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NEURAL CIRCUITS

Unpredictable turns in the worm

The response of an organism to a defined sensory stimulus can vary from one trial to the next, even if the average response is predictable. Bargmann and colleagues now show that the variable response of *Caenorhabditis elegans* to an attractive odour, an example of this type of probabilistic behaviour, can be explained by variability in the activity state of interneurons that convey the sensory input to motor neurons.

C. elegans do not move directly towards an attractive odour. Instead, their path towards such an odour is often characterized by distinct turns, including reversals, in which the animal initially moves backwards and then forwards in a new direction. Reversals in response to attractive odours are mediated by two AWC olfactory neurons, which detect the odour, and two AVA command interneurons, which activate motor neurons, but how these contribute to variability in reversals was not clear. Although there is a single direct synaptic connection from AWC to AVA neurons, most signalling occurs indirectly, including via two AIB interneurons, which receive direct AWC input. Furthermore, although AIB neurons can signal directly onto AVA neurons, they can also form many indirect connections with these command interneurons, including via two RIM interneurons; the precise contribution of RIM neurons to reversals was not clear, however.

Using optogenetics the authors showed that selective, independent activation of AWC, AVA and AIB neurons increased reversals in freely moving worms. RIM neuron activation also increased reversals, which clarified their role in the reversal circuitry. However, it was still not known how this circuit generates probabilistic reversals in response to a fixed stimulus.

To study the circuit further, the authors characterized calcium transients in AIB, RIM and AVA neurons in response to isoamyl alcohol, an attractive odour, using transgenic animals expressing the calcium indicator GCaMP3. On average, all neurons showed a decrease in calcium levels in response to the stimulus.

However, detailed examination of the changes in individual neurons revealed that the calcium responses underwent rapid transitions between prolonged periods of low and high calcium levels, defined as OFF and ON states, respectively, by the authors. Transitions between the two states often occurred at approximately the same time across the AIB, RIM and AVA neurons.

In the absence of a stimulus, three combinations of ON and OFF states occurred most frequently: all neurons ON, all neurons OFF, and AIB only ON. Notably, when the network was in the all ON state, either all neurons shifted from ON to OFF in response to odour, or none did, which could explain probabilistic reversals in response to the fixed odour. Interestingly, however, when the network state before the odour was AIB only ON, transition of AIB neurons to the OFF state always occurred, and such transitions occurred more rapidly, compared to the all ON state. Chemogenetic inhibition of RIM and/or AVA neurons also led to faster and more reliable ON–OFF transitions in AIB neurons. This suggested that in the ON state, RIM and AVA neurons antagonize AIB responses to odour.

By combining odour application with calcium imaging in freely moving animals, the authors found that in AIB, RIM and AVA neurons, rising calcium levels coincided with the start of reversals, whereas decreasing calcium levels coincided with their end. Importantly, specific synaptic silencing of RIM neurons increased reversals in response to odour exposure, indicating that the behavioural response is more variable when RIM neurons are active.

Together, these findings suggest that the activity state of the neuronal network receiving sensory input influences the response to a fixed stimulus, which may allow for behavioural flexibility and increase successful outcomes for the animal overall.

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> “the activity state of the neuronal network receiving sensory input influences the response to a fixed stimulus”

ORIGINAL RESEARCH PAPER Gordus, A. *et al.* Feedback from network states generates variability in a probabalistic olfactory circuit. *Cell* http://dx.doi.org/10.1016/j.cell.2015.02.018 (2015)

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