Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Multiple Properties of Drug-Paired Cues May Precipitate Reinstatement

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Review of Wheeler et al.

Reactivity to drug-paired cues is associated with increased severity of addiction and propensity to relapse (Jasinska et al., 2014). Consequently, animal models of addiction frequently investigate responses to drug-associated cues or contexts, using behavioral assays such as extinction–reinstatement or context-induced renewal. These experiments allow researchers to study the neural mechanisms by which extinguished drug-seeking behavior is reinstated or renewed when the animal is presented with drug-associated cues or returned to the original training context (Perry et al., 2014).

The exact role played by drug-paired cues is a contested topic in addiction science, and several competing explanations have been offered. Some hypotheses suggest that cues present during drug self-administration acquire properties of a conditioned reinforcer, while other hypotheses highlight the incentive-motivational properties of these cues or their ability to activate dysregulated neural circuits within the brain's stress system (Koob et al., 2014; Perry et al., 2014). According to Koob et al. (2014), although drug use is at first driven by the positive reinforcing and rewarding effects of the drug, the addicted state is driven by negative reinforcement, specifically, a desire to escape aversive motivational states that arise in the absence of the drug. Additionally, Su et al. (2012) have shown that contextual and discrete predictors of cocaine administration increase both approach and avoidance behaviors in rats. They argue cocaine produces an initial euphoric state followed by a homeostatically driven aversive state and both become associated with drug-paired cues. Drug-associated cues may therefore have both positive and negative associations.

Further evidence that drug-associated cues take on aversive properties comes from the finding that rats will show aversive reactions (e.g., gapes) to an otherwise palatable saccharin solution that predicts delayed (but not immediate) access to a drug of abuse (Wheeler et al., 2011; Colechio and Grigson, 2014). Wheeler et al. (2015) aimed to demonstrate that presentation of a saccharin delay cue (that appeared to acquire aversive properties) can reinstate drug-seeking behavior after extinction. Following placement in the operant chamber, rats in a "paired" group received experimenter-administered intraoral infusions of an appetitive saccharin solution before being allowed to lever press for tone-cued cocaine infusions, while "unpaired" rats received cocaine access after a waiting period (no saccharin). During extinction training, where saline was substituted for cocaine, paired rats experienced a waiting period before lever insertion, while unpaired rats received saccharin. This procedure resulted in rats in the paired, but not unpaired condition, displaying aversive taste reactivity to saccharin. After extinction, saccharin delivery induced reinstatement in paired rats, for whom saccharin signaled delayed access to cocaine, but not unpaired rats, which were tested under extinction conditions. Furthermore, using a combination of electrophysiology and fast scan cyclic voltammetry in the nucleus accumbens (NAc), the authors showed that for rats in the paired group, the saccharin delay cue decreased dopamine release and, importantly, simultaneously increased excitatory activity of neurons that also responded to the tone cue that was previously presented concurrently with cocaine delivery.

Wheeler et al. (2015) argue, in a similar vein to Koob et al. (2014), that the observed reinstatement is driven by attempts to alleviate the negative affective state (and the associated decrease in dopamine release) induced by presentation of the aversive saccharin delay cue. Such an interpretation is supported by the finding that the increase in responding during reinstatement over extinction was positively correlated with aversive reactions to the saccharin cue at test. In addition, electrophysiological recordings from the NAc showed that the same neurons that respond to the tone, a proximal and presumably appetitive cue (evidenced by the increase in

Received July 5, 2015; revised Aug. 13, 2015; accepted Aug. 19, 2015.
We thank Denovan Begg, Nathan Holmes, Kelly Clemens, Justine Fam and Fred Westbrook, for their helpful discussion and comments.
The authors declare no competing financial interests.
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DOI:10.1523/JNEUROSCI.2551-15.2015
 0270-6474/15/3512971-03$15.00/0

dopamine in the unpaired group), also respond to the saccharin, suggesting that these neurons might be sensitive to both appetitive and aversive stimuli. This provides a potential neurobiological mechanism through which cues that induce negative affective states can activate neural circuits involved in drug-seeking behavior.

The results of Wheeler et al. (2015) are consistent with the interpretation that reinstatement is spurred by the desire to avoid the negative affective state induced by aversive drug cues. However, such an account might miss important aspects of reward learning and appetitive motivation that could explain the observed results. Indeed, it may be that the saccharin cue has multiple properties and plays a more complex role in driving cocaine-seeking.

