

The hot ‘n’ cold of cue-induced drug relapse

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Environmental cues associated with rewards can acquire motivational properties. However, there is considerable variation in the extent to which a reward cue gains motivational control over behavior, depending on the individual and the form of the cue. When a discrete cue is paired with food reward, it acquires greater control over motivated behavior in some rats (sign-trackers, STs) than others (goal-trackers, GTs) as indicated by the propensity to approach the cue, the willingness to work to obtain it, and its ability to reinstate reward-seeking behavior. Here, we review studies that employ this ST/GT animal model to investigate characteristics of individuals that are especially susceptible to reward cue-elicited behavior and the involvement of dopamine and acetylcholine neuromodulator systems in the susceptibility to cue-induced drug relapse. First, we discuss individual differences in the attribution of incentive salience to different forms of reward cues and the involvement of the mesolimbic dopamine system. We then discuss individual differences in cognitive/attentional control and the contributions of the cholinergic system in processing reward cues. It is suggested that in STs a propensity to attribute motivational properties to a drug cue is combined with poor attentional control in the face of these cues, making them particularly vulnerable to transition from casual/experimental patterns of drug use to addiction and to cue-induced relapse.

Drug addiction is a chronically relapsing disorder in which a strong desire for drugs often leads to drug seeking and taking behavior despite significant adverse consequences, and often in the face of an expressed desire to abstain. This maladaptive behavior is associated with both increased reactivity to drugs and drug-related cues as well as poor cognitive/inhibitory control over behavior, especially in the presence of such cues (Ehrman et al. 1992; Childress et al. 1999; Jentsch and Taylor 1999; Field and Cox 2008; Epstein et al. 2009; Preston et al. 2009). This combination is thought to be the primary reason that individuals suffering from addiction have such difficulty abstaining from drug use, and even when they are successful, they remain vulnerable to relapse after months or years of abstinence. Relapse is not only a core feature of addiction, but it remains the most important and difficult clinical problem in addiction treatment. Drug relapse data show that more than 85% of individuals relapse to drug use following treatment (Brandon et al. 2007).

The role of drug cues in relapse is highlighted by reports that cues that have been associated with drug use not only unduly attract attention toward them (Field and Cox 2008) but evoke craving and autonomic arousal (Ehrman et al. 1992; Avants et al. 1995; Preston et al. 2009). There is some debate in the literature as to the extent to which cue-evoked craving is casually related to relapse. Some studies report a clear association between craving and cocaine relapse (Weiss et al. 2003; Rohsenow et al. 2007; Paliwal et al. 2008) while others have found no relationship (Weiss et al. 1995). But, most of these studies were performed in the laboratory setting. More recent studies performed in the “real world”—during the daily life in the drug user’s normal environment—have demonstrated a strong association between craving produced by exposure to drug-associated cues and subsequent drug use (Epstein et al. 2009; Preston et al. 2009), which can be exacerbated by stress (Preston et al. 2017a,b).

There is, however, considerable variation in the extent to which drug cues acquire control over behavior. This is due, in

part, to individual variation in the extent to which reward cues capture attentional resources and the degree of executive (attentional) control an individual has over their behavior in the presence of such cues as well as the propensity to attribute incentive motivational properties to such cues. In this review, we discuss preclinical studies investigating underlying sources of this individual variation including a bias for top-down (“cold”) versus bottom-up (“hot”) processing of reward cues and the role of two major neuromodulator systems—dopamine (DA) and acetylcholine (ACh).

