Sign Tracking and Drug Addiction
Sign Tracking and Drug Addiction

JONATHAN MORROW AND ARTHUR TOMIE
Contents

1. Introduction: The Role of Sign-Tracking in Drug Addiction 1
2. Sign-Tracking Model of the Addiction Blind Spot 8
3. The Neurobiological Mechanisms Underlying Sign-Tracking Behavior 35
4. The Propensity to Attribute Incentive Salience to Drug Cues and Poor Cognitive Control Combine to Render Sign-Trackers Susceptible to Addiction 75
5. Gambling Hijacks an Ancestral Motivational System Shaped by Natural Selection 106
6. Sign-Tracking, Response Inhibition, and Drug-Induced Vocalizations 129
7. Relevance of Sign-Tracking to Co-Occurring Psychiatric Disorders 162
8. Telling Stories about Sign-Tracking Boosts Awareness of Loss of Self-Control Related to Drug Use 186
Introduction: The Role of Sign-Tracking in Drug Addiction

Arthur Tomie

Corresponding Author:
Arthur Tomie, PhD, Associate Professor, Department of Psychology and Center of Alcohol Studies, Rutgers–The State University of New Jersey, New Brunswick, NJ 08903; e-mail: tomie@psych.rutgers.edu; phone: (848) 445-8885; fax: (848) 445-3500.

Keywords: addiction; autoshaping; conditioned approach; craving; drug cues; goal-tracker; sensitization; sign-tracker

Introduction: The Role of Sign-Tracking in Drug Addiction

Drug addiction is an enigma. Drug addiction is puzzling, mysterious, and difficult to understand. Particularly puzzling, and at the very heart of the matter, is the question, “How does drug addiction happen?” No one sets out to become an addict. Yet, somehow, through repetition and ritual, the controlled, decision-based, voluntary drug-taking of the social, recreational drug user mysteriously turns into the triggered, reflexive, and involuntary drug-taking that presages the downward spiral into full-blown, out-of-control drug addiction. This is the perplexing mystery of drug addiction that rightfully concerns us all. In this volume, addiction research scientists, working in the analytical experimental learning laboratory and in the biomedical neuroscience wet lab report insights they have gained through the study of sign-tracking, and, the drug addiction process.

What is sign-tracking? Sign-tracking like drug addiction is also difficult to understand. Those observing sign-tracking confess to being befuddled,
perplexed, and confused. Sign-tracking (also called autoshaping or Pavlovian conditioned approach) is a form of Pavlovian or classical conditioning (Locurto, Terrace, & Gibbon, 1981). The discovery of sign-tracking was historically significant because it revealed a novel form of Pavlovian conditioned response (CR). Notably, in studies of sign-tracking, the subject is freely-moving, an arrangement that is atypical of Pavlovian conditioning procedures. The freely moving subject receives repetitions of an object CS paired with a reward US and is free to adjust their location in response to these CS-US pairings in any way, including moving anywhere within the boundaries of the experimental chamber. The freely moving subject comes to develop a complex sequence, of CS-directed skeletal-motor orientations and actions. It is the targeting aspect of the response of the free-moving subject that allows the sign-tracking CR to uniquely model this potentially crucial feature of the drug addiction process. This includes, for some, but not all subjects (Flagel, Akil, & Robinson, 2009), the overwhelming, irresistible, attractiveness of drug-related cues (Berridge & Robinson, 2016; Robinson & Berridge, 1993). Sign-tracking procedures allow a form of CR expression that models crucial features of the behavior of the freely moving drug addict that contributes to their vulnerability to loss of self-control disorders, including drug addiction (Kuhn, Campus, & Flagel, this volume; Meyer & Tripi, this volume; Robinson, Carr, & Kawa, this volume), and behavioral addictions such as pathological gambling (Anselme, this volume), and vulnerability to neuropsychiatric disorders that are comorbid with substance use disorder (Morrow, this volume).

