

**Title:**

Neuroimaging as a tool for pain diagnosis and analgesic development

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## **Abstract**

Neuroimaging makes it possible to study pain processing beyond the peripheral nervous system, at the supraspinal level, in a safe, non-invasive way, without interfering with neurophysiological processes. In recent years, studies using brain imaging methods have contributed to our understanding of the mechanisms responsible for the development and maintenance of chronic pain. Moreover, neuroimaging shows promising results for analgesic drug development and in characterising different types of pain, bringing us closer to development of mechanism-based diagnoses and treatments for the chronic pain patient.

**Key Words: neuroimaging, pain, analgesia, drug development**

## Introduction

The pathophysiology of chronic pain conditions is not fully understood, which hinders development of new mechanism-based analgesic therapies. Unlike acute pain, there is no specific and effective medication to treat chronic pain. New drugs that appear on the market are mostly just refinements of existing drug classes.

Pain is not just a warning symptom informing our body of actual or potential damage to the tissue, although that is its primary function. Pain is also a complex, unpleasant sensation with sensory, emotional, and cognitive dimensions. Here, we will be concerned mostly with chronic pain. Pain is defined as chronic when it accompanies chronic disease or has lasted longer than three months, despite resolution of the disease or healing of the injury that caused it. The important characteristic of chronic pain is that it loses its warning function and becomes a disorder in its own right <sup>1</sup>, possibly even a disease <sup>2</sup>.

Over the last 20 years brain imaging methods, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have greatly contributed to our understanding of the perception and modulation of the pain experience with several recent reviews covering these developments <sup>3-7</sup>. It is now accepted that the central nervous system plays a crucial role in pain processing and many characteristics of chronic pain are caused by changes within the nervous system <sup>6, 8</sup>. Neuroimaging techniques provide a tool for understanding the mechanisms involved in generating and sustaining chronic pain. Moreover, neuroimaging can potentially be used as an objective, reliable and perhaps more sensitive method to assess the efficacy of analgesic drugs, compared to subjective reporting, and as such aid development of new treatment strategies <sup>9-14</sup>

Most of our current knowledge of pain processing is based on acute pain or pain-model studies in healthy volunteers. These studies are easier to interpret as a standardized stimulus is used in a homogeneous population. From the brain imaging studies on experimental pain in healthy volunteers, we know that acute pain evokes a largely bilateral

response in several brain regions including the primary and secondary somatosensory, and insular cortices, the anterior cingulate gyrus, the prefrontal cortex and the thalamus. Pain-related activation in these regions can be amplified/attenuated with further activation identified in the posterior parietal cortex, brainstem, basal ganglia, amygdala, cerebellum as well as other areas dependent upon the individual's mood, cognitive state and context of the situation<sup>3</sup>. From these studies, it is clear that there is no single "pain centre" in the brain, but rather there is an extensive, interconnected network of cortical and sub-cortical structures involved in the central processing and generation of a pain experience.

In short, pain is not a straightforward sensory process. Firstly, the pain experience does not necessarily linearly relate to magnitude of the intensity of the nociceptive stimulus. As nociceptive information is transmitted along sensory pathways it undergoes modulation, including both facilitation and inhibition, within the dorsal horn of the spinal cord. Secondly, pain is a multidimensional, unpleasant conscious experience strongly modulated by external (e.g. contextual) and internal (e.g. psychological, genetic) factors<sup>15-18</sup>. Neuroimaging studies have demonstrated that negative emotions, such as depression or anxiety, augment the perceived pain intensity<sup>18</sup> and increase the pain-related brain activation<sup>19</sup>. How the pain is experienced is also affected by attention<sup>20, 21</sup>, anticipation<sup>22</sup> and pain memories<sup>23</sup>. And of course the perception of pain changes in pathological states such as inflammation or after lesion to the sensory nervous system<sup>3, 24</sup>.

### **Experimental and clinical pain: Same or different brain regions?**

To date, relatively few studies have focused on the neural correlates of experimental, phasic pain in patients and even less on ongoing, tonic pain. Therefore, it is not certain whether the same brain regions that are associated with the experimental pain are also involved in pathological chronic pain syndromes<sup>25</sup>.