Individual variation in the propensity to attribute incentive salience to reward cues

Incentive stimuli

The importance of drug cues in addiction (Stewart et al. 1984) has led to considerable interest in understanding how such cues acquire incentive-motivational properties (incentive salience), and thus their ability to act as incentive stimuli capable of evoking complex emotional and motivational states (Robinson and Berridge 1993; Milton and Everitt 2010; Cardinal et al. 2002). It is now well established that when a cue (conditioned stimulus, CS) is associated with a reward (unconditioned stimulus; US), it can come to not only evoke a conditioned response (CR), but under some conditions, it can acquire incentive motivational properties. Thus, the cue (CS) acquires the ability to act as an incentive stimulus. Incentive stimuli have three defining characteristics: (i) they are attractive, biasing attention toward them and eliciting approach into close proximity with them (conditioned approach); (ii) they are desired in that they will reinforce new instrumental responses to get them (i.e., they act as conditioned reinforcers); and (iii) they evoke a conditioned motivational state that can instigate reward-seeking behavior or energize ongoing seeking behavior (conditioned motivation). Although these three defining

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characteristics of an incentive stimulus are dissociable, providing “three routes to relapse” (Cardinal et al. 2002; Milton and Everitt 2010), they often act in concert to motivate/control drug-seeking behavior and may do so either implicitly or explicitly (Robinson and Berridge 1993).

Sign and goal trackers

Studies on variation in the extent to which CSs acquire motivational properties have focused on rats that learn different CRs when a food cue (CS, often insertion of a lever) is paired with food delivery (the US). In these studies, the CS is located at a different place than the food cup. With repeated pairings of a lever-CS and food-US, some animals (sign-trackers, STs) learn to approach and interact with the lever-CS itself (i.e., they learn a sign-tracking CR). In contrast, others (goal-trackers, GTs) learn a goal-tracking CR, consisting of approaching and exploring the food cup during the CS period while awaiting food delivery (Zener 1937; Hearst and Jenkins 1974; Boakes 1977). The remaining animals are classified as intermediates (INs) because they show both sign-tracking and goal-tracking behavior, typically vacillating between these CRs within trials and between trials. Most of the studies discussed below did not include INs as the primary interest was comparing rats that strongly differed in their propensity to attribute incentive salience to food cues.

One reason different individuals acquire different CRs is because, although the CS evokes a CR in both STs and GTs, it acquires the attractive properties of an incentive stimulus preferentially in STs (Robinson and Flagel 2009; Robinson et al. 2014). This interpretation is supported by other studies showing that not only is a food cue more attractive in STs than GTs, but it is also a more effective conditioned reinforcer (Robinson and Flagel 2009; Yager and Robinson 2010; Meyer et al. 2012) and more effective in producing a conditioned motivational state that reinstates reward-seeking behavior (Saunders and Robinson 2010). Recent reports suggest similar variation exists in humans (Mahler and de Wit 2010; Styn et al. 2013; Garofalo and di Pellegrino 2015; Versace et al. 2016; Joyner et al. 2018).

The form of the CS matters

In most of the studies using STs and GTs, the CS is an illuminated, retractable, and manipulable lever, although similar individual variation in CRs is observed using a discrete light as the CS (Boakes 1977; Yager and Robinson 2013). Nevertheless, it has become clear that the specific features of a CS, including its modality, spatial arrangement, localizability, whether it includes motion, and the duration the CS-US interval influences the form of the CR (Holland 1977, 1980; Cleland and Davey 1983; Silva et al. 1992; Weiss et al. 1993; Costa and Boakes 2007) as well as the extent to which a CS is attributed with incentive salience (Meyer et al. 2014; Beckmann and Chow 2015; Singer et al. 2016a). For example, in rats, an auditory CS (e.g., tone) only results in a goal-tracking CR and a tone-CS is attributed with less incentive salience than a lever-CS (Holland 1977; Meyer et al. 2014; Beckmann and Chow 2015). Furthermore, by isolating the different modalities of the lever-CS (sound, visible movement, illumination), there is evidence that the nature of CRs varied based on the different properties of a CS (Singer et al. 2016a). Thus, despite being predictive of the same reward and presented in the same environment, the form and properties of the CS matter in regards to the extent to which it is attributed with incentive salience.

