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# Behavioral Characteristics and Neurobiological Substrates Shared by Pavlovian Sign-Tracking and Drug Abuse

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## Abstract

Drug abuse researchers have noted striking similarities between behaviors elicited by Pavlovian sign-tracking procedures and prominent symptoms of drug abuse. In Pavlovian sign-tracking procedures, repeated paired presentations of a small object (conditioned stimulus, CS) with a reward (unconditioned stimulus, US) elicits a conditioned response (CR) that typically consists of approaching the CS, contacting the CS, and expressing consummatory responses at the CS. Sign-tracking CR performance is poorly controlled and exhibits spontaneous recovery and long-term retention, effects that resemble relapse. Sign-tracking resembles psychomotor activation, a syndrome of behavioral responses evoked by addictive drugs, and the effects of sign-tracking on corticosterone levels and activation of dopamine pathways resemble the neurobiological effects of abused drugs. Finally, the neurobiological profile of individuals susceptible to sign-tracking resembles the pathophysiological profile of vulnerability to drug abuse, and vulnerability to sign-tracking predicts vulnerability to impulsive responding and alcohol self-administration. Implications of sign-tracking for models of drug addiction are considered.

### Keywords

Sign-Tracking; Pavlovian; Autoshaping; Drug abuse; Addiction; Salience

## 1. Introduction

Drug abuse researchers have noted striking similarities between behaviors elicited by Pavlovian sign-tracking (also called "autoshaping") procedures and prominent symptoms of drug abuse (Tomie, 1995a, 1996; Newlin, 2002; Uslaner et al., 2006; Flagel et al., 2007a, b). Moreover, key elements of sign-tracking procedures are likely experienced at the time that drugs are consumed. The traditional Pavlovian sign-tracking procedure consists of the presentation of a small object (conditioned stimulus, CS) that is followed by the response-independent presentation of reward (unconditioned stimulus, US). Crucial to the understanding of sign-tracking, the US is delivered regardless of what the subject does. Repeated CS-US pairings lead to the acquisition of the Pavlovian sign-tracking CR, which is a complex sequence of motor responses directed at the CS (Brown and Jenkins, 1968; for review, see Tomie et al.,

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1989). Thus, if presentation of a lever CS precedes the response-independent delivery of a food pellet US, rats approach and contact the lever CS, often grasping, licking, and gnawing the lever, as though it were food itself (Davey and Cleland, 1982; Tomie et al., 1989).

Sign-tracking has long been associated with seemingly maladaptive patterns of behavior that are elicited by and directed towards reward-related cues. Remarkably, these behaviors persist even though they serve only to delay or prevent the delivery of the reward, indicating that the sign-tracking CR performance is not under strict voluntary control. In their book, "The Misbehavior of Organisms", Keller and Marian Breland (1961) described how pairings of an object with reward lead to the development of bizarre and arguably compulsive responding. In a typical example, raccoons were trained to pick up wooden coins and deposit them through a slot into a metal box for a small morsel of crayfish, a highly prized food reward. Though initially things went well, with further training the raccoons began to experience problems. They were unable to let go of the coins, spending several minutes handling them with their forepaws, and dipping the coins into the slot only to pull them out again. In the end, the coins were licked, chewed, scratched and washed, but rarely deposited. This was not the distraction of an animal that has lost interest in eating, because making the raccoon hungrier merely made matters worse. Similar "misbehavior" has been described in squirrel monkeys, pigs, chickens, turkeys, otters, porpoises, and whales (Breland and Breland, 1961, 1966). Numerous investigators have now provided rigorous experimental evidence that sign-tracking CR performance is difficult to control or suppress (Williams and Williams, 1969; Hearst and Jenkins, 1974; Atnip, 1977; Schwartz and Gamzu, 1977; Holland, 1979; Davey et al., 1981; Tomie, 1995b; Killeen, 2003; for review, see Locurto, 1981).

Both sign-tracking and drug abuse may be described as poorly controlled consummatory-like responding that is elicited by and directed at a small object CS that has been repeatedly paired with reward US. In humans, for example, the alcohol abuser exhibits poorly controlled drinking responses that are directed at the cocktail glass CS that has been repeatedly paired with alcohol US, or the cocaine abuser exhibits poorly controlled sniffing responses that are directed at the coke tooter CS that has been repeatedly paired with cocaine US. This section presents evidence of additional similarities in the characteristics of behaviors exhibited by drug abusers that are induced by experience with sign-tracking procedures.

## 2. Behavioral characteristics

### 2.1. Relapse-like effects

After sign-tracking CR performance has been acquired, the behavior is not easily forgotten or eliminated, but rather appears to be quite durable and resilient. Evidence that sign-tracking CR performance is well retained is provided by reports that following its acquisition, the mere passing of time without additional training has little or no effect on the performance of sign-tracking CRs (Carr and Murtazina, 1994; Meneses et al., 2004; Tomie et al., 2002c, 2004a). For example, sign-tracking CR performance of alcohol drinking in rats is virtually unchanged following a 27-day retention interval (Tomie et al., 2002c) or following a 41-day retention interval (Tomie et al., 2004a). Maintenance of sign-tracking CR performance of sipper CS-directed alcohol drinking over time, without appreciable decay or deterioration in the performance, is similar to relapse in humans and reinstatement of drug-taking in animals (Kruzich et al., 2001; Stewart, 2004; for review of reinstatement as a model of relapse, see Epstein et al., 2006; Fattore et al., 2007). In each of these cases there is little evidence of loss of responding during the retention interval, even though responding is not practiced during this extended period of time.

