behavioral analysis alone could not have deciphered a role for head-scanning behavior in altering hippocampal mnemonic representations of space.

What might the behavioral utility of head-scanning behavior be, considering the findings of this work? Head scanning often occurs at behaviorally important locations, such as at reward locations. Thus, head scanning may facilitate the reward-oriented remapping of place cells, which, in turn, would ensure a more accurate spatial code for those locations[11]. Furthermore, in some of the experiments by Monaco *et al.*[1], there was confusion introduced between near-track and distal room cues. During head scanning, animals may have stopped to orient themselves relative to distal cues. Hence, the formation of new place fields could help the animal to keep track of its location amid conflicting cues. Finally, it is important to note that stable place fields were formed within a single trial in this study. Such one-trial encoding of new place cells is a requirement of episodic memory; thus, this type of place cell might represent a substrate for this process.

Head scanning–related place field formation could also provide a useful tool for studying the network mechanisms behind the formation and stabilization of new place fields. New spatial maps form rapidly when animals enter a novel environment, leaving limited opportunity to collect sufficient data to investigate place field formation. In contrast, tasks that involve numerous head scans can enable investigators to study place field formation processes in multiple instances.

How is it that new place fields were formed so abruptly following head-scanning behavior? Recent work performing intracellular recording in freely moving animals has demonstrated that hippocampal cells often exhibit place-related depolarization of their membrane potentials[13]. This depolarization is often below spike threshold, but once cells are depolarized further by intracellular current injections, these cells start to fire action potentials at these locations. Moreover, they maintain firing at these locations later, even when no further depolarization is applied. Thus, it is plausible that extra depolarization during head scanning could trigger certain cells to form new place fields. Increased firing of cells in the CA3 region of the hippocampus during SWRs could be a source of the necessary depolarization[14]. An alternative depolarizing source could be the transient increase of non-specific subcortical neurotransmitters. Indeed, acetylcholine levels may increase following head scanning, given that theta oscillatory power transiently increases at this time. Finally, a transient drop of interneuron firing rate noted during head scanning suggests that a transient disinhibition could also enable place cells to reach firing threshold during head scanning. Thus, as suggested for place field formation during other conditions[15], disinhibition could promote the development of new place fields during head scanning as well.

With the improvement of animal tracking methods and the development of machine vision algorithms to reconstruct the full body posture of animals, new avenues are opening to identify ethologically relevant behavioral patterns and relate them to circuit activity in the hippocampus and beyond. The recording of neuronal activity may further help to reveal new behavioral patterns or perhaps to divide existing patterns into subclasses on the basis of circuit activity patterns. The Monaco *et al.*[1] study provides a nice demonstration for the merit of such approaches by highlighting a role of head scans in the refinement of the hippocampal cognitive map of space.

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Loss of phasic dopamine: a new addiction marker?

Daniele Caprioli, Donna Calu & Yavin Shaham

A study finds that the loss of phasic dopamine signal in ventral, but not dorsal, striatum predicts escalation of cocaine self-administration. We discuss the study's implications for addiction theory and treatment.

What is the role of dopamine in addiction? This question has been in the forefront of addiction research during the last four decades. During this time, 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[1–5], 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 learning[5], in animal models of psychostimulant addiction. The development of fast-scan *in vivo* voltammetry to measure subsecond phasic dopamine release and the subsequent development of chronic implantable microsensors[6] to determine fluctuations in neurotransmitter release in behaving rodents over time have allowed Willuhn *et al.*[7] to address this question.

In a previous study[8], some of the same authors used the chronic implantable microsensor

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methodology to test a specific prediction of the dopamine-based aberrant habit learning addiction theory[5], which argues that dopaminergic 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 h 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 and 3. These data support the dopamine-based aberrant habit learning addiction theory.

In the present study, Willuhn *et al.*[7] further tested this influential theory by using an addiction-relevant self-administration procedure in which rats given extended cocaine access (6 h 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[9]. A straightforward prediction would be that, in the extended-access escalation procedure, the phasic dopamine signal will transfer 'faster' 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-h daily sessions; cocaine infusions were paired with a 20-s tone-light cue. During the subsequent 3 weeks, the rats were given extended, 6-h 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[6].

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. These data confirm and extend their previous findings for rats given short-access to cocaine[8]. However, in contrast with 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 (**Fig. 1**). These data suggest that loss of phasic dopamine signaling in ventral, but not