DA and incentive stimuli

There is considerable evidence that the mesolimbic DA system plays a central role in the attribution of incentive salience to cues

associated with both drug (for review, see Jasinska et al. 2014) and nondrug rewards (Flagel et al. 2011a; Lopez et al. 2015). Given that STs are more prone to attribute incentive salience to reward cues than GTs, it was hypothesized that DA would play a greater role in the acquisition and expression of a sign-tracking CR than a goal-tracking CR. Indeed, systemic administration of a DA antagonist impaired both the acquisition and expression of sign-tracking but not goal-tracking (Danna and Elmer 2010; Flagel et al. 2011b), and blocking DA neurotransmission in the NAc core was sufficient to degrade performance of a sign-tracking, but not a goal-tracking, CR (Di Ciano et al. 2001; Parkinson et al. 2002; Saunders and Robinson 2012). Additionally, the transfer of a phasic DA signal from receipt of an unexpected reward to the CS (predictor of reward; lever) was seen in rats that learn a sign-tracking CR, but not in rats that learn a goal-tracking CR (Flagel et al. 2011b; Singer et al. 2016a). These studies suggest that DA is not necessary for learning the CS-US association because both STs and GTs learn the association. Rather, DA is necessary for attributing incentive salience to reward cues, which happens preferentially in STs. Thus, DA plays a more important role in controlling behavior in STs than GTs (Danna and Elmer 2010; Flagel et al. 2011b; Saunders and Robinson 2012; Beckmann and Chow 2015; Chow et al. 2016; Singer et al. 2016a).

mPFC dopamine and Pavlovian drug cue processing

Incentive cue processing also requires prefrontal circuitry, particularly the mPFC (Stepien 1974; Kalivas and Volkow 2005). Imaging studies with individuals suffering from cocaine addiction reveal that the presentation of cocaine cues increases activation of the prefrontal cortex (Childress et al. 1999; Kilts et al. 2001), and the magnitude of this increased activation is predictive of the levels of reported craving and risk for relapse (Childress et al. 1999). Preclinical studies of drug relapse also show that prefrontal cortical regions contribute increased drug stimuli-evoked relapse (Ciccioppo et al. 2001; Zavala et al. 2008). It is important, therefore, that in animals DA release in the mPFC has been implicated in the reinstatement of drug-seeking behavior (Fuchs et al. 2007). Intra-PFC infusions of DA or DA receptor agonists elicit drug seeking, whereas DA receptor antagonists attenuate it (Park et al. 2002; Capriles et al. 2003; Fuchs et al. 2007; See 2009).

Pitchers et al. (2017a) investigated potential individual differences in prefrontal DA levels in response to the presentation of a Pavlovian cue (discrete light) formerly paired with cocaine infusions (Pitchers et al. 2017a). In line with DA transmission in the NAc core (Flagel et al. 2011b; Singer et al. 2016b), it was hypothesized that increased cortical extracellular DA levels would be associated with presentation of an incentive stimulus. STs and GTs underwent Pavlovian training in which a discrete, localizable light cue (CS) was either paired or explicitly unpaired with an IV infusion of cocaine (US). Over 14 d of Pavlovian cocaine training, STs (but not GTs) approached the Pavlovian cocaine cue suggesting that it was attributed with incentive salience in STs but not GTs. Following an abstinence period, STs and GTs were exposed to the Pavlovian cocaine cue (under extinction conditions) during 4-min blocks separated by 8-min periods void of cue presentations, while dialysate was collected from the mPFC. During this cue exposure test, the cue formerly paired with cocaine increased DA in STs but not GTs, and the magnitude of the increase in DA in STs predicted how avidly STs approached the cue during this test (for details see Pitchers et al. 2017a).

Cortical DA appears to be involved in the processing of motivational attributes of cocaine cues in rats (Pitchers et al. 2017a) and humans (Milella et al. 2016). When experiencing a high motivational state, there is a positive correlation between NAc and mPFC activation (Moscarello et al. 2007), which suggests that these

brain regions may act in concert to produce incentive motivational states (Carr et al. 1999; Milella et al. 2016; Otis et al. 2017). Prefrontal DA levels are speculated to be involved in the attractiveness of associated cues and stability of the cue-directed responding behavior (e.g., cue approach behavior) (Ellwood et al. 2017). Ventral striatal DA levels, on the other hand, may energize cue-associated behaviors, including instrumental responses to obtain cue access (e.g., test for conditioned reinforcement) or be involved with value-based decision making (Roesch et al. 2007; St. Onge et al. 2012). The involvement of the mesolimbic DA system, including increased DA levels in the mPFC and NAc core, mediating incentive stimulus-spurred behavior is consistent with sign-tracking behavior being controlled by DA and reflecting the output of an automatic, “bottom-up,” or “hot” motivational process (Sarter and Phillips 2018).