Further evidence of the resilience of sign-tracking CRs is provided by reports of spontaneous recovery and rapid reacquisition of sign-tracking CR performance. Spontaneous recovery is

observed following a rest interval and after sign-tracking CR performance has been thoroughly eliminated by extended experience with CS-only extinction procedures, during which the subject receives presentations of the CS but no US (Tomie et al., 1980, 1981; Robbins, 1990; Rescorla, 2004, 2005, 2006). Rapid reacquisition is observed following extensive training with response elimination procedures, when responding is rapidly reinstated by simply pairing the CS with the US (Tomie et al., 1980; Tomie and Kruse, 1980; Tomie et al., 1981). Relapse to drug-taking resembles spontaneous recovery and rapid reacquisition of sign-tracking CR performance because even after drug-taking has been thoroughly eliminated, mere exposure to the drug-paired cue or a brief lapse in abstinence, are sufficient to recover pre-elimination levels of drug-taking.

Drug abuse researchers have successfully employed Pavlovian CS-only extinction procedures to extinguish CRs indicative of reactivity to drug cues (for reviews see Tomie, 1995a, 1996). Nevertheless, there are many reports of spontaneous relapse of drug-taking, even though drug cue reactivity had previously been significantly reduced or eliminated by drug cue extinction procedures (Wikler, 1973; Monti et al., 2001; Junghanns et al., 2005; Loeber et al.., 2006), and Hammersley (1992) has attributed relapse to drug-taking following cue extinction therapy to spontaneous recovery. A role for spontaneous recovery of sign-tracking in relapse to drug-taking is suggested by reports that alcohol drinking glassware provides cues eliciting alcohol-related physiological responses (Carter and Tiffany, 1999) and subjective cravings for alcohol (Cooney et al., 1983; Fox, 2007), and the persistence of these cue-elicited responses contribute to relapse (Marlatt, 1990; Rohsenow et al., 1994; Sinha and Li, 2007).

Sign-tracking is a consummatory-like response directed at a small object CS paired with reward US, and because this resembles drug-taking, the analogies to relapse provided by long-term retention, spontaneous recovery, and rapid reacquisition seem particularly pertinent. It is, nevertheless, appropriate to acknowledge that addiction theorists have long noted, and prior to the discovery of sign-tracking, that the remarkable durability and persistence of Pavlovian CRs was addiction-like (Wikler, 1967). It is not surprising, therefore that several recent prominent theoretical formulations of addiction and relapse have explicitly emphasized the role of Pavlovian processes in general (Stewart, et al., 1984; Siegel, 1989; Robbins and Everitt, 1999; Robinson and Berridge, 1993; Corbit and Janak, 2007) and sign-tracking in particular (Tomie, 1995a, 1996; Newlin, 2002; Uslaner et al., 2006; Flagel et al., 2007a, b; Cunningham and Patel, 2007).

### 2.2. Vulnerability to impulsivity

Impulsivity is typically measured using delay discounting procedures, and in observed when human beings (Bickel and Marsch, 2001) or animals (Charrier and Thiebot, 1996; Evenden and Ryan, 1996) choose smaller but immediate rewards over larger but delayed rewards. Impulsivity is related to drug addiction by studies reporting that rats that are intolerant of reward delay subsequently acquire cocaine self-administration more rapidly and at lower doses (Perry et al., 2005) and also self-administer more alcohol (Poulos et al., 1995, 1998) than do delay-tolerant rats (for review, see Olmstead, 2006). In addition, Lewis rats, as compared to Fischer rats, exhibit more intolerance to reward delay (Anderson and Woolverton, 2005) and more readily self-administer drugs of abuse, including cocaine (Kosten et al., 1997; Haile and Kosten, 2001), morphine (Ambrosio et al., 1995; Martin et al., 1999), and alcohol (Suzuki et al., 1988). In humans, the trait of impulsivity has been proposed to predispose vulnerability to drug abuse (Zuckerman, 1993; Jentsch and Taylor, 1999; Svrakic et al., 1999; Volkow and Fowler, 2000; Kreek et al., 2005) and there is evidence that impulsivity, as measured by self-reports in humans, is higher in alcohol-dependent patients (Patton, et al., 1995; Chen et al., 2007), and in drug abusers (Allen et al., 1998; Fillmore and Rush, 2002), while recent evidence

implicates impulsivity is an important feature of early-onset alcoholism (Dom et al., 2006a, b).

Sign-tracking CR performance has been linked to impulsivity, as measured by delay discounting, in the same way that impulsive responding has been linked to alcohol drinking. The link between sign-tracking and impulsivity is based on the finding that individual differences in sign-tracking predict individual differences in impulsivity. Subject-to-subject variability in sign-tracking CR performance can be extreme, with large and reliable between-subject differences in sign-tracking CR performance reported in a number of species, including ring doves (Balsam, 1985), pigeons (Tomie, 1981), and rats (Locurto, 1981; Tomie et al., 1998a, b, 2000; Flagel et al., 2007a, b). Individual differences in sign-tracking CR performance were linked to individual differences in impulsivity, as measured by the tendency to choose small immediate rewards rather than larger delayed rewards (Tomie et al., 1998a). In that study, rats that performed more lever-press sign-tracking CRs were more impulsive, as measured by intolerance of reward delay. A similar type of within-subjects correlation between sign-tracking and delay discounting has been reported in a study of the effects of lesions of the subthalamic nucleus, which decreased impulsive choice and impaired sign-tracking CR acquisition (Winstanley, et al., 2005). Individual differences in impulsivity may also be substantial and predictive of between-subjects differences in alcohol drinking (Poulos et al., 1995, 1998). Poulos and his associates have shown that rats, exhibiting intolerance to reward delay by choosing small immediate rewards over larger delayed rewards, subsequently consumed more alcohol than rats that were less delay-intolerant. Their work reveals that impulsivity and alcohol drinking are linked phenomena (Poulos et al., 1997), and provides support for the hypothesis that those individuals that perform more sign-tracking CRs tend to be more impulsive and drink more alcohol.

