Pain: What Is It and Where Is It?

In the pain literature, the terms "nociception," "nociceptive activity," "pain signals," "pain pathways," and "pain" are often used interchangeably to mean the same or very similar things. Statements are frequently made, for example, that a painful stimulus applied to the body results in the generation of pain signals that travel along specific afferent pain pathways in the brainstem or spinal cord, and that this pain then generates a complex network of activity in thalamic and cortical regions. Statements are also made that chronic pain leads to changes in pain circuitry in the brain, that cortical networks are activated by pain, etc.

One problem with using the term "pain" in these contexts is that the stimulus applied to the body and the ensuing signals that travel along these pathways do not necessarily lead to the experience of pain. A classic example is the football player who becomes injured during a game, but only experiences the pain associated with the injury after the game has finished. Another example is that of a nonpainful stimulus (eg, light touch to a trigger zone on the face) leading to extreme pain in individuals with trigeminal neuralgia.

The International Association for the Study of Pain (IASP) has defined pain as a sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.[1] Therefore, pain is an experience that requires consciousness. Pain may be experienced when certain parts of the brain interpret incoming processed afferent information (often, but not always, traveling along nociceptive A-delta and C afferent nerve fibers) to indicate that tissue damage is occurring or has occurred. Sometimes this information is processed to the extent that those regions of the brain responsible for the experience of pain do not register that tissue damage is occurring, and pain is not experienced. Other times, these same regions might register that a lot of tissue damage is occurring when in fact there is little or no damage, as appears to occur in chronic or persistent pain states or in fearful individuals. Other times still, activity is not needed at all in these nociceptive primary afferents in order for a person to experience pain, as occurs in patients with post-stroke pain[2] or as has been shown with electrical stimulation of higher regions of the brain such as the thalamus.[3] In both these examples, despite the fact that there appears to be no activity in nociceptive primary afferents, the individual still experiences pain.

Therefore, activity in these so-called pain pathways is not strongly linked to the sensory and emotional experience described as pain. This is one of the reasons why the terms "nociception" or "nociceptive pathways" are better used when dealing with any form of processing of nociceptive information, particularly at the lower levels of the brain, which are not thought to subserve the experience of pain. Questions that arise then are: Where in the brain is the experience of pain? That is, what is the neuronal activity that is the experience of pain?

Much research has been directed toward determining which regions of the brain might encode the sensory-discriminative, motivational-affective, and cognitive-evaluative dimensions of the painful experience.[4,5] The primary and secondary somatosensory cortical regions (SI and SII) are considered to play a major role in encoding the sensory-discriminative aspects of a painful experience (ie, intensity, location, duration, quality), while the anterior and mid-cingulate cortices (ACC/MCC), insula, and prefrontal cortex (PFC) appear to be important for the motivational-affective dimension.

Are all these regions of the brain responsible for the pain experience, or is it only a subset of these regions? Or are there other regions that do not light up in imaging studies but are the real seat of the experience of pain? Does it matter for the management of pain patients?

The picture, however, is even more complicated, because just as there is a mismatch between the pain experience and the amount of tissue damage (as described above), there also appears to be a mismatch between the pain experience and changes in brain structure and/or function, particularly when acute and chronic pain states are compared and even between different chronic pain states.[4,6,7] There is added complexity in that studies have shown that observing another individual in pain, anticipating a painful experience, or imagining a painful hand movement in an amputated arm can be associated with activation in some pain-related brain regions.[5] Despite these regions becoming activated when observing another individual in pain, these observers do not experience pain themselves.

One recent view of the normal perception of any form of sensory information portrays "conscious perception as the result of an active interpretative process by the brain, rather than a passive reflection of the environment."[8] Meyer suggests that top-down signals along corticocortical pathways from higher-order cortical areas to primary sensory cortices are important for conscious perception. Early neuronal activity in the primary cortical areas appears to correlate more with the properties of the stimulus, while later neuronal activity appears to correlate more with the

subject's conscious perception.[8] With this in mind, the higher centers (eg, association cortical regions, PFC, insula[9]) would be responsible for the actual experience of pain, and these regions are interpreting or "looking at" the activity that is processed in the other cortical (eg, SI, SII, ACC) and subcortical (eg, thalamus, brainstem, and spinal cord somatosensory nuclei) areas that light up in imaging studies when individuals are experiencing pain. These higher-order brain regions responsible for the experience of pain may or may not undergo the structural and functional changes that have been identified in individuals experiencing pain.

If the neuronal network responsible for the experience of pain is separate from or even overlaps with the parts of the brain that change in chronic pain, then in the management of a patient's pain, it may only be necessary to target the neurons that are actually responsible for the pain experience. This approach might be of value, particularly in intractable pain states and/or if there are changes in the brain mechanisms involved in chronic pain states (eg, a change in the relative contribution of central and peripheral drivers to the pain experience). Targeting these constantly changing brain mechanisms might not be as useful as targeting the regions actually involved in the pain experience.

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