

Published in final edited form as:

*Neurosci Biobehav Rev.* 2013 November ; 37(0): . doi:10.1016/j.neubiorev.2013.02.008.

## Individual variation in resisting temptation: implications for addiction

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### Abstract

When exposed to the sights, sounds, smells and/or places that have been associated with rewards, such as food or drugs, some individuals have difficulty resisting the temptation to seek out and consume them. Others have less difficulty restraining themselves. Thus, Pavlovian reward cues may motivate maladaptive patterns of behavior to a greater extent in some individuals than in others. We are just beginning to understand the factors underlying individual differences in the extent to which reward cues acquire powerful motivational properties, and therefore, the ability to act as incentive stimuli. Here we review converging evidence from studies in both human and non-human animals suggesting that a subset of individuals are more “cue reactive”, in that certain reward cues are more likely to attract these individuals to them and motivate actions to get them. We suggest that those individuals for whom Pavlovian reward cues become especially powerful incentives may be more vulnerable to impulse control disorders, such as binge eating and addiction.

### Keywords

rat; human; sign-tracking; goal-tracking; addiction; binge eating; obesity; motivation; dopamine; individual differences; learning; accumbens; Pavlovian; relapse

## 1. Introduction

“I couldn’t help it. I can resist everything except temptation.” (Oscar Wilde, *Lady Windermere’s Fan*, 1892)

To survive animals must navigate a complex, ever-changing environment. Stimuli associated with different behavioral outcomes help organisms do this, in part by coordinating approach towards desirable stimuli and avoidance of potentially harmful stimuli (Hebb, 1955; Ikemoto, 2010; Moltz, 1965; Schneirla, 1959). Thus, from worms to humans, environmental cues play an important role in guiding individuals to successfully seek out what is critical for survival, by signaling the current or future availability, location, quality, and/or quantity of rewards. The sensory systems of different animal species have

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evolved specifically to enable efficient processing of particular types of reward cues important for their survival. Color vision, for example, is thought to have evolved in many species, including insects and primates, due to selection pressures favoring the ability to visualize colorful flowers and fruits, which facilitates successful foraging. Thus, environmental cues serve a phylogenetically ancient purpose: to increase the probability of acquiring rewarding stimuli and avoiding aversive stimuli.

Cues, while serving this vital role in directing adaptive reward-seeking behavior, under certain conditions, may also serve as powerful temptations that can promote maladaptive patterns of behavior (Nesse and Berridge, 1997). This is best illustrated in many types of human psychopathology, where cues can instigate pathological reward seeking in disorders such as compulsive eating, gambling, hypersexuality, and drug abuse. Here, we review evidence from human and nonhuman animal studies demonstrating the role reward-associated cues play in controlling behavior, with a special emphasis on food and drug-seeking behavior. Furthermore, we emphasize that there is considerable individual variation in the extent to which reward-related cues, including drug-associated cues, gain motivational control over behavior. That is, we address why some individuals (such as Oscar Wilde's character above), have much more difficulty resisting temptation than others.

## 2. The role of Pavlovian cues in reward seeking

In now classic studies, Pavlov (1927) demonstrated that if a previously neutral stimulus (conditional stimulus, CS) reliably predicts the delivery of a reward (unconditional stimulus, US), over time the CS will come to elicit a conditional response (CR). Pavlov found that in hungry dogs if the ticking of a metronome were paired with food delivery the sound of the metronome itself (the CS) came to elicit salivation (the CR). Given that the dogs initially salivated unconditionally when presented with the US, Pavlov referred to the CS-elicited CR as a *conditional reflex* (Pavlov, 1927). For many years after these experiments, researchers described Pavlovian conditioned behavior largely in terms of stimulus – response (S-R) *habits* (Berridge, 2001). That is, as a consequence of learning, a Pavlovian CS comes to evoke a rigid, inflexible behavioral response. Researchers have long known, however, that beyond eliciting simple, reflexive CRs, CSs may also be attributed with *incentive motivational properties* (“incentive salience”), becoming *incentive stimuli*, and thus acquire the ability to activate complex emotional and motivational states (Berridge, 2001; Bindra, 1978; Bolles, 1972; Cardinal et al., 2002; Konorski, 1967; Rescorla, 1988; Toates, 1986; Trowill et al., 1969; Young, 1959; Young, 1966). Incentive salience refers specifically to the acquired perceptual and motivational properties of a stimulus that render it attention grabbing and “wanted” (Berridge and Robinson, 1998). Thus, Pavlovian CSs not only have predictive or associative value, signaling upcoming rewards, but they can also acquire powerful motivational properties, acting as incentive stimuli. Importantly, the motivational properties of a reward or reward cue are not simply a fixed characteristic of the stimulus itself, but are modulated by the physiological state of the individual (Cabanac, 1979; Toates, 1986; Young, 1959). For example, when one is hungry, the incentive value of rewards and their cues is potentiated, when sated, their value is relatively diminished. Various circumstances, therefore, such as hunger, thirst, or even drug-induced states can modulate the motivational value of learned reward cues (Berridge, 2001; Richard et al., 2013). The complexity of these psychological responses to rewards and cues – well beyond simple S-R habits – can have the effect of greatly increasing the flexibility and diversity of an individual's behavioral repertoire, allowing for adaptive reward seeking (Toates, 1986).

Here, we will focus specifically on the *Pavlovian* incentive motivational properties that stimuli can acquire, but it should be noted that stimuli can also develop what Dickinson and colleagues have termed *instrumental* incentive value (Berridge and Robinson, 2003;

Dickinson and Balleine, 1994; Dickinson et al., 2000). The latter refers to an explicit cognitive expectation of a reward, and we will not focus on this psychological process here (see Berridge and Robinson, 2003; Dickinson et al., 2000 for a discussion of the difference between so-called Pavlovian versus instrumental incentives). We should also note that Pavlovian reward cues are broadly defined, and can be discrete and localizable, or diffuse and contextual, and can exist in any sensory modality. Depending of the physiology of the sensory systems of a given species, and the evolutionary niche it occupies, certain stimulus modalities may be more or less important for behavior (Timberlake, 1984), which is an important consideration for experiments. Additionally, reward cues do not have to be external to the individual, and may include reward-associated interoceptive states. Finally, in experimental settings, a cue is often a relatively simple stimulus, such as a light, tone, or image, but in reality, reward cues are often complex compound stimuli.

Barry Everitt and colleagues (e.g., Cardinal et al., 2002; Everitt et al., 2001; Milton and Everitt, 2010) have developed a useful conceptualization of Pavlovian incentive stimuli that defines their three fundamental properties. An incentive stimulus 1) is attractive and attention grabbing, drawing individuals into close proximity with it. 2) It is itself desirable, in the sense that it can reinforce novel actions to obtain it. 3) Its presence can evoke a conditioned motivational state capable of both instigating reward-seeking behavior, and invigorating ongoing behavior. Collectively, these properties define an incentive stimulus but, importantly, they are psychologically dissociable, and rely on overlapping but different neural systems (Cardinal et al., 2002). Taken together, if a reward-associated cue acquires these properties it is, in effect, transformed from a predictive but motivationally “cold” CS into a “hot” incentive stimulus, which can exert motivational control over behavior (Cardinal et al., 2002; Meyer et al., 2012a).

### 3. Incentive stimuli

#### 3.1. Conditioned Approach

An important feature of an incentive stimulus is its ability to grab one’s attention and attract, which has the effect of drawing individuals into close physical proximity with it, and thus usually with the reward itself. Experimentally, this phenomenon is measured as Pavlovian conditioned approach behavior. It was demonstrated several decades ago that if a localizable Pavlovian CS reliably predicts the presentation of a reward, some animals will learn to approach the CS itself, even though no response is necessary to obtain the reward (Brown and Jenkins, 1968; Zener, 1937). This CS-directed approach behavior was called “sign-tracking” (Hearst and Jenkins, 1974), the word “sign” referring to the cue, and often includes vigorous engagement with the cue that mimics the consummatory response associated with the type of reward delivered (Davey and Cleland, 1982; Jenkins and Moore, 1973; Pavlov, 1932). Originally, the term “autoshaping” was used to describe the procedure that produces this type of Pavlovian CR (Brown and Jenkins, 1968), but this is actually a misnomer, because during the Pavlovian procedure no responses are ever reinforced (i.e., shaped). Indeed, the development of conditioned approach is not due to accidental reinforcement or “superstitious” behavior (Skinner, 1948). This was neatly demonstrated in Pavlovian conditioning studies in which a negative contingency was implemented, whereby contact with the CS resulted in omission of the reward. Under these conditions, animals continue to approach and sometimes even contact the CS, despite no longer receiving reward (Killeen, 2003; Lajoie and Bindra, 1976; Schwartz and Williams, 1972; Timberlake and Lucas, 1985; Williams and Williams, 1969).

Many species of animals, including birds, fish, rats, mice, monkeys, and humans, are known to exhibit sign-tracking behavior (Breland and Breland, 1961; Brown and Jenkins, 1968; Burns and Domjan, 1996; Cole and Adamo, 2005; Gamzu and Schwam, 1974; Hearst and

Jenkins, 1974; Nilsson et al., 2008; Pithers, 1985; Tomie et al., 2012; Wilcove and Miller, 1974; Williams and Williams, 1969). However, there is considerable individual variation in the extent to which CS-US pairing leads to the development of a strong sign-tracking (ST) CR (Tomie et al., 2000). Zener (1937) first described such variation in dogs, for which a bell was paired with the delivery of food. These studies were nearly identical to those done by Pavlov, but in his case Zener released the dogs from their harnesses, allowing them to move freely. Zener found that the type of CR the CS elicited varied across dogs. Some dogs exhibited “small but definite movement of approach toward the conditioned stimulus... followed by a backing up later to a position to eat”; similar to what was later called sign-tracking behavior (Hearst and Jenkins, 1974). Other dogs, however, exhibited “an initial glance at the bell” followed by “a constant fixation...to the food pan” (p. 391). Studies after this described similar individual variation in approach behavior, but Boakes (1977) was the first to systematically describe goal location-directed conditioned approach in the context of autoshaping experiments, which he termed “goal-tracking (GT)”. We will use this ST/GT terminology here in respect of historical precedence.

Individual variation in conditioned approach behavior in rats has recently been explored in a series of studies utilizing a simple Pavlovian conditioning procedure, in which the extension of a lever (the CS) is paired with delivery of a food pellet (the US) into an adjacent food hopper. Under these conditions, in which a discrete localizable cue that can also be manipulated is presented (versus, for example, a tone), some rats come to preferentially approach and engage the lever-CS itself (sign-trackers; “STs”), as described above. However, upon lever-CS presentation other rats (goal-trackers; “GTs”), initially glance at the lever-CS, but then go immediately to the food hopper (Figure 1), and make head and mouth movements in the hopper while awaiting food delivery (Mahler and Berridge, 2009). Yet other rats are ambivalent, alternating responses (Flagel et al., 2007; Meyer et al., 2012a). Both STs and GTs learn their respective CRs at the same rate, indicating that the food cue is an equally effective CS – it evokes a reliable approach CR in both – the conditioned approach response is just directed to different locations in the environment (Robinson and Flagel, 2009). Critically, the different approach behaviors of STs and GTs are not a reflection of differential learning capabilities, as both groups learn a variety of tasks equally well (Morrow et al., 2011; Robinson and Flagel, 2009; Saunders and Robinson, 2010). Rather, we have suggested that variation in the topography of the CR reflects underlying variation in the propensity to attribute incentive salience to discrete Pavlovian CSs (Flagel et al., 2009; Flagel et al., 2007; Meyer et al., 2012a; Robinson and Flagel, 2009). Thus, only for STs does the CS acquire those incentive stimulus properties that make it attractive.