Rat strains that exhibit more impulsive responding as measured by intolerance to reward delay or delay discounting also perform more sign-tracking CRs. For example, Lewis rats exhibit more intolerance to reward delay than Fischer rats (Anderson and Woolverton, 2005), and Lewis rats also exhibit more rapid acquisition and higher asymptotic levels of sign-tracking CR performance than Fischer rats (Kearns et al., 2006). Intolerance to reward delay or delay discounting is one of several indices of impulsivity, and there is evidence that sign-tracking resembles impulsive responding on other behavioral tasks as well (Monterrosso and Ainslie, 1999). For example, depletions of forebrain serotonin in rats increased the number of sign-tracking approach responses to a CS paired with food and also increased impulsive responding as measured by conditioned locomotor activity to food (Winstanley et al., 2004).

### 2.3. Psychomotor sensitization

Behavioral sensitization is defined as an increase in the locomotor-stimulating effect of a drug after repeated administration (Robinson and Becker, 1986) and is proposed to be a determinant factor in addictive behavior in rats (Robinson, 1984; Salamone, 1992; Robinson and Berridge, 1993; Stewart, 2000, 2003, 2004) and in humans (Newlin and Thomson, 1991; Hunt and Lands, 1992). In rats, sensitization has been shown with cocaine, morphine, and alcohol, and cross-sensitization has been shown between alcohol and morphine (Nesby et al., 1997) and between abused drugs and stress (Sorg and Kalivas, 1991; Tidey and Miczek, 1997; Araujo, et al., 2003). Repeated activation of the mesolimbic dopamine system may mediate the development of behavioral sensitization to psychomotor stimulants (Vezina and Stewart, 1990; Robinson and Berridge, 1993) and to alcohol (Nesby et al., 1997). Alcohol-induced behavioral sensitization has been shown in human beings (Zack and Vogel-Sprott, 1995), some strains of mice (Masur et al., 1986; Phillips et al., 1997) and in some strains of outbred rats (Hoshaw and Lewis, 2001; Correa et al., 2003); however, the conditions conducive to the induction or expression of behavioral sensitization of locomotor activation in rats remain unclear.

Sensitization of psychomotor activation has been more reliably reported with drugs other than alcohol, including cocaine (Pecins-Thompson and Peris, 1993; Mattingly et al., 1994; Schenk and Partridge, 2000; Zavala et al., 2000; Erb et al., 2003; Haile et al., 2003; Matell et al., 2004), amphetamine (Robinson, 1984; Paulson and Robinson, 1991; Serwatkiewicz et al., 2000; Vezina and Queen, 2000; Crombag et al., 2001; Fukami et al., 2004), and opiates (Balcells-Olivero and Vezina, 1997; Ojanen et al., 2005).

Sign-tracking CR performance and sensitization of psychomotor activation are similar in the topographical forms of the behaviors expressed. Sign-tracking CRs (Tomie et al., 1989) and the psychomotor activation syndrome (Wise and Bozarth, 1987; Piazza and Le Moal, 1996) are skeletal-motor responses, including actions of forward locomotion and directed approach, that include contact and manipulation responses, culminating in consummatory-like responses, including gnawing, licking, sniffing, chewing, and swallowing. Conditions conducive to sign-tracking of alcohol drinking and to alcohol-induced sensitization of psychomotor activation share a number of elements. For example, both are enhanced by exposures to alcohol that are repeated and spaced. In sign-tracking procedures, alcohol drinking is enhanced by Intermittent Sipper procedures and longer intertrial interval (ITI) durations (Tomie et al., 2003c, Exp. 2; 2005a, 2006b). These are not unlike procedures most conducive to the induction of the psychomotor activating effects of alcohol, where repeated and spaced injections of alcohol (i.e., intermittent schedules of alcohol exposures), induce stronger psychomotor activating effects than in controls provided with massed exposures to alcohol (Pecins-Thompson and Peris, 1993; Lessov and Phillips, 1998; Quadros et al., 2003). Similarly, other abused drugs induce psychomotor activation effects (Robinson, 1984; Wise and Bozarth, 1987; Wise and Rompre, 1989) that are exaggerated by repeated and spaced exposures to the drug, relative to controls receiving fewer but massed exposure to similar amounts of the drug (Salamone, 1992; Stewart, 2003).

Sign-tracking of alcohol drinking and sensitization of alcohol's psychomotor activating effects are similar in that both are behavioral models of addiction that emphasize similar properties of the inducing experience. They do, however, differ in a number of important ways. For example, sign-tracking procedures provide for oral alcohol drinking of small amounts of alcohol per exposure, with relatively short inter-exposure intervals. In contrast, sensitization procedures provide for systemic or intraventricular injections of larger doses of alcohol per exposure, with longer inter-exposure intervals. Despite these dosing differences, the ratio of the duration of the inter-exposure interval to the amount of drug delivered per exposure is similar for both sign-tracking and sensitization procedures. Furthermore, both procedures demonstrate the direct relationship between the duration of the inter-exposure interval and the amount of sign-tracking or sensitization observed.

