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Critical Review

How Neuroimaging Studies Have Challenged Us to Rethink: Is Chronic Pain a Disease?

Irene Tracey* and M. Catherine Bushnell†

*Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, Nuffield Department of Anaesthetics and Department of Clinical Neurology, University of Oxford, John Radcliffe Hospital, Headington, England, UK.
†Alan Edwards Centre for Research on Pain, Department of Anesthesia and Faculty of Dentistry, McGill University, Montreal, Quebec, Canada.

Abstract: **In this review, we present data from functional, structural, and molecular imaging studies in patients and animals supporting the notion that it might be time to reconsider chronic pain as a disease. Across a range of chronic pain conditions, similar observations have been made regarding changes in structure and function within the brains of patients. We discuss these observations within the framework of the current definition of a disease.**

Perspective: ***Neuroimaging studies have made a significant scientific impact in the study of pain. Knowledge of nociceptive processing in the noninjured and injured central nervous system has grown considerably over the past 2 decades. This review examines the information from these functional, structural, and molecular studies within the framework of a disease state.***

Key words: *Chronic pain, disease, neuroimaging, central nervous system.*

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Neuroimaging studies have made a huge impact scientifically. The techniques and paradigms are now penetrating the fields of clinical medicine,[65] diagnosis,[12] and even drug discovery.[13,88,103]

The pain field is no exception to these exciting developments, and our knowledge of nociceptive processing in the noninjured and injured central nervous system has grown considerably over the past 2 decades. To date, the focus has been to measure functional correlates of the human pain experience using either blood flow based methods, such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (FMRI), or via electrophysiological methods, such as magnetoencephalography (MEG) and electroencephalography (EEG). Many excellent reviews and several meta-analyses have been written summarizing the findings to date,[1,2,16,99] with more recent reviews focusing on the neural basis of pain modulation and its relief.[10,60,93,100,101] Techniques that focus on the structural architecture of the brain, in terms of gray matter density,[3,4] white matter connections,[8,47] receptor density,[50,56] brain biochemistry,[41,43] and neurotransmitter availability[56,91,105,108] have been applied also to the field of pain with often surprising results.

In this review, rather than regurgitate much of the information already reviewed and current regarding human central pain processing, we want to examine the information from these functional, structural, and molecular studies within the framework of a disease state. This is partly motivated by the observation that treatment options are pharmacologically and behaviorally similar for many patients, despite aetiologies for the pain, particularly when neuropathic, being different.[49,70] This has been taken as evidence that the symptoms likely share some overlapping mechanisms, common to the chronic-pain condition, which the various drugs target irrespective of the cause. Certainly, the focus on mechanism-based analgesic drug development and treatment,[73,106] reinforces this concept that some shared changes occur during the

Address reprint requests to Irene Tracey, Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, Nuffield Department of Anaesthetics and Department of Clinical Neurology, University of Oxford, John Radcliffe Hospital, Headington, OX3 9DU, England, UK. E-mail: irene@fmrib.ox.ac.uk or M. Catherine Bushnell, Alan Edwards Centre for Research on Pain, Department of Anesthesia and Faculty of Dentistry, McGill University, 3640 University Street, Room M19, Montreal, Quebec, Canada H3A 2B2. E-mail: catherine.bushnell@mcgill.ca

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transition to a chronic-pain status. The question is whether these changes are detectable using current or advanced techniques, and if so, do the changes that reflect common underlying mechanisms, constitute a diseaselike process.

Why is any of this important? Well, chronic pain is an enormous medical-health problem. Current statistics estimate that approximately 20% of the adult population have chronic pain,[14] and separate to the physical and emotional burden it brings, the financial cost to society is huge, currently estimated at over €200 billion per annum in Europe, and $150 billion per annum in the USA. Treatment options are limited with many patients either not responding or having incomplete pain reduction.[31,71,96] A paradigm shift in our thinking is needed if we are to better diagnose, manage, and treat chronic pain. Certainly beyond the immediate pain community, we need to encourage people to consider chronic pain in a new light and very possibly as a disease in its own right. This review presents the data, but we leave the reader to decide whether sufficient evidence exists to reclassify chronic pain as a disease.

