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Loss of phasic dopamine signaling: a new addiction marker

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Abstract

A study finds that a loss of phasic dopamine signal in ventral but not dorsal striatum predicts escalation of cocaine self-administration. Restoring phasic dopamine in ventral striatum with L-DOPA reverses this escalation. The implications of these results to addiction theory and treatment are discussed.

What role does dopamine play in addiction? This question has been in the forefront of addiction research during the last four decades. During this time period, numerous studies have implicated mesolimbic and nigrostriatal dopamine transmission in the rewarding effects of psychostimulant drugs and conditioned drug effects. In parallel, several prominent dopaminergic-centered addiction theories, which argue that dopamine transmission in ventral and/or dorsal striatum is critical for psychostimulant addiction^{1,2}, have emerged. These theories were primarily derived from studies using lesion, receptor pharmacology and microdialysis techniques that do not have the temporal resolution to assess the role of fast phasic dopamine transmission, which is critical to reward learning³, in animal models of psychostimulant addiction. The development of fast-scan *in vivo* voltammetry to measure sub-second phasic dopamine release and the subsequent development of chronic implantable microsensors to determine fluctuations in neurotransmitter release in behaving rodents over time have allowed Willuhn *et al.* to address this question.

In a previous study⁴, the research group used the chronic implantable microsensor methodology to test a specific prediction of the dopamine-based aberrant habit learning addiction theory⁵, which argues that dopamine control of cocaine self-administration shifts from ventral to dorsal striatum over time. They found that in the ventral striatum of rats trained to self-administer cocaine for 1 hour per day (limited-access condition) the phasic dopamine signal immediately after the lever-press for cocaine injection was higher on week 1 than on weeks 2 and 3. In contrast, phasic dopamine signal was not observed in the dorsal striatum on week 1 but emerged during weeks 2–3. These data support the dopamine-based aberrant habit learning addiction theory.

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In the present study, Willuhn *et al.* further tested this influential theory by using an addiction relevant self-administration procedure in which rats given extended cocaine access (6 hours or more daily) increase or escalate their cocaine intake over time. This procedure is thought to model the transition from intermittent, limited drug use to excessive drug use in humans . A straightforward prediction would be that, in the extended-access escalation procedure, the phasic dopamine signal will transfer ‘sooner’ from ventral to dorsal striatum. The results of their study, however, ran contrary to this prediction.

The authors implanted voltametric electrodes into the ventral striatum (nucleus accumbens core region) and dorsal striatum (dorsolateral region) of rats. They then trained them for 1 week to nose-poke (an operant response) for intravenous cocaine during short-access 1-hour daily sessions; cocaine infusions were paired with a 20-second tone-light cue. During the subsequent 3 weeks, the rats were given extended, 6-hour daily access to cocaine. During these 3 weeks the authors measured phasic dopamine signaling immediately after each nose-poke response. The phasic dopamine signal is thought to reflect the conditioned dopamine response to the drug-associated cues .

On week 1, the authors observed a phasic dopamine signal in ventral striatum immediately after the reinforced nose-poke; this signal progressively declined during weeks 2 and 3. The data confirm and extend their previous findings for rats given short-access to cocaine . However, in contrast to their previous findings for phasic dopamine signaling in dorsal striatum during short access to cocaine, during extended access the phasic dopamine signal weakly emerged during the second week and completely disappeared during the third week (Figure 1). These data suggest that loss of phasic dopamine signaling in ventral but not dorsal striatum predicts escalation of cocaine self-administration.

The authors further supported this conclusion with *post-hoc* analyses of data from both the present, extended-access study and the previous short-access study , showing that the loss of phasic dopamine signaling in ventral but not dorsal striatum is associated with escalation of cocaine self-administration, independent of the daily access conditions. In other words, there was no loss of the phasic dopamine signal over time in rats from both access conditions that maintained stable cocaine self-administration during the 3-week period. Additional support to the authors’ conclusion is the provocative observation that systemic or ventral striatum injections of L-DOPA, a precursor of dopamine, decrease escalated cocaine self-administration to ‘pre-escalated’ levels, and remarkably, L-DOPA also restored the phasic dopamine signal in ventral striatum. Taken together, the results suggest that escalated cocaine self-administration is due to compromised ventral striatal dopamine function, which is reflected in the loss of phasic dopamine signaling in this brain region. The unexpected results of Willuhn *et al.* may have implications for both addiction theories and cocaine addiction treatment.

Regarding addiction theories, let us consider the degree to which the present data fit with three influential classes of addiction theories: incentive sensitization , aberrant habit learning and opponent process (Figure 1). The incentive sensitization theory predicts that escalation of cocaine self-administration would be associated with heightened ventral striatal dopaminergic responses to drug-associated cues, a predication that is directly opposite to the

Willuhn *et al.* data. As mentioned above, the dopamine-based aberrant habit learning addiction theory predicts that escalation of cocaine self-administration would be associated with heightened dorsal striatum dopaminergic response to drug-associated cues, this prediction was not confirmed either. By contrast, opponent-process theories predict that extended access to cocaine and escalation of drug intake would be associated decreased phasic dopamine signaling due to a drug-induced hypodopaminergic state, leading to a dysphoric withdrawal that drives cocaine seeking to restore dopamine signaling to normal, drug-naïve levels¹. However, it is too early to discard any of these theories on the basis of the results from Willuhn *et al.*: their study only assessed one facet of presynaptic dopamine transmission, and all assessments were limited to daily self-administration sessions.