Recently additional relationships between sign-tracking and psychomotor sensitization have been reported. For example, Flagel and her associates have reported that those rats that develop sign-tracking CR performance show enhanced propensity to exhibit cocaine-induced psychomotor sensitization, relative to goal-tracking rats that moved to the location of the food receptacle rather than to the lever CS (Flagel et al., 2007b). They suggested that sign-trackers are susceptible to a form of cocaine-induced plasticity that may contribute to the development of addiction. In support of this hypothesis, Flagel and her associates have reported that sign-trackers exhibited higher levels of D1 mRNA in NAC core relative to goal-trackers after the first day of training with sign-tracking procedures (Flagel, et al., 2007a), but after 5 days of training, sign-trackers showed blunted dopaminergic expression patterns relative to goal-trackers, including lower levels of tyrosine hydroxylase, dopamine transporter, and dopamine D2 mRNA relative to goal-trackers (Flagel et al., 2007a). These data are consistent with the hypothesis that behavioral changes induced by sign-tracking procedures are related to changes in the dopamine system, and in a manner noted by addiction researchers. For example, lower

levels of D2 receptor have been associated with increased craving (Heinz et al., 2004), and increased reports of "drug-liking" in humans (Volkow et al., 2002). Finally, Flagel and her associates (unpublished data) have noted that rats selectively bred for high responsivity to environmental novelty stress are almost exclusively sign-trackers in food US procedures and rats selectively bred for low responsivity to environmental novelty stress exhibit almost exclusively goal-tracking, moving to the location of the food receptacle rather than to the lever CS. When these rats are employed in sign-tracking procedures employing cocaine US, the same results are observed. The high-responders to novelty all acquire sign-tracking CR performance, while none of the low responders do so. Thus, the high responsivity phenotype exhibits sign-tracking in procedures employing either food US or cocaine US, while the low responsivity phenotype does not exhibit sign-tracking to signals for either food US or cocaine US.

### 2.4. Sign-Tracking induced by abused drugs

Our hypothesis is that sign-tracking CR performance is induced by experience with repeated pairings of an object CS with drug reward US. There is evidence of precisely this effect in animal studies of drug abuse. The most compelling evidence of this is provided by Uslaner et al. (2006), who used the insertion of a retractable lever as CS and intravenous administration of cocaine as US. They reported that when lever CS and cocaine US were paired in a sign-tracking procedure, rats approached and sniffed the lever CS more than pseudoconditioning controls that received the lever CS and cocaine US in an unpaired fashion (Uslaner, et al., 2006). Other drug abuse investigators have employed modified sign-tracking procedures to induce lever-pressing of drug self-administration in rats. For example, Carroll and her associates have reported that pairings of the insertion of a lever CS with intravenous administration of drug reward US induced the automatic "shaping" of lever-pressing for drug self-administration in rats. Procedures of this sort have been employed to induce reliable lever-pressing for the self-administration of the cocaine US (Carroll and Lac, 1993, 1997, 1998; Specker et al., 1994; Gahtan et al., 1996; Lynch and Carroll, 1999; Lynch et al., 2001; Campbell and Carroll, 2001; Campbell et al., 2002; Carroll et al., 2002; Roth et al., 2002; see also Panlilio et al., 1996; Weiss et al., 2003 c.f., Di Ciano and Everitt, 2003; Kearns and Weiss, 2004), orthe self-administration of the amphetamine US (Carroll and Lac, 1997) or the self-administration of the heroin US (Lynch and Carroll, 1999; Carroll et al., 2002; Roth et al., 2002). In all of these studies, rats developed increasingly frequent lever-pressing as a function of experience with repeated pairings of lever CS with rewarding drug US. The role of sign-tracking, however, remains unclear, because when lever-pressing occurred, the drug reward US was administered more quickly than when lever-pressing was not observed. Thus, the drug reward US was not presented independently of responding, as is the case during sign-tracking procedures. An additional problem is that none of these studies included controls for pseudoconditioning, leaving open the possibility that the development of lever-pressing was due to mere experience with repeated presentations of the lever CS *per se* or to repeated presentations of the drug reward US *per se*.

Pairing a visual CS with alcohol US induces sign-tracking CR performance in rats. For example, after provided rats with pairings of a light CS with alcohol US, Krank (2003) observed that they approached the location of the light CS, resulting in increases or decreases in operant lever-pressing for alcohol reinforcement, when the light CS was located either near or far away from the operant lever, respectively. Sign-tracking using alcohol US has also been reported by Cunningham and Patel (2007), who reported that only three pairings of a star CS with alcohol US were required to induce reliable Pavlovian conditioned approach to the star CS as revealed by place conditioning procedures in mice. Tomie and his associates have employed sign-tracking procedures consisting of alcohol sipper CS paired with food US to induce alcohol sipper CS-directed consummatory responding, resulting in alcohol drinking (Tomie et al., 2002a Exps 1 and 2, 2002c, 2003c Exps 1 and 2, 2004a, 2005b, 2006b). Similar procedures

have been employed with chlordiazepoxide in the sipper CS to induce sign-tracking of sipper CS-directed chloridazepoxide drinking in rats (Tomie et al., 2004e). Most significantly, there is evidence that the drinking of alcohol from the sipper CS, an action that provides the rat with pairings of sipper CS with alcohol US, induces a pattern of alcohol drinking that is indicative of sign-tracking of sipper CS-directed alcohol drinking in rats (Tomie et al., 2002c, 2003c Exps 1 and 2; Tomie et al., 2005a, 2006b Exps 1 and 2; see also Tomie et al., 2006a). Thus, the hypothesis that sign-tracking CR performance develops as a function of repeated pairings of an object CS with drug reward US is well supported. Our view is that repeated pairings of an object CS with drug reward US are experienced by humans during the drug-taking sequence, and this leads to the development of sign-tracking CR performance of reflexive and poorly controlled drug-taking.