Distinguishing Disease From Syndrome

According to the Compact Oxford English Dictionary (http://www.askoxford.com/), the most common definition of the noun 'disease' is "a disorder of structure or function in a human, animal, or plant, especially one that produces specific symptoms." A more expansive definition includes it being a "cause of discomfort or distress" (Oxford English Dictionary). In contrast, the definition of syndrome is "a group of symptoms which consistently occur together." The main distinction here is that in order for something to be a disease there must be an identifiable disorder of structure or function and not just a grouping of symptoms. The factors leading to the disorder of structure or function might vary, as is the case with cancer, but the end result must be a disordered system. In the case of chronic pain, the disorder would be within the nervous system. Historically, chronic pain has been labeled as a syndrome (or group of syndromes), but recent evidence, mainly from neuroimaging studies, strongly suggests that chronic pain could be labeled as a disease.

Disordered Function Producing Discomfort and Distress: Evidence from Functional Imaging

Chronic pain is discomforting and distressing for most patients. Providing objective proof that this is the case, in addition to listening to the patient or examining their behavior, can be obtained using functional imaging. Areas of the brain involved in processing and controlling affect, negative emotions like depression, anxiety, and aversion, are now better understood and include structures like the amygdala, anterior insular cortex, prefrontal cortices, parahippocampal region, amongst others. Recruitment of these regions could be taken as evidence for the patient's pain causing discomfort or distress. For instance, the processing of experimental heat pain in patients with somatoform pain disorder compared to matched controls revealed, despite similar behavioral ratings, a hypoactive state of the ventromedial prefrontal/orbitofrontal cortex (BA 10/11) and a hyperactive state of the parahippocampal gyrus, amygdala, and anterior insular.[45] An earlier study by Gracely et al[40] on fibromyalgia patients showed that pain catastrophizing, independent of depression, was significantly associated with increased activity in similar brain regions, particularly those associated with attention and anticipation to pain, as well as emotional aspects of pain. Interestingly, such findings are found across different patient types supporting common disturbances in function. For instance, in patients with Irritable Bowel Syndrome (IBS), Mayer et al[68] found that compared to patients with ulcerative colitis and control subjects, the IBS group had increased activity in response to rectal distention within the amygdala and prefrontal cortices, amongst other limbic and paralimbic regions. Kulkarni et al found that osteoarthritic knee pain was associated with increased activity in the cingulate cortex, thalamus, and the amygdala when compared to experimental knee pain.[58] Finally, focusing on the neural correlates underpinning the patients' ongoing, tonic pain, Baliki et al[5] again emphasized the relevance of the medial prefrontal cortex, including rostral ACC, during episodes of sustained, high, ongoing pain. Furthermore, its activity was strongly related to the intensity of chronic back pain.

These findings of an altered cerebral processing of either experimentally induced or disease-related pain in patients support previous findings identifying the relevance of these structures in pain anticipation,[15,77,79,80] and anxiety-induced pain amplification.[29,76]

Evidence of disturbed prefrontal activity and a dysfunction of emotion regulation during experimental pain stimulation in depressed patients have been shown in recent studies.[7,95]

Such data forces us to think about how factors associated with chronic pain conditions, like depression, can become part of the overall condition itself and contribute to the discomfort and distress via increased activity within relevant brain regions. For instance, in patients with fibromyalgia, it has been shown that their degree of depression was related to amygdala and anterior insular activity during experimental pain,[38] as well as medial prefrontal cortex activity during disease-relevant induced pain in patients with rheumatoid arthritis and suffering depression.[90]

The anterior insular cortex is particularly intriguing because of its role beyond pain perception. Current thought links activity within the anterior insula to, among other factors, interoception, body awareness, anxiety, depression, fear, and possibly even consciousness.[18-21] There is therefore a potential link to a sense of body disturbance, discomfort, and distress. In a meta-analysis performed by Schweinhardt et al,[89] it was shown that the peak coordinate of activity in clinical pain was shifted to the anterior insular cortex compared to nociceptive pain in healthy volunteers, whose activity was more

midposterior insular. This apparent maladaptive plasticity and shift in brain activity towards the more affective division of the insular cortex is perhaps indicative of a functional disturbance.

