Pain, Heat, and Emotion with Functional MRI
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Pain, in its various manifestations, is our most distressing human experience. A large volume of evidence extending from psychology to neuroimaging emphasizes the powerful influence of both social and physical pain on mammalian well-being and survival.1 Although pain is defined as an unpleasant sensation caused by noceptive stimuli,2 the concept encompasses social

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as well as physical pain. Painful emotional feelings are associated with the loss of social connection owing to rejection, exclusion from a group, personal failure, or the death of a loved one. We often describe the experience of social pain by using terms for physical pain,\(^1\) making reference to broken hearts, hurt feelings, heartache, or being crushed or wounded to the quick. Moreover, social pain activates neural circuitry that is related to somatosensory pain, and analgesic agents have ameliorating effects on both physical pain and pain caused by social rejection, providing mechanistic links between them.\(^1,3\)

However, a dissociation between the sensory and affective components of physical pain has long been known from clinical work, in which lesions of the lateral thalamus render a person insensate on the opposite side of the body while still permitting a display of grimacing, restlessness, and autonomic responses to pain. Functional magnetic resonance imaging (fMRI) studies have confirmed this separation by showing a neural circuitry for physical pain that has two disparate ensembles: first, a sensory system in the primary and secondary somatosensory cortices and posterior insula that codes for the qualitative and quantitative characteristics of a stimulus, and second, an affective system in the dorsal anterior cingulate cortex, anterior insula, and the limbic system that signals aversive states.\(^1,4-6\) The insula, which is embedded in both systems, is a pivotal hub of a salience network that identifies the most relevant internal and external stimuli, including pain, from moment to moment, in order to guide attention and behavior.\(^6,7\)

The question of whether particular regions of the brain are specific for physical pain and whether activity in these regions can be quantified are the main issues addressed by Wager and colleagues in this issue of the Journal.\(^8\) The investigators, using fMRI and machine-learning methods, identified a widely distributed, multi-regional pattern (or signature response) that was activated by physical pain applied in the form of heat to the forearm of healthy volunteers. The pattern that Wager and colleagues detected had high sensitivity and specificity in discriminating painful heat from nonpainful warmth, pain anticipation, pain recall, and provocatively, social pain. In addition, activity in these regions in response to pain was reduced by an opioid analgesic agent.

These results may be of great practical importance, because physical pain is the most common reason for consultation with a physician. We comprehend our own pain only as a subjective phenomenon and recognize that the experience and affective display of pain differ from person to person and from culture to culture. Physicians are flummoxed by pain because of a paucity of objective manifestations and are reduced to using clinical instruments, such as the visual-analogue scale to quantitate pain. Imagine how all fields of medicine would be altered if pain could be objectified by a measure that did not require direct patient reporting. For example, what would be seen in patients with fibromyalgia, depression, or narcotic addiction, who have both physical and emotional pain? Wager and colleagues describe potential applications of their method, including detecting and quantifying pain in persons who cannot communicate and in those for whom the self-report of the intensity of pain is suspect.

The results, however, require cautious evaluation for several reasons. First, the authors make it clear that they have studied only cutaneous pain and not pain in the context of disease, so their findings may not apply to clinical circumstances. They also do not shed light on the issue of chronic pain, one of the most vexing problems in general medicine. Second, their assessment of social pain, in which participants recalled a recent romantic breakup while viewing a photograph of their ex-partner, used an uncertain stimulus with respect to the neural processes that are engaged. Participants in these studies may have experienced many feelings, including social rejection, love, or attachment, which led to changes in the activity of reward centers in the brain.\(^9\) Finally, the spatial resolution used in this study was limited, reflecting the low sensitivity of the 1.5-T fMRI system that was used for most of the testing, and this may have led to the misidentification of small deep-brain structures that contributed to the neurologic signature response for pain. Therefore, further studies in diverse clinical circumstances with the use of more-sensitive MRI acquisition techniques will be necessary to validate any pain biomarker.

The studies conducted by Wager and colleagues serve as an example of how functional neuroimaging may help clinicians assess clinical symptoms, such as somatic and emotional...
pain, that were previously thought to be impenetrable. Being doctors, though, we may ultimately have to acknowledge that “pain is pain” and can be reported only by the patient.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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