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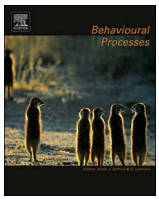

Review

Alcohol-seeking and relapse: A focus on incentive salience and contextual conditioning

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ABSTRACT

Environmental stimuli that reliably accompany alcohol intake can become associated with the pharmacological effects of alcohol through classical (Pavlovian) conditioning. Of growing interest to addiction researchers is whether or not this process results in the attribution of incentive salience to alcohol-predictive cues, which could motivate alcohol-seeking behavior and relapse. To evaluate this question, we present a review of rodent behavioral studies that examined the capacity of alcohol-predictive cues to (i) support sign-tracking behavior, (ii) serve as conditioned reinforcers, and (iii) produce Pavlovian-to-instrumental transfer. A second, emerging area of research is focused on delineating the role of context in alcohol-seeking behavior and relapse. Here, we review studies showing that alcohol-associated contexts (i) support conditioned place preference, (ii) renew extinguished alcohol-seeking behavior, and (iii) modulate alcohol-seeking responses elicited by discrete alcohol-predictive cues. These behavioral effects may be mediated by unique psychological processes, and have important implications for cue-reactivity studies and neurobiological research.

Much attention has been given to the hypothesis that classical (Pavlovian) conditioning is integral for the development and maintenance of alcohol use disorder, and facilitation of relapse (Anton, 1999; Drummond, 2000; Glautier and Drummond, 1994; Monti et al., 2000; Tiffany and Conklin, 2000). There is broad agreement that stimuli that routinely accompany alcohol intake, and therefore precede the pharmacological effects of alcohol, can become established as cues that predict alcohol. For example, visual and orosensory stimuli (e.g., sight, smell, taste) experienced with each sip of an alcoholic beverage can become associated with alcohol (Field and Duka, 2002), and trigger physiological, behavioural and psychological conditioned responses in abstinent individuals (Field and Duka, 2002; Miranda et al., 2016; Pomerleau et al., 1983; Staiger and White, 1991). Stimuli that occur in close temporal proximity to the pharmacological effects of drugs are referred to as 'discrete' or 'proximal' cues (Conklin et al., 2008), and presenting proximal drug-predictive cues to abstinent individuals is an established protocol for eliciting conditioned cue-reactivity (Conklin et al., 2015; Cooney et al., 1984; Kwako et al., 2015; Pomerleau et al., 1983; Staiger and White, 1991).

In addition to signaling the unconditional stimulus (US), an appetitive Pavlovian conditional stimulus (CS) can accrue incentive salience, a property that renders the CS capable of motivating conditioned responding (Bindra, 1974, 1978; Robinson and Berridge, 1993; Stewart et al., 1984). Indications that a CS has acquired incentive salience include (i) CS-directed approach and contact, (ii) responding with conditioned reinforcement and (iii) CS-induced invigoration of instrumental responding in the absence of primary reinforcement (Cardinal et al., 2002; Milton and Everitt, 2010; Robinson et al., 2014). While there is considerable evidence in human and non-human animals that discrete alcohol-predictive cues evoke reactivity and prompt alcohol-seeking behaviour, far fewer studies have determined if these cues also become attributed with incentive salience. In this review, we provide a comprehensive overview of rodent studies that have used the three behavioural indices described above to investigate this question.

An emerging literature suggests that, like discrete drug-predictive cues, environmental contexts in which drugs-of-abuse are routinely used can also elicit craving and influence drug-seeking behaviour (Conklin et al., 2008; Stevenson et al., 2017). Indeed, rodent studies have found that contexts associated with alcohol intake can exert multiple, potentially dissociable effects on alcohol-seeking behaviour. Specifically, alcohol-associated contexts (i) support conditioned place preference, (ii) renew extinguished alcohol-seeking behaviour, and (iii) invigorate alcohol-seeking responses elicited by non-extinguished,

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discrete alcohol-predictive cues. Here, we review this literature and outline potential psychological processes that could underlie these effects. In addition, we elucidate the implications of these data for cue-reactivity studies and research on the neural mechanisms underlying cue-driven behaviour.

1. Do discrete alcohol-predictive cues acquire incentive salience?

A prominent theory in the field of addiction research is that environmental stimuli that are reliably associated with abused drugs can acquire incentive salience, which engenders affective states that motivate drug-seeking and drug-taking behaviours (Stewart et al., 1984). Evidence for this theory comes from three related lines of research that culminate in the notion that cues can become 'desirable' and 'attractive' by virtue of their association with the primary reinforcing effects of drugs (Berridge and Robinson, 2003; Robinson and Berridge, 1993). Specifically, upon acquiring these properties, a drug-associated CS can elicit CS-directed approach and interaction, reinforce new instrumental behaviours, and/or invigorate non-reinforced, drug-seeking behaviour (Milton and Everitt, 2010; Robinson et al., 2014; for a review of relapse models with alcohol see Martin-Fardon and Weiss, 2013)

Only a handful of laboratories have investigated the attribution of incentive salience to discrete alcohol-predictive cues, and results must be viewed in light of two parametric considerations. First, the use of sweetened alcohol in many studies raises the possibility that incentive salience accrued by the CS might be related to its association with the sweetener (e.g., sucrose or saccharin), and not the alcohol (Samson et al., 1982). Second, the use of food-restriction, while standard in the field of incentive learning, is deemed problematic in alcohol studies because incentive salience in food-restricted subjects might be driven by calorie repletion from alcohol, and not the pharmacological effects of alcohol (Fedorchak and Bolles, 1987; Lockie and Andrews, 2013). These caveats aside, our synthesis of the literature supports the view that alcohol-predictive cues can accrue incentive salience, with considerable individual variability in this effect. Moreover, the attribution of incentive-salience to a discrete alcohol-predictive cue may be augmented by extended exposure to alcohol, the CS or both.