Individual variation in the influence of contextual cues

The propensity to attribute incentive salience to a food cue predicts the extent to which a discrete cocaine cue acquires the three properties of an incentive stimulus (discussed above). Thus, STs attribute greater motivation value to a discrete cocaine cue (e.g., a light) than GTs (Flagel et al. 2010; Saunders and Robinson 2010; Yager and Robinson 2013). However, another class of cues that acquires substantial control over behavior is one that signals reward availability, such as a context or occasion-setter (i.e., discriminative stimulus, DS). Like a discrete cue, a contextual stimulus is known to elicit a conditioned motivational state that can renew drug-seeking behavior in humans (O'Brien et al. 1992; Foltin and Haney 2000; Mayo et al. 2013) and rats (McFarland and Ettenberg 1997; Crombag and Shaham 2002; Fuchs et al. 2005). Interestingly, a drug-paired context was found to exert greater control over behavior in GTs compared to STs, as indicated by a greater level of conditioned hyperactivity in a drug context and greater context-induced renewal of cocaine-seeking behavior (Saunders et al. 2014). In line with these findings, GTs also show greater context fear conditioning compared to STs (Morrow et al. 2015).

More recently, several experiments investigated the influence of an occasion setter (referred to as a DS in an instrumental or operant setting) on behavior of STs and GTs (Ahrens et al. 2016; Kawa et al. 2016; Pitchers et al. 2017b,c). Occasion setters provide higher order discriminative or contextual-like information that predicts a positive relationship between a stimulus (e.g., CS) or response (e.g., nose poke) and an outcome (e.g., drug infusion). The ability a cue (house light) that signaled periods of reward or nonreward on conditioned responding was compared in STs and GTs. During the first training session, GTs' behavior during reward and nonreward periods differed dramatically as they rapidly decreased responding (less goal-tracking CRs) during nonreward periods yet resumed making goal-tracking CRs during reward periods. In contrast, STs did not modify their behavior between reward and nonreward periods during the first training session as they continued to make sign-tracking CRs throughout the session. With more training, STs learned to modify their behavior, like GTs, between reward and nonreward periods (for details see Ahrens et al. 2016). It seems likely that STs were slower to extinguish their CR compared to GTs because they were less aware of the informative cues in the environment (e.g., occasion setter) and consequently, were delayed in learning about the changing reward conditions.

In a related experiment, the degree of DS control over drug-seeking behavior in STs and GTs was tested (Pitchers et al. 2017b). In this study, rats were trained to self-administer cocaine using an Intermittent Access (IntA) drug self-administration procedure during which all animals learned to discriminate two spatially

distinct light cues that either signaled drug available (DS+) or drug not available periods (DS−). When the DS+ was on, a nose-poke response resulted in a cocaine infusion, whereas when the DS− was on, a nose-poke had no consequence. As also found in other IntA studies (Kawa et al. 2016; Pitchers et al. 2017c), both STs and GTs learned to discriminate DS+ versus DS− periods at similar rates, making significantly more active responses during drug available compared to no drug available periods. After 14 d of IntA training, animals underwent extinction training (no cue, no cocaine) before a reinstatement test that involved brief DS+ presentations. Compared to STs, the DS+ evoked significantly more drug-seeking responses in GTs (for details see Pitchers et al. 2017b).

