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Review

Enhanced dorsolateral striatal activity in drug use: The role of outcome in stimulus–response associations

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HIGHLIGHTS

- Dorsolateral striatal activity has been proposed to underlie habitual drug use.
- This region supports stimulus–response (S–R) based behaviors.
- Behavioral evidence is described showing that reward value can regulate S–R behaviors.
- This is consistent with a maintained interaction between ventral and dorsal striatum.

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ABSTRACT

Prolonged stimulant exposure leads to enhanced dorsolateral striatal (DLS) dopaminergic activity in response to the drug and drug-associated cues. This effect has been interpreted in light of evidence that this brain region supports the generation of habitual stimulus–response (S–R) based behaviors to propose the idea that prolonged drug use leads to the development of drug taking and seeking habits that are insensitive to the value of the rewards they procure. In this review, we discuss evidence supporting a continued role for reward value in the performance of S–R based behaviors. We describe how caching of reward value and Pavlovian to instrumental transfer can provide mechanisms for past and current reward values to regulate the performance of S–R habits. The contribution of these constructs is consistent with evidence indicating the continued interaction between ventral incentive processing and dorsal S–R processing striatal regions in the generation of habitual drug seeking behaviors.

Contents

Abbreviations: CS, conditioned stimulus; DA, dopamine; DLS, dorsolateral striatum; PIT, Pavlovian to instrumental transfer; R–O, response–outcome; S–R, stimulus–response; UCS, unconditioned stimulus; VS, ventral striatum.

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1. Introduction

A large body of research has demonstrated the sensitizing effects of psychostimulant drugs in the striatal regions of the basal ganglia. Two stages have been observed [1,2]. Following several days of drug use, drugs and associated cues elicit an enhanced dopaminergic response in the ventral aspect of the striatum (VS). As drug use continues, this enhancement radiates to include the dopamine (DA) projections to the dorsolateral aspect of the striatum (DLS) [1–4]. These effects have proven to be fairly reliable and have been demonstrated in rats and primates as well as in humans [5–9].

These findings have served as the basis for a highly influential theory of habitual drug use [10,11]. Based on research linking the DLS to the formation and expression of stimulus–response associations [12,13], this theory argues that drug-induced sensitization of DA overflow in the DLS leads to the emergence of stimulus–response associations that mediate pathological drug seeking and taking.

Dual process theories of behavior posit that two types of associations underlie behavior: stimulus–response (S–R) and response–outcome (R–O) associations. S–R associations differ from R–O associations regarding the role played by reward in controlling behavior. Behaviors based on R–O associations are conceptualized as being directly motivated by the value of the outcome procured by the behavior. In contrast, S–R behaviors are conceptualized as habitual or reflexive responses to environmental stimuli that are not driven by the value of the outcome resulting from the behavior [14,15].

One readily observable difference between S–R versus R–O based behaviors stems from their differential sensitivity to reward, that is the degree to which the intensity of the behavior emitted shifts in response to changes in the value of the contingent reward. R–O associated behaviors tend to be reward-sensitive while S–R associated behaviors generally are not [14,15]. If pushing a lever produces food, devaluation of that food will either decrease lever pressing or have no effect depending on the association underlying the behavior. Table 1 provides key terms and definitions as they relate to habitual drug use.

According to the theory of habitual drug use of Everitt and Robbins [10,11], enhancement of stimulant-induced DA activity in the DLS increases the degree to which drug seeking and taking behaviors are under the control of S–R associations. As a result, these behaviors occur in response to environmental stimuli and are relatively unaffected by the value of the rewards subsequently obtained. A constellation of drug procuring behaviors can conceivably be perceived in this way (e.g. reaching for a crack pipe, cigarette, or alcoholic beverage). These 'habits' are cued by environmental stimuli and occur irrespective of the outcomes that have become linked to drug use. Such habitual reward insensitive behavior is argued to be an essential component of addiction [10,11,16]. It has also been suggested that reliance on S–R associations increases the cognitive automaticity of behavior so that it may require fewer attentional resources [7,8,10,11,16,17].

These arguments suggest that as drug use progresses, the degree to which both positive and negative outcome value plays a role in the behavioral mediation and cognitive experience of drug seeking and taking declines. This theory has significant ramifications for therapies that try to focus drug users on the negative consequences of the drug use lifestyle. If drug pursuit occurs as a habitual response to environmental cues then these therapies are not likely to be very effective.

Here we argue that outcome value can continue to influence the emission of drug procuring behaviors despite the development of drug induced S–R associations. While increased reliance on S–R associations heralds a shift in the role of reward in mediating behavior, it remains that the value of previous rewards as well as competing values of multiple current rewards can continue to influence S–R behaviors. In the first section of this review, we outline a mechanism by which previously learned reward value may continue to influence behaviors that have become habitual. We also describe a mechanism by which different current reward values associated with multiple reinforcers can influence S–R responding. As it has not yet been demonstrated unequivocally that S–R based behaviors recruit fewer attentional resources, we review in the second section the respective determinants of S–R and automatic behaviors and discuss overlaps and distinctions between these two constructs. Finally, we review relevant neurobiological findings to support the assertion that reward value continues to play a role in chronic habitual drug use. These findings demonstrate maintained interactions between R–O and S–R substrates in striatum.

Table 1
Key terms and definitions.

R–O. An operant association in which the probability of a response is linked to a rewarding outcome. These associations can be identified by varying the value of the outcome and measuring variations in response amplitude [14].
S–R. An operant association in which a stimulus is linked to a response independent of outcome. These associations can be identified by varying the value of the outcome and demonstrating a lack of variation in response amplitude [14].
Reward value sensitivity. The degree to which operant responses are influenced by changes in the value of reinforcers associated with operant stimuli. Reward-sensitive behaviors are considered reflective of R–O associations while reward-insensitive behaviors are considered reflective of S–R associations [14].
DLS/S–R development. The suggestion that over the course of drug use neural activation radiates from ventral to dorsal striatal regions. The latter regions are associated with the performance of habitual S–R behaviors. Hence, DLS activation is suggested as a mechanism by which drug seeking and use become increasingly under the control of S–R modes [11].
Interval training. A reinforcement schedule that rewards operant behavior in timed intervals. This type of schedule distances behavior from reward as behavior is not always involved in making the reward available. This type of schedule has been associated with the development of S–R associations [14].
Overtraining. Refers to the extent that a given training paradigm is repeated. The role of overtraining in S–R development is unclear. It appears to be sufficient [26] but not necessary for S–R development [12,13]. Other studies, however, have found that overtraining produces no effect on the development of S–R associations [27,28].
Ratio training. Reinforcement schedule that rewards operant behavior according to the amount of behavior produced. This type of schedule establishes a strong relationship between reward and behavior as all responses are related to reward provision. This schedule is more likely to produce R–O associations [14,15].

2. Outcome as a modulator of S–R based behaviors

There are different ways in which outcome can influence S–R behavior. Two different types of outcome value have been proposed: cached and current value [18,19]. While definitions of cached value vary, common among them is the idea that it indexes a memory of some general aspect of reward associated with a given reinforcer experienced in the past [18–20]. Current value refers to the significance of the actual reinforcer based on a representation of reward as it is relevant to the organism at the present time [21]. The following results suggest that both cached and current reward values may be able to influence the performance of S–R behaviors.

2.1. Role of cached outcome values in S–R responding

Theoretical arguments have been made to suggest that cached outcome value can influence the generation of S–R behavior [18–20]. While these arguments did not provide unequivocal evidence for outcome representation during S–R performance, they did introduce the possibility that memories of the value of reinforcers could come to influence the expression of the respective S–R