In sign-tracking studies, repeated pairings of a small object (conditioned stimulus, CS) that precedes the delivery of the reward (unconditioned stimulus, US) induces some subjects to approach, contact, and “consume” the small object CS. Important to the understanding of sign-tracking is that the reward US is delivered on each trial regardless of what the subject does. For a brief video showing the acquisition of sign-tracking CR performance in a laboratory rat, see www.youtube.com/watch?v=x38b0R6TZxM. As revealed in the video, the retractable lever CS is inserted into the chamber for 5 seconds, followed immediately by the response-independent delivery of the food pellet US. As a result of lever CS–food US pairings, the rat associates the lever CS with the food US, as revealed by the development of sign-tracking CR performance. The sign-tracking rat behaves toward the lever CS as though it were the food US. The rat approaches the lever CS, contacts the lever CS, and licks and gnaws the lever CS. Remarkably, the rat
does this more and more on trial after trial, even though these actions serve no purpose and are a complete waste of time and energy. Many students, upon first observing sign-tracking seem puzzled and comment that it makes no sense. They wonder why the rat is attempting to “eat” the lever.

The sign-tracking CR is a Pavlovian acquired reflex. The sign-tracking CR is an involuntary Pavlovian response that is triggered automatically by the presentation of the CS and performed regardless of the intention of the subject. Sign-tracking CR performance is so poorly controlled that the subject is often unable to restrain the performance even at the cost of losing the reward US (Breland & Breland, 1961; Locurto, 1981). For a brief video of misbehaving raccoons exhibiting sign-tracking behavior resulting in the loss of food rewards, see https://tailoftheraccoon.com/the-integrated-reward-system/. As can be seen in the video, gnawing and chewing the coin CS causes the raccoon to earn virtually no food rewards. Presumably the hungry raccoon intends to eat a tasty treat, but due to sign-tracking, its actions are disconnected from intentions. The behavior of the raccoon is puzzling because it results in the loss of food and simply because the raccoon is unable to exercise self-control. The video is telling. The video reveals that the compulsive performance of the sign-tracking reflex is stronger than the intention of the hungry raccoon to simply deposit the coins in order to eat.

According to the Sign-Tracking Model of Addiction (STM) proposed by Tomie and his associates (Tomie, 1995, 1996; Tomie, Badawy & Rutyna, 2016; Tomie, Grimes, & Pohorecky, 2008; Tomie & Sharma, 2013), drug-taking begins as a voluntary operant drug self-administration response that, due to repetitions of Pavlovian pairings of cue CS with reward US, inadvertently recruits Pavlovian sign-tracking CR performance (Hearst & Jenkins, 1974; Schwartz & Gamzu, 1977). In this way, sign-tracking offers an account of how impulsive and involuntary behavior begins and is triggered by cues. It offers a theory of how addiction gets started, while, at the same time, explaining why the erosion of self-control induced by sign-tracking goes largely unnoticed. According to Tomie, Jeffers, and Zito (this volume), the sign-tracking CR is camouflaged or masked to pass for operant drug self-administration. The masking effect is based on the striking resemblance between the physical topographies of the performances of the operant and Pavlovian responses as well as their common targeting, both of which are directed at the object employed to consume the drug. Tomie, Jeffers, and Zito (this volume) provide a sign-tracking account of the addiction blind spot, the widespread failure of drug users to recognize when they are starting to lose control of their drug-
taking. Their failure to recognize the loss of self-control due to sign-tracking allows them to spiral further downward into the pit of drug addiction. A possible way to address the blind spot problem is offered by Levitch, Marcinkowski-Paulis, and Tomie (this volume). They report that, in 9th–12th grade students, using scientific short stories about sign-tracking and drug addiction as an educational tool is effective in boosting awareness of the loss of self-control and the relationship between loss of self-control and drug addiction.

Individual subjects differ greatly from one another in their vulnerability to drug addiction. Subjects also differ greatly in their tendency to exhibit sign-tracking CR performance. Addiction scientists have found that these tendencies co-vary within an individual, suggesting that sign-tracking is a behavioral marker of vulnerability to drug addiction (Flagel, Akil, & Robinson, 2009; Flagel & Robinson, 2017). Some subjects respond to repeated lever CS-food US pairings by approaching and contacting the lever CS. These subjects, called sign-trackers (ST rats), learn that the lever CS signals the impending delivery of the food US, and ST rats express this learning in an emotional way, revealing their attraction to the lever CS and their need to be in close proximity to it. This is the case even though approaching the lever CS serves no purpose and actually moves them to a location removed from the site of the delivery of the food US.