## 3. Neurobiological substrates

### 3.1. Stress-related effects

Stressful events play a prominent role in alcohol and drug abuse in humans (Fouquereau et al., 2003; Goeders, 2004; Kreek et al., 2005) and animals (Stewart, 2003; Capriles et al., 2003; Kabbaj, et al., 2004; Mantsch and Katz, 2007). Experience with stressful events provokes neuroendocrine responses as well as changes in neurotransmitter systems (Koob, 2006), and drug abuse is related to neurobiological responses to stress, including the release of the glucocorticoid stress hormone corticosterone (Martinelli and Piazza, 2002; Yang, et al., 2004; Le et al., 2005), and changes in monoamine neurotransmitter activity (Heinz et al., 2002; Kalivas and McFarland, 2003; Zhang and Kosten, 2005; Salomon et al., 2006; Sorge and Stewart, 2005). This section reviews evidence that sign-tracking procedures induce changes in corticosterone levels and monoamine neurotransmitters that resemble the stress-related responses known to accompany alcohol and drug abuse.

**3.1.1. Corticosterone—**There are relationships between corticosterone and sign-tracking in many animal studies that resemble those observed between corticosterone and the self-administration of abused drugs. For example, addiction researchers have noted that higher plasma corticosterone levels are associated with higher levels of alcohol intake (Morin and Forger, 1982; Fahlke et al. 1994a, b; Hansen et al., 1995; Prasad and Prasad, 1995; Higley and Linnoila, 1997), and with more self-administration of other abused drugs (Wise and Bozarth, 1987; Robinson and Berridge, 1993; Piazza and Le Moal, 1996; Koob, 1999; Stewart, 2003). A similar type of relationship between plasma corticosterone levels and sign-tracking has been documented in several ways. For example, pretreatment with ketoconazole, a corticosterone synthesis inhibitor, decreased the rate of acquisition of sign-tracking CR performance of cocaine self-administration in rats (Campbell and Carroll, 2001), and adrenalectomy reduced sign-tracking CR performance in rats that was previously established by pairings of lever CS with food US (Thomas and Papini, 2001).

There is also evidence that mere experience with sign-tracking procedures induces corticosterone release in rats (Tomie et al., 2002b Exp 1, 2003a, 2004b), and this finding is particularly intriguing in view of the postulated relationships between sign-tracking and drug-taking and between corticosterone and drug-taking. In these studies, rats trained with sign-tracking procedures that consisted of pairings of lever CS with food US showed higher post-session plasma corticosterone levels than controls trained with lever CS and food US presented randomly with respect to one another (Tomie et al., 2002b Exp 1, 2003a, 2004b). For example, in a number of studies, plasma samples collected immediately following the 20$^{th}$ daily sign-tracking session revealed higher corticosterone levels in the Paired group relative to the Random control group (Tomie et al., 2002b Exp 1, 2003a, 2004b). Most significantly, group differences in plasma corticosterone levels in rats were also observed in plasma samples collected immediately following the first sign-tracking session (Tomie et al., 2002b Exp 2),

which preceded the acquisition of sign-tracking lever-press CR performance in the Paired group. This indicates that the effect of training with sign-tracking procedures on plasma corticosterone levels is not a by-product of group differences in lever-pressing frequency. Corticosterone release is induced by experience with lever CS - food US paired sign-tracking procedures and is evident prior to the expression of sign-tracking CR performance. One possibility is that corticosterone induces a state of arousal (Merali et al., 1998; see also Killeen et al., 1978) that is conducive to the expression of sign-tracking CR performance (Tomie et al., 2002b, 2004b); moreover, higher levels of corticosterone are related to higher levels of alcohol drinking (Fahlke et al, 1994a, b) and the tendency to self-administer abused drugs (Piazza et al., 1989; Rouge-Pont et al., 1993; Lucas et al., 1998; for reviews see Piazza and Le Moal, 1996; Koob, 1999).

The performance-enhancing effects of corticosterone on sign-tracking CR performance are also revealed by the relationship between individual differences in corticosterone release and sign-tracking CR performance. Rats that showed higher novelty stress-induced corticosterone release acquired the lever-press sign-tracking CR more rapidly and maintained higher asymptotic levels of lever-press sign-tracking CR performance (Tomie et al., 2000). The effect of vulnerability to novelty stress-induced corticosterone release on sign-tracking CR performance resembles this effect on drug self-administration (Piazza and Le Moal, 1996). Corticosterone is thought to activate mesolimbic dopamine neurons. Between-subjects differences in sign-tracking CR performance (Tomie et al., 2000) and amphetamine self-administration (Piazza and Le Moal, 1996) are positively correlated with indices of increased dopaminergic function (i.e., elevations in accumbal levels of dopamine (DA) and DOPAC). This pattern of results suggests that corticosterone release, postulated to activate mesolimbic DA neurotransmission producing psychomotor activation (Robinson and Berridge, 1993; Wise and Bozarth, 1987), may also be involved in promoting the expression of sign-tracking CRs and drug-taking responses. The possibility that elevated plasma corticosterone levels may contribute to sign-tracking CR expression as well as to vulnerability to drug abuse adds to the growing list of common features shared by both (Tomie 1995a, 1996, 2001). The pathophysiological profiles of vulnerability to sign-tracking and drug abuse are considered in more detail in Section 3.3.

