RESEARCH HIGHLIGHT

How uncertainty sensitizes dopamine neurons and invigorates amphetamine-related behaviors

Mike J. F. Robinson [1] and Patrick Anselme [2]

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Over the last two decades, a growing body of evidence has revealed that reward uncertainty, a major component of human gambling, stimulates the brain similarly to addictive drugs. However, many questions relative to the exact neuronal, psychological, and behavioral effects of uncertainty remain unanswered, especially after prolonged exposure. In this issue of *Neuropsychopharmacology*, Mascia et al. (2018) provide important insights into the role played by reward uncertainty in creating behavioral and neural changes associated with addiction. Two groups of rats were trained to nose-poke for a non-caloric saccharin reward under an increasing variable- (VR) or a fixed-ratio (FR) schedule (1–20) across 55 days. Although the rats performed similarly under the VR and FR schedules, exposure to a VR schedule resulted in a sensitized locomotor response and greater dopamine release in the Nucleus Accumbens (NAc) following amphetamine. It also induced greater drug-seeking and amphetamine self-administration under a progressive ratio.

Interestingly, the authors reported larger dopamine outflows during training under VR (uncertain) conditions that exponentially increased in conjunction with the growing variability associated with larger response ratios. However, this uncertainty-induced increase in dopamine outflow occurred despite no apparent behavioral change during training, suggesting that it did not directly affect motivated behavior. Instead this increased dopamine outflow appears to be a consequence of the training conditions, which raises interesting questions regarding the role of dopamine in encoding this form of uncertainty. Although the authors highlight that dopamine tracks the variability of ratios, it remains to be determined how what appears to be something more akin to an error prediction-like signal, turns into enhanced incentive motivation when animals are later tested on a progressive ratio reinforcement schedule for a drug. Indeed, prediction error does not account for the uncertainty-induced sensitization of dopamine neurons or the increases in locomotion in response to amphetamine and in self-administration of amphetamine. In the current study, microdialysis does not provide the precise temporal resolution that might help answer some of these questions, which is why techniques such as fast-scan cyclic voltammetry or even very recent dopamine-targeted neural imaging techniques might be useful to further probe at these questions [1].

In addition, refining behavioral analysis could reveal differences that, if present, are not shown here. Ferster and Skinner found that response rates are equivalent when the VR is the same as the FR on average [2]. But they also found that the distribution of the responses, not analyzed here, is different: The pause-run pattern commonly found with FR schedules is generally not shown with VR schedules, in which animals seek rewards continuously. Whether or not this behavioral difference is a consequence of differential NAc dopamine overflows under FR and VR has yet to be demonstrated. Another possibility is that uncertainty mainly sensitizes the ability of amphetamine to increase NAc dopamine overflows with respect to non-instrumental behaviors such as locomotion [3]. In a Pavlovian task, there is indeed behavioral evidence that sign-tracking under uncertainty can be sensitized independent of subsequent changes in reward contingency [4, 5].

The current findings further strengthen the case of the effect of reward uncertainty on dopamine activity and incentive sensitization, when one considers that the current design only incorporates one form of uncertainty (effort). As the authors mention, the impact of loss along with the variable magnitude of reward may further compound this effect, as it has been suggested by the literature [6]. This is in addition to our previous work [5, 7] that shows that the combination of probability and magnitude uncertainty, which carries both a loss component and the impact of large wins, could further impact dopamine activity and incentive sensitization.

Interestingly, it appears that uncertainty-based incentive sensitization of drug-seeking during a progressive ratio task, not only increases motivation, but appears to also increase resilience to uncertainty. Based on Figure 2C, rats trained under certain conditions appear to decrease motivation across repeated progressive ratio testing, whereas uncertain animals seem to maintain and possibly increase the effort to which they will work for drug. The greater response rates under progressive ratio after prolonged uncertainty treatment are apparently compatible with frustration theory [8], which predicts that unexpected non-rewards—which occasionally occur in a VR schedule—can boost the dominant response. However, the uncertainty-induced sensitization of dopamine neurons suggests that the invigorated response under progressive ratio is motivated by the opportunity for amphetamine rewards rather than being the consequence of the exasperation that may have resulted from past non-rewarded trials in the VR task.

It is also important to note that the authors found that exposure to uncertainty during training sensitized the dopamine system in a way that was specific to reward-seeking conditions. Meaning that increased dopamine outflow required the presence of a

[1]Department of Psychology, Wesleyan University, Middletown, CT, USA and [2]Department of Biopsychology, University of Bochum, Bochum, Germany
Correspondence: Patrick Anselme (Patrick.Anselme@rub.de)

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reward or at a minimum reward-seeking conditions for these effects to transpire, rather than being the product of a general increase in dopamine tone across the board.

These findings raise the question as to whether the changes due to uncertainty are the same as those one would expect from drug sensitization or whether they simply have a similar behavioral output, yet have the possibility of being complimentary or additive. More research is needed to solve this issue. But the present findings represent a significant step forward for the understanding of the motivational and behavioral effects of reward uncertainty as a powerful determinant of animal and human activities, and further validate the inclusion of gambling disorder alongside substance abuse in the DSM V.

ADDITIONAL INFORMATION

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