One consequence of this discomfort and distress is the impact it has on a patient's cognition,[28] and is perhaps a direct way of confirming the presence of centrally induced alterations in normal cognitive functioning due to pain. While many neuroimaging studies examine the neural basis for how attention and distraction modulate the pain experience, they have largely been done in healthy control subjects and not patients.[101] The reverse has rarely been examined,[93] namely identifying a disruption in normal cognitive brain processing due to the presence of pain, except for 1 study in healthy controls.[11] Studies looking at how pain alters your capacity to make rational decisions due to biases in cost and reward calculations identify, again in healthy subjects, that pain is clearly disruptive to normal cognition,[94] and one can readily extrapolate these findings to testable experiments in patients that might produce further evidence to support functions being disturbed.

In summary, these findings strongly support the case for dysfunctional pain processing, especially in affect-regulating regions, and that these patterns of brain activity strongly reflect patients being in true discomfort and distress.

Disordered Functions and Departure from State of Health: Evidence from Functional Imaging

We shall examine 3 areas where normal physiological functions have been shown to be disturbed in chronic pain states, indicating a departure from a state of health: 1) resting state networks; 2) descending inhibition and facilitation; and 3) thalamic asymmetry.

Resting State Networks

Several years ago, it was observed that subjects undergoing neuroimaging data collection while at rest displayed functional connectivity of specific cortical regions,[32,44] and that this observation was robust across subjects and modalities. These connectivities are now considered as components of the default mode network (DMN), a set of brain regions including medial prefrontal cortex, medial temporal lobes, and posterior cingulate cortex /retropslenial cortex that display balanced positive and negative correlations and are disrupted in several neurological and psychiatric disorders.[22,32,82,84] In response to task performance, certain areas within the DMN reliably deactivate, and in an early study, we found complete abolishment of normal nociceptive-induced deactivation in the capsaicin model of central sensitization in the presence of gabapentin,[54] suggesting a possible interaction with the default mode network. Baliki et al[6] more specifically investigated whether long-term pain alters the functional connectivity of these cortical regions known to be active at rest. During execution of a simple visual task, which patients with chronic back pain performed as well as controls, they found that patients displayed reduced deactivation in several key default-mode network regions. Their findings demonstrate that chronic pain, like other major neurological and psychiatric diseases, has a widespread impact on overall normal brain function.

Descending Inhibition and Facilitation

The descending pain modulatory system is a well-characterized anatomical network that enables us to regulate, largely within the dorsal horn, nociceptive processing in varying circumstances to produce either facilitation or inhibition.[30,48,100] The relevance of descending facilitation in chronic-pain states has gathered considerable momentum over the past few years,[37,78,97] and our human work in models of central sensitization confirm that this facilitatory system becomes active and underpins the maintenance of the centrally sensitized state.[54,59,107] In parallel, many studies in chronic-pain patients have highlighted also a dysfunction in the normal descending inhibition displayed by healthy volunteers, indicating a dysfunction in this powerful and dedicated endogenous pain modulatory system in chronic pain.[9,39,46,63,83,92]

Thalamic Asymmetry

Experimentally induced tonic pain has previously been reported to result in less thalamic activation when compared to acute phasic pain in PET studies.[25] However, controversy exists, as increased blood flow to the thalamus has also been reported and thought to reflect an arousal reaction to pain,[75] and to be involved in the processes of attention and vigilance.[33,81] Evidence from patient studies, however, supports the fact that blood flow to the thalamus is reduced: A common finding has been a relative decrease in thalamic CBF during ongoing pain, which then receded after analgesia and symptom improvement.[26,34,35,52,53,74] Indeed, historically, thalamic infarcts have long been recognized as a cause of spontaneous pain[24] and more recently, atrophy of the thalamus has also been reported in patients with chronic back pain using voxel-based morphometry (see section below).

Therefore, perhaps the most convincing data directly to support the idea that pain is a disease, rather than a syndrome, involves evidence that it is a disorder of structure, as well as function. This is consistent with the definition of disease ("a disorder of structure or function in a human, animal, or plant, especially one that produces specific symptoms.")