It has become clear that not all animals process motivationally salient information similarly, which may contribute to such cues spurring different behavior in different individuals (for review, see Robinson et al. 2014; Sarter and Phillips 2018). The studies reviewed to this point suggest that discrete reward cues exert greater control over behavior in STs via the engagement of “hot” incentive motivational processes mediated by the mesolimbic DA circuit (Flagel et al. 2011b; Saunders et al. 2013; Singer et al. 2016b). In contrast, GTs appear to be more capable of incorporating higher order cues, including contextual stimuli and occasion setters, that may require “top-down” or “cold” cognitive processing to modify behavior appropriately based on situational demands (for review, see Sarter and Phillips 2018).

Susceptibility to cue-evoked behavior: beyond incentive salience

The above section emphasizes how individual variation in the propensity to attribute incentive salience to drug cues may predispose some individuals to relapse. However, as emphasized by so-called dual-systems views of addiction, behavior is often the result of a competition for control between “bottom-up” and cue-driven (“hot”) psychological processes versus more deliberative, “top-down,” and goal-oriented (“cold”) cognitive processes (e.g., Jentsch and Taylor 1999; McClure and Bickel 2014; Bickel et al. 2016; Sarter and Phillips 2018). Thus, relapse to drug use may result from the excessive attribution of motivational properties to drug cues and impaired or biased processing of drug-associated cues. Therefore, in the discussion of individual variation in the propensity to relapse it is important to emphasize that STs and GTs also differ on measures of cognitive (attentional) control over behavior (Lovic et al. 2011; Paolone et al. 2013; Koshy Cherian et al. 2017; Sarter and Phillips 2018).

Individual variation in attentional control

To investigate the attentional capacities of STs and GTs, Paolone et al. (2013) evaluated performance on a task requiring sustained attention that has been validated in humans (Demeter et al. 2008), rats (McGaughy and Sarter 1995; Demeter et al. 2008), and mice (St. Peters et al. 2011). The task involves signal (illumination of a central panel light; 25, 50, or 500 msec light ON) and non-signal (no illumination) trials. Following a signal (or nonsignal) event, two levers on either side of light are deployed until a response on either lever is made or up to 4 sec if no response is made (trial omission). A response on one lever indicates a signal was detected, and a response on the other lever indicates no signal was detected. Correct responses (hits, correct rejections) on each trial are reinforced, while incorrect responses (misses, false alarms) are neither reinforced nor punished. On this task, poor cognitive control of attention is characterized by distractibility, attentional lapses, impulsive action, low motivation, or attentional fatigue (see Fig. 1 in Sarter and Paolone 2011).

Both STs and GTs improved their task performance over time until reaching asymptotic performance levels. However, STs performed more poorly at the beginning of training, and despite improving over time, their task performance remained lower than GTs even after 75 d of training. This relatively poor performance by STs was characterized by a lower hit rate during reoccurring shifts between periods of good performance to periods of poor (or near-chance) performance within a session. In fact, performance was negatively correlated with strong sign-tracking behavior (according to earlier Pavlovian conditioned approach training). The relative number of correct rejections or trial omissions did not differ between STs and GTs indicating that STs and GTs were similarly motivated to perform the task (for details, see Paolone et al. 2013). STs and GTs were also tested on a more attention-demanding version of task involving the introduction of a distractor (housetlight flashing ON/OFF at 0.5 Hz). While the distractor was on, all animals performed the task at near-chance levels. However, following removal of the distractor GTs quickly recovered task performance to predistractor levels, whereas STs remained at low, near-chance levels for the remainder of the session (Kim et al. 2016). Overall, STs, compared to GTs, have weakened cognitive control over attention indicated by their inability to sustain periods of good performance (attentional lapses/fluctuations) and limited recovery of performance during a post-distractor period.

