Probing neural circuits underlying the socially 'contagious' nature of pain and pain relief

By Rennie Kendrick

Empathy is often thought of as a uniquely human trait, but a recent study led by Dr. Monique Smith (now an Assistant Professor at University of San Diego) and Dr. Robert Malenka at Stanford University calls this long-held notion into question. The study, published in *Science* last year, found evidence for what Dr. Malenka refers to as a "primitive form of empathy" in mice.

One common definition of empathy is the tendency to understand, or even take on, the experience of others. The researchers asked if this latter form of empathy, the transfer of physical states between individuals, occurred in mice. They examined two physical states, pain and pain relief. They found that both states were socially transferred between mice. That is, mice that were not experiencing pain or pain relief began to show signs of pain or pain relief simply after interacting with a mouse experiencing one of those states. Importantly, they tied this social transfer of pain and pain relief to a circuit in the brain that has been implicated in human empathy.

Probing neural circuits underlying the social transfer of pain

Dr. Malenka remembers the awe he felt when Dr. Smith first told him about her PhD research related to the social transfer of pain between mice, remarking that, "To be honest, I had never really heard of it, and I was kind of blown away by it." Not only that, but Dr. Malenka saw a powerful point of synergy between Dr. Smith's research into pain and his longstanding interest in studying prosocial behavior. He thought that this social transfer of pain experiment could be a foothold into dissecting neural mechanisms of empathy, and perhaps ultimately prosocial behaviors.

The researchers first wanted to replicate that pain could be socially transferred. They induced arthritis-like pain in one mouse, and then allowed the mouse to interact for one hour with a mouse that was not experiencing pain. As expected, this previously pain-free mouse soon began to show signs of pain.

While this transfer of pain had been previously observed, the neural mechanisms underlying this transfer remained black-boxed. To examine the neural basis of this social transfer of pain, the researchers turned to two powerful tools pioneered here at Stanford, Targeted Recombination in Active Populations (TRAP) and optogenetics.

TRAP labels cell populations that are active during a specific time window and was used to label cells that were active while mice were interacting. Strikingly, cells in both the anterior cingulate cortex (ACC) and nucleus accumbens (NAc) were active during this social interaction, two regions previously implicated in other social behaviors. Importantly, ACC has also been implicated in human studies of empathy.

To causally tie these cell populations to the social transfer of pain, the researchers turned to optogenetics. Optogenetics allows for selective stimulation or inhibition of neural populations or connections. The researchers used optogenetics to inhibit the ACC cell population that was active during social interactions and found that this blocked the social transfer of pain. Inhibiting neural connections from ACC to NAc also impaired the social transfer of pain, and activating these connections prolonged how long mice experienced the transferred pain.

Common circuits for the social transfer of pain and pain relief

Armed with new information about the neural basis of the transfer of one physical state in mice – pain – the researchers were curious to see if other states could be transferred via this ACC□NAc circuit. In particular, they were curious to see if this circuit could mediate the transfer of pain relief between mice.

At this point, it wasn't even known if pain relief could be transferred between mice, let alone if this transfer would leverage the same circuits as in the transfer of pain. So, to ask this question, the authors had to develop a new behavioral experiment. In this study, the researchers induced pain in two mice, and then administered an analgesic dose of morphine to one of the mice. When these two mice were then allowed to interact, remarkably, the mouse that did not receive pain relief showed diminished pain signs. Moreover, they found that inhibiting ACC populations active during this social interaction, as well as the ACC□NAc circuit, also prevented the social transfer of pain relief, suggesting common circuit mechanisms underlying the social transfer of pain and pain relief.

Social transfer of pain and pain relief as windows into empathy and prosocial behaviors

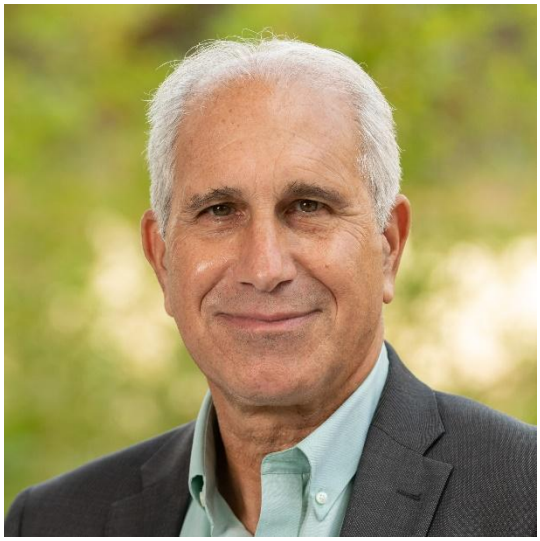
The fact that the same circuit is necessary for the social transfer of two distinct, opposing physical states – pain and pain relief – is striking. Importantly, this diverse action of the ACC□NAc circuit suggests that it may constitute a more general neural substrate of empathy and prosocial behaviors.

Dr. Malenka would be the first to admit that it is impossible to capture the nuances and intricacies of human social interaction in mice. Still, the wealth of tools available to access and manipulate neural activity in mice makes the study of this approximation of empathy in mice especially attractive. For example, current work in Dr. Malenka's lab asks if drugs thought to potentially promote empathy and prosocial behaviors – such as 3,4-Methylenedioxy methamphetamine (MDMA) – modulates these neural circuits and the social transfer of states between mice.

It is Dr. Malenka's hope that this rich mechanistic research in mice could ultimately be back-translated to humans. After all, he cares first and foremost about gaining insight into the human condition, noting, "If somebody told me, 'I have proof that the mechanisms you're studying in mice are not relevant to human neurobiology,' I would stop doing it in mice."

Dr. Smith and Dr. Malenka's research paves the way for further mechanistic and causal research into neural mechanisms of empathy, which has significant implications for individuals and society. Deficits in empathy are a socially debilitating component of neuropsychiatric disorders such as autism and schizophrenia, and better understanding of these neural circuits could spur better development of new treatments for these disorders.

Even among individuals without a neuropsychiatric diagnosis, it isn't hard to see how pronounced deficits in empathy continue to fuel prejudice and harm in our society. Dr. Malenka wonders if tangible evidence of the neural basis of empathy could be used to motivate individuals to improve their empathy and compassion. He notes, "Do you need the neuroscientific understanding to do this? Probably not. But maybe saying, 'this is not fluffy stuff. This is not philosophy, this is science' maybe we can convince political leaders to pay a little more attention and understand we all have empathy in us."



Prof. Robert Malenka, Stanford U.

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