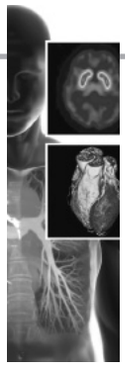

Investigating pain networks in the spinal cord using functional MRI

"In order to obtain information noninvasively about the complete pain processing network throughout the brain, brainstem and spinal cord, there is only one method available, namely functional MRI."

KEYWORDS: BOLD ■ function ■ human ■ imaging ■ SEEP

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Pain research is particularly challenging due to the fact that pain is subjective, being the net effect of physical, emotional and cognitive influences. Two people might perceive the pain caused by a noxious stimulus quite differently, or a person may perceive an identical stimulus to be more or less intense, depending on their attention focus or emotional state. It is a fairly common to say that 'pain is in the mind' or, alternatively, that 'pain is in the brain'. However, these two statements do not mean the same thing. Regions outside of the brain, including the brainstem region, such as periaqueductal gray (PAG) matter and the rostral ventromedial medulla (RVM), have been known for decades to play an important role in the perception of pain [1]. Electrical stimulation of the PAG appears to eliminate pain, but the effect of this stimulation is incompletely blocked when areas of the RVM are inactivated with anesthetics. The PAG and RVM project descending input to the spinal cord to modulate the responses of neurons to input from the periphery. The descending modulation can either inhibit or facilitate the transmission of pain, and there is tonic input to the spinal cord when the normal healthy balance in this network is maintained. A key part of the pain response also includes the ascending input from the spinal cord to the brainstem and thalamus via the spinothalamic tract. From the thalamus, there are projections to the key areas in the brain, termed the 'pain matrix', such as the somatosensory, insular and anterior cingulate cortices. It has been argued that the role of brain regions in the emotional and cognitive aspects of pain have received too little attention compared with the role of the spinal cord in pain [2]. However, relatively few functional MRI (fMRI) studies of pain in humans have extended outside the brain. It appears from the anatomical pathways that are now known to be involved with the perception of pain, that the complete integrated network spanning the brain, brainstem and spinal cord is necessary to explain the pain experience. While pain may be in the mind, it is certainly not solely in the brain.

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Based on the emotional and cognitive components of pain, it could be argued that a complete understanding of pain processing in humans can only be achieved with research involving human volunteers, as opposed to with laboratory animals. Clearly, however, extremely valuable pain research has been carried out in animals, and accounts for most of our knowledge of pain to date, with the limitation that only certain aspects of pain can be studied in such models. Studies of the neural processes involved with pain processing in humans must be carried out using noninvasive methods, in order to avoid the need for analgesics or anesthetics that would necessarily alter the pain response, and of course, must be within ethical limits for the treatment of research volunteers. As a result of these requirements toward human pain research, the range of techniques that can be used is narrowed considerably. In order to obtain information noninvasively about the complete pain processing network throughout the brain, brainstem and spinal cord, there is only one method available, namely fMRI.

Functional MRI of the brain has become well established over the past two decades, and fMRI of the spinal cord (spinal fMRI) has also been under development for approximately

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15 years, but its usage is far less widespread and its development has progressed more slowly as a result. Nonetheless, some important studies of pain processing in the spinal cord have been carried out using spinal fMRI. These studies have demonstrated the network of areas involved with thermal sensation/pain [3–5], as well as the network of areas involved with pain caused by light touch and brush sensations on skin that has been sensitized with capsaicin, and how the responses are different than those observed prior to sensitizing the skin [6]. In a subsequent study, differences were demonstrated in the descending modulation of pain responses in the spinal cord, in people with carpal tunnel syndrome [7,8]. Both of these studies highlighted the importance of the descending modulation signals from the brainstem, including the RVM and the dorsolateral pontine tegmentum.

> *"The optimal method for brain fMRI is well established as being T_2*-weighted gradient-echo EPI with BOLD contrast, whereas the optimal method for spinal cord fMRI is the proton-density-weighted fast-spin-echo imaging method with SEEP contrast."*

Two other relevant studies did not focus specifically on pain, but rather on attention and cognitive/emotional factors related to being within the MRI system and participating in fMRI studies that are not particularly mentally engaging (i.e., participating in these studies is boring) [3,9]. The results showed that activity in the spinal cord is altered significantly depending on whether or not a person focuses their attention on a sensation or focuses their attention on something else. Therefore, the difference in pain that you experience when you 'block it out' by not thinking about it, does not happen only in the brain, but involves control in the spinal cord. While this result is somewhat expected based on the known anatomy, it reveals the importance of the role of the spinal cord in the experience of pain, and confirms that the spinal cord is not a mere relay point for information on its way to the brain. Variations in descending modulation from the brainstem and local processing in the spinal cord may contribute to a wide range of effects, such as chronic pain after spinal cord injury, phantom limb pain and the placebo effect [10].

