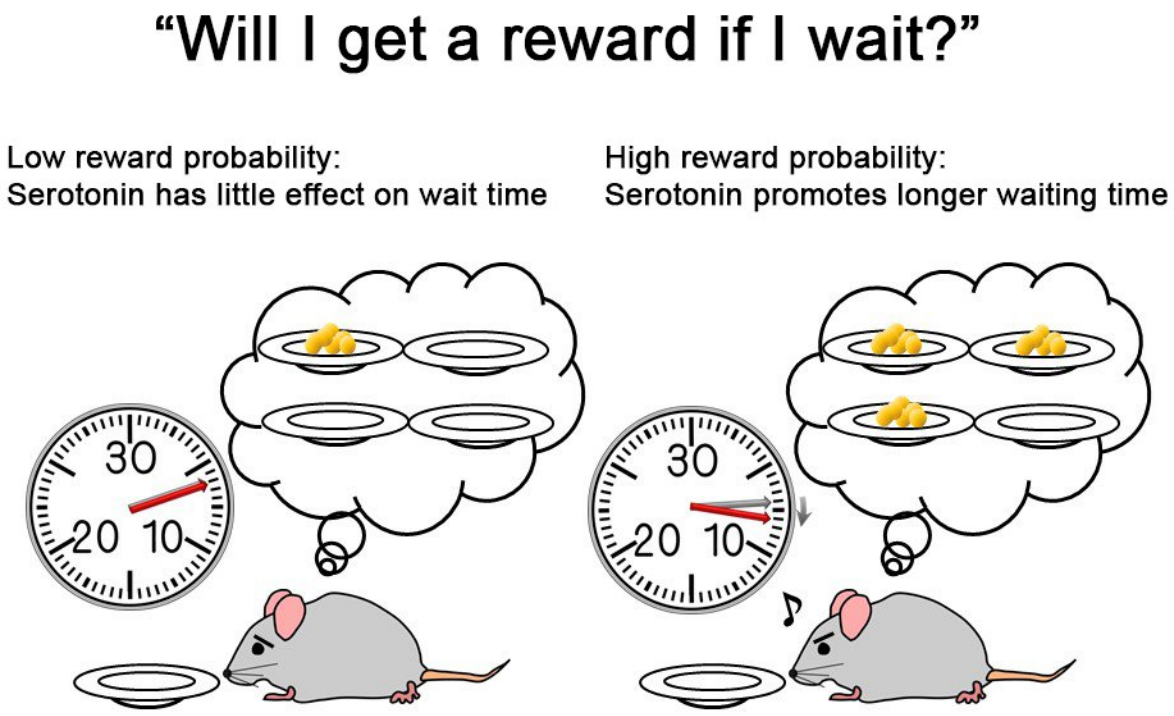
Serotonin and confidence underlie patience in new study

June 1 2018



With a 25 percent probability of reward, the nose-poke time in no-food trials did not change even if serotonin neurons were activated (left). But with a 75 percent reward probability, the nose-poke time during no-food trials increased when serotonin neurons were activated (right). Credit: OIST

People usually have the ability to put aside the desire for immediate gratification in anticipation of something good. But this isn't just a human trait—a new study shows that mice can be patient, too, revealing a link between the brain's chemical system and the mice's belief about how waiting will pay off.

The effect of the neuromodulator serotonin on mice's ability to stay patient when waiting for a reward is at the core of a new study published in *Nature Communications*. The authors, Dr. Katsuhiko Miyazaki and Dr. Kayoko Miyazaki, analyzed how the rodents behaved under the influence of serotonin, as part of a study conducted in the Neural Computation Unit at the Okinawa Institute of Science and Technology Graduate University (OIST).

Serotonin is a chemical messenger that influences neuron functions. It has been linked to a wide array of behaviors encompassing mood, sleep, cravings and spontaneity. The power of the chemical over human behavior has made it a key focus in the treatment of mental conditions such as depression by selective serotonin receptor inhibitors (SSRIs), which slow down the reabsorption of serotonin and keep it active in the brain.

"Serotonin has had a lot of study in pharmacology, and serotonergic drugs are commonly prescribed," said Katsuhiko Miyazaki, "but the role that serotonin has over behavior isn't clear." The team investigated for a causal relationship between serotonin levels and behavior in mice.

The mice were trained to perform a task to obtain a food reward, placing their noses into a small hole and waiting—a behavior called a "nose poke." After a pre-set duration, the reward was delivered. In a previous study, the team used a method called optogenetics, a method allowing scientist to use light to stimulate specific neurons with precise timing. These neurons are genetically modified to a produce a light-sensitive

protein and are then stimulated by shining light along a fiber optic implanted in the brain. In the study, serotonin-producing neurons were optogenetically stimulated in a part of the brain called the dorsal raphe nucleus (DRN). These neurons then fired widely into the forebrain. The result was that increasing the activity of serotonin neurons in the DRN drastically increased the amount of time mice were willing to wait for a food reward.

In a test where food rewards were always delivered after 6 seconds, serotonin's effect of extending nose-poke time was small (left). But in tests where food goes was delivered after two, six, or ten seconds later, serotonin boosted nose poke times significantly (right). Credit: OIST

While the study showed that serotonin increased patience, the latest study tested whether mice respond similarly in circumstances when getting a reward was uncertain. Would mice wait for food regardless of the probability and timing of its presentation, or would they give up if they predicted a low chance of return on their time investment?

The new trials showed there are limits to serotonin's ability to enhance patience. Mice were given a nose-poke trial with a 75 percent chance of a reward, with a three second waiting period before the reward was delivered. When these mice were subject to a no-reward outcome, their waiting time was prolonged, as expected from the previous paper. However, in tests where the chance of reward delivery following a nose-poke was 50 percent or 25 percent, increasing serotonin had no effect on the mice's waiting time. "The patience effect only works when the mouse thinks there is a high probability of reward," said Dr. Miyazaki.

They also found that serotonin stimulation made the mice to wait longer when the timing of a reward was harder to predict. In some sessions with a 75 percent chance of getting a reward, mice were rewarded after precise periods, while in other sessions, they were rewarded after randomized timing. The extended waiting times by serotonin neuron stimulation were more prominent when the reward timing was randomized. (Fig. 2).

To explain the results of their experiment, the team constructed a computational model to explain the experimental data. In the model, the mice were able to expect when a food reward would be delivered, and to judge when they were subject to a no-reward trial. The model could reproduce the experimental results by assuming that serotonin affects confidence of receiving a reward when subjective confidence is high. In a 75 percent reward probability trial, for example, serotonin made the mice behave as if there was a 95 percent chance of reward.

The model also reproduced the result of timing uncertainty. When the mice were uncertain of the timing of reward delivery, it became difficult for them to judge whether they were waiting in a reward trial or no-reward trial. Serotonin stimulation increased the mice's belief that they were in a reward trial, delaying their judgment further as reward timing was less clear.

The findings show that the relationship between the activation of serotonin and subsequent behavior is highly dependent on the animals' belief about the circumstances. These results may have implications for our understanding of how humans taking serotonin boosting drugs can also be affected. "This could help explain why combined treatment of depression with SSRIs and Cognitive Behavior Therapy (CBT) is more effective than just SSRIs alone," said Dr. Miyazaki. "The psychological boost of the therapy is enhanced by raised serotonin levels."

More information: Katsuhiko Miyazaki et al, Reward probability and timing uncertainty alter the effect of dorsal raphe serotonin neurons on patience, *Nature Communications* (2018). DOI: 10.1038/s41467-018-04496-y

Provided by Okinawa Institute of Science and Technology