Disturbed Structure of the Brain: Evidence from Anatomical MRI

In 2004, Apkarian et al[3] reported that chronic-pain patients had less brain gray matter than age-matched control subjects. That study was conducted in chronic low-back pain patients and showed that such patients had reduced gray matter in the thalamus and in the lateral prefrontal cortex, a region involved in descending pain modulation. The gray-matter loss was greater in patients who had neuropathic type symptoms than ones who did not, and the

decrease in gray matter correlated with the duration of the symptoms. Similar studies have now been conducted in patients with chronic headache, fibromyalgia and irritable bowel syndrome (IBS), and chronic regional pain syndrome (CRPS).[66] Although the details of which brain regions show the largest effects differ among studies, gray-matter decreases have been observed in all of these populations.[23,36,57,61,85,86] The predominant gray-matter decreases observed in patients with chronic pain contrast with usage-related increases in brain gray matter that has been observed during learning,[27] and during repeated painful stimulation in healthy subjects.[98] Similarly, patients with cluster headache who show increased hypothalamic activation have increased gray matter in the region of increased activation.[67]

Another anatomical neuroimaging method, diffusion tensor imaging (DTI), allows in vivo mapping of the anatomical connections in the human brain. Hadjipavlou et al[47] used this method to identify anatomical circuitry involved in the top-down influence on pain processing, involving the periaquaductal grey (PAG) and its connections with the prefrontal cortex, amygdala, thalamus, and rostroventral medulla. This method has now been applied to chronic-pain patients, where we see disruptions of structure within brain regions involved in normal modulatory influences on pain.[36,61]

Together, these anatomical studies show that chronic pain is associated with structural changes in the brain. Nevertheless, the current cross-sectional studies tell us little about cause and effect. This is particularly important, since chronic-pain patients frequently have comorbid conditions, including anxiety and mood disorders, altered life-styles so are generally more sedentary, and are also taking various drugs that themselves might be contributing to these measured changes. Thus, it is possible that the gray matter changes are related to the comorbid factors and not to the pain itself. Although some studies have excluded patients with major comorbid conditions such as depression,[57] other studies suggest that such factors are important to the gray-matter changes. For example, Schmidt-Wilcke et al[87] observed that when depression and age were included as nuisance factors, most of the observed gray-matter changes were no longer significant, Similarly, we cannot identify from these neuroimaging studies the cellular basis for changes in grey-matter size—is this a neurodegenerative phenomenon, or are the structural changes related to non-neural cells? In order to answer these questions, animal studies are needed. Animal models are available to address a number of chronic pain conditions, including neuropathic pain, headache, CRPS, arthritis, inflammatory visceral pain conditions, and back pain. On the other hand, such models do not completely mimic functional pain conditions, where the etiology is unknown. Nevertheless, the use of rodents with short life spans will allow us to conduct longitudinal studies lasting only months, but covering a large part of the animal's life span. A recent 5-month longitudinal study of rats undergoing a nerve injury (spared nerve injury—SNI) revealed reductions in the size of frontal cortex, but not until 20 weeks after the injury. Although the rats showed mechanical and thermal hyperalgesia from the time of the injury, they began demonstrating anxiety-like behavior at approximately the same time as the changes in frontal cortex became manifest (Seminowicz et al, in press). Many chronic-pain patients show anxiety-like behavior after their pain has persisted for months or years, so it is interesting to speculate that some of these secondary effects of chronic pain may well be associated with structural changes in the brain.

Rodent studies also allow for histological analysis of the tissue, thus helping us interpret the anatomical changes seen with neuroimaging methods. Metz et al[69] investigated layer 2/3 pyramidal neurons in acute slices of the medial prefrontal cortex (mPFC) in the rat SNI model of neuropathic pain. These investigators found changes in dendritic branching and spine density of the neurons, providing the first direct evidence of anatomical changes at the cellular basis associated with chronic pain.

