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Craving, context and the cortex

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Abstract

A new study challenges the idea that the ventromedial prefrontal cortex inhibits drug relapse, by selectively inactivating a subpopulation of neurons in this brain area and showing attenuation of context-induced reinstatement of heroin seeking.

Drug addiction is a chronically relapsing disorder characterized by a compulsion to seek and take drugs, a loss of control over intake and the emergence of a negative emotional state during drug abstinence. One key aspect of drug addiction is the very high relapse rate observed in addicted individuals who try to quit[1]. High relapse rates are driven by many factors; these include reexposure to the environmental context previously associated with the drug, which can trigger a powerful craving for the drug and provoke relapse. A new study in this issue of *Nature Neuroscience* identifies a neuronal network responsible for context-induced relapse of heroin seeking[2]. This study represents a major step toward understanding the neurobiological mechanisms of relapse and may lead to the identification of individuals vulnerable to addiction, as well as the development of new strategies for treating addiction.

Converging lines of evidence point to prefrontal cortex (PFC) function in drug addiction and particularly relapse[3,4]. Previous work with cocaine in rodents led to the hypothesis that a specific subregion of the PFC, the ventromedial prefrontal cortex (vmPFC), inhibits drug relapse. This work showed that pharmacological activation of the majority of neurons in the vmPFC prevents cocaine-induced reinstatement of cocaine seeking, whereas pharmacological inactivation of the vmPFC promotes relapse to cocaine seeking[5]. In this issue, Bossert *et al.*[2], using a new and elegant pharmacogenetic approach, challenge this hypothesis by identifying a specific subpopulation of sparsely distributed neurons in the vmPFC that are activated by the environmental context associated with heroin, activation that may mediate context-induced relapse to heroin seeking.

The authors first used an animal model of context-induced relapse to heroin, combined with a classic brain mapping technique (Fos immunohistochemistry), to demonstrate that reexposure to the context previously associated with heroin intake recruits a small population of neurons in the vmPFC. The authors trained rats to self-administer intravenous heroin by pressing on a lever for 3 hours per day for 12 days in one context (context 1). Response for heroin was then extinguished by exposing rats to a different context (context 2). In context 2, which differed from context 1 with regard to its visual, auditory, tactile and circadian features, rats could still press a lever, but received no heroin. As such, rats progressively stopped pressing the lever as they learned that the lever in context 2 was not associated with heroin delivery. After this extinction training, rats were reexposed to the heroin-associated context (1) or the non-drug context (2; Fig. 1) and given access to the

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lever, although no heroin was provided. This allowed measurement of heroin seeking, inferred by the number of lever presses) induced by reexposure to the drug-associated context. The authors found that reexposure to context 1 was associated with Fos induction in a subpopulation (~6%) of neurons in the medial PFC, both dorsal and ventral. Of importance, the majority (~71%) of the neurons recruited by reexposure to the heroin-associated context were excitatory glutamatergic neurons (presumably pyramidal neurons), and only a minority (~13%) were inhibitory GABA neurons (presumably interneurons). This result demonstrates that reexposure to the context associated with heroin recruits a small population of excitatory pyramidal neurons in the medial PFC.

These results suggest that this small population of neurons, activated specifically by reexposure to drug-associated context, encodes the learned association between the environmental cues and effects of heroin, and this activation may drive the motivation to seek heroin. However, testing this hypothesis is very challenging and, indeed, requires the experimenter to inactivate the subpopulation of neurons specifically activated by the context without affecting other, 'silent' neurons. To overcome the limitation of available inactivation methods (for example, pharmacological inactivation, lesion, and optogenetic or transgenic manipulations), Bossert *et al.*[2] used a novel pharmacogenetic neuroanatomical method to selectively inactivate vmPFC neurons that were recruited (that is, neurons that expressed Fos) when exposed to the context associated with heroin.

To specifically inactivate these neurons, the authors previously used a *Fos-lacZ* transgenic rat that expresses the protein β-galactosidase driven by the activity-dependent promoter of the *Fos* gene. When the prodrug Daun02 is locally injected, β-galactosidase converts Daun02 to daunorubicin, which then decreases subsequent cellular excitability for several days[6]. Here, the authors used the same transgenic rats and locally infused Daun02 into the vmPFC after reexposure of the transgenic rats to the heroin context. This manipulation allowed enough time for the experimenter to reextinguish the behavior in the non-drug context (2) before testing the motivation to seek heroin when the rat was reexposed to the heroin context (1). When tested in context 1 a second time, rats that had received Daun02 in the vmPFC immediately after reexposure to the heroin context (1) the first time exhibited decreased context-induced activation of vmPFC neurons and decreased heroin seeking. In contrast, rats that received Daun02 immediately after exposure to the non-drug context (2) the first time showed no change in context-induced activation of vmPFC neurons and heroin seeking when reexposed to the heroin context.

These results are exciting for several reasons. First, the authors identify a neuronal ensemble in the vmPFC that mediates context-induced reinstatement of heroin seeking. Second, they suggest that the neuronal network mediating relapse to heroin seeking differs from the neuronal network mediating relapse to cocaine seeking. Third, these results raise hope that focusing specifically on a neuronal ensemble within the majority of neurons of a key structure in the brain for decision making may be a promising strategy for identifying biomarkers of individuals vulnerable to addiction.

However, several questions remain to be addressed. It is critical to determine why the same inactivation of the vmPFC promotes cocaine seeking[5] while preventing heroin seeking. How does the neuronal ensemble in the vmPFC that promotes heroin seeking relate to the one that inhibits cocaine seeking in these rats? Additionally, pyramidal neurons in the vmPFC send projections to many key structures of the brain reward/stress systems that control drug seeking, taking and relapse, including the nucleus accumbens, ventral tegmental area, central nucleus of the amygdala, bed nucleus of the stria terminalis, and basolateral amygdala[7]. It is then critical to determine the projection pattern of this specific neuronal ensemble that

controls context-induced relapse and how this specific neuronal network integrates with the well known role of the vmPFC in decision making in general.

