# Study reveals brain mechanism behind chronic pain's sapping of motivation

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Robert Malenka and his colleagues found that chronic pain changed the brain circuitry in mice, making them less willing to work for rewards. Credit: Steve Fisch

Chronic pain is among the most abundant of all medical afflictions in the developed world. It differs from a short-term episode of pain not only in its duration, but also in triggering in its sufferers a psychic exhaustion best described by the question, "Why bother?"

A new study in mice, conducted by investigators at the Stanford University School of Medicine, has identified a set of changes in key parts of the brain that may explain chronic pain's capacity to stifle motivation. The discovery could lead to entirely new classes of treatment for this damaging psychological consequence of chronic pain.

Many tens of millions of people in the United States suffer persistent pain due to diverse problems including migraines, arthritis, lower back pain, sports injuries, irritable bowel syndrome and shingles. For many of these conditions, there are no good treatments, and a crippling loss of mojo can result.

"With chronic pain, your whole life changes in a way that doesn't happen with acute pain," said Robert Malenka, MD, PhD, the Nancy Friend Pritzker Professor in Psychiatry and Behavioral Sciences and the study's senior author. "Yet this absence of motivation caused by chronic pain, which can continue even when the pain is transiently relieved, has been largely ignored by medical science."

A series of experiments in mice by Malenka and his colleagues, described in a study published Aug. 1 in *Science*, showed that persistent pain causes changes in a set of nerve cells in a deep-brain structure known to be important in reward-seeking behavior: the pursuit of goals likely to yield pleasurable results. Malenka's lab has been studying this brain structure, the nucleus accumbens, for two decades.

"We showed that those brain changes don't go away when you transiently relieve the mice's pain," Malenka said. The experiments also indicated that the mice's diminished motivation to perform reward-generating tasks didn't stem from their pain's rendering them incapable of experiencing pleasure or from any accompanying physical impairment, he said.

## How pain and reward interact

"This study is important—to my knowledge, the first to explain how pain and reward interact. It begins to get to an understanding of why it's such a struggle for people undergoing chronic pain to get through the day," said Howard Fields, MD, PhD, a professor of neurology at the

University of California-San Francisco and founder of that school's pain management center.

Fields, who did not participate in the Malenka group's study but wrote an accompanying perspective piece published simultaneously in *Science*, described the psychological effect of chronic pain as "the clouding of the future. There's no escape from it. You want it to end, but it doesn't." As a result, people become pessimistic and irritable, he said. "People come to expect the next day is going to wind up being painful. It just takes the edge off of life's little pleasures—and big pleasures, for that matter."

The experiments were spearheaded by the study's first author, Neil Schwartz, PhD, a postdoctoral scholar in Malenka's lab. "You can't just ask a hungry mouse how motivated it is to pursue its heart's desire," Malenka said. "But there are ways of asking that mouse, 'How hard are you willing to work for food?'"

Schwartz, Malenka and their associates looked at lab mice enduring chronic paw pain due either to persistent inflammation or to nerve damage. The mice also happened to be hungry. The scientists trained the mice to poke their noses into a hole to get a food pellet. At first, a single nose poke earned a pellet. But over time, the number of nose pokes required for a reward was increased. In essence, the researchers were asking these mice: How hard are you willing to work for food? Will you poke your nose into that hole once to satisfy your hunger? Ten times? Even 150 times?

## Fading motivation

Within a week after the onset of chronic pain, the animals grew increasingly less likely to work hard for food than pain-free control animals were. The researchers next explored three possible explanations:

Were the mice unable to work because their pain was too severe? Did something about being in pain cause them to not value the food reward as much? Or was their failure to seek food due simply to a lack of motivation? Additional tests showed that the mice had no movement problems. "Like other research groups, we found that they can scamper around just fine," said Malenka. Also, when the mice were given free access to food, they ate just as much as the animals who weren't in pain—so they still valued the food. But they were less willing to put in an effort to obtain food than mice who'd suffered no pain.

Moreover, the difference didn't disappear even when the scientists relieved the mice's pain with analgesics. "They were in demonstrably less pain, but they were still less willing to work," Malenka said.

The Stanford scientists then focused on the nucleus accumbens, a brain structure known to be involved in computing the behavioral strategies that prompt us to seek or avoid things that can affect our survival. They found that chronic pain permanently changed certain connections to the nucleus accumbens, causing an enduring downshift in the excitation transmitted by them. Importantly, Malenka's group showed that a particular brain chemical called galanin plays a critical role in this enduring suppression of nucleus accumbens excitability.

Galanin is a short signaling-protein snippet secreted by certain cells in various places in the brain. While its presence in the brain has been known for a good 60 years or so, galanin's role is not well-defined and probably differs widely in different brain structures. There have been hints, though, that galanin activity might play a role in pain. For example, it's been previously shown in animal models that galanin levels in the brain increase with the persistence of pain.

## Possible therapies?

Schwartz, Malenka and their peers identified receptors for galanin on a set of nerve cells in the nucleus accumbens and demonstrated that disabling galanin's signaling via this receptor prevented the long-term suppression of motivation seen in mice—and people—with chronic pain. This suggests that therapeutic compounds with similar effects could someday be developed, although they would have to be carefully targeted so as to not disrupt galanin signaling in other important brain circuits.

"There's no reason to think this finding won't generalize to people," said Fields of UCSF. "Our brains have galanin, and a nucleus accumbens, just as mouse brains do. However, before jumping from mice to humans it would be wise to test other animal species. If the same things happen in a non-rodent species that happen in mice, then it's probable they happen in humans, too."

**More information:** *Science*, dx.doi.org/10.1126/science.1253994

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