Motivation to achieve goals may depend on anxiety level

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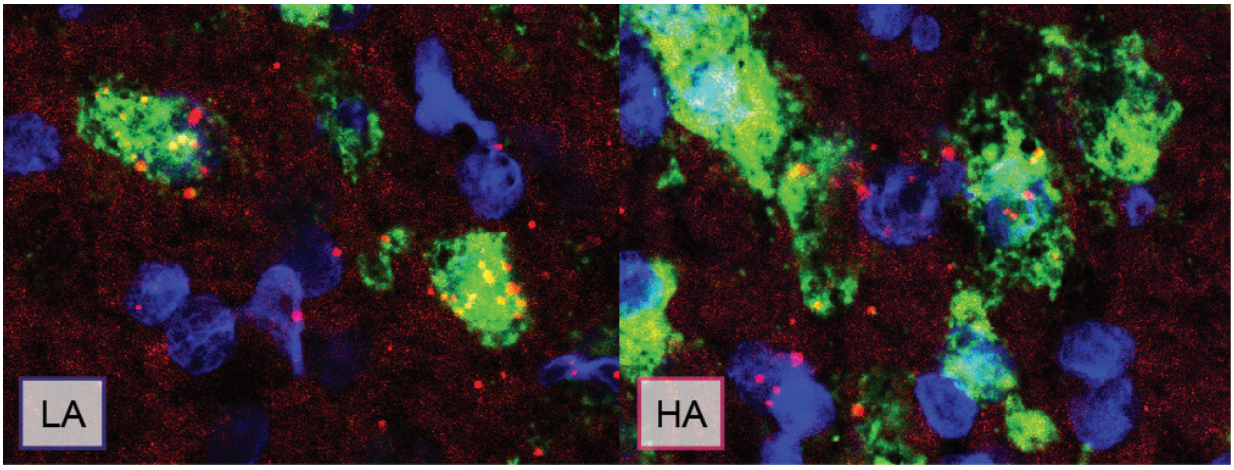

The dopaminergic neurons of low-anxiety rats (LA) show a stronger expression of the corticotropin-releasing hormone receptor 1 (CRHR1, red points) in the ventral tegmental area, as opposed to the rats with high anxiety (HA). The dopaminergic cell groups are shown in green and the clusters of all the neural cells in blue. Credit: CARMEN SANDI/EPFL

People often have different responses to stress. These distinct behavioral reactions could represent factors that indicate different individual susceptibility to develop certain pathologies such as depression. A research team from the EPFL, member of the Swiss Synapsy national center of competence in research (NCCR-Synapsy) on mental health, demonstrated that the motivation to exert sustained effort to obtain goals

after stress exposure depends on the individual's level of trait anxiety.

The study, performed in rats, shows that whereas stress motivates animals with low anxiety to make a physical effort, it mines the capacity to exert effort in highly anxious animals. The cellular mechanisms that underlie these behavioral differences, which can be read in the journal *Science Advances*, involve the corticotropin-releasing hormone receptor 1 (CRHR1), expressed by the dopaminergic cell group in the ventral tegmental area, a cerebral region known to be involved in regulating motivation.

The study shows that the expression of these receptors is directly connected to the rats' anxiety level, with the first consequence being a modulation in the neuronal activity, leading to boosted or diminished motivation. These results help explain the individual differences in susceptibilities to stress and could provide better patient stratification for developing more personalized treatments against depression.

Exposure to stress activates a group of natural physiological and cerebral responses that orchestrate the necessary behavioral changes for facing threats to one's life, such as fleeing or fighting when confronted by a potential aggressor. Exposure to situations of intense or repeated stress can nonetheless have insidious effects and trigger psychiatric problems characterized by an alteration in motivation, such as depression.

The studies conducted on motivation after exposure to stress have until now provided contradictory results. Some studies show that stress causes a decrease in motivation while others indicate an improvement in performance. Carmen Sandi, neuroscientist at the EPFL's Brain Mind Institute, and her research team tried to determine if these contradictory results may be due to variations in the individuals' personality traits, such as anxiety, which has proved to be a key moderator in the effects of acute stress on learning and social behavior. Her lab performed a study

to determine if different individuals' trait anxiety could promote or inhibit motivation under stress.

Anxiety influences motivation

Like humans, rats have more or less anxious personality traits. "We took this natural variation as a basis for selecting a population of very anxious rats and another set with low anxiety traits," Carmen Sandi said. The EFPL researchers first trained rats in a task pressing a lever to obtain a treat.

Then, they submitted these two different test populations to a stressful challenge consisting on exposing animals to an elevated platform where they could not escape during a quarter of an hour. Immediately afterwards, they tested their motivation by making the effort to activate the lever harder each time. The capacity of the highly anxious rats to keep a steady performance was considerably lower than the one shown by the less anxious ones.

The mechanism of Willpower

Using this newly acquired information, the neuroscientists then looked into the underlying mechanisms. Through the genetic analyses of the two rat populations, they found that the expression of the CRHR1 was different between the high-anxiety rats and the low-anxiety rats. This receptor is activated when animals are exposed to stress and influences the activity of the dopaminergic cell groups in the ventral tegmental area (VTA), a cerebral region recognized for its role in regulating motivation. The higher levels of CRHR1 in low anxious rats explains why their performance is better after stress exposure.

To verify their findings, the researchers used genetic and

pharmacological strategies to "play" with the level of expression, and to inhibit and activate this receptor. Regardless of whether the experimental manipulations were done on mice or on rats, the results were consistent with the conclusion that, as Ioannis Zalachoras, postdoc at EPFL and co-author of the study, said, "motivation under stress moves in opposite directions in individuals according to their level of anxiety".

Taking diversity into account

So, when considering anxiety as a character trait, the diversity of personalities could reflect the diversity of behavior, represented in this study by willpower. "Life sciences until now had the tendency to avoid the question of diversity, particularly the one linked to gender. Aside from its main aim, our study is also a way of looking into the question of diversity," Carmen Sandi said.

These results are also promising for treating depression. The CRHR1 receptor was actually the subject of a lot of studies for developing medicinal treatments. Due to a lack of efficacy and the variability of the obtained results, no molecule has yet managed to get over the first hurdle of clinical studies. "Our results show that we need to take into account individual anxiety traits to get a better picture of behavioral performance. This will certainly help develop clinical trials that are more focused on genetic profiles and individuals' variability in anxiety, increasing their chances of success," Carmen Sandi said.

More information: Ioannis Zalachoras et al, Opposite effects of stress on effortful motivation in high and low anxiety are mediated by CRHR1 in the VTA, *Science Advances* (2022). DOI: 10.1126/sciadv.abj9019. www.science.org/doi/10.1126/sciadv.abj9019