Humans also find reward cues “attractive”, such that they receive greater perceptual and attentional resources, even outside volitional awareness (Hickey et al., 2010a; Hickey and van Zoest, 2012; Raymond and O'Brien, 2009). This is often measured by their ability to bias attention relative to neutral cues (Field and Cox, 2008). Interestingly, studies in humans also demonstrate substantial individual variation in the degree to which reward cues are allocated with visual and attentional resources. For example, Hickey et al. (2010b) found that individuals with “reward-seeking” personality characteristics, as measured by the Behavioral Inhibition/Activation Scale (Carver and White, 1994), allocated more visual resources to reward-associated visual stimuli. A few studies have even attempted to examine individual differences in reward-cue approach tendencies in humans (Christiansen et al., 2012; Field et al., 2008; Field et al., 2005; Palfai, 2006; Thewissen et al., 2007; Van Gucht et al., 2008; Wiers et al., 2009). Direct measures of behavioral approach are difficult to examine in people, so investigators have developed experimental paradigms that allow for approach to be inferred. For example, Field et al. (2005) found that individuals with high levels of alcohol craving had more pronounced “approach” to alcohol-related pictures, as measured by the speed at which they moved a character on a computer screen toward the

pictures. Wiers et al. (2009) found a similar relationship between alcohol drinking history and the tendency to use a computer joystick to “approach” alcohol-related images on a screen.

### 3.2. Conditioned Reinforcement

In addition to being attractive, incentive stimuli can also become desirable, in the sense that they will reinforce actions to obtain them. In experimental terms, incentive stimuli act as conditioned or secondary reinforcers. Conditioned reinforcers are capable of maintaining responding for long periods of time in the absence of the primary reward, and can support the learning of new and complex behavioral chains (Fantino, 1977; Hall, 1951; Hull, 1943; Kelleher and Gollub, 1962; Mackintosh, 1974); thereby greatly increasing the persistence and complexity of behavior. Pavlovian CSs are thought to produce conditioned reinforcement via two mechanisms: 1) by triggering a general motivational state, independent of particular outcomes, and/or 2) by evoking a representation of a specific rewarding outcome that reinforces further behavior (Burke et al., 2007, 2008; Parkinson et al., 2005).

The conditioned reinforcing properties of reward cues can become quite powerful. For example, they maintain behavior in the absence of rewards (Di Ciano and Everitt, 2004), they are also resistant to extinction (Arroyo et al., 1998; Di Ciano and Everitt, 2005; Panlilio et al., 2005), and they continue to reinforce responding even after US devaluation (Davis and Smith, 1976). The ability of cues to act as conditioned reinforcers is clearly illustrated by self-administration studies utilizing traditional extinction-reinstatement procedures to model relapse behavior (Nair et al., 2009; Shaham et al., 2003). In these studies, animals are trained to self administer a reward in the presence of an explicitly associated cue (often a light or tone), after which instrumental responding is extinguished in the absence of the cue. The cue’s ability to reinstate and maintain reward-seeking behavior is examined in a reinstatement test, wherein responses again produce the reward-paired cue, but under extinction conditions (that is, they do not receive the primary reward). Using this procedure, many studies have demonstrated that cues associated with a variety of rewards promote reward-seeking behavior (de Wit and Stewart, 1981; Kruzich et al., 2001; Milton and Everitt, 2010; Nair et al., 2009; Shaham et al., 2003). We should note that these studies typically refer to this effect as “cue-induced reinstatement”, but the way these procedures are usually applied (but see de Wit and Stewart, 1981; Deroche-Gamonet et al., 2002; Grimm et al., 2000) the cue does not “induce” an action, but the action produces the cue, and therefore it is presumably the conditioned reinforcing properties of the cue that primarily increases drug-seeking actions.

Reward cues also serve as conditioned reinforcers in humans. Indeed, in day-to-day life, most of human behavior produces no immediate primary reward, and thus cues must have the ability to maintain responding for prolonged periods of time. This has been formally demonstrated in several studies (Fantino and Case, 1983; Panlilio et al., 2005; Perone and Baron, 1980; Pithers, 1985; Wyckoff, 1952).

Interestingly, there is considerable individual variation in the extent to which reward-associated cues acquire conditioned reinforcing properties. For example, for STs, the same food CS that was attractive is also an effective conditioned reinforcer (i.e., these rats will learn a new instrumental response for presentations of just the CS). However, for GTs, who did not approach the CS but instead the food hopper, the CS is a less effective conditioned reinforcer (Lomanowska et al., 2011; Meyer et al., 2012a; Robinson and Flagel, 2009). Furthermore, Yager and Robinson (2010) found that a cue associated with food during an instrumental task was more effective in reinstating responding after extinction in STs than in GTs. These studies provide additional support for the hypothesis that STs and GTs differ in



their propensity to attribute incentive salience to reward-associated cues (Meyer et al., 2012a).

### 3.3. Conditioned Motivation

Finally, incentive stimuli can arouse or evoke a conditioned motivational state that spurs reward-seeking behavior (Bindra, 1968; Cardinal et al., 2002; Milton and Everitt, 2010). This is an important mechanism by which cues produce craving, which may not only instigate new actions to procure the reward, but also invigorate ongoing actions. We should note here that craving, in the context of this review, refers to the conscious subjective state of desire for rewards, often directly measured in human studies, while “craving”, in quotations marks, refers to inferred implicit conditioned motivation. Importantly, conditioned motivational states need not reach conscious awareness to affect behavior or physiology (Childress et al., 2008). The ability of a Pavlovian CS to invigorate instrumental behavior has traditionally been examined using Pavlovian-to-instrumental transfer (PIT) procedures (Estes, 1943; Estes, 1948; Holmes et al., 2010; Lovibond, 1983; Ostlund and Maidment, 2012; Rescorla and Solomon, 1967). Typically, individuals first receive Pavlovian training, where a discrete CS is paired with reward delivery independent of any action. This is followed by an instrumental training phase, where the individual learns to make a response (e.g., lever press) for a reward. Subsequent *noncontingent* presentations of the Pavlovian CS (under extinction conditions) increase the rate, or “vigor”, of instrumental responding for reward. Similar to conditioned reinforcement, two varieties of this transfer effect have been described. First, PIT can occur in an outcome-*independent* manner (Dickinson and Dawson, 1987), where a CS enhances instrumental responding for any appetitive outcome, even those the CS was never paired with. For example, Balleine (1994) demonstrated that rats trained to self administer water responded at a higher rate when presented with either a water-associated CS, or a food-associated CS. Importantly, this general ability of CSs to invigorate instrumental behavior is tied to internal motivational states, such that transfer is greatest when the individual is highly motivated for the associated rewards. If rats have been stoned on food, for example, a food-associated CS does not increase responding for water (Balleine, 1994). Second, an outcome-*specific* form of transfer can occur (Colwill and Rescorla, 1988; Kruse et al., 1983), where a CS biases instrumental actions to favor the one that produces the same outcome that was paired with that CS. This form of transfer appears to be somewhat less dependent on internal motivational states (Corbit et al., 2007). Therefore, Pavlovian CSs can directly modulate instrumental actions via multiple, dissociable processes.

As described above, most reinstatement studies typically use procedures in which the conditioned reinforcing properties of cues control behavior (that is, the cue is presented contingent upon an action). But noncontingent presentation of rewards can also produce a conditional motivational state that invigorates or reinstates extinguished reward seeking. Skinner (1938) demonstrated that, following extinction, non-contingent presentation of a food pellet to rats reinstated responding. Similarly, Rescorla and Skucy (1969) found that giving rats noncontingent food retarded the rate of extinction of food-seeking, and this occurred even if continued responding delayed the next availability of food. Many of these reward “priming” studies have now demonstrated that exposure to even small amounts of a variety of rewards can renew extinguished or long abstinent instrumental behavior (de Wit, 1996; Jaffe et al., 1989; Konorski, 1967; Skinner, 1938).

The notion that reward cues can produce conditioned motivation that invigorates instrumental behavior has also been demonstrated in humans (Bray et al., 2008; Hogarth et al., 2007; Holmes et al., 2010; Nadler et al., 2011; Paredes-Olay et al., 2002; Talmi et al., 2008). One of the first clear demonstrations of this came in a study by Talmi et al. (2008). They found that noncontingent presentation of a Pavlovian-conditioned money cue

invigorated responding for money rewards. Another recent study by Bray et al. (2008) showed that Pavlovian CSs can also bias instrumental behavior in a outcome-specific way. Furthermore, reward “priming” also occurs in humans. As demonstrated by Cornell et al. (1989), people who were primed with a small amount of food subsequently ate significantly more food, relative to those who were not primed, even though these individuals had just eaten until satiation.

While several studies have characterized individual variation in the propensity to attribute incentive salience to reward cues by assessing their ability to motivate approach behavior, and act as conditioned reinforcers, few have assessed variation in the ability of cues to evoke a conditioned motivational state, as measured specifically with PIT procedures. To our knowledge, only one study has examined individual variation in PIT. Barker et al. (2012) recently found that mice vary in the degree that a food-associated CS invigorates food-seeking behavior. Interestingly, high PIT mice showed greater resistance to extinction of alcohol taking behavior and greater cue-induced reinstatement of alcohol seeking behavior than low PIT mice, suggesting that high PIT mice, like STs, attributed greater motivational value to both food and alcohol cues.

In summary, many studies in human and non-human animals, using a variety of procedures, indicate that Pavlovian stimuli, in addition to informing an individual about upcoming rewards, can acquire powerful incentive properties. While there is little disagreement about this general concept, it is important to point out that it is often assumed, either explicitly or implicitly, that a CS will also necessarily function as an incentive stimulus. We argue, however, that the individual differences in reward-cue responsivity described above demonstrate that this assumption is not valid. For both STs and GTs a discrete localizable Pavlovian cue serves as an effective CS, evoking CRs, but it is attributed with incentive salience to a much greater degree in STs than GTs. Thus, a reward cue acquires the ability to instigate conditioned approach towards it, to act as a powerful conditioned reinforcer, and to arouse a conditioned motivational state to a greater extent in STs than GTs. This leads us to conclude: *the conditional, predictive relationship between a CS and a US is not sufficient to confer motivational properties to the CS.* The fact that the motivational and predictive properties of reward cues are dissociable has considerable implications for thinking about the psychology and neurobiology of reward, as in most situations these properties are confounded, and tend to change together.

## 4. Individual variation in drug-cue responsivity

The transformation of a predictive CS into a motivationally significant incentive stimulus is important for normal reward-seeking behaviors, as described above, but may become especially relevant to the persistence of maladaptive reward seeking, characteristic of disorders such as compulsive drug use, overeating, and gambling. Several theories of addiction have emphasized the importance of drug cues (Di Chiara, 1998; Robinson and Berridge, 1993; Stewart et al., 1984; Tomie, 1996), as it is known that encounters with drug-associated cues can instigate craving and relapse behavior (DeJong, 1994; Hser et al., 2001; O'Brien et al., 1998; Shaham et al., 2003). We will now shift our discussion to the role that *drug-associated stimuli* play in drug-seeking behavior, and individual variation in the extent to which drug cues acquire motivational control over behavior.

