To flee or not to flee: How the brain decides what to do in the face of danger

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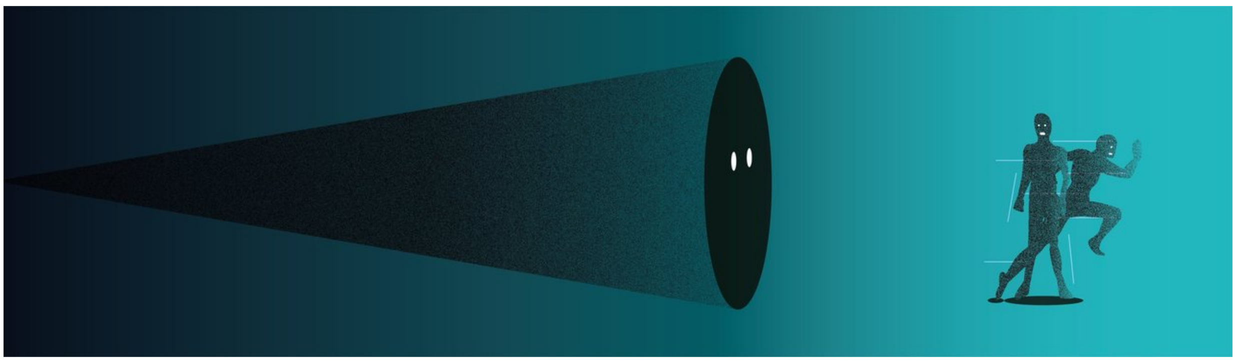

How the brain decides what to do in the face of danger? Credit: Gil Costa, Champalimaud Centre for the Unknown

Though it has been many millennia since humans were regularly threatened by predatory wild animals, the brain circuits that ensured our survival then are still very much alive within us today. "Just like any other animal in nature, our reaction to a threat is invariably one of the following three: escape, fight or freeze in place with the hope of remaining unnoticed," says Marta Moita, who together with Maria Luisa Vasconcelos led the study conducted at the Champalimaud Centre for the Unknown in Lisbon, Portugal.

"These behaviours are fundamental, but we still don't know what the rules of the game are. In each situation, how does the brain decide which of the three strategies to implement and how does it ensure that the body carries it through?" says Ricardo Zacarias, the first author of the study, published September 12 in the scientific journal *Nature Communications*.

Remarkably, unprecedented insight into these questions came from the common fruit fly. "When we started working on these issues, most people believed that flies only escape, but we wondered if that was really true. Even though it's an insect, the fruit fly is an incredibly powerful model organism that has shed light on many difficult problems in biology. So when we decided to delve into the neural basis of defensive behaviour, we asked, what will happen if we expose flies to a threat in a situation where they couldn't just fly away?" Moita says.

The results were immediately clear. "When we placed the flies in a covered dish and exposed them to an expanding dark circle (which is how a threat looks like to a fly), we saw something completely new: they froze. In fact, just like mammals, they would remain perfectly motionless for minutes on end, sometimes in very awkward positions, such as half crouching, or with a leg or two suspended in the air," she explains.

But the story didn't end there. Many of the flies froze, but some didn't—some ran away from the threat. "This was very exciting," says Vasconcelos, "because it meant that similarly to humans, the flies were choosing between alternative strategies."

The team decided to take a closer look at what triggered these different responses by using machine vision software that produced a highly detailed account of the behaviour of the fly. With this information, they discovered something quite unexpected: the flies' response hinged on their walking speed at the moment the threat appeared. If the fly was moving slowly, it would freeze, but if it was walking quickly, it would run away from the threat. "This result is very important: it is the first report showing how the behavioural state of the animal can influence its choice of defensive strategy," Vasconcelos points out.

These observations opened the door to identifying the actual neurons that determined whether the fly would flee or freeze. Using state-of-the-art genetic tools, the team found a single pair of neurons important for the flies' defensive behaviours. "It was quite incredible. There are hundreds of thousands of neurons in the brain of the fly, and among all of those, we found that freezing was controlled by two identical neurons, one on each side of the brain," she explains.

When the team turned the neurons off, flies didn't freeze anymore, but they still escaped from the threat. But what was even more remarkable is what happened when they turned the neurons on (without the presence of a threat): flies would freeze in a manner that depended on their walking speed. "If we turned the neurons on when the fly was walking slowly, it would freeze, but not if it was walking quickly. This result places these neurons directly at the gateway of the circuit of choice," says Zacarias.

"This is exactly what we were looking for: how the brain decides between competing strategies. And moreover, these neurons are of the type that sends motor commands from the brain to the 'spinal cord' of the fly. This means that they may be involved not only in the choice, but also in the execution," Moita points out.

According to the team, this series of findings starts a whole new field of research in flies. "We can now study directly how the brain makes choices between very different defensive behaviours," says Moita. "And because defensive behaviours are common to all animals, our discoveries provide a good starting point towards identifying the 'rules of the game' that define how all animals choose to defend themselves."

More information: Ricardo Zacarias et al, Speed dependent descending control of freezing behavior in Drosophila melanogaster, *Nature Communications* (2018). DOI: 10.1038/s41467-018-05875-1

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