Dopamine modulation could help to treat stress-induced anhedonia

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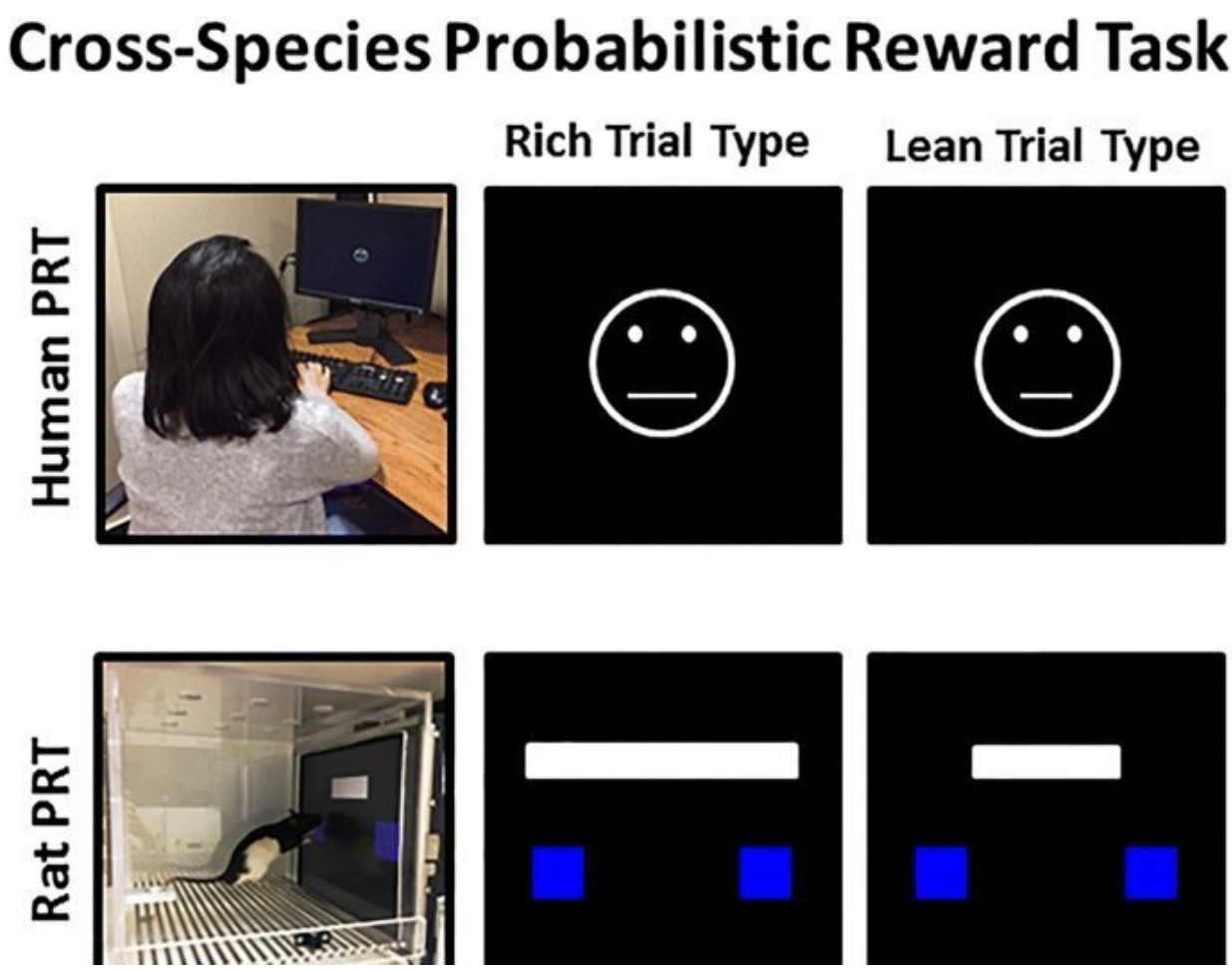

A picture of the PRT task that the researchers used in their experiments. Credit: Luc, Pizzagalli & Kangas, *Perspectives on Behavior Science* (2021). link.springer.com/article/10.1007/s40614-021-00288-w

The term anhedonia is used to describe the inability to feel pleasure and a disinterest in activities that previously brought positive feelings. This lack of interest and pleasure is a very common symptom of depression, as well as other widespread mental health disorders.

