resolution and the fact that no contrast agents or radioactive substances are required to image neural activation. The current review focuses on MRI findings, while acknowledging that other methods such as single photon emission computed tomography and PET have also