### 4.1. Nonhuman Animal Studies

For a large part of the second half of the twentieth century, the predominantly held psychological explanation for why addicts continue to self administer drugs despite many adverse consequences was because doing so alleviated an aversive state associated with withdrawal symptoms (Koob and Le Moal, 2001; Lindesmith, 1968; Solomon and Corbit,

1974; Wikler, 1973). This was partly due to the prevalence of drive-reduction theories at the time (Hull, 1943), but also because the majority of early drug self-administration studies utilized opiates, which produce physical dependence that leads to marked withdrawal symptoms upon abstinence. Many studies (e.g., Deneau et al., 1969; Stewart et al., 1984; Woods and Schuster, 1971) eventually demonstrated, however, that opiate use – and that of other drugs – develops and progresses in the absence of physical dependence and withdrawal symptoms. Furthermore, studies began to demonstrate that relapse of drug seeking could be instigated through presentation of drug-associated cues or contexts, or by “priming” individuals with small amounts of drug, even in users who had been long abstinent (de Wit and Stewart, 1981; Hodgson et al., 1979; Stretch and Gerber, 1973). Based on studies like this, consensus began to shift to the view that drug use, similar to consumption of biologically relevant rewards such as food and water (Bindra, 1978), is usually – though not always – mediated by the positive incentive motivational properties of drugs and associated cues, rather than an internal drive to reduce a negative withdrawal state. In regard to drug use, this conceptual change was summarized by Stewart et al. (1984), who noted, “Need and drive views of motivation are gradually being replaced by a view ... that ascribes a primary role to incentive stimuli as the generators of motivational states and elicitors of actions”. It is, “the drug itself, or the presentation of a stimulus previously paired with the drug, that acts to create a motivational state that facilitates drug-seeking behavior” (p. 251, 256), a view that currently has broad support (Milton and Everitt, 2010; Robinson and Berridge, 1993). Indeed, we now know that if drug cues act as incentive stimuli, they may become especially critical for the development and persistence of addiction, in part because they facilitate three “routes to relapse” (see Figure 4 in Milton and Everitt, 2010). They may 1) bias attention, eliciting approach to drug-associated places and paraphernalia; 2) reinforce actions that lead to obtaining drugs; and 3) spur intense drug seeking by evoking a conditioned motivational state (e.g., implicit “craving” or explicit craving). Though dissociable, these incentive motivational properties of drug cues in addicts may work in concert to promote relapse, such that maintaining abstinence becomes overwhelmingly difficult in addicts.

**4.1.1. Conditioned Approach: Drug Cues**—Until recently, there was no clear evidence that discrete drug cues would support conditioned approach behavior directed towards the drug cue itself (i.e., sign tracking) in non-human animals, as is readily demonstrated with food cues (see above). Indeed, as late as 2005, Everitt and Robbins (2005) speculated with regard to Pavlovian drug cue approach, “it may...be that the behavioral influence of CSs associated with drugs and natural reinforcers differ fundamentally in this regard” (p. 1482). Nevertheless, several studies using rats have now demonstrated that drugs delivered in a variety of fashions do in fact support conditioned approach behavior (Cunningham and Patel, 2007; Krank et al., 2008; Tomie et al., 2008; Uslaner et al., 2006). Tomie (1996) was amongst the first to suggest that the ability of drug cues to instigate approach and engagement is important in the development of maladaptive drug use, given that many drug-associated stimuli (e.g., drinking containers, needles, and pipes, etc) are embedded within drug-delivery apparatuses. If these cues become attractive and facilitate approach and engagement, the likelihood of continued drug use will be high.

Recent studies have demonstrated that variation in the extent to which individuals assign incentive salience to food cues predicts the degree to which drug-associated cues motivate approach. For example, in a study using selectively bred rats, STs, who developed robust approach behavior directed at a discrete food, also readily approached a discrete visual cue that had been paired with noncontingent intravenous cocaine infusions, while GTs did not (Flagel et al., 2010), and similar results have been found in outbred rats (Yager and Robinson, 2012).



**4.1.2. Conditioned Reinforcement: Drug Cues**—The ability of drug cues to act as conditioned reinforcers is an important mechanism contributing to persistent drug-seeking behavior. A variety of studies have demonstrated that, as with food cues, cues associated with drugs will maintain drug-seeking behavior for long intervals between drug delivery events, and support complex drug-seeking behavioral sequences (Arroyo et al., 1998; Di Ciano and Everitt, 2003, 2004; Di Ciano and Everitt, 2005; Everitt and Robbins, 2005; Goldberg and Tang, 1977; Katz, 1979; Kelleher, 1966; Kelleher and Goldberg, 1977; Schindler et al., 2002). Di Ciano and Everitt (2004) found, for example, that a discrete visual CS associated with cocaine can actually reinforce the learning of a novel instrumental action, and maintain responding in the absence of the drug across two months of intermittent testing. Consistent with this, other studies demonstrated that self administration of drugs is more robust when a cue is associated with drug delivery, compared to when drug delivery is un signaled (Caggiula et al., 2009; Caggiula et al., 2001; Panlilio et al., 1996; Schenk and Partridge, 2001). Many further studies using the traditional extinction-reinstatement procedure showed that animals will reinstate extinguished drug-seeking behaviors in order to receive presentations of a drug-associated CS alone (e.g., de Wit and Stewart, 1981; Shaham et al., 2003).

Recently, several studies have demonstrated that there is considerable individual variation in the degree to which drug cues serve as conditioned reinforcers. Barker et al. (2012) found that for mice that exhibited high levels of PIT in a test using food reward, an alcohol cue served as a more effective conditioned reinforcer, as measured by its ability to reinstate alcohol seeking. Additionally, Saunders and Robinson (2010) trained STs and GTs to self administer cocaine, in sessions where a discrete visual cue was explicitly paired with drug infusions. Following the acquisition of stable self-administration behavior, the cocaine cue was removed, though cocaine remained available. This manipulation caused a dramatic reduction in the rate of drug self-administration in STs, but not GTs, suggesting that the cocaine cue had acquired considerable motivational power of its own, but only in STs (Figure 2). Further evidence for such differences came in a follow-up experiment (Saunders and Robinson, 2010), where it was found that a cocaine cue reinforced much greater reinstatement in STs than GTs. Additionally, Yager and Robinson (2012) found that a cocaine cue acquired greater ability to reinstate drug seeking behavior in STs than GTs, even if it had only been paired with cocaine in separate Pavlovian conditioning sessions. Furthermore, using a conditioned cue preference procedure, Meyer et al. (2012b) showed that STs preferred a tactile cue that had been paired with cocaine injections to one paired with saline, while GTs did not show this preference. Importantly, in all of these experiments, both total drug intake and cue exposure were held equivalent across groups. Additionally, using these controlled procedures (e.g., Saunders and Robinson, 2010), STs and GTs were found to acquire self administration behavior equally well, providing further evidence that any behavioral differences were not a reflection of differences in learning. We should note, however, one recent study reported that when total drug intake was not limited by the experimenter, rats that preferentially exhibit sign-tracking responses acquired self administration at a faster rate than rats that preferentially goal-track (Beckmann et al., 2011). However, this effect was found using only low doses and a self-administration training procedure that is a modified version of Pavlovian approach training, so there is as yet no clear evidence that STs and GTs acquire drug self administration differently.

**4.1.3. Conditioned Motivation: Drug Cues**—The presence of drug-associated cues in the environment can elicit conditioned motivational states that instigate drug-seeking behavior (Milton and Everitt, 2010). Such cue-evoked conditioned motivational states are thought to result in drug craving, which is an important way that drug cues promote relapse behavior. Additionally, exposure to small amounts of drug itself can instigate craving and relapse (de Wit and Stewart, 1981; Hodgson et al., 1979; Jaffe et al., 1989). As mentioned

above, the ability of cues to produce conditioned motivation is often measured in tests of Pavlovian-instrumental transfer, where the presence of a Pavlovian CS invigorates current instrumental behavior. However, until recently there was no clear experimental evidence that a drug-associated cue can produce a PIT effect. In an important study addressing this issue, LeBlanc et al. (2012) demonstrated drug cue PIT, showing that presentations of a cocaine-associated CS acutely increased the rate of ongoing self-administration behavior in rats (see also Cortright et al., 2012). Interestingly, they found that the presence of a Pavlovian cocaine CS invigorated behavior during both the “seeking” and “taking” phases of the self administration behavioral chain, which are analogous to the approach/preparation and consumption phases of drug taking. Though this topic requires more investigation, the results of LeBlanc et al. (2012) suggest that Pavlovian drug cues directly invigorate behavior at multiple points along the progression of drug use.

As with the other incentive motivational properties of drug cues, there are also individual differences in the degree to which drug cues acquire the ability to evoke a conditioned motivational state. For example, Saunders and Robinson (2011a) trained STs and GTs to self administer cocaine, where a discrete visual cue was paired with drug infusions. Next, instead of extinction training, an aversive consequence to drug seeking was introduced to eliminate self-administration behavior. While cocaine was still available, the front two-thirds of the experimental chamber was electrified, with the current increasing over days (see also Cooper et al., 2007). Thus, to make a response that produced a cocaine infusion, the rat was required to cross this electric “barrier”, experiencing foot shock. After the current was high enough so that responding fell to a low level, the ability of the cocaine cue to instigate drug seeking was assessed with a procedure functionally equivalent to PIT. The cocaine cue was presented *noncontingently*, under extinction conditions, but with the electric barrier still in place. Noncontingent cocaine cue presentations spurred robust reinstatement of drug seeking in STs, but not GTs. In another study, Saunders and Robinson (2011b) trained STs and GTs to self administer cocaine in the absence of any explicitly paired cues. Following extinction, we found that a “priming” injection of cocaine instigated greater reinstatement behavior in STs than GTs. Thus, cocaine and discrete cocaine cues produce a state of conditioned motivation to a greater extent in some rats, and this motivational state is powerful enough to reinstate drug-seeking behavior, even overcoming aversive consequences.

#### 4.2. Individual differences in reward cue responsivity underlie addiction vulnerability

Not all individuals experience temptation to consume drugs in a maladaptive way. Only a small subset of the general population ever becomes addicted to drugs, even though the vast majority of people use a potentially addictive substance at some point in their lives (Anthony et al., 1994). Given the enormous cultural and public health costs associated with addiction and other impulse control disorders, it is important to understand the mechanisms that engender these behaviors in order to understand the individual variation. The studies described above demonstrate that in individuals with a tendency to attribute exaggerated incentive salience to food cues, drug cues also acquire powerful motivational control over behavior – as measured by their ability to instigate approach, maintain drug self administration, and reinstate drug seeking. We propose that this variation is a contributing factor (of many) to individual differences in vulnerability to addiction. Specifically, we hypothesize: *individuals for whom drug cues acquire exaggerated incentive salience will find them difficult to resist, and will therefore be more vulnerable to developing the persistent and compulsive patterns of drug seeking characteristic of addiction.* Thus, one source of variation in susceptibility to maladaptive drug use may be variation in the ability of drug cues to gain motivational control over behavior. We will now turn our focus to an evaluation of the evidence for this prediction in human studies.

### 4.3. Human studies

The degree to which humans find drug cues attractive, as measured by their ability to bias attention, relative to neutral cues, predicts subjective craving for drugs, prospective drug use, and likelihood of relapse (Cox et al., 2002; Field and Cox, 2008; Franken et al., 2000; Marissen et al., 2006; Simon et al., 2010; Vezina and Leyton, 2013; Waters et al., 2003). For example, Field and Eastwood (2005) found that when subjects were experimentally manipulated into exhibiting greater attentional bias to alcohol cues, they experienced greater subjective craving, and drank more alcohol during a subsequent taste test. By training subjects to exhibit less attentional bias to alcohol cues, Fadardi and Cox (2009) reduced their subsequent alcohol consumption. Similarly, Attwood et al. (2008) found that smokers could be trained to show more or less attentional bias, and the degree of bias was positively associated with subjective craving. These studies suggest there is a direct correlation between the extent that a drug cue is attractive and attention grabbing and its ability to spur motivation to take drugs. The causal connection between drug-cue attentional bias and drug craving/intake is somewhat unclear, however, because some studies (e.g., Duka and Townshend, 2004; Schoenmakers et al., 2008) have reported that drug exposure increases subsequent attentional bias to drug cues, suggesting there may be a reciprocal relationship. One possibility is that while the development of an attentional bias for drug cues may be essential for those cues to later instigate craving and drug consumption, once attentional bias is established, further drug use can produce conditioned motivation that potentiates the bias.

