# When our world turns 'upside-down,' serotonin helps us deal with it

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Serotonin, one of the major chemical messengers serving neuronal communication, is usually associated with the direct regulation of affective states and mood in general. But growing evidence suggests that one of the core functions of this neurotransmitter may be to facilitate our adaptation to changes in the world around us - which, in turn, may indirectly impact mood.

Previous studies have shown that an animal's flexibility to adapt to an unfamiliar environment is in fact related to the amount of serotonin available in certain areas of the brain. When those amounts are decreased, adaptability is impaired. However, the mechanisms underlying this phenomenon remain unknown.

To begin elucidating them, neuroscientists at the Champalimaud Centre for the Unknown, in Lisbon, Portugal, analyzed the activity of serotonin-producing neurons in the mouse brain (located in an area called the raphe nuclei), when the animals' familiar environment was suddenly turned "upside-down".

More specifically, the team developed a so-called "reversal learning" task, a type of learning in which the animals start by learning certain rules that lead to a reward and then, after an inversion of the rules, find themselves having to alter their behavior (in this case, licking the source of water) in order to continue obtaining the reward.

"We trained the mice to associate different odors to a reward or to the absence of reward", says Sara Matias, first author of the study, to be published on March 21st in the open-access online journal *eLife*.

When the odor cues were suddenly reversed, the mice started out by making many mistakes, anticipating a reward when it was no longer there and vice-versa. But eventually, they learned the new rules. "It takes three to four days for them to become good at performing the reversed task", says Sara Matias.

## Inadequate behavior

In a first series of experiments, the authors blocked the activity of the serotonin-producing neurons while mice were learning the tasks and found that, following the reversal of the odor cues, the animals persisted in their licking behavior even though it was no longer followed by a reward. In other words, in the absence of the normal serotonin activity, their behavioral flexibility was impaired.

In a second series of experiments, the team simply measured the evolution of the natural activity of the serotonin-producing neurons throughout the initial learning task and the reversal learning task. For this, they used a tool called a "genetically-encoded calcium indicator", that makes a specific type of cell, in this case serotonin-producing neurons, glow when illuminated. To access these glowing serotonin neurons, which reside deep in the brain, they implanted a tiny optical fiber.

After two weeks of initial training, they found that, right after the mice were exposed to an odor cue - but only when the cue allowed them to predict a rewarding outcome -, there was a spike of activity in the population of serotonin neurons. On the other hand, "when the odor was associated to a non rewarding outcome, their activity did not increase", explains Sara Matias.

## Surprise effect

After a given mouse had learned the rules of the game, the scientists abruptly broke them. How was this done? "On a certain day, everything starts as usual - until, after 50 repetitions of the task, I simply invert the odor/reward pairings", replies Sara Matias.

And then, something happened which the team had not been expecting: right after the rules were changed, there was a second serotonin spike. According to the authors, this increase in the neurons' activity is exclusively due to the "surprise effect" brought about by the sudden reversal of the environmental conditions with which the mice are familiar - and not to any prediction of the outcome. "This spike only appears when the outcome is unexpected", says Sara Matias, "independently of the outcome being for better or for worse".

The increased neuronal activity persists as long as it takes the mice to become familiarized with their new reality, acting during the learning period as an alert signaling the existence of altered circumstances. It gradually decreases as the mice learn to deal with the new situation and disappears when the reversal learning process is over.

## The flexibility molecule

Now, the scientists want to know more about how serotonin works to help "unlearn" a previous behavior. Does it act by simply putting a break on the "old" behavior? Does it function instead as a wake-up call, by anticipating possible behavioral errors stemming from an altered situation? Or does it exert its effect through a combination of these two mechanisms?

The new study also suggests a possible way to explain the antidepressant effects of so-called selective serotonin reuptake inhibitors (SSRIs, of which Prozac is the best-known), which are drugs that inhibit the normal clearance of serotonin from the brain.

"Most people overcome the loss of a loved one, but for those who are unable to do it, it may be that serotonin, by promoting behavioral flexibility, opens the door to an increased adaptability to change", says Zach Mainen, who led the study.

Depression can be seen as an inability to adapt to adverse situations, leaving its victims trapped in a downward behavioral spiral. The increase in behavioral flexibility resulting from a long-term increase in serotonin levels may thus help these patients to alter their negative behaviors.

"We think serotonin is not the happiness molecule", says Sara Matias. "It is the neural and behavioral flexibility molecule. It gives us the opportunity to change, but we still have to do something for that change to go in a positive direction. Maybe that's why SSRIs work much better when combined with behavioral psychotherapies than when used alone."

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