One area that needs future integration with the present study is the well documented roles of the vmPFC and other cortical structures, such as the insular cortex, in emotional decision making. Emotional decision making can be defined as the selection of responses on the basis of the expected valence, magnitude and probability of available response options. The disruption of emotional decision making can lead to risk-prone behavior despite adverse consequences, a hallmark of addiction. The vmPFC has long been known to be critical in decision making in general; and the insular cortex has been hypothesized to mediate emotional decisions, holding the representations of bodily states associated with different choice options[8]. Subjects with damage to the vmPFC display poor judgment, socially inappropriate behavior and impulsivity. For example, such subjects perform poorly when tested for decision making under risk, such as in the Iowa Gambling Task[9] and the Cambridge Gamble Task[10]. Most intriguingly, damage to the vmPFC and insular cortex disrupt performance on the Cambridge Gamble Task by means of a different mechanism[10]. Although lesions both to the vmPFC and insula lead to risky behavior (that is, increased betting in the gambling task) compared with healthy controls, only subjects with vmPFC damage were able to adjust to the odds of winning when the probability of losing increased, whereas insular subjects maintained high bets even when the probability of losing was high. This result suggests that a neuronal ensemble in the vmPFC may control risky behavior by setting the level of acceptable risk on the basis of the cognitive context (positive and negative outcomes), while a specific neuronal ensemble in the insula may control risky behavior on the basis of the internal context by encoding the visceral and somatic representations associated with aversive outcomes necessary to guide decision making.

The identification in the Bossert *et al.* study[2] of vmPFC neuronal ensembles that mediate craving for the rewarding effects of a drug (type 1 craving, or reward craving[11]) has tremendous implications for the neurobiology of addiction; however, with opioids (and other drugs), as dependence develops, other sources of reinforcement evolve, such as the negative reinforcement associated with the removal of the aversive emotional state of withdrawal (type 2 craving, or withdrawal-relief craving)[11]. This negative emotional state can be conditioned[12], contribute to craving[13] and motivate drug seeking[14]. One intriguing possibility is that other cortical ensembles that involve structures such as the insular cortex may be recruited with the development of opioid dependence and contribute to the powerful drug seeking during protracted abstinence observed in those addicted to opioids. Such a hypothesis could easily be tested by combining the innovative techniques applied to the context-specific reinstatement outlined by Bossert *et al.*[2] with animal models for the transition to drug dependence that have been developed recently[15].

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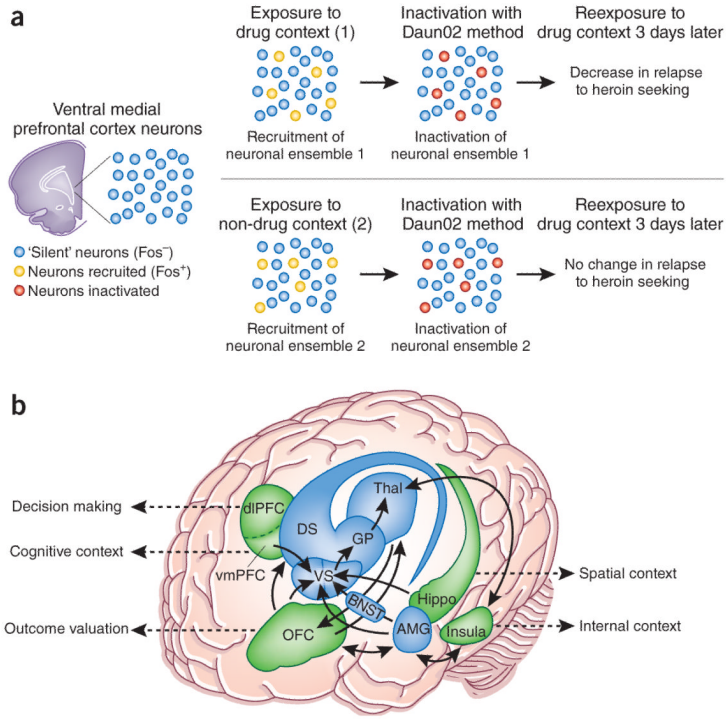

Figure 1.

Cortical neuronal ensembles underlying context-induced reinstatement of drug seeking. (**a**) Pharmacogenetic inactivation of vmPFC neurons that have been recruited by the drug-associated context prevents relapse to heroin seeking. After drug-seeking is extinguished in a non-drug context, rats are exposed either to the drug context (1) or the non-drug context (2). Exposure to the different contexts results in recruitment of different ensembles of neurons, ensembles 1 and 2 (Fos^+ neurons, gold). Local infusion with the compound Daun02 selectively inactivates the neuronal ensemble (red neurons) that was previously activated while leaving the remaining, 'silent' neurons (Fos^-, blue) functional. (**b**) Neural circuitry of context-induced relapse to drug seeking. Different types of contextual representations are hypothesized to be processed in the different areas: cognitive context in the ventromedial prefrontal cortex (vmPFC), internal context in the insula and spatial context in the hippocampus. These representations, together with the representation of the outcomes and their values in the orbitofrontal cortex (OFC), may influence the dorsolateral PFC (dlPFC) and contribute to risky decision making and relapse to drug seeking. Green, cortical areas; blue, subcortical areas. AMG, amygdala; DS, dorsal striatum; VS, ventral striatum; GP, globus pallidus; BNST, bed nucleus of the stria terminalis; hippo, hippocampus; thal, thalamus.