Additionally, a large number of studies have demonstrated that drug cue-induced craving is positively correlated with intensity of abuse history and/or future intake, and likelihood of relapse (for review, see Carter and Tiffany, 1999; Tiffany and Wray, 2012), though the relationship between craving and subsequent drug use is somewhat controversial, as some studies have also demonstrated weak or insignificant correlations between cue-induced craving and drug-related behaviors. Most of these studies, however, measure craving in the laboratory setting, where the context has never been associated with drug use, and thus may not be conducive to the generation of robust craving. Interestingly, recent studies have examined the relationship between craving and drug use in the addict's "natural environment". For example, Epstein et al. (2009) monitored use of cocaine and heroin in outpatient subjects, using an ecological momentary assessment method (Stone and Shiffman, 1994), where subjects themselves reported real-time behavioral and subjective data on handheld electronic devices. They found that cocaine use was predicted by a variety of antecedent "triggers", such as seeing the drug, or being reminded of drug use. Addicts who used more cocaine reported the most intense craving associated with these triggers (though this relationship was less clear for heroin use). Similar positive predictive associations between reported cue-induced craving and subsequent real-life drug use have been found in other studies (Epstein et al., 2010; Preston et al., 2009; Shiffman, 2009; Shiffman et al., 2002).

In addition to biasing attention and instigating craving, drug cues also become desirable. For example, Panlilio et al. (2005) demonstrated that a brief cocaine-associated stimulus maintained robust drug-seeking behavior – on the order of thousands of responses – in subjects with a history of cocaine abuse, even in the absence of actual drug delivery. The ability of the cue to maintain high levels of behavior persisted even though individuals reported being consciously aware that cocaine was not available. Related to this finding, Moeller et al. (2009) found that, relative to healthy controls, cocaine addicts preferentially chose to view images related to cocaine use over pleasant (e.g., smiling faces, nude bodies) non-drug images. Among cocaine addicts in this study, the amount of reported drug use in the past month and subjective arousal upon viewing cocaine images were positively correlated with the intensity of cocaine image preference. In another recent study on abstinent smokers, Freeman et al. (2012) found that presentation of smoking cues

“overshadowed” (Mackintosh, 1976) neutral cues, in that smoking cues had greater perceived reward value, even though both sets of cues were equally predictive of the rewarding outcome.

Many of these studies demonstrate there is considerable individual variation in the ability of drugs and drug cues to bias attention, produce craving, and instigate relapse in humans (Abrams et al., 1988; Carpenter et al., 2009; Carter and Tiffany, 1999; de Wit et al., 1986; de Wit et al., 1987; Kirk and de Wit, 2000; Lloyd and Salzberg, 1975; Niaura et al., 1998; Payne et al., 2006). Indeed, there is growing evidence that some humans are more reactive to cues. For example, Mahler and de Wit (2010) examined food and cigarette craving in a groups of smokers (see also Styn et al., 2012). They found that those individuals that showed the highest craving in response to discrete food cues, when hungry, also showed the highest craving to discrete smoking cues, after a period of abstinence (Figure 3). This individual variation parallels that in the rat studies described above (e.g., Saunders and Robinson, 2010; Saunders and Robinson, 2011b), suggesting that some humans may be more “cue reactive”, prone to assigning high incentive salience to certain types of cues in general, regardless of the reward they are associated with.

Together, this research demonstrates the important role drug cues play in human substance use, and highlight how the degree to which cues gain motivational control over behavior increases with increased drug use – experienced drug users show greater attentional bias and cue-induced craving and relapse than new or non users – consistent with an incentive motivational account of addiction (Robinson and Berridge, 1993; 2001; Stewart et al., 1984). In the context of the preclinical studies described above, it appears that similar individual variation in the tendency to attribute incentive salience to reward cues can be found *in both humans and non-human animals*. Analogous parallels between humans and non-humans are evident in studies of the neural systems that mediate the motivational properties of reward cues, which we will now discuss.

## 5. Neural mechanisms of Pavlovian reward cue processing

Considerable research suggests that the neural systems recruited by motivationally significant events are very similar across many different classes of rewards, such as food, sex, and drugs (Cardinal et al., 2002; Childress et al., 2008; Haber and Knutson, 2010; Ikemoto, 2010; Ikemoto and Panksepp, 1999; Kalivas and Volkow, 2005; Kelley, 2004a; Kelley, 2004b; Kelley and Berridge, 2002; Kelley et al., 2005; Kenny, 2011; Kuhn and Gallinat, 2011; Nair et al., 2009; Volkow and Wise, 2005). These reward circuits comprise a wide, distributed network, including mesocorticolimbic dopamine pathways, which we will discuss in detail below. Though each may have specific functional roles in different reward-related processes, several brain regions, including the ventral tegmental area (VTA), dorsal and ventral striatum, ventral pallidum, thalamus, habenula, amygdala, and prefrontal/ anterior cingulate/orbitofrontal cortex (PFC/ACC/OFC) are all known to be “engaged” by reward-associated cues (Cardinal et al., 2002; Kalivas and Volkow, 2005; Kelley et al., 2005; Koob and Volkow, 2010; Schiltz et al., 2007). Together, these regions constitute a motivational circuit, comprised of cortico-striato-pallido-thalamic loops with extensive reciprocal interregional connectivity (Belin and Everitt, 2008; Belin et al., 2009; Haber et al., 2000; Haber and Knutson, 2010; Kalivas and Volkow, 2005; Zahm, 2000, 2006). Specifically, VTA dopamine neurons project to subcortical targets in the ventral pallidum, amygdala, and nucleus accumbens core and shell, and also to frontal-cortical areas such as the PFC (Beckstead et al., 1979; Britt et al., 2012; Fields et al., 2007; Ikemoto, 2007; Swanson, 1982). The VTA and the adjacent VTA “tail”/rostromedial tegmental nucleus receive GABAergic inputs from the nucleus accumbens, ventral pallidum, and habenula, and glutamatergic inputs from hippocampus and PFC, all of which regulate dopamine signaling

(Barrot et al., 2012; Carr and Sesack, 2000; Geisler and Zahm, 2005; Kalivas, 1993; Watabe-Uchida et al., 2012). The nucleus accumbens in particular sits at an important junction within this system, receiving the densest dopamine projections from VTA, as well as having reciprocal connections with the ventral pallidum, amygdala, hippocampus, and PFC/ACC/OFC (Berendse et al., 1992; Brog et al., 1993; Fields et al., 2007; Heimer et al., 1991; Hurley et al., 1991; Ikemoto, 2007; Kelley and Domesick, 1982; Kelley et al., 1982; Nauta et al., 1978; Zahm, 2000). Within the thalamus, the mediodorsal nucleus acts as a relay between these cortical and subcortical structures, as it receives input from the ventral pallidum, and sends projections to frontal cortical areas (Groenewegen, 1988; Ongur and Price, 2000; Ray and Price, 1992).

The ability of cues to act as incentive stimuli is dependent on the functional integrity of this motivational circuit, though the specific cells and systems required for each psychological property of an incentive stimulus are somewhat dissociable (Cardinal et al., 2002; Milton and Everitt, 2010). *Conditioned approach*: Pavlovian conditioned approach is dependent on neural signaling within the nucleus accumbens, central amygdala, ACC, and OFC (Blais and Janak, 2009; Chudasama and Robbins, 2003; Parkinson et al., 1999; Parkinson et al., 2000a; Parkinson et al., 2000b), although the distinction between a ST and GT CR is not always considered in these studies. *Conditioned reinforcement*: The conditioned reinforcing properties of reward cues are dependent on the ventral striatum, OFC, and basolateral amygdala (Burke et al., 2007, 2008; McDannald et al., 2011; Parkinson et al., 2001). *Conditioned motivation*: The neural systems supporting the ability of reward cues to produce a conditioned motivational state have been most clearly examined using PIT procedures. These studies suggest that the general and outcome-specific versions of PIT have somewhat dissociable neural substrates. For example, while both forms require an intact VTA, general PIT is dependent on the nucleus accumbens core, central amygdala, and dorsolateral striatum, while outcome-specific PIT requires the nucleus accumbens shell, basolateral amygdala, OFC, mediodorsal thalamus, and dorsomedial striatum (Corbit and Janak, 2007; Corbit and Balleine, 2005, 2011; Corbit et al., 2007; Corbit et al., 2001; Hall et al., 2001; Holland and Gallagher, 2003; Murschall and Hauber, 2006; Ostlund and Balleine, 2007, 2008).

While extensive studies implicate the neural systems mentioned above in mediating the motivational properties of cues, there appear to be large individual differences in the extent to which cues associated with reward engage these neural systems. For example, Flagel et al. (2011a) measured c-fos mRNA expression – an indirect measure of neuronal activity – in the brains of STs and GTs following exposure to a cue that had been paired with food (under extinction conditions). Exposure to the food cue produced significant increases in c-fos mRNA expression in the nucleus accumbens core and shell, dorsal striatum, lateral habenula, lateral septum, OFC, and the paraventricular, mediodorsal, and central medial nuclei of the thalamus in STs, relative to rats who received an equivalent number of unpaired presentations of the CS and US. Interestingly, in GTs c-fos mRNA expression in these regions was not different from unpaired control rats, even though for GTs the food cue was a perfectly effective CS, as indicated by its ability to reliably evoke a GT CR. This suggests that the acquisition of predictive value, via Pavlovian conditioning, is not sufficient for a CS to significantly “engage” these brain reward systems. For that to occur it appears that the cue must also be attributed with incentive salience.

### 5.1. Cue processing within dopamine systems

Within the larger, distributed reward circuits described above, signaling in dopamine neurons projecting from the VTA to ventral striatal regions such as the nucleus accumbens is thought to be central to motivated behavior. Considerable debate exists, however, about dopamine’s exact role, or roles, in reward processing (Beeler et al., 2012; Berke and Hyman,



2000; Berridge, 2007; Berridge and Robinson, 1998; Bromberg-Martin et al., 2010; Di Chiara, 1998; Ikemoto, 2010; Robinson et al., 2005; Salamone et al., 2007; Saunders and Richard, 2011; Schultz, 2007; Wise, 2004). One view is that phasic signaling of dopamine neurons provides a “prediction-error” signal necessary for learning stimulus-reward associations (Bayer and Glimcher, 2005; Montague et al., 1996; Schultz et al., 1997). This hypothesis stems from electrophysiological recordings of dopamine neurons in the VTA and substantia nigra, as well as electrochemical measurements of actual dopamine release within the nucleus accumbens, showing that a phasic dopamine response that initially occurs to an unexpected reward (US), transfers in time to the CS that predicts reward delivery (Cohen et al., 2012; Day et al., 2007; Pan et al., 2005; Schultz, 1998; Schultz et al., 1997; Waelti et al., 2001). Additionally, these studies suggest that dopamine signaling also modifies learned predictive associations. For example, if a reward is bigger than expected based on the CS’s learned predictive value, dopamine neurons fire more, if it is smaller than expected, they fire less (i.e., a negative prediction error), leading to new learning (Pan et al., 2005; Schultz et al., 1997; Waelti et al., 2001).