Other rats respond to repeated lever CS-food US pairings in a different way. They do not develop sign-tracking CRs. Instead, they react to the insertion of the lever CS by approaching the location of the food trough, where the food US is delivered. These subjects, called goal-trackers (GT rats), also learn that the lever CS signals the delivery of the food US, but GT rats respond in a more cognitive way, reacting to the information provided by the appearance of the lever CS. GT rats show little evidence of being attracted to the lever CS or having the need to be in close proximity to it. Most significantly, the two behavioral phenotypes differ in their tendency to subsequently self-administer an abused drug. ST rats, relative to GT rats, more rapidly acquire the drug-taking response, and self-administer the abused drug more frequently. In addition, ST rats are more vulnerable to relapse to drug-taking following periods of drug abstinence. ST rats also exhibit a constellation of other addiction-like behaviors (Beckmann, Marusich, Gipson, & Bardo, 2011) as well as physiological traits (Tomie, Grimes, & Pohorecky, 2008) and neurobiological markers that are associated with drug addiction (Flagel & Robinson, 2017).
The tendency to perform sign-tracking CRs confers vulnerability to drug addiction, but why is this so? What is the basis for the addiction vulnerability of the ST rat? According to incentive sensitization theory (IST) proposed by Robinson and Berridge (1993), the cue-elicited emotional reaction of "craving" or "wanting" the drug is sensitized due to repeated activations of the dopamine reward pathways by abused drugs. Consequently, drug cues increasingly trigger the feeling of "wanting," which is responsible for the dramatically exaggerated motivation for drugs displayed by addicts. Sign-tracking reveals, in the form of overt physical skeletal action, the sensitization of the incentive value or attractiveness of drug cues. The emotional feelings of drug craving, wanting, and needing elicited by drug cues are therefore revealed by the physical expression of orientation and skeletal action of the target-directed behaviors of the freely moving ST rats. Thus, the propensity to attribute incentive salience to reward cues renders sign-trackers susceptible to drug- and behavioral addictions, including pathological gambling (Anselme, this volume).

The neurobiological pathways that differentiate ST rats from GT rats have been extensively studied. Kuhn, Campus, and Flagel (this volume) map the distinctive neurobiological substrates associated with the two behavioral phenotypes, while Robinson, Carr, and Kawa (this volume) show that in addition to activation of dopamine systems, ST rats also exhibit weak cholinergically-mediated cognitive/attentional control.

The ST and GT phenotypes model individual differences in vulnerability to substance use disorder. Investigators have noted in other paradigms additional examples of behaviors that are differentially associated with sign-tracking and goal-tracking, including initial differences in the value of the rewarding US, differences in inhibitory control related to impulsivity, and differences in cocaine-induced vocalizations (Meyer & Tripi, this volume). Symptoms of ST-like and GT-like responding are also observed in a number of other neuropsychiatric disorders.

Based on the strong relationship between addiction and other psychiatric disorders, it is not surprising that sign-tracking, in particular, has relevance to a broad range of neuropsychiatric disorders beyond just substance use disorders. Morrow (this volume) notes overlapping behavioral symptoms and neuropsychiatric diagnostic criteria of ST-like effects observed in co-occurring neuropsychiatric disorders, including behavioral addictions, such as pathological gambling (see also Anselme, this volume), anxiety disorders,
PTSD, psychotic disorders, and OCD, while GT-like symptoms are prominent in individuals diagnosed with OCPD, eating disorders, and depression.

References


2. Sign-Tracking Model of the Addiction Blind Spot

Arthur Tomie, *a,b Peter Jeffers, a and Barbara Zito c

a Department of Psychology, Rutgers University, New Brunswick, NJ 08901
b Center of Alcohol Studies, Rutgers University, New Brunswick, NJ 08901
c ZT Enterprises LLC, Cranbury, NJ 08512

Corresponding Author:
Arthur Tomie, PhD, Associate Professor, Department of Psychology and Center of Alcohol Studies, Rutgers–The State University of New Jersey, New Brunswick, NJ 08903; e-mail: tomie@psych.rutgers.edu; phone: (848) 445-8885; fax: (848) 445-3500.