The results of the present study raise questions for future research. One question is whether the phasic dopamine signaling in ventral and/or dorsal striatum would re-emerge during periods of abstinence when the response to cocaine cues progressively increases over time. Another question is whether the loss of ventral striatum phasic dopamine signal would predict escalation of opiate (e.g., heroin) self-administration. As evidence suggests that ventral striatum dopamine does not play a critical role in heroin self-administration², we predict that this may not be the case.

Finally, the provocative results of chronic administration of L-DOPA demonstrated by Willuhn *et al.* may have implications for the development of medications for cocaine addiction. There are as yet no FDA-approved medications for cocaine addiction. However, several clinical studies have suggested that agonist-based substitution treatment (e.g., prescription oral amphetamine) decreases illegal cocaine use³. The data of Willuhn *et al.* provide additional preclinical

Figure 1 Comparison of in vivo observations of phasic dopamine changes by Willuhn *et al.* with the predictions of three prominent addiction theories for phasic dopamine neurotransmission during escalation of cocaine self-administration. Predictions for incentive-sensitization (blue shading), aberrant-learning theories (orange shading) and opponent-process theories (red shading), as well as the observed phasic dopamine changes of Willuhn *et al.* (turquoise shading, bold traces) for the ventromedial striatum (VMS, blue brain area and traces) and dorsolateral striatum (DLS, red brain area and traces). Phasic dopamine signal is aligned (time 0) on rats' reinforced nose-poke responses, which result in delivery of a cocaine infusion paired with a tone-light cue. All traces associated with theory predictions are hypothetical, and empirical traces are representative of the findings of Willuhn *et al.* Top: week 1 of extended 6-hour access to cocaine self-administration. Middle: week 2. Bottom: week 3. The observed dopamine changes in VMS most closely match the predictions of opponent-process theories. CC, corpus callosum. In *incentive-sensitization* theories, addictive drugs increase dopamine neurotransmission in the mesolimbic dopamine system that attributes incentive salience to contexts and cues. Long-lasting drug-induced adaptations in the dopaminergic system render it hypersensitive to drugs and drug-associated cues⁴. In *aberrant-learning* theories, repeated exposure to drugs heightens Pavlovian and instrumental responsiveness to drug-associated cues through actions in ventral striatum⁵, dorsal striatum or both⁶. The heightened responsiveness is insensitive to outcome devaluation, leading to continued drug use despite adverse consequences, a process mediated by a progressive dopamine-dependent ventral-to-dorsal striatal shift in control over drug

seeking and taking . In *opponent-process* theories, initial drug use is primarily controlled by the drug's rewarding effects, but chronic drug use is associated with decreased functioning of the mesolimbic dopamine reward system, leading to a dysphoric withdrawal state that drives cocaine seeking to restore dopamine function to normal, drug-naïve levels . Note: we do not indicate dopamine signal predictions in dorsal striatum for incentive-sensitization theories, because these theories only made specific predictions regarding ventral striatum dopamine.

References

1. Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. *Psychol. Rev.* 1987; 94:469–492. [PubMed: 3317472]
2. Stewart J, de Wit H, Eikelboom R. Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. *Psychol. Rev.* 1984; 91:251–268. [PubMed: 6571424]
3. Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Brain Res Rev.* 1993; 18:247–291. [PubMed: 8401595]
4. Di Chiara G. Drug addiction as dopamine-dependent associative learning disorder. *Eur. J. Pharmacol.* 1999; 375:13–30. [PubMed: 10443561]
5. Everitt BJ, Dickinson A, Robbins TW. The neuropsychological basis of addictive behaviour. *Brain Res. Rev.* 2001; 36:129–138. [PubMed: 11690609]
6. Clark JJ, et al. Chronic microstimulation for longitudinal, subsecond dopamine detection in behaving animals. *Nature methods.* 2010; 7:126–129. [PubMed: 20037591]
7. Willuhn I, L.M B, Groblewski PA, Phillips PEM. Excessive cocaine use results from decreased phasic dopamine signaling in the striatum. *Nat Neurosci.* 2014 this issue.
8. Willuhn I, Burgeno LM, Everitt BJ, Phillips PE. Hierarchical recruitment of phasic dopamine signaling in the striatum during the progression of cocaine use. *Proceedings of the National Academy of Sciences of the United States of America.* 2012; 109:20703–20708. [PubMed: 23184975]
9. Ahmed SH, Koob GF. Transition from moderate to excessive drug intake: change in hedonic set point. *Science.* 1998; 282:298–300. [PubMed: 9765157]
10. Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology.* 2001; 24:97–129. [PubMed: 11120394]
11. Dackis CA, Gold MS. New Concepts in Cocaine Addiction - the Dopamine Depletion Hypothesis. *Neuroscience and Biobehavioral Reviews.* 1985; 9:469–477. [PubMed: 2999657]
12. Badiani A, Belin D, Epstein D, Calu D, Shaham Y. Opiate versus psychostimulant addiction: the differences do matter. *Nat. Rev. Neurosci.* 2011; 12:685–700. [PubMed: 21971065]
13. Grabowski J, et al. Agonist-like or antagonist-like treatment for cocaine dependence with methadone for heroin dependence: two double-blind randomized clinical trials. *Neuropsychopharmacology.* 2004; 29:969–981. [PubMed: 15039761]
14. White NM. Addictive drugs as reinforcers: multiple partial actions on memory systems. *Addiction.* 1996; 91:921–949. discussion 951–965. [PubMed: 8688822]
15. Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology.* 1999; 146:373–390.

Figure 1.

Comparison of in vivo observations of phasic dopamine changes by Willuhn et al.⁷ with the predictions of three prominent addiction theories for phasic dopamine neurotransmission during escalation of cocaine self-administration.