Alternatively, others have argued that mesolimbic dopamine is not necessary for learning stimulus-reward associations per se, but for conferring learned reward cues with incentive salience, transforming them into “wanted”, motivationally potent incentive stimuli (Berridge, 2007; Berridge, 2012; Berridge and Robinson, 1998). An important prediction from the incentive salience hypothesis of dopamine is that changes in dopamine signaling can modify the motivational value of learned CSs ‘on-the-fly’, without the need to re-experience CS-US pairing (Zhang et al., 2012; Zhang et al., 2009). This is in contrast to learning-based accounts (Daw et al., 2005; Schultz et al., 1997; Sutton, 1988), which state that dopamine prediction errors update the learned value of a CS incrementally, on a trial-by-trial basis. It has been difficult to separate the potential contribution dopamine makes to learning from its contribution to incentive salience, because reward cues often acquire these properties together. However, recent studies have exploited individual variation in the tendency to attribute cues with motivational value, as discussed above, to dissociate these properties of reward cues (Berridge and Robinson, 2003; Robinson and Flagel, 2009).

Flagel et al. (2011b) used fast-scan cyclic voltammetry (FSCV) to measure rapid dopamine signaling within the nucleus accumbens core (Phillips et al., 2003b), during Pavlovian training in which a lever-CS was paired with food delivery, independent of any action, as described above. In rats that learned a sign-tracking CR the phasic dopamine signal transferred from the US to the CS, as a function of learning, similar to previous reports (see also Clark et al., 2012; Day et al., 2007). However, in rats that learned a goal-tracking CR, no such US-to-CS transfer occurred (Figure 4), even though for these rats the CS-US association was learned, as indicated by the fact that the CS came to reliably evoke a CR directed at the location of food delivery, as a function of training. Similarly, Parker et al. (2010) found that mice with disrupted phasic dopamine signaling learned a goal-tracking CR normally, even though no clear US-to-CS transfer in dopamine signaling occurred. To test whether dopamine is necessary for learning a ST vs. GT CR, Flagel et al. (2011b) treated rats with systemic injections of the dopamine antagonist flupenthixol prior to each training session, which would block dopamine activity in all brain regions that receive a dopaminergic input. They found that flupenthixol blocked learning of a sign-tracking CR, but it had no effect on learning the CS-US association that underlies a goal-tracking CR (Figure 4; see also Danna and Elmer, 2010).

In their supplemental materials Flagel et al. (2011b) also reported that the *performance* of already acquired sign- and goal-tracking behavior were both impaired by systemic dopamine antagonism. However, this result is difficult to interpret, because the effects occurred at doses that also produced non-specific reductions in motor activity. Thus, based on this

study, the role of dopamine in the performance of sign- and goal-tracking behavior remained unclear. To directly address this issue, and to reduce non-specific effects of dopamine antagonism on behavior, Saunders and Robinson (2012), administered flupenthixol directly into the nucleus accumbens core of rats after they had acquired stable sign- and goal-tracking behavior. The administration of flupenthixol dose-dependently attenuated a sign-tracking CR, but had little to no effect on a goal-tracking CR (Figure 4; see also Di Ciano et al., 2001; Parkinson et al., 2002). Additionally, after administration of flupenthixol into the accumbens, sign-tracking behavior was fully impaired on the very first trial, before new learning via updated prediction-errors could occur. Consistent with the incentive salience hypothesis, this suggests that fluctuations in mesolimbic dopamine signaling can dynamically modify the motivational value of reward cues, without the need to re-experience the CS-US association (see Berridge, 2012; Richard et al., 2013; Zhang et al., 2012; Zhang et al., 2009). Similar learning-independent performance effects of dopamine manipulations have been found in recent studies of Parkinson's disease patients (e.g., Shiner et al., 2012). Finally, even in STs, dopamine antagonism did not attenuate performance of a different CR, a conditioned orienting response in the direction of the CS, suggesting that even in STs some stimulus-reward associations remained functional after dopamine blockade in the core of the accumbens.

Earlier studies provide further evidence that dopamine is not necessary for stimulus-reward learning. For example, Berridge and Robinson (1998) completely depleted dopamine in the dorsal and ventral striatum of rats using the neurotoxin 6-OHDA, and found they were still able to learn a new value of a food reward just as well as intact control rats. An important series of studies by Richard Palmiter and colleagues similarly demonstrated that genetically engineered dopamine-deficient (DD) mice, whose brains cannot produce dopamine, learned normally on a variety of tasks, such as conditioned place preference (Cannon and Palmiter, 2003; Hnasko et al., 2007; Hnasko et al., 2005; Robinson et al., 2005). From these studies, Robinson et al. (2005) concluded: "dopamine is not necessary for animals to learn to associate salient cues with rewards"...but it "is necessary for reward-related cues to attain motivational significance".

Several other studies suggest that dopamine controls the degree to which cues act as incentive stimuli. For example, potentiation of dopamine release, via administration of psychostimulant drugs, increases sign-tracking behavior (Hitchcott et al., 1997; Holden and Peoples, 2010; Palmatier et al., 2012; Phillips et al., 2003a; but see Simon et al., 2009), but not goal-tracking behavior (Doremus-Fitzwater and Spear, 2011), and also potentiates the conditioned reinforcing effects of food and drug-associated cues (Collins et al., 2012; Hill, 1970; Kelley and Delfs, 1991; Robbins, 1975, 1976; Taylor and Robbins, 1984). Additionally, injection of amphetamine increases the ability of a Pavlovian CS to spur ongoing food-seeking behavior, as measured by a general PIT procedure (Wyvell and Berridge, 2001), and increases neuronal firing in the ventral pallidum in response to an incentive CS, but not a purely predictive CS (Smith et al., 2011; Tindell et al., 2005; Tindell et al., 2009). This is consistent with reports that administration of dopamine receptor antagonists suppress general PIT effects (Dickinson et al., 2000; Ostlund and Maidment, 2012; Smith and Dickinson, 1998; Wassum et al., 2011), suggesting that dopamine signaling is necessary for Pavlovian CSs to invigorate instrumental responding. Dopamine appears to be somewhat less important for the outcome-selective version of PIT. For example, Yin et al. (2006) found that hyperdopaminergic mice failed to show elevated outcome-specific PIT, relative to wild type control mice (see also, Shiflett, 2012). Furthermore, Ostlund and Maidment (2012) reported that dopamine antagonists did not influence the ability of CSs to bias action selection for a specific outcome. Dopamine's role in mediating the conditioned motivational effects of CSs may be relatively localized to the ventral striatum, however, as

elimination of dopamine cells projecting to the dorsal striatum had no effect on either general or outcome-specific PIT (Pielock et al., 2011).

It is important to acknowledge that dopamine clearly has other functions in the brain besides regulating Pavlovian incentive motivation. For example, dopamine is implicated in arousal, action selection, cognitive flexibility, and behavioral effort, particularly during instrumental conditioning (Beeler et al., 2012; Cools, 2008; Day et al., 2010; Redgrave et al., 1999; Robbins and Everitt, 1992; Salamone et al., 2007; Wassum et al., 2012). We should note, though, that even for instrumental behaviors, dopamine can modulate responding by scaling performance vigor, or by regulating PIT effects, independent of learning (Cagniard et al., 2006; Yin et al., 2006). Also, we have focused our discussion on appetitive cue processing, but dopamine is also involved in processing aversive or dysphoric motivational states (Aragona and Wang, 2009; Badrinarayan et al., 2012; Chaudhury et al., 2012; Faure et al., 2008; Kapur et al., 2005; Lemos et al., 2012; Oleson et al., 2012; Pezze and Feldon, 2004; Pezze et al., 2001; Richard and Berridge, 2011; Roitman et al., 2008; Tye et al., 2012).

Additionally, while we have emphasized dopamine signaling from the VTA to nucleus accumbens, midbrain dopamine neurons in the VTA, as well as substantia nigra, project to a variety of regions outside of the ventral striatum, including the dorsal striatum, amygdala, prefrontal cortex, and hippocampus, and different dopamine neurons have different patterns of activity and functions (Britt et al., 2012; Bromberg-Martin et al., 2010; Fields et al., 2007; Lammel et al., 2011; Li et al., 2012; Margolis et al., 2006; Watabe-Uchida et al., 2012; Witten et al., 2011). Finally, dopamine is but one of many neurotransmitters systems involved in general reward-related processes, and even in mediating the incentive motivational properties of reward cues (Bakshi and Kelley, 1993; Berridge, 2012; Cardinal et al., 2002; DiCiccioantonio and Berridge, 2012; Kelley et al., 2002; Mahler and Berridge, 2009; Novak et al., 2010; O'Connor et al., 2010; Puglisi-Allegra and Ventura, 2012; Smith et al., 2010; Ventura et al., 2007; Wassum et al., 2009). Thus in future research it will be necessary to fully investigate the contribution of other systems, such as glutamate, GABA, and endogenous opioids, in individual differences in reward cue processing, as well as their interactions with dopamine.

Nevertheless, while a complex and distributed set of brain systems are involved in reward-cue processing, the mesolimbic dopamine system has thus far been an important focal point. Interestingly, there is growing evidence that endogenous individual variation in dopaminergic systems may underlie variation in the tendency to attribute incentive salience to reward cues. Specifically, rats that attribute greater incentive salience to discrete cues, as indicated by sign-tracking behavior, exhibit greater sensitization of stereotyped head movements – thought to reflect sensitization of dopamine pathways (Paulson and Robinson, 1995; Robinson and Becker, 1986) – following a series of cocaine injections (Flagel et al., 2008). In the striatum, STs have higher levels of mRNA for the D1 dopamine receptor, and lower levels of dopamine transporter (DAT) mRNA, than GTs, which has the functional consequence of greater dopamine receptor activation (Flagel et al., 2007). Other studies, using selectively bred rats, have shown that within the nucleus accumbens core STs generate more spontaneous dopamine release events (“transients”), and have a greater number of high affinity dopamine D2 receptors, relative to GTs (Flagel et al., 2010). Finally, variation in dopamine signaling within the nucleus accumbens core is associated with variation in the propensity to approach a reward cue. The best illustration of this thus far is a study by Aragona et al. (2009), who paired a light cue with intravenous infusions of cocaine. They reported that the magnitude of cue-elicited dopamine release in the accumbens core was positively correlated with the propensity to approach the cocaine cue; i.e., to show a sign-tracking CR (Figure 5). Taken together, these studies suggest that variation in dopamine

activity is associated with variation in the propensity to attribute incentive salience to reward cues, although this topic requires much more research.

Importantly, the role dopamine plays in modulating the incentive salience of reward cues has implications for understanding human disorders such as addiction. Robinson and Berridge (1993; 2000; 2001; 2003; 2008) have argued that changes in the mesolimbic dopamine system associated with drug use play a critical role in the development of persistent drug seeking as seen in addiction. With repeated drug use, brain dopamine systems become hypersensitive, resulting in the exaggerated attribution of incentive salience to drugs and drug cues, making them irrationally desirable and “wanted”. The neurobiological changes associated with repeated drug exposure are long lasting (Paulson et al., 1991; Robinson and Kolb, 2004; Wolf et al., 2004), and thus the threat of relapse persists for a considerable time after the discontinuation of drug use. We will now review evidence of the role of dopamine in processing drug cues in humans.