One possibility is that presentation of saccharin during test recreated the conditions experienced by the paired group during cocaine self-administration, when saccharin predicted the future, albeit delayed, availability of cocaine. Therefore, it is plausible the saccharin cue exhibits some of the properties of an occasion setter and that the reinstatement of cocaine-seeking may be attributable, at least in part, to a contextual renewal effect. Meanwhile, the unpaired group were tested under conditions identical to extinction and hence showed no reinstatement. Although reinstatement is correlated with aversive taste reactions, the relationship may be mediated by the strength of the association between the saccharin and cocaine access, where rats with stronger associations show greater aversive taste reactivity because the saccharin is a good predictor of delayed cocaine access. As a result, these rats show greater reinstatement, but not necessarily because of the aversive properties of the cue.

A second possibility could be that the reinstatement is the result of a combination of the appetitive and aversive properties of the saccharin delay cue. It may be that in some cases, the aversive properties of the saccharin cue drive compensatory cocaine-seeking, while in others they augment the renewal of drug-seeking induced by returning the animals to the original training context. Such an interpretation would be consistent with studies of stress and cue-induced reinstatement, as Buffalari and See (2009) found that presentation of an aversive stimulus precipitates reinstatement alone, but also augments a cue-induced reinstatement response when combined with a cocaine-associated cue. This could be tested using intra-amygdaloidal β-adrenoceptor antagonism, which has been shown to attenuate the negative/anxiogenic effects of cocaine without affecting its acute hedonic properties (Wenzel et al., 2014). If the aversive properties of the saccharin are necessary for reinstatement, their modulation should attenuate reinstatement.

Given that the saccharin cue may possess multiple properties, it is not clear whether the electrophysiological data reflect the aversive nature of the saccharin per se. The authors interpret the finding that NAc neurons respond to both the proximal drug cue and the saccharin as evidence that this circuitry is sensitive to aversion. While D_2 receptor-expressing neurons in the NAc are known to be preferentially activated by aversive stimuli (e.g., footshock; Xiu et al., 2014), it is clear that the NAc also responds to cues associated with reward. Indeed, NAc neurons have been shown to integrate information from a number of brain regions about the value of an expected reward, and the excitability of these neurons increases even when there is a delay (in the range of seconds) between the cue and reward delivery (Roesch et al., 2009). As a result, it is unclear whether the neurons excited by the tone are also sensitive to aversion, or are merely encoding the value of the reward that is predicted by the presence of the saccharin.

Group comparisons regarding the effect of saccharin presentation on the neural response to the proximal tone cue are further complicated by the fact that there are different associative relationships between the saccharin and the tone for the paired and unpaired groups. Wheeler et al. (2015) speculate that the aversive saccharin-induced decrease in dopamine response to the tone may be contributing to the reinstatement observed among rats in the paired group. However, while the paired group received 12 sessions of saccharin exposure followed by response-contingent tone presentations during acquisition, rats in the unpaired group received as few as five extinction sessions (where response rates, and hence tone presentations, were significantly lower than during self-administration). Therefore, it may be argued that the two groups differ not only their affective response to the saccharin, but also in the extent to which they have learned the associative relationship between the saccharin and the tone. Since some dopamine responses are thought to encode prediction error (Schultz, 2013), it may be that the increase in dopamine response to noncontingent presentations of the tone merely reflects the surprise experienced by rats in the unpaired group: that is, they have no expectation the tone will be presented. However, for the rats in the paired group, the saccharin delivery could have predicted the upcoming tone presentations as they did during self-administration, and the lack of prediction error prevented cue-related dopamine efflux in the NAc.

The paper by Wheeler et al. (2015) provides insight into the neural mechanisms underlying reinstatement by providing a potential neurobiological mechanism through which cues that induce negative affective states may activate neural circuits involved in drug-seeking behavior. However, there is some uncertainty surrounding which properties of the saccharin are involved in precipitating reinstatement of cocaine-seeking. This complicates the interpretation of the neurophysiological results because the group differences could be due, at least in part, to a contextual renewal effect arising from the saccharin cue's role as an occasion setter for the paired group. The differences in electrophysiological and dopaminergic responses to the proximal tone cue may also stem from the different predictive and associative relationships between the saccharin cue and the proximal tone. Regardless of whether the results are considered with respect to the role of negative reinforcement or contextual and associative learning, further work along this line will be of great interest to experimental psychologists and addiction neuroscientists alike.

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