Abstract

No one sets out to become an addict. Drug use begins voluntarily, but somehow, through repetition and ritual, drug-taking becomes unstoppable. The most obvious characteristic of addiction is that drug use takes on a life of its own, but how and why this happens remains a mystery. The voices of addicts serve only to deepen the mystery. Many tell us that their drug use escalated, even as they were trying very hard to keep it under control. Despite repeated failed attempts to maintain self-control, when addiction closed in, they were stunned, because all along they were certain that they could quit drug use if they really wanted to. There is something mysterious and stealthy about the drug addiction process that allows addiction to prey upon the unsuspecting. Based upon our research, we have concluded that there is an addiction blind spot in the form of a psychological scotoma, which enables the gradual erosion of self-control to proceed unrecognized. Due to this blind spot the loss of self-control
occurs in the background, at a preconscious level, without awareness. The addiction blind spot obscures the loss of self-control that fuels the transition from social, recreational, and voluntary drug use into the realm of the habitual and automatic drug-taking of the drug abuser.

Keywords: autoshaping; drug addiction; misbehavior; reflex; self-control; sign-tracking

Introduction

Addiction nosologists (Babor, 1995; Jellinek, 1960) and addiction researchers (Barker & Taylor, 2014; Corbit & Janak, 2016; de Wit et al., 2012; Tiffany, 1990; Tiffany & Conklin, 2000) have long noted that repeated drug use sets the stage for the gradual progression from voluntary and intended drug use into reflexive and poorly controlled drug abuse. Our hypothesis is that repeated drug use induces Pavlovian sign-tracking of drug-taking, which accounts for the increase in vulnerability to drug cues that accompanies the habitual and automatic drug-taking of the drug abuser (Corbit & Janak, 2016). The sign-tracking model (STM) has previously been presented in a number of theoretical reviews (Tomie, 1995, 1996; Tomie, Badawy, & Rutyna, 2016; Tomie, Grimes, & Pohorecky, 2008; Tomie & Sharma, 2013) where we have proposed that the development of sign-tracking conditioned response (CR) performance of drug-taking provides a unified account of prominent features of drug abuse, including escalation into excessive drug-taking and the loss of control of drug-taking.

In the present chapter, we expand on the role of sign-tracking to account for the blind spot in the drug addiction process. The drug addict is in the dark, unaware that sign-tracking has developed and is gradually robbing him or her of his or her free will. The addiction blind spot is evidenced by their lack of awareness that their actions have become triggered and reflexive due to sign-tracking. They remain confident in their ability to control their drug use, even as they lose their grip. While treatment specialists have made reference to the addiction blind spot (Formica, 2012; Reich, 2015), their focus was on relapse and the ego-hypertrophic overconfidence that encourages
risk-taking. In contrast, our focus is on a much earlier phase of the drug addiction process. It is when the user chooses to use drugs again and again, that this ritualized experience leads to the development of sign-tracking, which is a form of drug-taking that the user cannot control. We propose that the development of sign-tracking of drug-taking goes unnoticed because the reflexive use of drugs closely resembles and passes for voluntary drug-taking. Thus, the naïve user is oblivious to the emergence of sign-tracking of drug-taking, as sign-tracking integrates seamlessly with ongoing voluntary drug use. This is the addiction blind spot, where drug-taking is slipping out of control and the user is unable to see it.

Sign-tracking is especially likely to go undetected because of representational and cognitive momentum (Hubbard, 2015; Miura 1990), the tendency to see what we expect to see and to see it as that which we have seen all along. The user has already established a history of performing voluntary acts of intended drug-taking and continues to see it that way. When sign-tracking CR performance of drug-taking does emerge, the user will perceive it as just another ordinary routine act of voluntary and intended drug-taking. In other words, sign-tracking is simply overlooked because it is camouflaged as voluntary drug use and is virtually invisible, allowing sign-tracking of drug-taking to hide in plain sight.

The following discussion will focus on these fundamental questions: What is sign-tracking? What role does sign-tracking play in the compulsive use of drugs? How does sign-tracking contribute to the blind spot, that is, to the misguided belief of the drug abuser that they are in control of their drug-taking?