In recent years, there have been an increasing number of clinical pain studies

providing new insights into pathological mechanisms of chronic pain. The results of an early meta-analysis done by Apkarian and colleagues <sup>6</sup> suggest that there are differences between pain processing in healthy volunteers versus chronic pain patients. The regions most frequently observed in connection with acute pain in healthy volunteers were the primary and secondary somatosensory cortices, the anterior cingulate cortex, the insular cortex, and the thalamus, whereas in chronic pain patients activation in these regions was reported less often (activated in 82% of healthy volunteers' studies versus 42% of patients' studies). The region most often reported activate in clinical pain studies was the prefrontal cortex (81% in patients versus 55% in healthy controls) <sup>6</sup>.

The prefrontal cortex is involved in pain control mechanisms, in processing the ascending input from the spinothalamic tract, and it is a source of descending modulation via its connections to the brainstem's descending pain modulatory system <sup>5</sup>. This region plays an important role in interoception, cognition, and processing of negative emotions and outcomes <sup>7, 26, 27</sup>. Activation in the medial prefrontal cortex was reported during ongoing lower back pain, and correlated with the intensity of the pain <sup>28</sup>. The thalamus is another region affected by chronic pain. Several studies reported a decrease of cerebral blood flow and metabolic rate in the thalamus contralateral to the clinical pain <sup>29-31</sup>. These changes normalise after successful pain treatment <sup>32</sup>. Apkarian and colleagues <sup>6</sup> suggest that, in patients there is a decrease in the sensory aspect of pain processing and an increase in affective and cognitive processing of pain. This may be a result of clinical pain having a stronger emotional value <sup>33</sup>. Another possible explanation is that the ongoing pain leads to more generalised changes, affecting the baseline state and leading to an altered response to evoked pain <sup>6</sup>. This explanation is congruent with a study by Baliki and colleagues <sup>34</sup> who reported changes in the default brain activity in chronic pain patients in comparison to healthy controls. This disruption of the default state network may explain the different activation pattern observed

in clinical pain studies than in healthy controls, as well as the cognitive and behavioural impairment reported in chronic pain patients<sup>35</sup>.

Pain is not passively transmitted to the brain. The nociceptive inputs are changed and modulated at each level of the pain neuraxis. The inputs from the dorsal horn of the spinal cord are modulated (inhibited or facilitated) by the powerful and endogenous descending pain modulatory system. This system involves monoaminergic projections from the higher brain regions including the prefrontal cortex, the anterior cingulate cortex, the insular cortex, the amygdala, the hypothalamus, and the brainstem. It has been demonstrated, in human models of pain, that the pain modulatory system is critical for sustaining central sensitisation in menthol<sup>36</sup> and capsaicin-evoked allodynia<sup>37, 38</sup>. In a study on capsaicin-evoked allodynia and its modulation by gabapentin, the brainstem was the main region where the effect of the drug on sensitisation<sup>38</sup>. The pain modulatory system is also crucial for sensitisation and maintaining chronic pain in patients<sup>39</sup>. Patients with chronic pain, either neuropathic or inflammatory, have impaired endogenous control of pain with increased descending facilitation or impaired inhibition<sup>40-42</sup>.

From the above, it's clear that several potential brain regions and networks might serve as objective, non-invasive 'biomarkers' for specific aspects of the pain experience, and as such be used to aid diagnosis and as surrogates for determining analgesic efficacy.

### **Evoked versus spontaneous pain in chronic pain patients**

In chronic pain patients, there are differences in the brain activation pattern in response to evoked (i.e. acute) pain in comparison to the ongoing, tonic pain. The evoked pain results in similar brain activation as the acute pain in healthy controls<sup>43-45</sup>. Tonic clinical pain results in different brain activity pattern, than evoked clinical pain; for example dynamic mechanical allodynia in patients with post-herpetic neuralgia results in different activation patterns than the ongoing pain<sup>43, 46</sup>. Also the evoked pain differs from the ongoing, tonic pain

in patients with arthritis <sup>44</sup>. This observation is very important for treatment development as it highlights the fact that the evoked pain typically used in pain studies, even though it is disease-related, is not the same as the ongoing pain the patients experience during the course of their disease and often describe as their most problematic symptom.

In a study on chronic back pain it was shown that ongoing, tonic pain correlates with stronger activation in the regions involved in emotion, cognition and motivational drive, such as, the medial prefrontal cortex, the rostral anterior cingulate cortex, as well as the thalamus and amygdala <sup>28</sup>. However, the increase of the intensity of their clinical pain correlates with activation in the regions observed during acute pain processing, i.e. the somatosensory cortices and the insular cortex <sup>28</sup>. Kulkarni and colleagues also observed differences between ongoing arthritic pain and evoked pain. Both conditions activated several brain regions, sensory, affective and motivational, but the tonic pain was associated with activation in the brainstem and greater activation in the regions involved in affective processing of pain <sup>44</sup>. The long-term treatment effect and reduction of tonic pain correlates with activation in the areas processing emotions and reward <sup>46</sup>.