Individual variation in impulsivity

Given that STs (relative to GTs) have particular difficulty resisting discrete reward cues, it was investigated whether STs were more impulsive than GTs using two tests of impulsive action: two-choice serial reaction time task (2-CSRTT) and a differential reinforcement of low rates of responding (DRL) task. During both tests, STs proved to be more impulsive than GTs as they demonstrated a greater tendency to make premature responses (not waiting the appropriate length of time between trials) resulting in them being less efficient in obtaining rewards. In fact, a greater propensity to make sign-tracking CRs during Pavlovian conditioned approach training positively correlated with greater number of premature responses (for details, see Lovic et al. 2011). A potential explanation for greater impulsivity in STs is their bias toward stimulus-driven responses. However, an alternate, but not mutually exclusive, explanation is that STs may be impulsive because they possess relatively poor "top-down" control over behavior. This latter explanation was suggested by STs' inability to recover task performance after a distractor (discussed above) and to suppress premature and inappropriate/competitive responses.

Susceptibility to cue-evoked behavior: beyond DA

As discussed above, STs appear to be influenced by discrete cues paired with rewards and process their environment via "hot" DA incentive salience systems. In contrast, GTs appear to better incorporate more complex contextual information, which may be due to better attentional control over behavior and being less prone to impulsive action. Since there is evidence that cortical cholinergic neurotransmission is modulated as a function of "top-down" control (for review, see Sarter and Paolone 2011), we investigated potential differences in frontal cortical cholinergic activity in STs and GTs.

The relatively poor attentional control demonstrated by STs was associated with relatively low cortical cholinergic neuromodulation (Paolone et al. 2013). Despite no differences in basal levels of cortical ACh between STs and GTs, STs have a relatively unresponsive cholinergic neuromodulatory system compared to GTs (Koshy Cherian et al. 2017). More specifically, STs' BF cholinergic neurons

have an attenuated capacity to release cortical ACh upon stimulation, potentially due to unresponsive cellular trafficking of the choline transporter (CHT) to the synapse (Koshy Cherian et al. 2017). Presynaptic CHT is the rate-limiting step for the synthesis of ACh (Ennis and Blakely 2016). It is a major determinant of the capacity of cholinergic neurons to sustain release of ACh (Sarter et al. 2016), as a CHT inhibitor was found to attenuate increases in prefrontal ACh. As a result, we tested the hypothesis that low levels of cholinergic activity are involved in the development of sign-tracking behavior using the same inhibitor. When the CHT inhibitor was administered during Pavlovian conditioned approach testing, it increased the likelihood of animals developing a sign-tracking CR (for details, see Koshy Cherian et al. 2017).

mPFC acetylcholine and Pavlovian drug cue processing

In addition to DA levels, Pitchers et al. (2017a) also measured prefrontal ACh levels in response to presentations of a Pavlovian cocaine cue (discrete light). In direct contrast to prefrontal DA levels (discussed above), a Pavlovian cocaine cue did not influence prefrontal ACh levels in STs. Thus, STs' cue approach behavior appeared to be mediated via DA mechanisms and the absence of ACh may have augmented the bias toward cue-driven behavior. Conversely, presentations of the Pavlovian cue increased prefrontal ACh levels in GTs, but not DA, despite no detected changes in behavior, including locomotor activity during or after cue presentation. Thus, increased ACh levels did not appear to be connected to a specific behavior (like DA with cue approach in STs). Instead, the increase in cue-evoked ACh, indicative of recruitment of the cholinergic cognitive system, may have mediated GTs' resistance to behavioral control by the Pavlovian cue (for details, see Pitchers et al. 2017a).

In summary, there was a double dissociation in the effect of a cocaine cue on prefrontal DA and ACh in STs and GTs. A cocaine cue increased prefrontal DA but not ACh in STs, but increased ACh but not DA in GTs. Together, the DAergic and noncholinergic processing of drug cues by STs may mediate their susceptibility to discrete cue-directed behavior. It is possible that the lack of cholinergic response permitted the elevation of DA and consequently, approach to the cue. Alternatively, the cholinergic and non-DAergic processing of drug cues by GTs may be indicative of higher order processing of the stimulus situation. Thus, a bias for "top-down" processing of cues might provide GTs with the ability to deprioritize a Pavlovian cue allowing them to override the potentially maladaptive and automatic response of approaching it.

mPFC ACh and discriminative stimuli

A better functioning BF-cortical cholinergic system may not only make GTs resistant to power of simple reward-predictive cues (CSs), but it may increase their ability to process more complex stimuli (compared to STs). A DS, unlike a CS, precedes both the behavioral response and any drug effect, so it may require a relatively complex analysis to properly guide behavior. Thus, it was hypothesized that the processing of DSs by GTs may depend on cholinergic mechanisms.