Sign-tracking is a form of Pavlovian conditioning. Pavlov's dogs learned to salivate to the tone conditioned stimulus (CS) that signaled food unconditioned stimulus (US). During sign-tracking procedures, the subject learns to react to the presentation of the object CS that signals the delivery of the food US as though the object CS was the actual food US (Brown & Jenkins, 1968). For example, when food is the US, the subject will approach the lever object CS, contact the lever object CS, and then lick, gnaw, and chew (i.e., “consume”) the lever object CS. However, regardless of what the subject does, the food reward US is delivered. This is important to the understanding of sign-tracking. Even though lever-pressing for food reward is a widely employed operant reward training procedure, sign-tracking is not a voluntary goal-directed operant response (Locurto, 1981; Tomie, Brooks, & Zito, 1989), and therefore does not serve the instrumental purpose of
acquiring the food reward US. It is important to note that sign-tracking may be induced during operant reward training procedures and may resemble operant responding, but sign-tracking induced during operant procedures does not increase operant goal-directed behavior; rather, sign-tracking increases non-instrumental performance of instrumental-like responding.

It bears repeating that sign-tracking is an acquired Pavlovian reflex. It is a complex sequence of directed skeletal-motor responses that are conditioned to be triggered by the object CS and, in addition, to be performed regardless of the intention of the subject (D. Williams & H. Williams, 1969; for reviews, see Herrnstein & Loveland, 1972; Locurto, 1981; Locurto, Terrace, & Gibbon, 1976, 1978). For a brief video showing the acquisition of sign-tracking in a laboratory rat, see www.youtube.com/watch?v=x38b0R6TZxM.

Herein lies the crux of the matter, the erroneous presumption of the drug abuser, who all along thought that quitting was simply a matter of deciding to do so. The drug abuser is baffled and confused because the actions of sign-tracking of drug-taking, which are reflexive and involuntary, were mistaken for and misconstrued as the actions of voluntary and intended drug-taking (Tomie & Sharma, 2013). Figure 2.1, using alcohol drinking as an example, illustrates how voluntary operant drug-taking brings about the development of sign-tracking CR performance of drug-taking.
STM emphasizes the role of the tool used by humans as a conduit to aid in consuming the drug (Tomie, 1995, 1996). For example, through repetitions of drug-taking, the cocktail glass CS comes to signal the impending drug reward US. In this way, repeated voluntary acts of alcohol drinking from the cocktail glass CS provide the user with numerous Pavlovian CS-US pairings, which are conducive to the induction of Pavlovian sign-tracking CR performance. What does the topography, the sequence of physical movements, of sign-tracking CR performance of alcohol drinking look like?

Consider the case of the alcohol user who is in the early stages of exhibiting sign-tracking of triggered, reflexive, and automatic alcohol drinking. He comes home after a stressful day, walks straight to his home bar, and begins the well-practiced routine of pouring a drink. He reaches for his favorite bottle of bourbon, takes the tumbler glass from the cabinet and as he drops the ice cubes into the glass, he hears the familiar clink of the ice hitting the glass. He then pours the bourbon over the ice cubes and proceeds to bring to his lips his favorite drink, bourbon on the rocks. This ritual is performed over and over again. How does this physical process,
the actual preparation of and consumption of the drink, differ from his bourbon-drinking prior to the acquisition of the triggered, reflexive, and automatic habit of doing it? The problem is, it doesn't. This is exactly how he made his drink before he developed the habit, and due to the development of sign-tracking, it's exactly how he will make his drink now and in the foreseeable future. In other words, the voluntary action and the reflexive action appear the same. Despite the fact that the subject's routine of pouring and consuming the drink has become reflexive and is now performed mindlessly and automatically, nothing in his actual skeletal-motor response sequence appears any different from before, when it was all performed as a voluntary and intended action. For this reason, drinking beyond what was intended is likely to be misinterpreted as “I changed my mind,” indicating that I believe that I am still in control of my drinking. Note that the physical movements of sign-tracking of alcohol drinking and the physical movements of voluntary intended alcohol drinking appear to be identical. Sign-tracking of drug-taking, therefore, is inconspicuous, easily overlooked, and virtually invisible because sign-tracking of drug-taking looks very much like voluntary operant drug self-administration.