### **Are we closer towards using imaging for a mechanism-based classification of chronic pain?**

Different types of allodynia can result in distinct brain activation patterns, which is congruent with results of psychophysical studies and the hypothesis that different types of allodynia have different pathophysiological mechanisms. From a study on syringomyelia by Ducreux and colleagues <sup>47</sup>, they reported different results of psychophysical tests, as well as distinct activation patterns between patients with cold allodynia, and patients with tactile allodynia. The only region that was consistently activated during both types of allodynia in this study was the pre-frontal cortex. Cold allodynia evokes responses in dorsolateral prefrontal cortex and brainstem (regions usually involved in sensitization), in addition to the

regions activated in response to the noxious cold <sup>48</sup>. Activation in the prefrontal cortex was found also by Schweinhardt and colleagues <sup>49</sup> in their study on neuropathic pain patients, as well as in other studies on capsaicin-evoked allodynia in healthy volunteers <sup>50</sup>.

As with many preclinical models of disease there are always limitations regarding how well they mirror the patient condition. This is certainly the case for preclinical pain models, which despite displaying key symptoms of chronic pain patients well, are difficult to behaviorally assess regarding the presence and severity of these symptoms, in particular the affective components. Furthermore, models usually reflect a single mechanism or symptom of pain whereas, in chronic pain conditions there is usually more than one symptom and mechanism driving the pain <sup>51</sup>. Likely these shortcomings have contributed to the low predictive capacity of analgesic efficacy in patients of these preclinical models of pain. Neuroimaging *per se* or when coupled to standardized psychophysical assessments, such as quantitative sensory testing, may help to diagnose which mechanism is responsible or dominant for pain in a particular patient <sup>52</sup>. For many years it has been known that there is a need for better characterization and mechanism-based classification of pain <sup>53</sup>.

### **Neuroimaging as a tool for assessing drug-induced analgesia and “reverse-translation” to preclinical models**

Currently, in order to measure pain we have to rely on a patient’s subjective report using unidimensional rating scales. These scales, although easy to use and accepted in clinical and research settings, are imprecise, relative, context-dependent and vary significantly between and within patients. Moreover, pain scales do not provide information about the underlying pain mechanisms <sup>54</sup>. Neuroimaging offers an objective and quantitative method to assess pain by measuring the magnitude of pain-related brain activation <sup>55</sup>. This method has its limitations, but it is a step forward from using the patients’ report.



Arguably the same argument can be made for animal models of chronic pain where the behavioural read-out is even more difficult to relate to underlying mechanisms. There is now increasing enthusiasm to apply functional imaging methods in preclinical models of pain in combination with drugs <sup>12, 54, 56, 57</sup>. The body of knowledge we've gleaned from human studies regarding central pain mechanisms could be more aggressively "reverse-translated" to guide these preclinical models. We believe this to be a promising future direction and potential opportunity for neuroimaging methods in the next decade.

As described above, neuroimaging is promising as a tool to study mechanisms sustaining and exacerbating chronic pain. It is still poorly understood how chronic pain is maintained and why it persists. At the same time treatment depends on mechanisms rather than aetiology <sup>58</sup>. Understanding the neurophysiological mechanisms of pain would lead to optimisation of therapy, help to better identify patients who would respond to treatment, and potentially help identify new treatment strategies.

Neuroimaging may be used as a tool to assess the effects of peripherally and centrally acting analgesics. Brain imaging studies are able to demonstrate effects of drugs on the central nervous system comparable with the behavioural measures. There are several studies published on remifentanyl, a rapidly acting opioid receptor agonist, and its effect on pain processing. Functional MRI has proven to be sensitive enough to detect changes in brain activity with increased concentration of the drug, and to demonstrate the correlation between the brain activation, and both drug dose and pain ratings <sup>59-62</sup>. Functional neuroimaging can be also used to study the pharmacodynamics and pharmacokinetics of analgesic drugs <sup>63</sup>. Furthermore, imaging is a tool that can improve or clarify our understanding of the likely mechanism of action of approved analgesic drugs, as well as their side effect profiles; for example, the study on capsaicin-evoked sensitisation model and gabapentin by Iannetti and colleagues <sup>38</sup>. Moreover, and as mentioned above, neuroimaging is useful for translation and reverse translation between preclinical models, healthy volunteer models, and patients <sup>64</sup> as

illustrated in Figure 1. Furthermore, brain imaging techniques may be used in drug development as a measure of drug efficacy with assessment of plasma drug concentration as a measure of exposure. This would provide an objective marker of treatment effect in Phase I and II of drug development, therefore improving and accelerating the drug discovery process (see Figure 1).