To test this hypothesis, rats were trained using the IntA cocaine self-administration procedure described above, in which there were periods of drug availability interspersed with periods of nonavailability, signaled by DSs (discrete lights) (Zimmer et al. 2012). After IntA and subsequent extinction training, STs and GTs received infusions of the choline-specific toxin 192 IgG-saporin to partially (~50%) remove BF cholinergic neurons, primarily in the nucleus basalis of Meynert. Next, a reinstatement test involving DS+ presentations was conducted under extinction conditions to quantify drug-seeking behavior. Both STs and GTs with reduced BF cholinergic neurons were able to perceive the

cue (all animals oriented to it) and remember the cue-reward association (number of responses were greater than last extinction session). However, the DS+ was differentially imbued with motivational properties by STs and GTs. In STs, the DS+ produced only low levels of drug seeking, potentially due to their already relatively unresponsive cholinergic systems (Paolone et al. 2013; Koshy Cherian et al. 2017), and they were unaffected by the cholinergic lesions in the BF. In contrast, in GTs the ability of the DS+ to evoke significantly more drug-seeking behavior (compared to STs) was severely disrupted by loss of BF cholinergic neurons (for details, see Pitchers et al. 2017b).

It is interesting to compare prefrontal cholinergic transmission in GTs in response to CSs versus contextual stimuli. With a CS, prefrontal ACh was associated with a lack of behavioral response—a resistance to the automatic approach to the cue. Whereas, with a DS, cholinergic input to the prefrontal cortex was necessary for the cue to induce drug seeking. In both conditions, it seems that the drug-associated cue was inserted into the cortical circuitry to mediate a cognitive expectation of drug (its availability). As a result, GTs appear to act accordingly in both situations whether it was to do nothing (since no action was required to obtain reward under Pavlovian conditions) or have pertinent environmental cues produce a state of heightened motivation or craving.

Summary and conclusions

STs have a bias for cue-driven (“hot”) psychological processing as their reward cue-associated behavior is mediated by prefrontal and ventral striatal DA and a relatively unresponsive cholinergic system (Flagel et al. 2011b; Saunders and Robinson 2012; Chow et al. 2016; Singer et al. 2016b; Koshy Cherian et al. 2017; Pitchers et al. 2017a). Their susceptibility to cue-induced drug relapse may be a result from the excessive attribution of incentive properties to drug cues, poor attentional control, and a propensity for impulsive action. GTs, on the other hand, have a bias for cognitive or controlled (“cold”) psychological processing. Their goal-directed behavior in the face of cues depends on cholinergic neurotransmission and is not dependent on DA (Flagel et al. 2011b; Saunders and Robinson 2012; Singer et al. 2016b; Koshy Cherian et al. 2017; Pitchers et al. 2017a,b). GTs’ bias for more cognitive cholinergic processing seems to minimize potentially maladaptive behavior driven by a reward cue, which does not only empower GTs to more appropriately navigate their

environment, but it may also make them less susceptible to cue-induced relapse to drug use (see Fig. 1 for a summary of results).

Taken together, it is clear that STs and GTs process motivationally salient information in different ways that, in part, depend on reward-cue associated changes in extracellular prefrontal DA and ACh levels. It remains to be tested whether elevations of the prefrontal ACh directly limit increases in DA transmission in GTs, or vice versa (in STs). From a clinical perspective, it will be critical to better understand the DAergic and cholinergic mechanisms and their interactions in mediating the susceptibility to drug relapse in order to identify novel pharmacological targets capable of reducing the likelihood of ever-present threat of relapse.

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Figure 1. A summary of contributing factors, that make sign- or goal-trackers relatively susceptible or resistant, respectively, to cue-induced drug relapse.

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