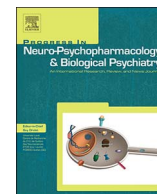




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An extended history of drug self-administration results in multiple sources of control over drug seeking behavior

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ABSTRACT

It is widely recognized that across the development of drug addiction, cues associated with drug use come to exert increasing control over drug seeking and taking behaviors. However, there remain gaps in our knowledge regarding how the different types of drug related cues affect drug seeking and taking behaviors, and how the emergence of cue control over these behaviors relates to the onset of drug seeking compulsions. This paper reviews the literature on drug self-administration in animals to address these gaps. It first identifies the different types of cues that acquire control over reward seeking behavior generally, and examines whether the same types of cues acquire control over drug seeking behavior specifically. It then examines how the role of drug related cues in motivating and reinforcing drug seeking behavior changes across an extended drug-taking history, with a particular focus on the case of nicotine. The evidence reviewed shows that, after an extended history of drug taking, drug seeking behaviors are controlled by contextual cues associated with the development of drug seeking habits, response contingent cues that accompany delivery of the drug, as well as internal states that correlate with levels of drug intake. These multiple sources of control over drug seeking are discussed in relation to the generation of an addicted phenotype in animal models and the hypothesized progression from internal control over drug use to compulsive drug seeking.

1. Introduction

People start using drugs of abuse for reasons that are complex and varied. Many abandon drug use over time, but a significant minority continue using in spite of explicit knowledge (or experience) of ill health, economic, family and social consequences, a hallmark of substance abuse disorders. In general, a substance use disorder is a progressive and chronic disease, characterized by an early stage of voluntary or recreational drug use, followed by a stage of regular drug use, and finally, a loss of control over intake (Everitt and Robbins, 2005). This progression across drug use is thought to involve disturbances in reinforcement and motivational processes, onset of withdrawal syndromes, and an increased sensitivity to drug related cues. However, there is a surprising lack of evidence regarding the conditions under which different types of drug-related cues control drug seeking, how the impact of drug-related cues change across the course of drug use, and how these changes relate to compulsive drug-seeking.

This paper selectively reviews the literature regarding how different types of drug-related cues control drug seeking, and how this cue control changes across time and with drug exposure. It does not cover the neural substrates of drug-seeking, as there are already several

excellent reviews of this literature (Everitt et al., 2008; Wickens et al., 2007). Like an earlier paper by Hogarth et al. (2013), the paper views drug seeking behavior as the product of “multiple controllers” in the form of the different types of drug related cues. However, it differs from the earlier review in considering the broader range of cues that control drug seeking behavior (i.e., those beyond contextual cues that become associated with a drug seeking response), and how the role of these cues in sustaining drug-seeking changes over time.

This paper has five parts. The first describes the different types of cues that acquire control over reward seeking behavior generally. The second reviews the types of cues that acquire control over drug seeking behavior specifically (e.g., those that precede drug-use, those that are encountered contingent on the drug taking response, and those produced by variations in an internal drug state), including the evidence that an extended history of drug self-administration brings about changes in their control over drug seeking. The third focuses on the case of nicotine, as this drug consistently ranks among the most harmful in terms of its health effects, and given the usual route of administration (i.e., smoking), the different types of cues described above are clearly defined (e.g., the pub, sensation of smoke in the throat, and blood level of nicotine). The fourth considers other types of changes that occur

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across a history of extended drug self-administration, such as the regulation of drug seeking in relation to blood levels of a drug or its metabolites. Finally, the fifth part considers the relationship between the emergence of cue control over drug seeking and the expression of drug seeking compulsions.

2. Cue-controlled drug seeking

There is widespread recognition that drug seeking and taking behaviors gradually come under the control of cues in the environment, and further, that the emergence of cue control over these behaviors is a fundamental feature of substance use disorders (Hogarth et al., 2012; Robinson and Berridge, 1993). Three broad categories of cues can be distinguished, each defined by their temporal relation to drug use. First, there are *distal cues* that signal the possibility or availability of the drug (i.e., they serve as discriminative cues). These cues are often, but not always, associated with drug use: e.g., in their everyday circumstances, a drug user encounters places where drug taking is possible (e.g. a bar) and others where it is not (e.g. work), thus imbuing particular environments with the capacity to draw people in, elicit cravings and trigger or initiate drug-seeking. The user may then enter into a complex and varied set of behaviors specifically aimed at procuring the drug reward. Second, there are cues encountered *proximal* to drug use that are nearly always associated with drug taking: e.g., drug-taking paraphernalia and other drug users. These cues can trigger specific sequences of events that lead to drug consumption. Third, there are internal or sensory cues that accompany delivery of the drug, and are therefore always associated with drug use: e.g., cues that are experienced contingently on the drug-taking response (such as the taste, smell or sensation of ingestion, as well as the internal state that occurs as a consequence of drug use) and therefore influence drug seeking by acting as conditioned reinforcers.

Associations between drug-related cues and various drug effects form rapidly, often within a few drug taking experiences, and are strengthened across repeated drug use. Based on this strengthening, it has been suggested that cues that signal the availability of the drug may trigger drug seeking, approach and intake independently of the value of the drug, and response contingent cues may become rewarding or reinforcing in their own right, sustaining drug seeking independently of the drug itself.

