Should I run or not? The neural basis of aggression and flight

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A brain hovers over a chess board, symbolizing control over location-specific defensive responses. Credit: Holly Joynes/EMBL

Our brains are wired to protect us from threats. For social animals like humans, threats often come from other members of our own species when there is conflict over food, mates, or territory. Animals with a strong sense of territory will attack anyone who enters their territory, but will flee if caught in the territory of another individual. In such animals, the decision to stand their ground and attack or to run away and escape depends on where the animal is. How is the decision between these two types of defensive responses made? How does our sense of territory drive our instinctive behavior?

Previous studies from the Gross group at the site of the European Molecular Biology Laboratory in Rome have revealed the crucial function of a specific brain region, the ventromedial hypothalamus (VMH), in social fear. The VMH is a central node in the brain that receives sensory inputs from the amygdala—a region involved in organizing sensory information related to emotional behavior—and sends outputs to motor areas of the brainstem. This position midway between sensory inputs and motor outputs makes the VMH an ideal subject to understand how threats drive behavior.

To investigate the possibility that the VMH is involved in the decision between attacking and escaping a social threat, scientists in the Gross group measured the activation of neurons while the mice were exposed to a more aggressive mouse. When the mice were in this situation, activity of a large class of neurons increased proportionally with the threat intensity, confirming that the VMH may encode an internal state of threat that is necessary to trigger defensive responses.

Unexpectedly, the scientists also observed activation of the same neurons when the animal returned to explore the place where it had been threatened previously, even though there was no longer any threat present. And, surprisingly, a second set of neurons now became active when the animal returned (via a corridor) to its home cage. Under these circumstances, the researchers could predict precisely where the animal was located—threat cage or home cage—by looking at the firing of neurons in the VMH. This demonstrates that the VMH encodes spatial context—a function that has never before been attributed to the hypothalamus.

Finally, the researchers showed that exposure to a more aggressive mouse dramatically increased the ability of the VMH to promote flight. When the VMH was artificially activated after such a situation, the animal rapidly ran away from a threat, but not when the VMH was activated before this situation. This shows that social experience can change the VMH. The researchers are currently trying to understand what mechanisms might be involved in this transformation, which allows the neural networks in the VMH to be rewired in response to experience—a process known as neural plasticity.

"This finding has important implications for the field, because previous work had argued that the VMH is hardwired to respond to threats," says group leader Cornelius Gross. "Our view holds that the VMH is dedicated to controlling both attack and flight, and that this choice is driven by its encoding of social space. When an animal is in its own territory it favors attack, but when it is in the territory of another animal it favors flight."

"These results can contribute to understanding how emotions like fear and aggression are regulated, especially in the context of territory," says Piotr Krzywkowski, who conducted the research as a Ph.D. student in the Gross group and is now Senior Data Scientist at the company IQVIA. The results also suggest a novel role of the hypothalamus in behavior. Rather than being viewed as an innate behavioral response region, the hypothalamus should be seen as a region that integrates present and past sensory and contextual information, processing the level of threat and adapting survival behaviors to a changing environment.

More information: Piotr Krzywkowski et al, Dynamic encoding of social threat and spatial context in the hypothalamus, *eLife* (2020). DOI: 10.7554/eLife.57148

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