**3.1.2. Monoamines—**Additional stress-like effects induced by sign-tracking procedures are the changes associated with monoamine neurotransmitter levels and monoamine neurotransmitter turnover in forebrain areas. In addition to the release of corticosterone, sign-tracking procedures induce stress-like changes in forebrain norepinephrine and serotonin. For example, sign-tracking procedures induce changes in central monoamine systems that resemble stress-induced sensitization effects. Paired sign-tracking procedures induce higher levels of norepinephrine (NE) and serotonin (5-HT) in the prefrontal cortex (PFC) but not in the striatum relative to Random controls (Tomie et al., 2004b), and this pattern of results bears a striking similarity to the effects of stressful events, like electric shock (Adell et al., 1988; Yoshioka et al., 1995; Koob, 1999). Stress may play a crucial role in drug addiction, by sensitizing crucial neuronal substrates to the activating effects of abused drugs (Piazza and Le Moal, 1996; Koob, 1999; Stewart, 2003); therefore, these stress-like changes induced by experience with CS-US paired sign-tracking procedures may also serve to accentuate the activating effects of abused drugs.

A stress-like effect on 5-HT receptor binding has also been observed in sign-tracking (Tomie et al., 2003a; Meneses et al., 2004). The relationship between stress and reduced 5-$HT_{1A}$ receptor function has been documented in several ways. Chronic mild stress reduced adrenocorticotrophic hormone responses to 8-OH-DPAT, a 5-$HT_{1A}$ receptor agonist (Grippo et al., 2005). Stress reduces 5-$HT_{1A}$ messenger RNA gene expression in hippocampus in rats (Lopez et al., 1999) and 5-$HT_{1A}$ receptor binding, as measured by autoradiography, in the

hippocampus in rats and humans (Lopez et al., 1998). Sign-tracking investigators have reported that corticosterone levels are elevated by omission procedures providing for cancellation of the food US on trials that the rat performs the lever-press sign-tracking CR, relative to non-omission controls (Tomie et al., 2003a), suggesting that the omission procedure is stressful. Autoradiography revealed lower post-synaptic 5-$HT_{1A}$ receptor binding in the omission group than in the non-omission controls, in several brain areas, including frontal cortex, septum and caudate putamen (Tomie et al., 2003a). More recently, it has been reported that $^{3}$H-8-OH-DPAT-labeled binding of 5-$HT_{1A}$ receptors was lower in septum and caudate putamen in rats receiving lever CS - food US sign-tracking procedures than in untrained controls (Meneses et al., 2004). Several studies suggest 5-$HT_{1A}$ receptors may mediate drug-taking responses in rats. For example, ipsapirone, a 5-$HT_{1A}$ partial agonist reduced ethanol intake in rats (for review, see Schreiber et al., 1999), while NAN-190, a selective 5-$HT_{1A}$ receptor antagonist decreased intravenous self-administration of methamphetamine in rats (Novakoval et al., 2000). Furthermore, it is known that repeated administration of alcohol (Rothman et al., 2000; Chastain, 2006) or psychomotor stimulants (Weiss et al., 1992; Levy et al., 1994; Rothman et al., 2000; Marshall et al., 2007) result in synaptic deficits in 5-HT. Thus, these stress-like changes in corticosterone and monoamine levels and 5-HT receptor binding induced by sign-tracking are not unlike the profile of neurobiological features associated with drug abuse (Piazza and Le Moal, 1996; Marinelli and Piazza, 2002; Stewart, 2003).

## 3.2. Dopamine pathways

**3.2.1. Nucleus accumbens—**The addictive properties of various drugs depend on the mesocorticolimbic DA system (Wise and Bozarth, 1985; Koob and Bloom, 1988; Carelli, 2002; Saal et al., 2003) and its projection to the nucleus accumbens (NAC) from the ventral tegmental area (VTA) in the brainstem (Zito et al., 1985; Wise and Rompre, 1989; Everitt et al., 2001; Marinelli and Piazza, 2002; Ghitza et al., 2004). The NAC has been shown to be crucial for the development of Pavlovian conditioned responses to natural rewards (for review see Day and Carelli, 2007), abused drugs (Ghitza et al., 2003; Cardinal and Everitt, 2004; Di Chiara et al., 2004), and to sign-tracking CR performance (Parkinson et al., 1999, 2000, 2002; Di Ciano et al., 2001; Dalley et al., 2002; Cardinal et al., 2002; Everitt and Robbins, 2005).

Lesions of the NAC disrupt the acquisition of sign-tracking CR performance in rats (Parkinson et al., 2000; Di Ciano et al., 2001; Parkinson et al., 2002; Dalley et al., 2002; Cardinal et al., 2002) and the maintenance of performance of previously learned sign-tracking CRs (Parkinson et al., 1999; Parkinson et al., 2002). For example, in rats, DA-depleting lesions of the NAC, induced by bilateral infusions of 6-hydroxydopamine directly into the NAC, impaired the acquisition of sign-tracking of light CS-directed contact CRs during training with light CS - food US sign-tracking procedures (Dalley et al., 2002).

