further help in the application of this concept.

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Neuroscience

Flies sense the world while sleeping

Wanhe Li & Alex C. Keene

High-throughput analyses of how sleeping fruit flies respond to a variety of odours show that the brains of these insects continue to process the value of the signals conveyed by sensory information during sleep. **See p.479**

Sleep is a complex behaviour nearly ubiquitous among animal species[1,2]. Many animals, including humans, are less responsive to sensory stimuli during sleep than when they are awake. However, human sleep is unlikely to involve a complete loss of consciousness, because people respond to salient stimuli – such as the sound of names[3] or a baby crying – during sleep, while filtering out more-trivial sensory cues. But whether other animals can evaluate the importance or value signalled by different sensory stimuli during sleep is not clear. On page 479, French *et al.*[4] show that the fruit fly *Drosophila melanogaster* also actively processes sensory information during sleep, and that the salience of different sensory stimuli can be affected by whether it is fed or starved.

Sensory processing during sleep can be studied in humans by repeatedly awakening participants and asking them to recall their most recent sensory experience before waking, while monitoring their brain activity[5]. Although such a 'serial awakening' approach cannot be used in other animals, sensory processing during sleep can be investigated in certain model animals using high-throughput behavioural analyses and approaches to manipulate the activity and gene expression of various populations of neurons.

A few years ago, researchers from the same group as French *et al.* developed an open-source robotic machine called an ethoscope that can deliver behaviourally triggered stimuli to flies in a feedback-loop mode, allowing high-throughput analysis of how sensory stimuli affect individual flies during sleep[6]. Using this machine, French *et al.* delivered sensory stimuli to each fly whenever they fell asleep, akin to the 'serial awakening' experiments typically performed in humans.

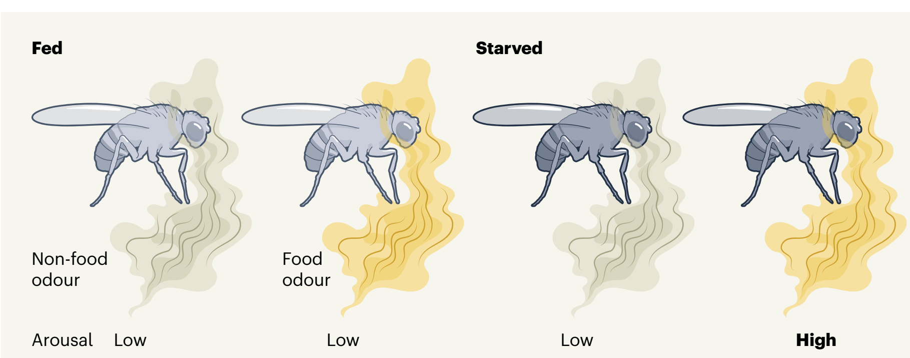

Figure 1 | A fly's internal state affects its response to sensory information during sleep. Using a machine called an ethoscope, French *et al.*[4] delivered various odorants to *Drosophila melanogaster* fruit flies when the insects were asleep, and tracked the flies' behavioural responses. The authors found that food odours and non-food odours awakened the flies at a similarly low rate. However, if the flies were starved of food, they woke up much more readily in response to food odours, but not to non-food odours. This finding implies that flies continue to process olfactory information, as well as the value attached to different odorants, during sleep.

The authors assembled a panel of various odorants, and tested whether the sleeping flies woke up in response to each of the odorants delivered at different concentrations, and at different times of day and night. They found that sleeping flies were more likely to be awoken by odours that, when the insects were awake, they found aversive than by those they found attractive or neutral (that is, neither attractive nor aversive).

But when flies were starved before sleep, their responses changed (Fig. 1). Food odours, but not non-food odours, were more likely to wake the flies when they had been starved than when fed, suggesting that the odours were more salient to the starved flies. These findings suggest that flies process complex sensory information during sleep, and that their responses are modulated by their internal state. The results thus reveal a previously unknown feature of sleep in a non-mammalian model that is analogous to sensory processing in sleep by humans.

To identify the neuronal cells involved in this process, French *et al.* searched for cells that connect two parts of the fly brain involved in sleep: the mushroom body and the fan-shaped body[7,8]. The neurons that transmit information from the mushroom body have been comprehensively identified, and several tools are available to label and manipulate specific populations of these neurons[9,10].

French and colleagues identified two populations of neurons in a circuit that regulates arousability during sleep: neurons that carry output from the mushroom body, and their putative target neurons in the fan-shaped body. Blocking neural communication by either of these populations of neurons made flies more easily woken by odorants, suggesting that these neurons are active during sleep to prevent odour-triggered awakening.

Next, the authors found two sets of neurons that act to 'gate' the effects of starvation on the arousal evoked by food odours. The first set are olfactory neurons that detect odorants through receptor proteins expressed on the neuronal-cell surface. The other gating population of neurons releases the neurotransmitter molecule dopamine and forms synaptic connections with the output neurons of the mushroom body. Artificially deactivating either the olfactory neurons or the dopamine-releasing neurons stopped starved flies from being more easily aroused by food odours than by other odours. These findings suggest that the fruit fly, with a brain of only about 100,000 neurons, could be used to investigate how sensory processing differs between sleeping and waking states.

A remaining question is whether a fly's internal state modifies its responsiveness to sensory cues of other modalities, such as auditory or mechanical sensations. Information about different senses might converge on the circuit identified by French and colleagues or be regulated by separate circuits.

Fruit flies can form odour-conditioned memories (for example, they can associate a previously unfamiliar odour with an electric shock), and such memories depend on sleep[11,12]. Whether flies are 'hard-wired' to wake up in response to food odours when they are hungry, or whether the effects of food odours on starved sleeping flies depend on the flies' previous experience, is not clear. Understanding whether the effects of internal state on olfactory processing during sleep is generalizable to other senses and modifiable by experience could advance our understanding of the relationship between sensory perception, sleep and memory.

The finding that fruit flies can assess the value signalled by sensory information during sleep suggests that complex processes associated with sleep are evolutionarily conserved across species. Although flies have long been used to study the function of sleep and to identify genes involved in its regulation, French and colleagues' findings suggest that studying non-mammalian species – including the zebrafish *Danio rerio*[13] and the nematode *Caenorhabditis elegans*[14] – might help us to understand some of the most complex cognitive processes in sleep. The continued application of these genetic models to the study of brain processing during sleep has the potential to uncover conserved biological mechanisms that regulate and underlie many of sleep's crucial functions.

"The fruit fly could be used to investigate how sensory processing differs between sleeping and waking states."

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