# Identification of brain region responsible for alleviating pain could lead to development of opioid alternatives

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Prescription bottle for Oxycodone tablets and pills on metal table. Credit: Penn State

Researchers from the UK & Japan have identified how the brain's natural painkilling system could be used as a possible alternative to opioids for the effective relief of chronic pain, which affects as many as one in three people at some point in their lives.

The team, led by the University of Cambridge, have pinpointed an area of the brain that is important for endogenous analgesia – the brain's intrinsic pain relief system. Their results, published in the open access journal eLife, could lead to the development of pain treatments that activate the painkilling system by stimulating this area of the brain, but without the dangerous side-effects of opioids.

Opioid drugs such as oxycodone, hydrocodone and fentanyl hijack the endogenous analgesia system, which is what makes them such effective painkillers. However, they are also highly addictive, which has led to the opioid crisis in the United States, where drug overdose is now the leading cause of death for those under 50, with opioid overdoses representing two-thirds of those deaths.

"We're trying to understand exactly what the endogenous analgesia system is: why we have it, how it works and where it is controlled in the brain," said Dr. Ben Seymour of Cambridge's Department of Engineering, who led the research. "If we can figure this out, it could lead to treatments that are much more selective in terms of how they treat pain."

Pain, while unpleasant, evolved to serve an important survival function. After an injury, for instance, the persistent pain we feel saps our motivation, and so forces us towards rest and recuperation which allows the body to use as much energy as possible for healing.

"Pain can actually help us recover by removing our drive to do unnecessary things—in a sense, this can be considered 'healthy pain'," said Seymour. "So why might the brain want to turn down the pain signal sometimes?"

Seymour and his colleagues thought that sometimes this 'healthy pain' could be a problem, especially if we could actively do something that

might help—such as try and find a way to cool a burn.

In these situations, the brain might activate the pain-killing system to actively look for relief. To prove this, and to try and identify where in the brain this system was activated, the team designed a pair of experiments using brain scanning technology.

In the first experiment, the researchers attached a metal probe to the arm of a series of healthy volunteers—and heated it up to a level that was painful, but not enough to physically burn them. The volunteers then played a type of gambling game where they had to find which button on a small keypad cooled down the probe. The level of difficulty was varied over the course of the experiments—sometimes it was easy to turn the probe off, and sometimes it was difficult. Throughout the task, the volunteers frequently rated their pain, and the researchers constantly monitored their brain activity.

The results found that the level of pain the volunteers experienced was related to how much information there was to learn in the task. When the subjects were actively trying to work out which button they should press, pain was reduced. But when the subjects knew which button to press, it wasn't. The researchers found that the brain was actually computing the benefits of actively looking for and remembering how they got relief, and using this to control the level of pain.

Knowing what this signal should look like, the researchers then searched the brain to see where it was being used. The second experiment identified the signal in a single region of the prefrontal cortex, called the pregenual cingulate cortex.

"These results build a picture of why and how the brain decides to turn off pain in certain circumstances, and identify the pregenual cingulate cortex as a critical 'decision centre' controlling pain in the brain," said

Seymour.

This decision centre is a key place to focus future research efforts. In particular, the researchers are now trying to understand what the inputs are to this brain region, if it is stimulated by opioid drugs, what other chemical messenger systems it uses, and how it could be turned on as a treatment for patients with chronic pain.

**More information:** Suyi Zhang et al. The control of tonic pain by active relief learning, *eLife* (2018). DOI: 10.7554/eLife.31949