

## Locked down, RNA editing yields odd fly behavior

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Because a function of RNA is to be translated as the genetic instructions for the protein-making machinery of cells, RNA editing is the body's way of fine-tuning the proteins it produces, allowing us to adapt. The enzyme ADAR, which does this editing job in the nervous system of creatures ranging from mice to men, even edits itself. In a new study that examined the self-editing process and locked it down at two extremes in fruit flies, Brown University scientists found some surprising insights into how this "fine-tuning of the fine-tuner" happens, including bizarre behavioral effects that come about when the self-editor can't edit.

Take mating, for instance. When the researchers fixed self-editing in dADAR (as drosophila fruit fly ADAR is known) at a very high level in males, they created fruit fly wallflowers. By contrast, when they fixed self-editing at a low level, they created shameless pick-up artists. Ultimately each kind of fly, as well as unaltered controls, spent comparable amounts of time mating, but the highly edited ones took twice as long to get started.

The speed of <u>courtship</u> may seem like a triviality, but not when a creature's most important function in the wild is to reproduce successfully, said <u>biologist</u> Robert Reenan, senior author of the study, which appears in the April 24 edition of *Nature Communications*.

"The females in nature may not like a male that has less interest in sex," Reenan said. "That's not going to be very adaptive."



Reenan, first authors Yiannis Savva and James Jepson, and the rest of the team observed other peculiar behaviors too. Stuck in a vial, as research <u>flies</u> often are, the highly self-edited ones would tend to congregate near the well-lit top, while the unedited ones would mill about at the bottom where the food was. Only the controls would consistently move about the whole vial.

The highly self-edited flies also seemed to lose the ability to anticipate morning, in that they failed to get going in the minutes before the light half of a 12-hour-dark, 12-hour-light cycle.

All of the strange behaviors provide evidence for the idea that the selfediting process can have significant effects on behavior in a living animal, Reenan said. "We're showing this is like an adjustment knob for some behaviors."

## The inner workings

In more fundamental experiments, Reenan's team observed that selfediting varied neuron by neuron. They also found that the more selfediting occurs in a fly's dADAR, the less RNA editing activity there is in a neuron. They even identified a mechanism for this, which is that more highly edited dADAR ends up becoming sequestered in a pocket of the nucleus — a phenomenon they saw under the microscope after tagging dADAR to fluoresce. Flies with less RNA editing activity still had levels of dADAR that were comparable to those of other flies. They were just editing their dADAR more and keeping it in a kind of nucleus dry dock.

Another surprising insight was that dADAR self-editing can be affected by external factors, such as the ambient temperature. After rearing flies in 25-degree Celcius temperatures, the researchers cranked up the heat by 10 degrees for some, kept it at 25 for others, and cooled others down to 15 degrees C. The hotter flies had 30 percent less self-editing than



controls, while the cooler flies showed a 20 percent increase.

"Auto-editing changes with temperature," Reenan said. "Out there in the wild, the same fly, at two different temperatures is going to express a different set of proteins in its brain."

One of the next questions Reenan said he'd like to ask is what other external, or "abiotic" factors, such as diet, might also lead to a fundamental change in dADAR self-editing levels. Given that some human mental illnesses, epilepsy, suicidal depression, and ALS (Lou Gehrig's Disease) have been associated with errant ADAR activity, it may help advance potential therapies to know how auto-editing could be modulated in behaving organisms.

Provided by Brown University

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