There are, however, certain limitations in the application of functional imaging methods in clinical studies. First, the disease or medication may affect the neurophysiological process we are measuring as a surrogate marker of brain activity; for example, changes in neurovascular coupling or changes in metabolic activity. Therefore, it is important to control for these effects while designing drug studies using neuroimaging methods. There are several ways of dealing with these limitations using control tasks to assess global haemodynamic effects, independently measure the baseline physiological state using arterial spin labelling methods, that directly and quantitatively measure regional blood flow changes, or measure physiological parameters. Secondly, none of the functional imaging methods have both superior temporal and spatial resolution. Using multi-modal imaging, for example combining fMRI with electroencephalography or with magnetoencephalography, allows us to establish in which order brain regions become active in response to a painful stimulus. Combining fMRI with PET makes it feasible to study neurochemical changes such as decrease in opioid binding that normalizes after reduction of pain<sup>65</sup>. Recently, it has become possible to collect whole brain data using arterial spin labelling rather than just a single slice<sup>66</sup>. This opens new possibilities; for example, controlling for baseline blood flow in fMRI studies, comparing global changes before and after treatment or studying ongoing, continuous pain; as this method allows quantitation of the blood flow not just relative changes as measured using fMRI.

Clearly there are many other, non-pharmacological ways of producing analgesia: surgical, cognitive behavioural therapy, alternative. Only a few imaging studies have

attempted to determine the neural basis for any analgesia produced <sup>67-69</sup>, but again these methods lend themselves to further study and improvements in our understanding of these additional lines of therapy. Understanding the neural basis of pleasure and relief provides alternative strategies and potential targets for intervention aimed at taking the “hurt” away <sup>70</sup>.

### **Consequences of not alleviating chronic pain: Structural brain changes**

The results of neuroimaging studies on brain structure or chemistry demonstrate that chronic pain affects not only the function of the brain, but can lead to long lasting changes. Some of these changes seem to be reversible, when the pain is alleviated <sup>8</sup>. However, some studies suggest that the pain-related changes may reflect neurodegeneration, rather than neuronal reorganisation <sup>71-73</sup>. The changes were observed in several brain areas and may be an acceleration of age-related brain atrophy. Apkarian and his group demonstrated that in patients suffering from lower back pain, the density of the grey matter decreases in several cortical and subcortical areas, including the prefrontal cortex <sup>71</sup>. There was also a decrease of the N-acetylaspartate concentration, a marker of neuronal well-being, in the prefrontal cortex of these patients <sup>74</sup>. The reduction of grey matter has been described not only in lower back pain <sup>16, 75</sup>, but also in several other chronic pain conditions such as migraine <sup>76, 77</sup>, chronic tension headache <sup>72</sup>, irritable bowel syndrome <sup>78</sup> and fibromyalgia <sup>79</sup>. It remains to be determined whether these changes are due to chronic pain conditions itself, the drugs the patients are taking, the lifestyle changes due to disuse or a combination of these factors. Current work attempts to disentangle the causal nature of this degeneration <sup>2</sup>.

### **Conclusions**

Neuroimaging is a non-invasive method that objectifies pain and allows the neurophysiology of pain processing, as well as the pathological changes that occur in chronic pain conditions, to be studied. There is a need to better understand the mechanisms

responsible for the generation and maintenance of chronic pain and for the development of new, effective therapies. In a relatively short time period, neuroimaging studies have contributed significantly to this goal and our understanding of the pathophysiology of chronic pain. We firmly believe that neuroimaging based methods may potentially improve mechanism-based classification of pain and lead to better diagnostic accuracy and identification of patients who would respond to treatment. Neuroimaging may improve drug development by making the evaluation of treatment efficacy easier and more objective, and critically by identifying new therapeutic targets. We believe therefore, that neuroimaging methods will become part of the pharmaceutical industry's analgesic development process, but that they will rapidly penetrate additional areas of application in the coming decade.

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