Most experimental evidence in support of these assertions comes from animal studies in which rats have been extensively trained to respond for a natural reward, such as food. These studies show that, after extended training, cues that usually accompany the delivery of food reinforce food seeking behavior even when the food itself is no longer liked (Parkinson et al., 2005), and cues that signal the availability of specific foods can trigger food-seeking when animals are sated (Corbit et al., 2007), or when the expected food has become disliked (Holland, 2004; Rescorla, 1994); for review, see (Holmes et al., 2010); for related findings, see (Delamater, 1996) and (Rescorla, 1992); but for opposite findings, see (Haddon and Killcross, 2006). That is, even after a target food has been devalued via pairings with gastric-induced illness, cues that previously signaled its delivery remain just as effective in triggering the seeking of *that* food (Holland, 2004; Rescorla, 1994) and can support the acquisition of a completely new response (Parkinson et al., 2005).

Given that drugs of abuse have an even more pronounced effect on the same reward systems that control feeding (Di Chiara and Imperato, 1988; Hernandez and Hoebel, 1988), drug-related cues are likely to be even more effective in acquiring control over behavior. Consistent with this suggestion, several studies in the past decade have shown that treatment with drugs of abuse facilitates the development of cue control over behaviors established and maintained by natural rewards (like food to a hungry rat). For example, Nelson and Killcross (2006) trained hungry rats to earn a food pellet reward by pressing a lever, devalued the food pellet via pairing with lithium chloride, and then tested lever

pressing under conditions of extinction (i.e., under conditions where lever-pressing could only be controlled by a retrieved representation of the food pellet). Nelson and Killcross (2006) found that pre-training sensitization to amphetamine reduced the impact of reward devaluation on lever-pressing in the extinction test: i.e., rats in the treatment condition exhibited a persistence of responding in extinction even though the food pellet reward had been poisoned and was no longer valuable to them (see also (Nelson and Killcross, 2013, Nordquist et al., 2007). Nelson and Killcross (2006)) confirmed that the poisoned food pellet was equally distasteful in the two conditions as rats in each refused to lever press when pressing procured that food pellet. These findings were taken to imply that, in the treatment group, cues that signaled the availability of food, including the context, had acquired control over rats' lever-pressing behavior; hence, the food seeking response was performed in the context regardless of the value of food that it had previously earned. That is, the amphetamine treatment facilitated the transition from goal-directed to habitual food-seeking.

The findings reported by Nelson and Killcross (2006) have since been replicated using regimes of systemically injected methamphetamine (e.g., (Furlong et al., 2017)) and cocaine (e.g., (Corbit et al., 2014a), LeBlanc et al., 2013); see also (Schmitzer-Torbert et al., 2015). These same regimes have also been shown to exaggerate the impact of more discrete reward related cues on rats' reward seeking behavior. One protocol used to illustrate this point is Pavlovian-to-instrumental transfer (PIT), where a stimulus predictive of a distinct reward biases the selection of responses that procure that same reward (for a review, see (Holmes et al., 2010)). A second protocol is conditioned reinforcement, in which animals learn to make a response in order to gain access to a cue that previously signaled delivery of some outcome (Williams, 1994). These two types of cue controlled behavior are both enhanced by systemic injections of amphetamine (Shiflett, 2012); see also (Shiflett et al., 2013; Wyvell and Berridge, 2001) and cocaine (LeBlanc et al., 2013). Hence, these findings show that treatment with drugs of abuse increases the impact of reward-related cues on reward seeking behavior, suggesting that drugs of abuse influence the neural circuits that mediate the impact of natural rewards (such as food to a hungry rat) on reward seeking behavior.

3. Cue-controlled drug seeking and loss of control with an extended training history

Reward devaluation procedures have been critical in demonstrating precisely how different types of food-related cues control food-seeking behavior. Such procedures include pre-test exposure to a maintenance diet (thereby shifting the motivational state of a subject from hungry to sated), pre-test exposure to the target food itself (thereby inducing a sensory specific satiety), and as described above, pairings of the target food with a nauseating agent such as lithium chloride (thereby conditioning a direct aversion). In principle, the same types of manipulations could be used to probe how different types of *drug*-related cues control *drug*-seeking behavior. However, in practice this strategy has been hampered by the fact that drugs of abuse are much more difficult to devalue than natural rewards. Specifically, manipulations of motivational state and sensory-specific satiety are difficult as the pharmacokinetics of the drug may not produce a long-lasting satiety signal, high levels of the drug may be aversive, and its sedative (e.g. opioids) or stimulatory (e.g. cocaine and amphetamines) effects may interact with behaviors at test. Furthermore, the conditioning of a gastric aversion to an abused drug can be difficult if it lacks the necessary features for association with feelings of nausea (e.g., intravenously administered drugs that lack consummatory or gustatory components).

For these reasons, researchers have developed other ways of illuminating the sources of control over drug seeking in rats. There are now a handful of studies showing that (i) drug-related cues control drug-seeking behavior in the same way that food-related cues control food seeking behavior; and (ii) the role of drug related cues changes across

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