

Beliefs modulate the effects of drugs on the human brain

Nora D. Volkow¹ and Ruben Baler

National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD 20892

Convergent neurobiological studies of value-based learning, and the computational models that flow from them, have long pointed to the existence of a reciprocal relationship between dopamine and beliefs. The complex interactions between the pharmacological (reinforcing) effects of addictive drugs and the conditioned responses (expectations) engendered by their continued use (1, 2) provide some of the most compelling examples of this dialogue between molecules and cognition. They help explain, among others, why drug abusers perceive the drug as more pleasurable when they expect it relative to when they do not (3, 4). The report by Gu et al. in PNAS (5) represents an important step forward in this context because it offers new insights into how the power of belief modulates nicotine-driven learning signals related

to nondrug rewards (money), as well as non-drug-related decisions (choice behavior). More specifically, this work illuminates the mechanisms whereby belief can influence nonconscious learned association by modulating how the brain performs risk decisions while under the effects of nicotine.

To investigate how pertinent beliefs can influence the brain's response to value-based learning and behavioral choices, the authors combined functional MRI with a task that involves two computationally explicit variables (one passive and market dependent and the other choice dependent) suitable for probing the inner workings of dopaminergic-driven learning processes. When subjects expected and received nicotine in their cigarettes, they displayed a much larger activation in the ventral striatum (brain reward region

modulated by dopamine) in response to either market value or to prediction reward error signals than after receiving nicotine when it was not expected. These attenuated patterns of ventral striatal activation led in turn to a diminished influence of the corresponding neural representations (of either the market value or reward prediction error) on future bets (choice behavior). Thus, expectation about the presence of nicotine influenced not only the responses to drugs (as had been shown previously) but also the brain response to the value of a nondrug reward, as well as the choice of behavior intended to maximize it (Fig. 1).

These new insights expand the importance of learning and memory in responses to drugs of abuse beyond that of conditioned responses to the drug and to drug-associated cues, to include conditioning to behaviors that occur while under the influence of the drug. For example, conditioning to the dopamine-mediated drug effects on biasing choices toward larger riskier rewards rather than smaller certain ones (6) could underlie the influence of belief in the behavioral choices while under the influence of nicotine reported by Gu et al. (5). These results have far reaching clinical implications. Drugs (including nicotine), by acutely increasing dopamine levels, temporarily enhance the salience value of other stimuli (7); thus, the conditioning to these effects will contribute to drug reinforcement via the expectation of a higher salience value for the activities with which they are associated. This could help explain why it is so difficult to quit smoking, particularly if we consider that smoking behaviors are intermingled with every day activities (and typically throughout the day and in multiple locations) to a greater extent than is the case for illicit drugs or alcohol, the intake of which is more constrained to specific places and times of day. It is also noteworthy that, although the natural tendency to engage in risky behaviors associated with drug intoxication is usually ascribed to drug-induced

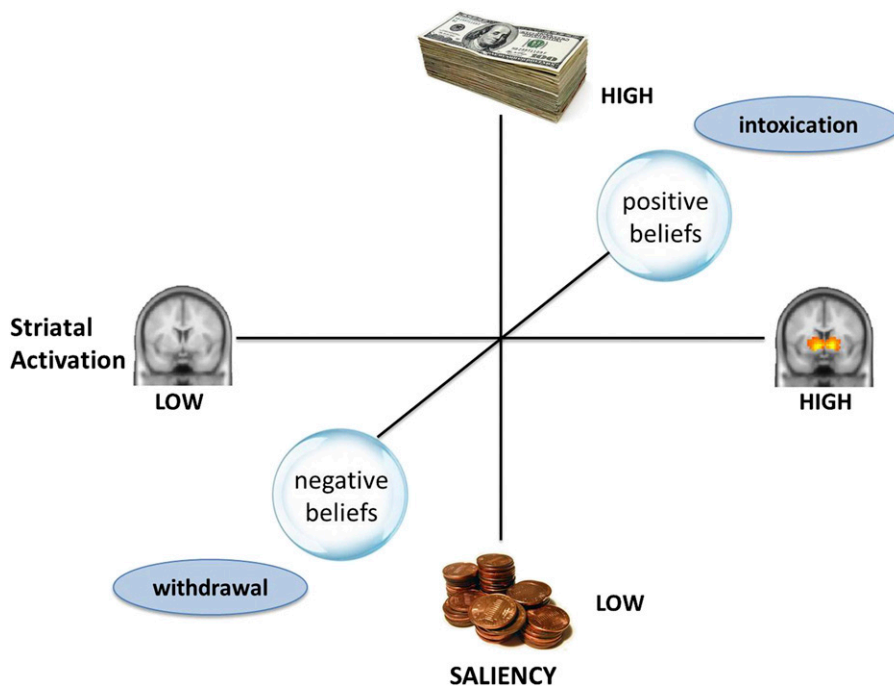


Fig. 1. Beliefs (in this case about nicotine content) that modify the expectation about a soon to be received reward (i.e., a cigarette) are powerful modulators of brain activity (and the dopamine response) in the ventral striatum and of the salience with which that reward is perceived. When combined, the effects of positive and negative beliefs can operate in two diametrically opposed spaces, phenomenologically related to drug intoxication and withdrawal states, respectively, and promote significantly different response behaviors, even if the administered reward is identical.

Author contributions: N.D.V. and R.B. wrote the paper.

The authors declare no conflict of interest.

See companion article on page 2539.

¹To whom correspondence should be addressed. Email: nvolkow@nida.nih.gov.

disinhibitory effects (presumably through the drug's actions on the prefrontal cortex), the findings from this paper would suggest that conditioned expectations could also influence risky choices.