Existing pharmacological treatments for depression, such as selective serotonin reuptake inhibitors (SSRIs) and other antidepressants, are not always effective for the treatment of anhedonia. In other words, while people taking them often feel an improvement in their overall mood, they do not always gain back the motivation to engage in rewarding activities.

Researchers at Queen's University have recently carried out a study on rats, exploring the possibility that drugs targeting dopamine receptors could be better suited for the treatment of anhedonia than those targeting serotonin receptors. Their findings, published in Springer Link's *Cognitive, Affective, & Behavioral Neuroscience* journal, suggest that the modulation of dopamine could help to reverse stress-induced anhedonia and reward dysfunctions.

"There are very few effective remedies for anhedonia, which is a debilitating condition that involves deficient motivation to pursue rewarding activities," Steven J. Lamontagne, Ph.D., one of the researchers who carried out the study, told Medical Xpress. "Current first-line drug treatments for depression target the serotonin system, but these are largely ineffective in treating anhedonia."

The main objective of the recent work by Lamontagne and his colleagues was to examine the effects of dopamine modulation on stress-induced motivational deficits in an animal model, specifically on rodents. Their new study was inspired by one of their previous papers, where they tested rodents on a probabilistic reward task and found that chronic stress impaired their reward learning, while amphetamine, which

potentiates dopamine transmission, improved it.

"A logical hypothesis derived from this finding was that we could rescue stress-induced reward dysfunction by enhancing dopamine signaling, but that hadn't been empirically tested," Lamontagne explained. "In our recent work, we completed two major projects to address this question."

In their experiments, Lamontagne and his colleagues exposed 48 male rats to stressful stimuli for a period of three weeks. Subsequently, they treated half of them using systemic, low-dose injections of the drug Amisulpride, which is known to increase dopamine transmission. The other half was treated using micro-infusions of Quinpirole, a chemical that acts as a selective D2-like receptor agonist, into either the nucleus accumbens or the medial prefrontal cortex, two brain regions known to be associated with motivation and goal-directed behavior.

"To determine whether dopamine modulation differentially affects reward learning based on susceptibility to stress, we measured adrenal gland weights as a proxy for stress reactivity," Lamontagne said. "Using immunohistochemistry, we measured D2 receptor expression in the mesolimbic and mesocortical pathways to shed light on stress-related changes at a receptor level."

In their experiments, the researchers gathered interesting results. Most notably, they found that the modulation of dopamine repaired motivational deficits elicited by stress. In addition, the most stress-reactive rats (i.e., those who appeared to have been most adversely affected by the 3-week stress-inducing period) had the best response to the treatment.

"We found higher mesolimbic D2 receptor expression in rats with high stress reactivity, suggesting differences in D2 receptor sensitivity could underlie these effects," Lamontagne said. "Overall, our findings suggest

that the dopaminergic system, particularly mesolimbic D2-like receptors, could be critical targets for drug interventions in the treatment of reward-related dysfunction."

Overall, the results gathered by this team of researchers suggest that patients with anhedonia who have a history of chronic stress exposure could benefit more from drugs that act on the mesolimbic dopamine system than from treatments acting on serotonin receptors. To confirm this and determine whether their findings on rodents can also be applied to humans, however, they will need to conduct further studies on human patients.

"The findings we collected offer exciting new directions in the pursuit of alternative pharmacological treatments for anhedonia," Lamontagne added. "Our next steps will involve clinical applications, where we aim to replicate these methods in a human population with anhedonia."

More information: Effects of dopamine modulation on chronic stress-induced deficits in reward learning. *Cognitive, Affective, & Behavioral Neuroscience* DOI: 10.3758/s13415-022-01001-3.