**3.2.1.1. Nucleus accumbens core:** The NAC is a heterogeneous structure that can be further divided into anatomically and functionally distinct core and shell subregions (Zahm and Brog, 1992; Zahm, 2000). Selective excitotoxic lesions of the core of the NAC during training impaired the acquisition of sign-tracking CR performance in rats (Parkinson et al., 2000). Lesioned rats failed to approach the light CS+ that had been paired with food US on more trials than sham controls, and lesioned rats failed to acquire a discriminative sign-tracking task, even though CS+ was paired with food and CS− was not (Cardinal et al., 2002). On the other hand, unilateral lesions of the medial PFC and the medial caudate-putamen produced attentional deficits, but had no effect on the acquisition of Pavlovian sign-tracking CR performance in rats (Christakou et al., 2005).

The involvement of the NAC core in Pavlovian sign-tracking has also been implicated by the deleterious effects on discriminative Pavlovian sign-tracking CR performance following infusions of glutamatergic or dopaminergic receptor antagonists (Di Ciano et al., 2001). Infusions of NMDA (N-methyl-D-aspartic acid) or the dopamine D1/D2 receptor antagonist alpha-flupenthixol into the NAC core during training impaired the acquisition of sign-tracking CR performance in rats. These rats performed fewer conditioned approach responses directed at the lever CS+ that was paired with food US, relative to vehicle controls, and, in addition, failed to discriminate between CS+ and CS−, even though CS− was not paired with food US (Di Ciano et al., 2001).

**3.2.1.2. Nucleus accumbens shell:** There is evidence that the shell of the NAC is also involved in the Pavlovian conditioning of appetitive approach CRs. Rats acquired a conditioned approach response to a compound light/auditory CS paired with sucrose US more rapidly when d-amphetamine was infused post-session into the shell of the NAC than into the core or dorsal striatum (Phillips, et al., 2003a). This finding is in agreement with immunohistochemical evidence showing that Pavlovian approach conditioning is associated with activation of dopaminergic terminals specifically within the shell of the NAC (Phillips et al., 2003b, c). DA activity in NAC shell and core was investigated immunohistochemically using antibodies raised against glutaraldehyde-conjugated DA (Phillips et al., 2003b). During acquisition of Pavlovian conditioned approach to a visual CS that preceded sucrose US, DA activity in NAC shell was more elevated than in NAC core during the initial stages of CR acquisition, and neither area was responsive during asymptotic CR performance (Phillips et al., 2003b).

The shell of the NAC may have an effect on the initial acquisition of Pavlovian conditioning of approach responses by influencing the rewarding effects of novelty. Single-unit recording using fast-scan cyclic voltammetry to assess DA release revealed that DA efflux increased only during the brief period of entry into novelty and the increase was confined to the shell of the NAC (Rebec, 1998). In this study, neither the accumbal core nor the overlying neostriatum showed a novelty-related DA change. Using single-unit recording to assess neuronal activity, approach to novelty was accompanied by roughly equal proportions of neuron excitations and inhibitions in core but a shift away from excitation toward inhibition in shell. Widespread activation of core units during approach to novelty suggested a role for core activation in the initiation of appetitive behavioral responses (Rebec, 1998; Wood and Rebec, 2004, see also Corbit et al., 2001; Sellings and Clarke, 2003; Ghitza et al., 2004; Balleine, 2005).

**3.2.2. Anterior cingulate cortex—**Anterior cingulate cortex (ACC) projects to NAC core and has been implicated as an area related to drug craving (Everitt and Robbins, 2005) and primed reinstatement of drug-taking responses (Kalivas and McFarland, 2003). In human cocaine addicts, imaging by positron emission tomography of synaptic activity related to addict-generated mental imagery of drug craving was associated with bilateral activation of ACC (Kilts et al., 2001), while in rats, bilateral lesions of the ACC produced a decrease in acquisition of heroin self-administration and a decrease in relapse of heroin-taking in rats (Trafton and Marquez, 1971). Lesions of ACC impair sign-tracking CR performance in rats (Bussey et al., 1997; Parkinson et al., 2000; Cardinal et al., 2002, 2003), and disconnection of the ACC from the core of the NAC also impaired the acquisition of sign-tracking CR performance (Parkinson et al., 2000). Lesions of ACC also impair differential responding to CS+ and CS− in discriminative sign-tracking procedures (Bussey et al., 1997; Cardinal et al., 2002). The effects of lesions of ACC on sign-tracking are unlikely due to general impairment of cognitive or motor function, as lesions of ACC impaired sign-tracking, but had no effect on a variety of Pavlovian conditioning tasks, including goal-tracking, conditioned reinforcement, conditioned freezing and Pavlovian-Instrumental transfer (Cardinal et al., 2003).