## 6. Dopamine regulates drug-cue responsivity in humans

Substantial evidence from human addiction studies, including many by Nora Volkow and colleagues, suggests that brain dopamine systems also play a key role in processing drug-related stimuli in addicts (Ersche et al., 2010a; Franken et al., 2005; Franken et al., 2004; Goldstein et al., 2009; Laruelle et al., 1995; Leyton et al., 2002; Vezina and Leyton, 2013; Volkow et al., 2006; Volkow et al., 1994; Volkow et al., 2008; Wong et al., 2006). Dopamine signaling is often measured by displacement of dopamine at the D2 receptor by the radiolabeled D2 antagonist, raclopride, using PET imaging. For example, Volkow et al. (2006) found that when cocaine addicts view images of cocaine use, dopamine signaling surged within the striatum (see also Wong et al., 2006). Interestingly, the magnitude of cue-evoked dopamine release correlated with subjective craving. Similar striatal dopamine increases have also been shown in response to amphetamine-associated stimuli (Boileau et al., 2007), as well as heroin cues (Zijlstra et al., 2008).

Dopamine signaling in humans also has a broad role in attentional processing of reward cues, including drug cues. Increases in dopamine transmission produce enhancements in performance on behavioral tasks that require selective attention to stimuli, while reductions in dopamine, via pharmacological manipulations, or as seen among Parkinsonian patients, results in selective attentional deficits (Clark et al., 1987; Franken et al., 2005; Hickey et al., 2010a; Nieoullon, 2002; Servan-Schreiber et al., 1998; Stam et al., 1993). A few recent studies have assessed the role of dopamine in attentional bias specifically for drug-related cues. For example, Franken et al. (2004) found that administration of haloperidol, a dopamine receptor antagonist, reduced attentional bias to heroin cues among heroin addicts. Reductions in drug-cue attentional bias were also found in smokers following acute tyrosine/phenylalanine depletion (Hitsman et al., 2008; Munafo et al., 2007). Complementary to this, administration of dopamine agonists increases drug-cue attentional bias (e.g., Ersche et al., 2010a).

Dopamine signaling may also serve to regulate the responses of other brain regions associated with attentional bias for drug cues, as recently demonstrated by Luijten et al. (2012). They found that, among smokers, haloperidol administration reduced smoking cue-evoked brain activity within ACC and dorsolateral PFC. After haloperidol administration, smoker’s cue-induced brain activity was identical to non-smoker controls. Consistent with this, Hermann et al. (2006) found that administration of the dopamine receptor antagonist anisulpride reduced alcohol cue-induced brain activity in the ACC and OFC in alcoholics, such that they were no longer different from control subjects. Indeed, many brain regions that receive dopaminergic innervation, such as the ACC, PFC, ventral striatum, and

amygdala are implicated in attentional bias for drug-related cues (Ersche et al., 2010a; Hester and Garavan, 2009; Janes et al., 2010; Luijten et al., 2012; Luijten et al., 2011), and striatal dopamine signaling, particularly in the ventral striatum, has been suggested to serve as an interface between so called “bottom-up” incentive motivational processes and “top-down” cognitive control of behavior (Aarts et al., 2010; Cools, 2008). Thus, it is possible that dopamine is involved in both the formation of attentional bias for drug cues, by “marking” them with incentive salience, and also in the maintenance of that bias, in part by regulating drug-cue detection that occurs in other brain regions. This has yet to be directly tested, however, and as Luijten et al. (2012) state, it will be important to “examine whether individual differences in dopaminergic activation...are associated with differences in attentional bias-related brain activation”. Given that largely overlapping brain circuits are involved in the detection and processing of cues associated with several classes of drugs (Kalivas and Volkow, 2005; Kuhn and Gallinat, 2011), dopamine likely has a fundamental role in drug-cue processing in humans.

The interaction between dopamine systems and other brain regions is complex, and not unidirectional. Dopamine systems, including the VTA, as well as its target regions, are also under regulation from fronto-cortical regions (Parikh and Sarter, 2008; Phillips et al., 2008; Richard and Berridge, 2012; Takahashi et al., 2011; Volkow et al., 2005; Volkow et al., 2007). An extensive literature has implicated abnormal activity in frontal cortical brain systems in addiction-like behaviors (Bolla et al., 2004; Bolla et al., 2003; Feil et al., 2010; Goto et al., 2010; Hester and Garavan, 2004; Kalivas and Volkow, 2005; Lucantonio et al., 2012). It remains unclear, however, the extent that dysfunction within frontal cortical circuits seen in addicts is a cause or consequence of long-term drug use, and, of course, both could be true. Further research is needed to better understand how variation in frontal cortical activity may interact with dopaminergic variation to underlie maladaptive reward seeking.

### 6.1. Individual differences in human dopamine systems

Several recent studies have found a relationship between individual differences in human dopamine systems, measured by brain activation patterns, and measures of incentive motivation like reward anticipation and craving (Aarts et al., 2010; Buckholtz et al., 2010a; Buckholtz et al., 2010b; Cools, 2008; Dagher and Robbins, 2009; Franken et al., 2005; Tomer et al., 2008; Treadway et al., 2012; van Schouwenburg et al., 2010). Leyton et al. (2002), for example, found individual differences in amphetamine-induced dopamine release within ventral striatum, and the magnitude of release was positively correlated with measures of subjective drug “wanting”. The results of this study are somewhat unique because this variability was found among healthy subjects, not experienced addicts, suggesting that an exaggerated responsivity of dopamine systems to drugs may be involved in predisposing certain people to have stronger drug craving.

Genetic variation in the dopamine systems of humans may explain some of the individual differences in reward-cue related brain activity. For example, Dreher et al. (2009) found that individuals with a polymorphism at the catechol-*O*-methyltransferase (COMT; a dopamine metabolizing enzyme) gene that produces a reduction in COMT enzyme activity, exhibited higher levels of activity in PFC and ventral striatum during cued reward anticipation and reward delivery. Similar elevations in brain activity were found among people with a polymorphism of the DAT gene that produces reduced DAT expression (Dreher et al., 2009). Other studies have shown similar relationships between DAT polymorphisms and drug cue-evoked brain activity in PFC and ventral striatum, as well as dorsal striatum, insula, ACC, and OFC (Aarts et al., 2010; Franklin et al., 2009; Wetherill et al., 2012). Though the exact mechanism that mediates these effects is unclear, changes in reward-



related brain activity in individuals carrying certain dopamine polymorphisms is presumed to be due to functional differences in dopamine release, reuptake, and/or metabolism.

Several studies have now addressed the relationship between dopamine-related polymorphisms and drug-cue induced neural activation and/or drug-related behaviors (Bogdan et al., 2012; Dagher and Robbins, 2009; Foll et al., 2009; Kreek et al., 2005; McClernon et al., 2007; Noble, 2000). Many, though not all (e.g., Guindalini et al., 2008) of these studies find that polymorphisms thought to produce elevated dopamine signaling are associated with greater drug cue-induced brain activity, and behavioral measures such as drug anticipation and/or craving, and drug use. Some of the strongest relationships between variation in dopamine-related genes and reward-related brain activity have been found when researchers analyzed multilocus genetic profiles, which consider the cumulative impact of multiple polymorphisms (Bogdan et al., 2012; Nikolova et al., 2011; Stice et al., 2012). People with multiple allelic variants that either increase or decrease dopamine activity tend to have the greatest or least cue-related neural activity, respectively. Thus, single polymorphisms themselves may not always contribute to individual differences in cue-evoked brain activity, and specific combinations may be necessary, indicating that a full genetic account of cue responsivity differences will be quite complex. Importantly, however, multilocus genetic profiling studies specifically examining responsivity to drug cues remain to be done.

We have focused here on compulsive drug use, but it is important to point out that individual differences in reward-cue processing have implications for understanding vulnerability to other maladaptive behaviors, such as over-eating (hyperphagia). Obesity brought on by binge eating is a growing problem, and now over a third of adults in the United States are considered obese (Flegal et al., 2010; Ogden et al., 2007). Exposure to food-associated cues can override satiety signals to promote overeating (Cornell et al., 1989), an effect that is more pronounced in obese individuals (Jansen, 1998; Jansen et al., 2003). Especially important for the subject of this review, there are individual differences in the ability of food cues to attract attention and motivate craving and eating. Individual differences in the ability of food cues to attract attention, motivate craving and eating, and elicit brain activity have now been reported in several studies (Carnell and Wardle, 2009; Fedoroff et al., 1997; Franken and Muris, 2005; Schachter and Gross, 1968; Tapper et al., 2010; Tetley et al., 2009). For example, Beaver et al. (2006) found that people reporting higher reward pursuit/seeking tendencies, as measured by the BAS/BIS scale, showed greater activity in ventral pallidum, ventral striatum, amygdala, midbrain, and OFC in response to viewing images of appetizing foods. Interestingly, Lawrence et al. (2012) reported recently that individual variation in food-cue induced activity in the nucleus accumbens predicted subsequent food intake, independent of subjective desire to eat. Several studies have now also shown that, compared to healthy controls, obese individuals show elevated striatal activation in response to food cues (e.g., Rothenmund et al., 2007). Additionally, there is a relatively high comorbidity between obesity and abuse of some drugs, especially alcohol (Gruza et al., 2010), suggesting that overlapping factors contribute to variation in vulnerability to both overeating and drug addiction. Indeed, while the existence of “food addiction” is debated (Avena et al., 2012; Davis and Carter, 2009), some are now calling for the implementation of public health strategies known to be successful at reducing rates of drug addiction to the treatment of compulsive overeating (Gearhardt et al., 2011).

Finally, we wish to point out that while the focus of this review is on individual differences in the propensity to attribute reward cues with incentive motivational properties, there are other relevant sources of individual differences relevant to compulsive reward-seeking disorders. For example, individuals vary greatly on measures of impulsive behavior (Belin et al., 2008; Dalley et al., 2011; de Wit, 2009; Evenden, 1999; Winstanley et al., 2010) and

novelty seeking (Bardo et al., 1996; Cami and Farre, 2003; Dagher and Robbins, 2009; Tomer, 2008), which have been studied extensively in preclinical and clinical populations as factors that may underlie variability in vulnerability to addiction-like disorders. Interestingly, variation in incentive salience attribution is associated with variation in these traits, in that STs tend to show more impulsive actions and novelty seeking, relative to GTs (Beckmann et al., 2011; Flagel et al., 2010; Lovic et al., 2011; Tomie et al., 1998). While details of the relationships between these traits are currently unknown, they all share the common characteristic of being associated with hyperreactivity to environmental cues. Furthermore, dopamine system differences have been associated with individual variation in each of these traits (Buckholtz et al., 2010a; Buckholtz et al., 2010b; Dalley and Roiser, 2012; Ersche et al., 2010b; Flagel et al., 2009; Leyton et al., 2002; Tomer et al., 2008), suggesting that related neural systems may underlie different behavioral manifestations of cue responsivity. Thus, investigation of the factors – genetic, epigenetic, environmental, and neural-systems-level – that facilitate individual variation in the tendency to attribute incentive salience to cues may shed light on other traits associated with psychopathology.

## 7. Implications for treatment: A focus on individual differences

The factors underlying individual variation in vulnerability to maladaptive reward seeking are complex. We have summarized some of the literature on variation that results in certain individuals attributing potentially maladaptive levels of motivational value to reward-associated cues, which may be a factor underlying individual differences in vulnerability to addiction and related disorders. Preclinical studies have been useful for furthering understanding the psychological and neural mechanisms associated with such aberrant reward-cue processing, and it will be important to exploit this information to improve treatment strategies in humans. We hope that in the development of future treatments, clinicians will consider 1) individual differences in the psychological factors that control pathological motivation for drugs, and 2) that in susceptible individuals drug cues may be especially insidious in instigating and maintaining drug-seeking behavior.