Although not discussed in the work of Gu et al., nicotine's ability to enhance the saliency of a stimulus is relevant in this context because it could make the expectation induced by information or misinformation to the subject more salient, either in the positive (you are getting nicotine) or negative (you are not getting nicotine) condition, respectively. Although the authors report seeing differences when placebo was used and the participants were told they would or wouldn't receive nicotine (belief while under the effects of placebo), these results were not compared with the magnitude of the effect of belief while under the effects of nicotine, which would have allowed them to determine whether the differences on the effects of expectation on brain response and behavioral choices differed between the nicotine and the placebo conditions. Further testing of this very point would allow us to explore how drugs (through their acute pharmacological dopamine enhancing effects and/or through their associated conditioning responses) influence the experience (level of excitement, interest, engagement) of everyday activities. In this respect, nicotine's fast pharmacokinetics are ideally suited, because a user would be able to precisely titrate optimal doses as might be needed throughout the day. Research on whether similar but opposite conditioned expectations might emerge during nicotine withdrawal (or other drug withdrawal) when the sensitivity of dopamine-modulated reward is decreased (8, 9) would also be clinically relevant. If this hypothesis is corroborated, novel approaches for enhancing the saliency of routine tasks and activities or extinguishing conditioned negative associations during drug withdrawal could emerge as the bases for more effective strategies for treating addiction.

A question for future research is whether the findings from Gu et al. will generalize to other associated behavioral effects of nicotine. Particularly relevant are nicotine's effects on attention, dysphoria, and appetite because

these effects are frequently cited as contributors to smoking among those addicted to nicotine. Thus, if beliefs about these learned responses could be clinically manipulated to either extinguish those associations, so as to make nicotine less reinforcing, or enhancing cognitive processes that can recreate these responses without

Gu et al. open up an exciting window into the largely hidden mechanisms by which beliefs and dopamine-driven value-based learning influence each other.

the need for nicotine administration, then this could be of significant therapeutic potential. This question has been extensively investigated for the placebo effect, particularly as it pertains to analgesia, including the relationships between anticipation of pain and the magnitude of the placebo/nocebo effect (10). As for prior studies on conditioning, the placebo analgesic effect also points to dopamine as a mediator of these learned responses (11).

Finally, the results are also relevant to our evolving conception of what constitutes a gateway drug, one of the main qualifications of which pertains to its ability to facilitate/potentiate the rewarding effects of other

drugs of abuse. Specifically, the learned experience of being prone to engage in risky behaviors while under the effects of nicotine could increase the likelihood of a smoker using other drugs, which combined with nicotine's pharmacological enhancement of other drugs' rewarding effects could facilitate transitioning into repeated abuse and addiction.

Our brains are optimized to predict future stimuli and mold our responses. Thus, in this respect, it is not surprising that learned responses play such an important role in drug-seeking behaviors. In the drug abuse field, such learning processes have been extensively investigated as they relate to conditioning to stimuli that predict a drug reward, in which dopamine is known to play a crucial role. The current findings extend the relevance of dopamine-guided learning processes to the experience of how drug intoxication influences the way the human brain works and orchestrates our behaviors. Gu et al. show that such learned responses can be manipulated, identifying a potential new target for developing therapeutic interventions for addiction.

Beliefs are powerful modulators of how humans experience the world and the differential value they ascribe to objectively identical objects or stimuli (12). Gu et al. open up an exciting window into the largely hidden mechanisms by which beliefs and dopamine-driven value-based learning influence each other.

- 1 Robinson TE, Berridge KC (1993) The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Res Brain Res Rev* 18(3):247–291.
- 2 Mitchell SH, Laurent CL, de Wit H (1996) Interaction of expectancy and the pharmacological effects of d-amphetamine: Subjective effects and self-administration. *Psychopharmacology (Berl)* 125(4):371–378.
- 3 Kirk JM, Doty P, De Wit H (1998) Effects of expectancies on subjective responses to oral delta9-tetrahydrocannabinol. *Pharmacol Biochem Behav* 59(2):287–293.
- 4 Volkow ND, et al. (2003) Expectation enhances the regional brain metabolic and the reinforcing effects of stimulants in cocaine abusers. *J Neurosci* 23(36):11461–11468.
- 5 Gu X, et al. (2015) Belief about nicotine selectively modulates value and reward prediction error signals in smokers. *Proc Natl Acad Sci USA* 112:2539–2544.
- 6 St Onge JR, Floresco SB (2009) Dopaminergic modulation of risk-based decision making. *Neuropsychopharmacology* 34(3):681–697.
- 7 Wise RA (1996) Addictive drugs and brain stimulation reward. *Annu Rev Neurosci* 19:319–340.
- 8 De Biasi M, Dani JA (2011) Reward, addiction, withdrawal to nicotine. *Annu Rev Neurosci* 34:105–130.
- 9 Small E, et al. (2010) Tobacco smoke exposure induces nicotine dependence in rats. *Psychopharmacology (Berl)* 208(1):143–158.
- 10 Palermo S, Benedetti F, Costa T, Amanzio M (2014) Pain anticipation: An activation likelihood estimation meta-analysis of brain imaging studies [published online ahead of print December 19, 2014]. *Hum Brain Mapp*, 10.1002/hbm.22727.
- 11 Schmidt L, Braun EK, Wager TD, Shohamy D (2014) Mind matters: Placebo enhances reward learning in Parkinson's disease. *Nat Neurosci* 17(12):1793–1797.
- 12 Koenke S, Pedroni AF, Dieckmann A, Bosch V, Jäncke L (2008) Individual preferences modulate incentive values: Evidence from functional MRI. *Behav Brain Funct* 4:55.