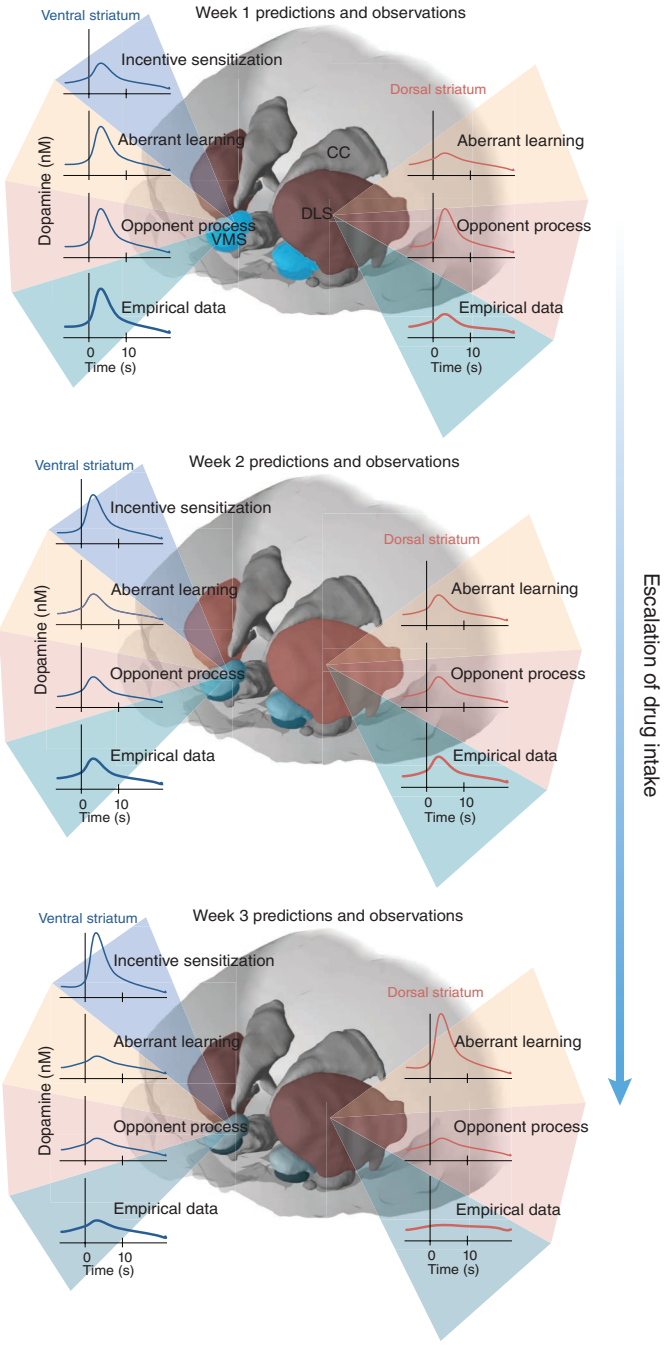

Figure 1 Comparison of *in vivo* observations of phasic dopamine changes by Willuhn *et al.*[7] with the predictions of three prominent addiction theories for phasic dopamine neurotransmission during escalation of cocaine self-administration. Shown are predictions for incentive-sensitization (blue shading), 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 (blue brain area and traces) and dorsolateral striatum (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.*[7]. Top, week 1 of extended 6-h 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. We do not indicate dopamine signal predictions in dorsal striatum for incentive-sensitization theories because these theories make specific predictions regarding ventral striatal dopamine only. CC, corpus callosum.

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[7] and the previous short-access study[8], 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, decreased escalated cocaine self-administration to 'pre-escalated' levels and, notably, that L-DOPA also restored the phasic dopamine signal in ventral striatum. Taken together, these findings suggest that escalated cocaine self-administration is a result of 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.*[7] 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[3], aberrant habit learning[5] and opponent process[10] (**Fig. 1**). 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 cues[2–4]. 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 prediction that was not supported by the data from Willuhn *et al.*[7].

In aberrant-learning theories of addiction, repeated exposure to drugs heightens Pavlovian and instrumental responsiveness to drug-associated cues through actions in ventral striatum[4], dorsal striatum[11] or both[5,12]. The heightened responsiveness is insensitive to outcome devaluation, leading to continued drug use despite adverse consequences, a process hypothesized to be mediated by a progressive dopamine-dependent ventral-to-dorsal striatal shift in control over drug seeking and taking[5]. As mentioned above, this theory[5] 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.

In opponent-process theories of addiction, 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 hypodopaminergic, dysphoric withdrawal state that drives cocaine seeking to restore dopamine function to normal, drug-naive levels[10,13]. These theories predict that extended access to cocaine and escalation of drug intake would be associated with decreased phasic dopamine signaling. This prediction appeared to be supported by the empirical data. However, it is too early to discard the other theories on the basis of the results from Willuhn *et al.*[7]: their study only assessed one facet of presynaptic dopamine transmission, and all of the 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 (for example, heroin) self-administration. As evidence suggests that ventral striatum dopamine is not critical for heroin self-administration[14], we predict that this may not be the case.

Finally, the provocative results of chronic administration of L-DOPA demonstrated by Willuhn *et al.*[7] may have implications for the development of medications for cocaine addiction. There are at present no FDA-approved medications for cocaine addiction. However, several clinical studies have suggested that agonist-based substitution treatment (for example, prescription oral amphetamine) decreases illegal cocaine use[15]. The data of Willuhn *et al.*[7] provide additional preclinical evidence for the utility of this agonist-based treatment modality.

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