Some preliminary evidence suggests manipulating attentional bias to drug cues via attentional control therapies may be an effective method for reducing some of the behavioral control drug cues have over addicts (Attwood et al., 2008; Fadardi and Cox, 2009; Schoenmakers et al., 2010). These studies demonstrate that by training addicts to explicitly avoid paying attention to drug cues, or by extensively extinguishing drug cues by presenting them repeatedly and in different contexts without drug exposure, a cue's relapse-provoking abilities may be lessened. Additionally, drug cue "reappraisal" procedures, where subjects are instructed to reinterpret the meaning of a cue, to make it less motivationally significant, may be effective at reducing cue-induced craving (Zhao et al., 2012). Intriguingly, these studies suggest that addicts may be able to exert some cognitive control over cue-induced urges, but important concerns exist over how generalizable and enduring such behavioral therapies are. Additionally, pharmacological interventions, particularly those targeting brain dopamine systems, have thus far shown some promise for diminishing drug-cue responsivity, though results are mixed (Cools, 2008; Ersche et al., 2010b), in part due to large individual differences in patient responses. Thus, a careful consideration of variation from subject to subject, behaviorally and neurobiologically, will be important for future development of targeted, patient-tailored interventions.

## 8. Conclusion

“Those who restrain desire do so because theirs is weak enough to be restrained.”  
(William Blake, *The Marriage of Heaven and Hell*, c. 1790–1793)

An important question arises from the exclamation of the character in Oscar Wilde's play "Lady Windermere's Fan", quoted at the beginning of this article. That is, why do some individuals have great difficulty restraining desires aroused by temptations? Why are some people unable to stop eating when they feel full, or can never limit themselves to just one drink? William Blake, above, provides us with somewhat of an answer, in pointing out that the strength of such desires may not be the same for everyone. Scientifically, we are just beginning to understand the basis of individual variation in the ability to resist temptations for rewards, but we suggest that one important factor, of many likely factors, is the extent to which reward-associated cues acquire incentive motivational properties. In those for whom reward cues become powerful incentives, cues will evoke desires that are difficult to suppress, potentially motivating maladaptive patterns of reward seeking, and these individuals will therefore be more vulnerable to compulsive behavioral disorders, such as addiction.

## Acknowledgments

The research by the authors reviewed here was supported by National Institute on Drug Abuse grants to B.T.S. (F31 DA030801) and T.E.R. (R37 DA004294 and P01 DA031656). We thank Shelly Fligel and Paul Meyer for helpful comments. We dedicate this manuscript to Ann Kelley, who, in a career cut short by untimely death, contributed many foundational discoveries about the neuroscience of motivated behavior. Her work informs much of our current understanding about brain reward circuitry. All of us who knew her personally (TER) will long remember not only her contributions to science, but as someone who's presence brightened any meeting or symposium she attended, because of her energetic, warm and delightful personality. She was, by any measure, a wonderful colleague and friend.

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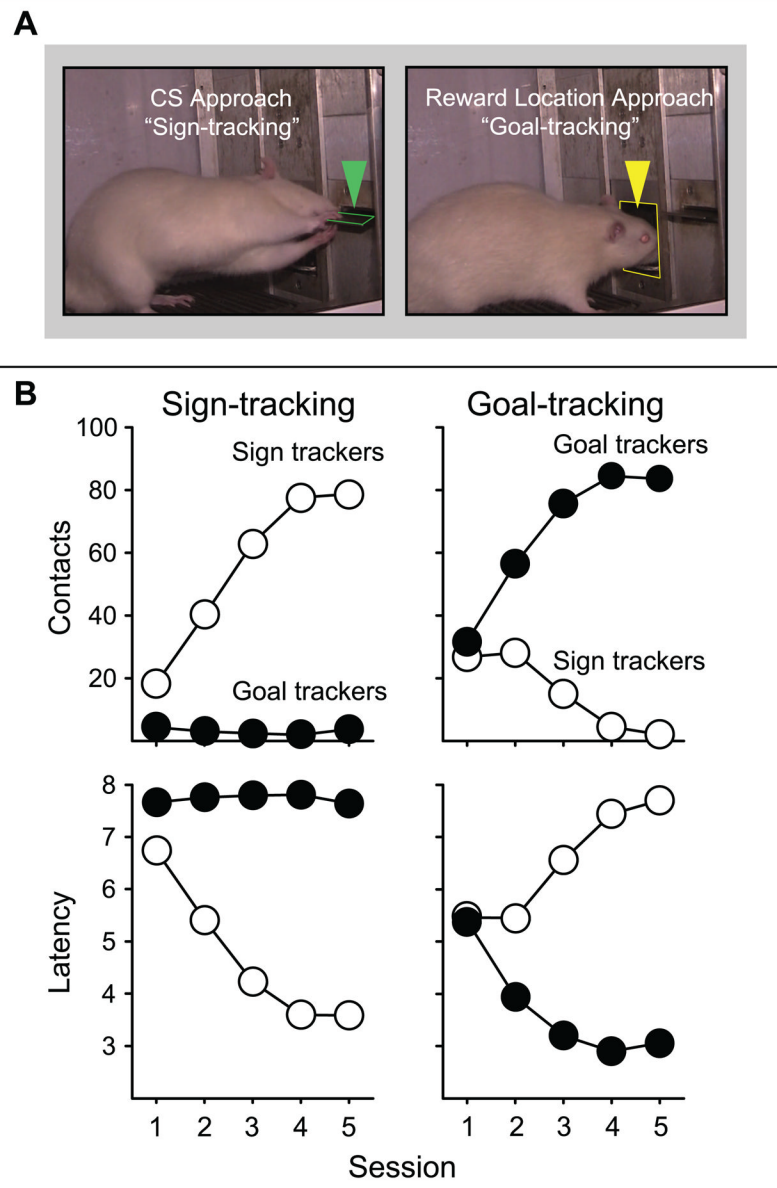
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- Individuals exhibit large variation in the strength of their reward temptations
- Reward cues acquire powerful motivational properties in only a subset of individuals
- Mesolimbic dopamine is causally involved in regulating cue motivational value
- “Cue reactive” individuals will be susceptible to developing binge eating and addiction

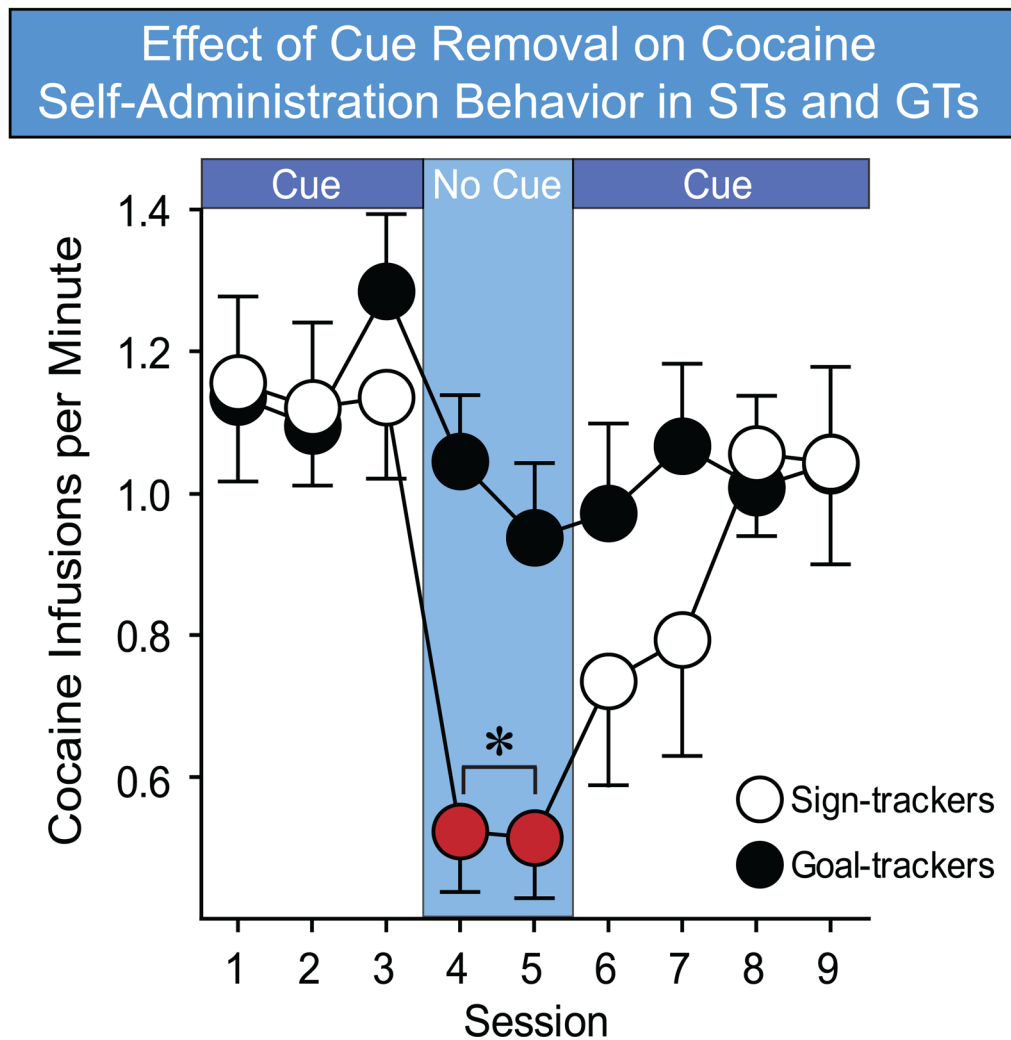
## Acquisition of a Sign-tracking and Goal-tracking CR in a Large Sample of Rats (N=1878)



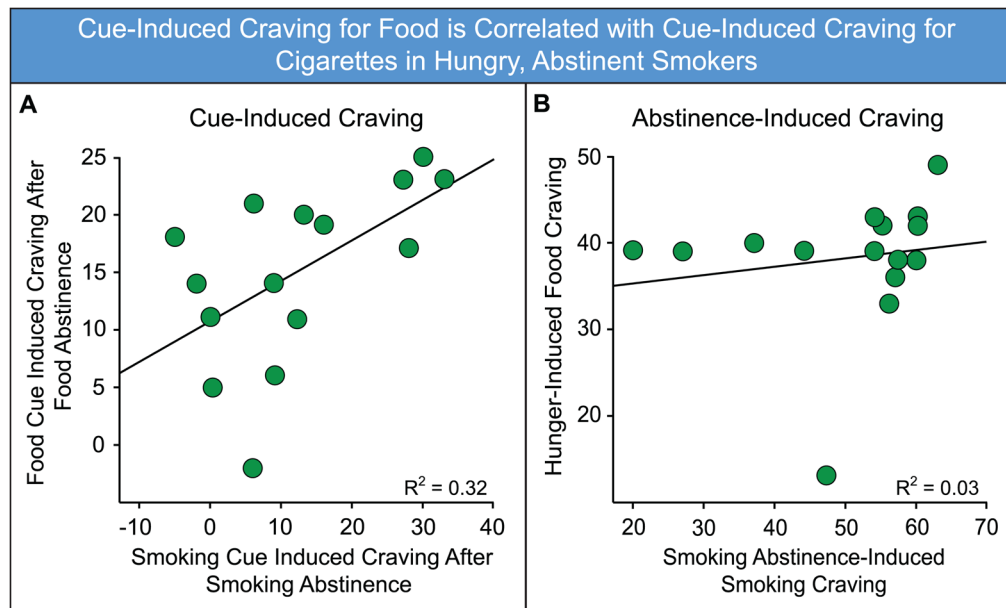
**Figure 1.** Acquisition of a cue (conditional stimulus, CS)-directed conditional response (CR; (sign-tracking, ST) versus a CR directed toward the location of reward delivery (goal-tracking, GT) in a large sample of rats (N=1878). Rats were defined as STs and GTs as described in detail in Meyer et al. (2012a). Briefly, we utilize a composite index score that incorporates three measures of Pavlovian conditioned approach: (1) the probability of either deflecting the lever or entering the food cup during each CS period [ $P(\text{lever}) - P(\text{food cup})$ ]; (2) the response bias for contacting the lever or the food cup during each CS period [ $(\# \text{lever deflections} - \# \text{food-cup entries}) / (\# \text{lever deflections} + \# \text{food-cup entries})$ ]; and (3) the latency to contact the lever or the food cup during the CS period [(lever deflection latency -