1.1. Conditioned approach and interaction with an alcohol CS

An appetitive Pavlovian CS that elicits CS-directed approach and interaction (Hearst and Jenkins, 1974) is said to have become 'desirable' and imbued with incentive salience (Cardinal et al., 2002; Milton and Everitt, 2010; Robinson et al., 2014). Such conditioned approach responses, called 'sign-tracking,' are revealed when a discrete, localizable CS is repeatedly paired with an appetitive US (Hearst and Jenkins, 1974). The CS is typically a visual stimulus, like the brief onset of a light or insertion of a retractable lever into the test chamber. Importantly, sign-tracking is not a necessary response, in that interacting with the CS does not impact the delivery of the US.

Our laboratory has reported sign-tracking behaviour elicited by a lever-CS that was paired with unsweetened alcohol in rats (Srey et al., 2015; Villaruel and Chaudhri, 2016). Importantly, rats were neither food- nor water-deprived, and conditioned responding was not observed in control groups that received explicitly unpaired presentations of the lever-CS and alcohol. Moreover, we observed marked individual differences in conditioned responding, with some rats rapidly acquiring sign-tracking, and others rapidly approaching the fluid port where alcohol was delivered for oral consumption (referred to as a 'goal-tracking' conditioned response; Boakes, 1977). Interestingly, a subset of rats initially exhibited robust goal-tracking behaviour, but with extended training switched to a predominantly sign-tracking response. This shift from goal- to sign-tracking behaviour suggests that even subjects that do not readily attribute incentive salience to alcohol-predictive cues may eventually do so when given sufficient exposure to alcohol, the CS or both.

These data corroborate earlier findings that a lever-CS that was paired with a sipper-tube containing sweetened alcohol elicited sign-tracking in food-restricted rats (Tomie et al., 2003a). The same study showed a positive within-subject correlation between the magnitude of sign-tracking and alcohol intake at different doses, supporting the idea that the incentive-motivational properties of the CS were related to the unconditional, pharmacological effects of alcohol (Tomie et al., 2003a). In addition to a lever-CS, sign-tracking has also been reported with a light-CS that was paired with sweetened (Krank, 2003) or unsweetened alcohol (Krank et al., 2008) in rats.

Tomie and colleagues have suggested that sign-tracking increases the likelihood of alcohol intake by attracting subjects to cues that also serve as the source of alcohol (Tomie et al., 2008; Tomie and Sharma, 2013). This hypothesis is based on an innovative procedure in which a retractable sipper containing alcohol served as the CS, and presentations of the sipper-CS were paired with food pellets. Rats developed robust sign-tracking in the form of approach and interaction with the sipper-CS, and alcohol intake via the sipper consequently escalated across sessions (Tomie et al., 2004, 2003b, 2002a, 2002b). Sign-tracking to the sipper-CS induced binge-like levels of drinking (Tomie et al., 2002a), and levels of sign-tracking remained stable over time (Tomie et al., 2004, 2002a). However, in this procedure contact with the sipper-CS was reinforced by alcohol intake, meaning that it was not a purely Pavlovian response. Results from these studies must also be viewed in light of caveats raised earlier regarding the use of sweetened alcohol and/or food restriction (but see Tomie et al., 2004).

Sign-tracking to a visual CS associated with systemic alcohol injections has been reported in mice (Cunningham and Patel, 2007), using a procedure in which mice received an intraperitoneal injection of alcohol immediately before placement into a chamber containing a spatially localizable visual cue (a drawing of a star). Across trials, mice came to approach the spatial cue (i.e., sign-track), and in a subsequent preference test spent more time near the cue only if it had previously been paired with alcohol. In this inventive model, conditioned approach developed rapidly; however, mice were unable to engage or interact with the visual cue. The latter provides important quantifiable information (e.g., number of contacts, latency, probability) that can be used to characterize individual differences in propensity to sign-track (Meyer et al., 2012; Robinson and Flagel, 2009; Villaruel and Chaudhri, 2016).

In summary, there is compelling evidence from several distinct behavioural procedures in rats and mice that a CS that is paired with alcohol will support CS-directed approach and interaction, which define sign-tracking behaviour. Recent data obtained in non-deprived rats that received unsweetened alcohol as the US suggest that there is considerable individual variability in this effect, with extended exposure to alcohol, the CS or both potentially facilitating the attribution of incentive salience to discrete alcohol-predictive cues (Villaruel and Chaudhri, 2016).

1.2. Conditioned reinforcement with an alcohol CS

An established way to determine if a CS that has been paired with an appetitive US has become an incentive stimulus is to investigate the capacity of the CS alone to reinforce a novel instrumental response. This procedure, called the 'acquisition-of-a-new-response task,' is a hallmark test for conditioned reinforcement (Di Ciano and Everitt, 2004; Taylor and Robbins, 1984). For a conclusive outcome, subjects must discriminate between two instrumental responses at test, making more responses on an 'active' device that is reinforced by the CS alone, relative to a second 'inactive' device that has no programmed consequences. In addition, a comparison between the behaviour of groups that received paired versus unpaired presentations of the CS and US prior to test is essential. This control rules out the possibility that response discrimination at test is caused by the CS having intrinsic