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Stanford Neuroscientists May Revolutionize Pain Management

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To be alive is to experience some form of pain. What we experience is a construction of the brain's interpretation of sensory input from touch, taste, sight, hearing, and movement. Pain is a survival mechanism that signals the brain. How the brain processes and responds to pain's sensory signal is a disagreeable and uncomfortable emotional experience. In January 2019, scientists Grégory Scherrer, Mark Schnitzer, Dong Wang, Benjamin Grewe, Biafra Ahanonu, and Gregory Corder from Stanford University published a neuroscience study in *Science* that identifies the cells in the brain that are responsible for the emotional "unpleasantness" of pain.

Pain is a two-part process. First, triggered nerve cells signal pain to the brain with sensory input messages—this is the physical component. Then the brain processes the information which generates the emotional discomfort associated with the pain sensation.

To put the duality of pain in context, let's use the example of an endurance athlete such as a triathlete, marathon runner, or an obstacle course racer. In each of these extreme athletic endeavors, it's inevitable that the racer will experience multiple forms of painful sensations during the course of the race. It's how the athlete responds to the sensory input of pain that determines performance. In other words, just because different parts of the body are signaling pain doesn't necessarily mean that a competitor needs to slow down or quit the race—it depends on the severity and situation. Savvy competitors know that pain is a signal and are able to "push through the pain" and manage the emotional response to the sensations in order to achieve performance goals.

The Stanford researchers sought to discover the neurons responsible for the emotional experience of pain. Using a combination of brain-imaging and molecular testing, the researchers discovered a group of cells in the amygdala that serves as an on-off switch to pain aversion in laboratory mice. The amygdala is the region of the brain's medial temporal lobe that processes emotions such as fear and pain.

The research team created a miniature microscope (miniscope) that recorded the cell activity of the amygdala of active mice through the measurement of neuronal calcium fluctuations. What they discovered was that the neurons of the basolateral amygdala (BLA) would be activated following pain stimuli of hot or cold water.

To eliminate the possibility that the basolateral amygdala would fire on any emotion, the team conducted a similar test using sugar water as the stimulus. The neurons in the basolateral region did not react to the non-painful stimulus of sugar water.

The researchers also tested the basolateral amygdala using non-painful but annoying stimuli on the mice. Again, the neurons in that area were muted.

To understand if the basolateral amygdala encoded the unpleasantness of pain, the researchers used advanced genetic techniques to switch the basolateral amygdala neurons on and off. The team discovered that by manipulating the basolateral amygdala neurons, the mice did not behave in a manner suggesting that they were experiencing the unpleasantness of pain. The researchers wrote, "disrupting neural activity in a nociceptive ensemble in the basolateral amygdala is sufficient to reduce the affective dimension of pain experiences, without altering their sensory component."

The Stanford scientists discovered neurons that are responsible for the emotional experience of pain. Pain is typically a temporary experience, but not for those suffering from chronic pain where the suffering can persist for three months or longer. Understanding the root cause of pain's discomfort may lead to innovative ways to solve a growing epidemic—the opioid crisis. Opioids are a class of drugs used for pain management. According to the Centers for Disease Control and Prevention (CDC), "two out of three drug overdose deaths involve an opioid," and nearly 400,000 Americans died from an opioid overdose during 1999-2017.

As next steps, the researchers plan to confirm the role of the basolateral amygdala in people. Eventually, the team hopes to identify a method to manage the neurons of the basolateral amygdala without impacting other neurons. The more insight into the mechanisms of pain, the better equipped scientists are to develop novel future medications that are non-addictive and do not dull the signal of pain itself, but do alleviate the unpleasant emotional experience of pain.