food-cup entry latency) / 8]. Thus, the Pavlovian conditioned approach index (PCA Index) score consisted of [(Probability difference score + Responses bias score + Latency difference score) / 3]. This formula produces values on a scale ranging from -1.0 to +1.0, where scores approaching -1.0 represent a strong food cup-directed bias and scores approaching +1.0 represent strong lever-directed bias. In this case, rats were designated STs if they obtained an index score of +0.5 or greater (which means they directed their behavior towards the lever at least twice as often as to the food cup), and as GTs if they obtained a score of -0.5 or less. Note that the specific index score cutoff used is somewhat arbitrary, and may change from experiment to experiment. **A**) Representative pictures of a rat engaged in a ST CR (left), directed at the CS (lever), and a rat engaged in a GT CR (right), directed at the food hopper, during the CS period (note the extended lever). **B**) Across training sessions (days), rats classified as STs (but not GTs) progressively increased the number of lever-CS contacts, and contacted the lever-CS faster and faster after its presentation. Rats classed as GTs also learned a Pavlovian approach CR, but it was characterized by approaching the food hopper more and more rapidly after CS presentation, and interacting with it more and more vigorously (as indicated by head entries). Symbols represent group means (SEM's are smaller than the symbols, and therefore not visible). Data in **B** adapted from Meyer et al. (2012a), with permission. Please see that paper for a more detailed analysis.

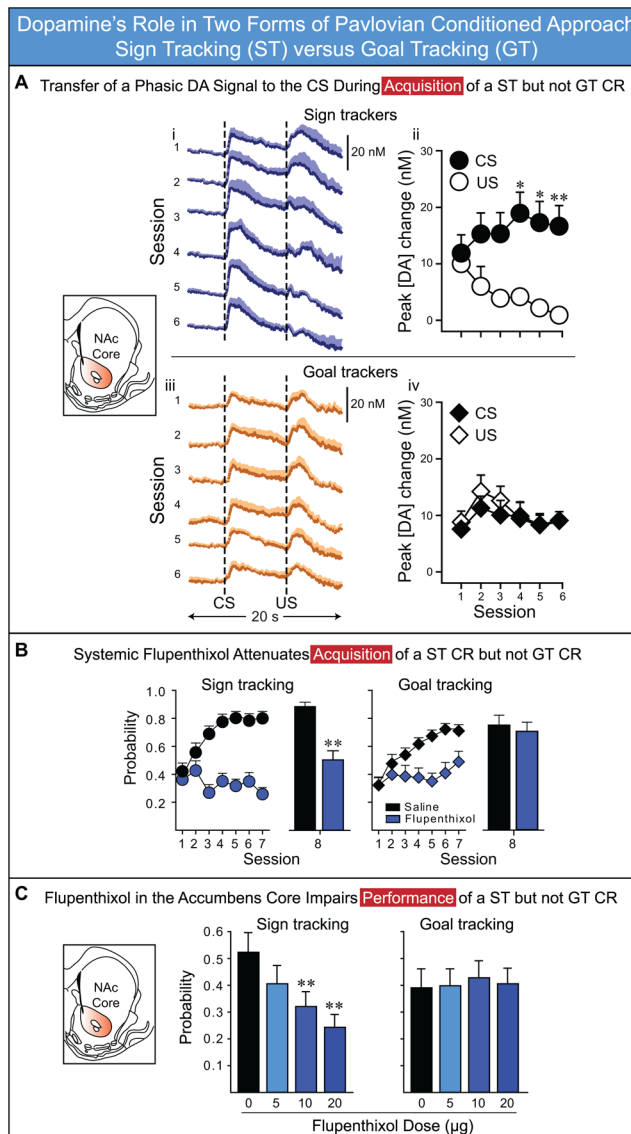


**Figure 2.** Effect of cue removal on cocaine self-administration behavior in STs (n=14) and GTs (n=16). STs and GTs have an equivalent rate of self administration when a light cue signaled drug delivery (sessions 1–3, 6–9), but on the two sessions when the light cue was omitted (sessions 4–5), the rate of self-administration in STs, but not GTs, was significantly reduced. Symbols represent the mean  $\pm$  SEM. \* $P < 0.05$ . Data adapted from Saunders and Robinson (2010), with permission.



**Figure 3.**

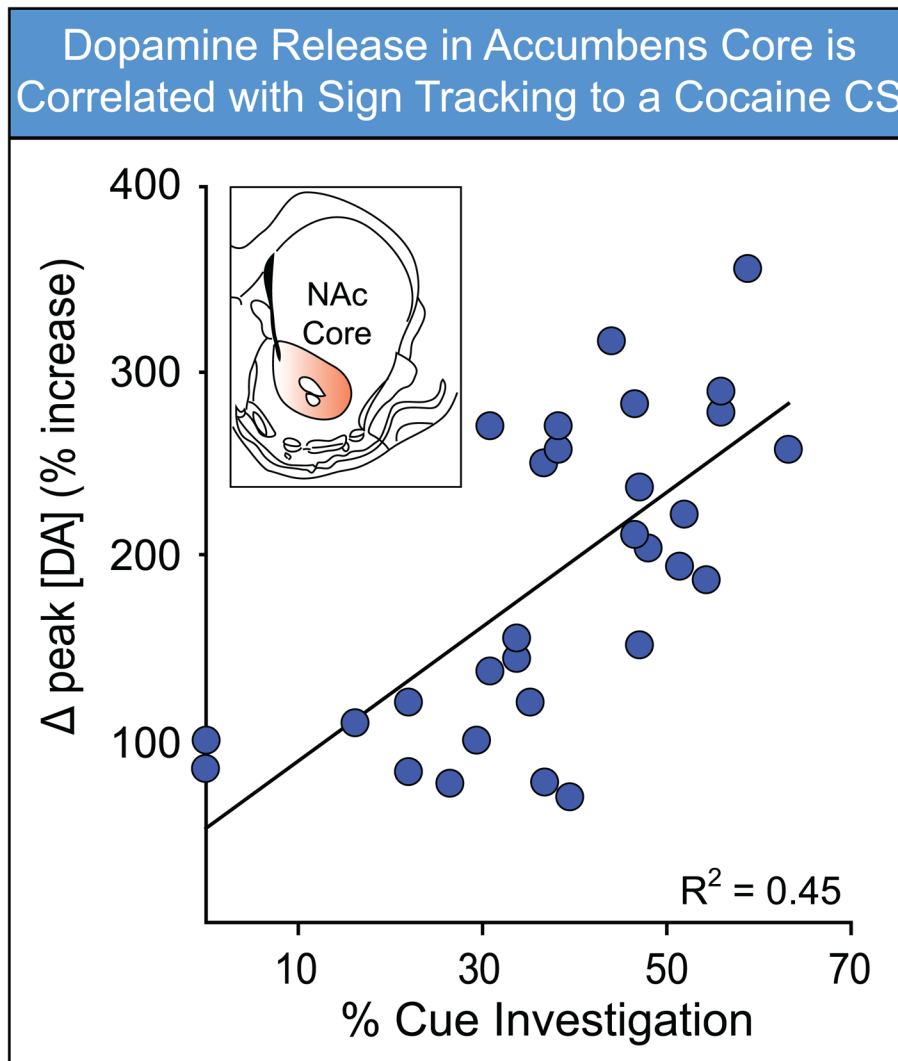
Cue-induced craving for food is correlated with cue induced craving for cigarettes in abstinent smokers. **A)** The amount of craving elicited by food images, when subjects were hungry, correlated with the amount of craving elicited by smoking images, after a period of smoking abstinence. **B)** Cravings associated by hunger or smoking abstinence alone, in the absence of cues, were not correlated. Data adapted from Mahler and de Wit (2010), with permission.



**Figure 4.** Dopamine's role in two forms of Pavlovian conditioned approach: sign tracking versus goal tracking. **A)** Transfer of a phasic dopamine signal from the US to the CS during acquisition of a ST CR but not GT CR in outbred rats. Dopamine concentrations in the nucleus accumbens core were measured using FSCV during six days of PCA training. **i, iii,** Changes in dopamine concentration in response to the CS and US for each day of Pavlovian conditioning for rats that learned a ST CR ( $n=6$ ) and rats that learned a GT CR ( $n=5$ ), respectively. **ii, iv,** Change in the peak amplitude of the dopamine signal in response to the CS and US across training sessions. In STs the phasic dopamine signal in response to the CS increased across days of training, while the response to the US decreased. In GTs there was no change in the dopamine response to the US or CS across days of training. **B)** Systemic administration of flupenthixol attenuates acquisition of a ST CR but not a GT CR in selectively bred rats. Flupenthixol or saline was administered via i.p. injections to bred high-responder rats (bHRs, left panel; these animals learn a ST CR) and bred low-responder rats (bLRs, right panel; these animals learn a GT CR) prior to the sessions 1–7 of Pavlovian

training. Relative to saline, flupenthixol impaired the performance of both ST and GT CRs during sessions 1–7. All rats received a final saline injection before session 8. On the Day 8 drug free test day bHRs (STs) treated with flupenthixol during training (n=22) had a significantly lower probability of making a ST CR than animals in the bHR saline group (n=10), and did not differ from the saline control group on Day 1 of training. This indicates that dopamine is necessary for the acquisition of a ST CR. On the other hand, on the Day 8 drug free test day bLRs (GTs) that received flupenthixol during training (n=16) did not differ from bLR saline rats (n=10) in the probability of making a GT CR, and had a significantly higher probability of making a GT CR than did the saline control animals on the first day of training. This indicates that dopamine was not necessary for the acquisition of a GT CR. C) Flupenthixol in the core of the nucleus accumbens attenuates the performance of a ST CR, but not a GT CR. Flupenthixol or saline was microinjected into the core of the accumbens of rats (N=42) after they had acquired stable Pavlovian conditioned approach behavior. Relative to saline, flupenthixol dose-dependently decreased the probability of animals making a ST CR (left panel), but not the probability of making a GT CR (right panel). Symbols represent the mean  $\pm$  SEM. \* $P < 0.05$ ; \*\*  $P < 0.01$ . Data in **A** and **B** adapted from Flagel et al. (2011b) and data in **C** from Saunders and Robinson (2012), with permission. Please see those papers for more detailed analyses.





**Figure 5.** Dopamine signaling within the nucleus accumbens core is associated with sign tracking to a cocaine cue. Dopamine concentrations within the nucleus accumbens core were measured using FSCV during Pavlovian conditioning of a light CS with i.v. cocaine infusions. On individual trials, the peak change in dopamine concentration was positively correlated with the percent of time rats spent investigating the light CS while it was illuminated (i.e., showed sign tracking behavior). Data modified with permission from Aragona et al. (2009).