Neurochemical Disruptions in the Brain: Evidence from PET Studies

Studies are now beginning to show that chronic-pain patients may have altered brain neurochemistry. Using in vivo proton magnetic-resonance spectrometry (^{1}H-MRS), Grachev et al[42] observed altered brain chemistry in the frontal cortices of chronic back-pain patients. Decreased levels of the neuronal marker N-Acetyl aspartate were observed in the dorso-lateral prefrontal cortex, a region in which gray-matter decreases were also observed in back-pain patients. Using similar techniques, Mullins et al[72] showed that glutamate is elevated in the cingulate cortex in response to painful stimuli in healthy humans, and Harris et al[51] showed that reductions in glutamate in the posterior insula in fibromyalgia patients is associated with reduced experimental and clinical pain. These neurochemical findings add further evidence to the idea that reduced gray-matter density in chronic-pain patients may be related to possible excitotoxicity and neuronal loss.

Other studies show possible changes in neurochemicals involved in pain modulation in chronic-pain patients. Two seminal molecular-imaging studies using positron emission tomography (PET) in chronic-pain patients showed cerebral decreases in opioid receptor binding in patients with central neuropathic pain and with rheumatoid arthritis.[55,56] More recent PET studies in fibromyalgia patients show alterations in both dopamine and opioid availability in the forebrain.[50,104] In the absence of external painful stimuli, fibromyalgia patients appear to have a reduction in the receptor availability of both dopamine D2 receptors and opioid mu-receptors in parts of the forebrain. For dopamine, it has also been shown that patients do not release dopamine in the basal ganglia in response to an external pain stimulus, whereas healthy subjects do release dopamine in that situation.[91,105] Such results may mean that patients have decreased receptor availability or have a heightened background tone or endogenous release of these neurotransmitters that is known to produce a reduced phasic release, but in either case, it appears that neurochemicals important for pain modulation are not responding as

they do in healthy individuals. Again, these findings are not specific to fibromyalgia but are shown for other chronic-pain conditions. Willoch et al[102] found in patients with central poststroke pain reduced opioid binding in pain-processing regions and Maarrawi et al[62] showed differential opioid-receptor availability in central and peripheral neuropathic-pain patients. Combined, these studies strongly support the case for disorder or dysfunction in the neurochemistry of chronic-pain patients' brains.

Does the Evidence Prove that Chronic Pain is a Disease?

This review has presented substantial functional, anatomical, and neurochemical evidence that chronic-pain patients have altered brains. But is what we see as altered and dysfunctional central nervous system processing more an adaptive response to the constant nociceptive barrage rather than a diseaselike process? The chicken and egg problem here is that for most "diseases" normally something within the body alters and changes function and possibly structure, and this process itself largely produces the symptoms and condition. For pain, we only have evidence of such changes after the transition to chronicity; therefore, it's difficult to know whether these mechanism-based changes are simply a normal adaptive response or are critical for the chronic-pain state itself. Reversibility of such changes with symptom improvement might help clarify this issue. However, if these changes could be induced without any initiating nociceptive input, would a chronic-pain-like state occur? In many conditions, chronic pain results after a clear tissue-damaging event, leading first to acute pain and then to chronic pain. Most neuropathic pain conditions have a clear nerve injury that precipitated the pain. Nevertheless, other painful conditions come about without a clear precipitating injury. These conditions, such as fibromyalgia, vulvodynia, interstitial cystitis, and irritable bowel syndrome, are sometimes referred to as functional pain syndromes, because the patient presents with pain without an obvious physiological cause. Could these conditions be related to pathophysiology of the central nervous system that is similar to that caused by a constant nocicieptive barrage in other pain conditions? Recent data from animal studies investigating stress-induced hyperalgesia[64] and peripheral hypersensitivity without peripheral inflammation after amygdala activation[17] provide support for this concept. Could an excitotoxicity of pain-modulatory circuitry be evoked not only by hyperexcitability of the afferent nociceptive system, but also, given the right genetic susceptibilitly, by activation of the stress, arousal, or attentional circuitry in humans? At this time, we can only speculate about these mechanisms.

Conclusion

By taking a multifactorial and longitudinal approach to the study of chronic pain, including in our analyses genetic and environmental factors, and merging data from the molecular to the clinical level, we may someday unravel the complexities of chronic pain. But for now, imaging studies have shown that chronic pain is associated with functional, structural, and chemical changes in the brain, thus putting it into the realm of a disease state.

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