**3.2.3. Pendunculopontine tegmental nucleus—**The pendunculopontine tegmental nucleus (PPTg) is a brain-stem output of the limbic system that projects to dopaminergic midbrain areas that connect to the nucleus accumbens (Steiniger-Brach and Kretschmer, 2005). The PPTg is involved in motor activity driven by the DA system (Steiniger, 2004) that is critical for the performance of complex motivated behavior (Bechara and van der Kooy, 1989). The PPTg exerts this influence by altering response selection processes in the NAC (Steiniger-Brach and Kretschmer, 2005). The PPTg has been implicated in the self-administration of abused drugs (Corrigall et al., 2002), including alcohol (Samson and Chappell, 2001). NMDA-lesions of the PPTg disrupt the learning of conditioned place preference based on injections of morphine or amphetamine (Olmstead and Franklin, 1994). In sign-tracking, PPTg may play a role in the learning of the association between the CS and rewarding US. PPTg-lesioned rats fail to respond differentially to CS+ that is paired with the US reward, as compared to CS−, which is not paired with US reward, as evidenced by the finding that rats approached the CS+ and CS− with equal frequency, and the latencies to respond to the two stimuli did not differ (Inglis et al., 2000). Thus, lesions of the PPTg disrupted the learning of conditioned approach responses in drug-seeking and sign-tracking procedures.

### 3.3. Vulnerability markers

The neurobiological characteristics of rats that perform more lever-press sign-tracking CRs (Tomie, et al., 2000) share much in common with pathophysiological markers of vulnerability to drug abuse (Piazza and Le Moal, 1996). Rats that performed more lever-press sign-tracking CRs showed more novelty stress-induced corticosterone release, higher DA levels in NAC, lower DOPAC/DA turnover ratios in caudate putamen, lower 5-HIAA/5-HT turnover in the VTA, but no evidence of elevated dopamine activity in PFC. Similarly, rats that more readily self-administer amphetamine showed more novelty stress-induced corticosterone release (Piazza et al., 1989; Rouge-Pont et al., 1993; Piazza and Le Moal, 1996; Lucas et al., 1998), higher indices of DA functioning in NAC (Piazza et al., 1989; Rouge-Pont et al., 1993; Piazza and Le Moal, 1996; Lucas et al., 1998), but not in PFC (Simon et al., 1988; Piazza et al., 1991) and lower indices of 5-HT functioning in VTA (Piazza et al., 1991; see also Kelland et al., 1990). These results add to the growing body of evidence suggesting that sign-tracking and drug abuse may be related phenomena (Tomie, 1995a, 1996; Tomie et al., 2000; Everitt et al., 2001; Uslaner et al., 2006; Flagel et al., 2007a, b).

## 4. Sign-tracking as attribution of incentive salience

Addiction researchers have long recognized that stimuli paired with abused drugs acquire incentive motivational properties (Wikler, 1967; Sherman et al., 1989; Robinson and Berridge, 1993; Robbins and Everitt, 1999; Glasner et al., 2005). These are typically viewed as Pavlovian CRs that activate subjective, emotional or motivation states that contribute to the incentive to consume the drug, thereby increasing the likelihood that the user will perform the physical actions of drug-taking. A more precise formulation of how Pavlovian incentive motivational processes may contribute to drug abuse is offered by Incentive Sensitization Theory (IST), which proposes that addictive drugs sensitize the neural reward function, increasing the positive reward value of drug-taking (Robinson and Berridge, 1993; Berridge and Robinson, 2003). Sensitization of the drug's rewarding effects may provide further incentive for increasing drug intake, causing the individual to increasingly crave the drug's effects (Robinson and Berridge, 2000, 2001). Most significantly, stimuli paired with the drug develop incentive salience, a motivational component of reward that, according to IST, makes objects paired with reward especially attractive and highly desired (Berridge, 2001). Thus, IST predicts that stimulus objects paired with reward will become motivational magnets (Berridge, 2001).

It has recently been proposed that sign-tracking CR performance may be the overt behavioral manifestation of the attribution of incentive salience to reward-related cues (Uslaner et al.,

2006; Flagel et al., 2007a, b). According to this view, repeated pairings of lever CS with food US leads to sign-tracking CR performance due to the attribution of incentive salience, which makes the lever CS highly salient and attractive and desired. Thus, the lever CS becomes a motivational magnet, compelling the rat to approach and contact the lever CS, even though the performance is not necessary to obtain food.

The hypothesis that sign-tracking reflects the attribution of incentive salience to the lever CS is supported by the finding that rats vulnerable to developing sign-tracking CR performance show greater propensity to exhibit cocaine-induced psychomotor sensitization (Flagel et al., 2007b), suggesting that individual differences in the tendency to sign-track are associated with differences in the tendency to attribute incentive salience to a discrete reward-related cue. This, in turn, suggests that sign-trackers are susceptibile to a form of cocaine-induced plasticity that may contribute to the development of addiction (Robinson and Berridge, 2000, 2001). These results suggest that drug abusers are individuals prone to develop pathological levels of incentive salience attributed to reward-related cues. Although further studies are required to develop more fully the possible relationship between sign-tracking CR performance and attribution of incentive salience, this approach may serve to integrate further our understanding of the behavioral and neurobiological determinants of drug abuse.

## Abbreviations

CS, conditioned stimulus
US, unconditioned stimulus
ITI, intertrial interval
DA, dopamine
DOPAC, 3,4-dihydroxy-phenylacetic acid
IST, Incentive Sensitization Theory
NE, norepinephrine
5-HT, 5-hydroxytryptamine
VTA, ventral tegmental area
NAC, nucleus accumbens
PFC, prefrontal cortex
8-OH-DPAT, 8-hydroxy-2-di-n-propylamino-tetralin
ACC, anterior cingulate cortex
NMDA, N-methyl-D-aspartic acid
PPTg, pendunculopontine tegmental nucleus
5-HIAA, 5-hydroxyindoleacetic acid

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