The method that has been used for the majority of the spinal cord fMRI studies published to date has received scepticism and criticism in the past, because it is different in some aspects from the established brain fMRI method. The method is based on signal enhancement by extravascular water protons (SEEP), which is caused by changes in tissue water content at sites of neural activity, and can be detected with proton-density-weighted imaging, as opposed to the blood oxygenation-level dependent (BOLD) contrast, which is the standard for fMRI and requires T_2* weighting. The necessity of relying on the SEEP contrast mechanism arises from the fact that T_2*-weighted imaging in the spinal cord gives poor image quality owing to the inhomogeneous magnetic field environment caused by bone–tissue interfaces within the spine. The image quality is further degraded when echo-planar imaging (EPI) schemes are used to achieve short image acquisition times, with the trade-off being high sensitivity to magnetic field distortions. Conventional BOLD fMRI using T_2*-weighted EPI methods have been shown to give poor image quality and poor spatial localization of areas of activity in the spinal cord. In the presence of metallic fixation devices used to stabilize the spine after trauma, the conventional BOLD fMRI method cannot be used at all. By comparison, fMRI data acquired in the spinal cord with single-shot fast-spin-echo imaging has been shown to give very good image quality, even in the presence of metallic fixation devices, and images can be acquired in sagittal planes to provide data from a large extent (~28 cm) of the spinal cord with a spatial resolution as fine as 1 × 1 × 2 mm. The advantages of the SEEP fMRI method for the spinal cord far outweigh those of the BOLD fMRI method, which are that BOLD can provide higher temporal resolution, and it receives less criticism from reviewers (the vast majority of whom are only familiar with brain fMRI). However, high temporal resolution data with very poor spatial fidelity cannot yield accurate maps of pain networks in the spinal cord. Moreover, recent studies have demonstrated the validity of the SEEP contrast mechanism, and the controversy over its existence has subsided [11,12]. The mechanism has been shown in fMRI studies of superfused tissue slices (i.e., no blood flow) to be distinct from the BOLD response and light-transmittance microscopy verified the link to cell swelling. *In vivo*, it has been shown that the BOLD mechanism does contribute a small proportion to the signal changes that are measured with essentially proton-density-weighted (or weakly T_2-weighted) spin-echo imaging. The reliability of the fMRI results obtained in the spinal cord and brainstem with SEEP fMRI has been demonstrated in a large number of studies [8],

including demonstrating the reproducibility and sensitivity of the results in individuals as opposed to grouped results [5]. After more than a decade of published research on spinal fMRI based on SEEP contrast, there is a large body of published evidence indicating the results it provides are sensitive, and reliably indicate areas of change in neural activity in response to a stimulus or task.

In order to obtain fMRI data spanning the entire pain network from spinal cord to cortex, it is necessary to acquire at least two sets of fMRI data, one optimized for the brain, and the other for the spinal cord and brainstem. The optimal method for brain fMRI is well established as being T_2*-weighted gradient-echo EPI with BOLD contrast, whereas the optimal method for spinal cord fMRI is the proton-density-weighted fast-spin-echo imaging method with SEEP contrast. Previous studies have compared SEEP and BOLD fMRI results in the brain, and have shown a high degree of correspondence of the spatial locations of activity that it detected. However, the SEEP activity tends to be more highly localized than that detected with BOLD. Nonetheless, the same areas of activity are demonstrated, and combinations of brain fMRI with BOLD and spinal cord and brainstem fMRI with SEEP are expected to be valid. The validity of the combination could be confirmed in overlapping areas of the acquisitions, such as in the thalamus and midbrain. In practice, it is expected that two fMRI acquisitions to reveal activity spanning from the spinal cord to the cortex could be achieved in approximately 15 min, and this approach is, therefore, practical for research with human volunteers.

Therefore, based on the nature of pain it appears that spinal cord fMRI of human volunteers who can report the pain they experience is an essential component (not a standalone method) of research that will ultimately lead to a much more complete understanding of pain and pain disorders in humans.

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