As alcohol use is repeated and loss of control of alcohol drinking begins to develop, voluntary acts of alcohol drinking will continue to take place as before. But now, in addition, due to the acquisition of sign-tracking CR performance, the drinker will absent-mindedly have a drink without intending to do it. This is not the same as deciding to have a drink. This is a triggered reflex. This is the first sign of the emergence of sign-tracking of alcohol drinking. Because the topography of the sign-tracking CR closely resembles the topography of voluntary drug-taking, the unconcerned user may drink excessively, having more than intended, but remain oblivious as to why. As sign-tracking develops further, alcohol drinking gradually becomes more reflexive, automatic, involuntary, mindless, thoughtless, and more difficult to stop. This is because, due to the strengthening of Pavlovian conditioning, the mere presence of the cocktail glass is now better able to trigger sign-tracking of alcohol drinking, resulting in reflexive drinking of the alcoholic beverage in the cocktail glass. Due to sign-tracking, an ongoing episode of alcohol drinking will be more difficult to stop, but the underlying cause of the actions of continued drinking will be overlooked. Having another drink will be seen as a voluntary and intended action that is regrettable, but correctable, an unfortunate consequence of a bad decision. This optimistic view allows the abuser to cling to the mistaken belief that
they are in control of their drug-taking when they are not. In this way, they remain blind to the erosion of their self-control and continue to slide down the slippery slope into the pit of drug addiction.

The complaints of the confused drug addict are telling. “I was blindsided,” “I never saw it coming,” “How did this happen to me?” Their words convey that they feel confused and cheated because they were unaware that their drug-taking would become unstoppable even when they were trying very hard to quit. Many addicts feel that they plummeted into the pit of addiction without fair warning because they were unaware that their control of their drug-taking was slipping away. This problem is addressed by Levitch, Marcinkowski-Paulis, and Tomie (this volume), who found that storytelling about sign-tracking significantly boosted awareness of the loss of self-control and improved understanding of how the loss of self-control contributes to the development of drug addiction.

Conduits

It should be noted that humans typically employ a tool as a conduit (i.e., tooter, bong, cigarette, syringe, capsule) to assist in the self-administration of abused drugs (i.e., cocaine, marijuana, tobacco, heroin, prescription painkillers). In addition, humans typically consume alcohol from a container (i.e., cocktail glass, ale mug, beer bottle) employed as a conduit to assist in drinking alcoholic beverages. An unintended role of the conduit, therefore, is to allow humans to self-administer drugs in a manner that is perfectly suited to the development of sign-tracking CR performance of drug-taking. Moreover, and crucial to the understanding of the blind spot, the conduit provides a common target at which both forms of drug-taking (voluntary operant drug-taking and reflexive sign-tracking of drug-taking) are directed. As noted earlier, the form of the sign-tracking CR resembles the form of the operant response performed when the subject decides to have a drink. Their shared common target, at the cocktail glass, serves to bring them together, merging them into a single unified stream of responding. In this way, the conduit triggers excessive use but, at the same time, camouflages sign-tracking, creating the blind spot that allows the user to believe that their excessive use of drugs is by choice. Thus, the user remains overconfident,
unconcerned, and oblivious, even as drug-taking becomes increasingly difficult to control.

Using a conduit to self-administer a drug plays a major role in the creation of the addiction blind spot. This is because repeatedly using the conduit to take the drug provides precisely the protocol that will lead to the development of sign-tracking of drug-taking. The reflexive and impulsive use of drugs is then able to masquerade as voluntary drug-taking when in fact it is due to sign-tracking. Using the conduit as the drug-taking tool allows the conduit to act as a drug cue, and this serves to obscure the distinction between voluntary and reflexive drug use. This provides the opportunity for sign-tracking to slip by unnoticed, so that the user fails to recognize that they are not acting by choice but losing control of their drug-taking.

**CAM and Masking**

When the conduit also serves as a drug cue, then the conduit provides a common target for sign-tracking of drug-taking and operant drug self-administration. To be clear, in the language of the animal learning literature, the conduit is the response manipulandum that the subject must contact in order to obtain the drug's rewarding effects. The response manipulandum, therefore, serves as the target at which the operant drug self-administration response is directed. Examples of the manipulandum in the animal learning laboratory are the pecking key in the operant chamber of the pigeon or the response lever in the operant chamber of the rat. The conduit induces sign-tracking to the extent that the conduit is a reward cue, that is, when the conduit CS predicts the rewarding effects of the drug US. In the animal learning laboratory, examples of the reward cue are the sound of a tone emanating from a loudspeaker, which signals that the reward is available for performing the instrumental response. Other examples are the color (i.e., wavelength) of a light stimulus projected onto the pigeon's pecking key, or the illumination of a small light located inside or just above the rat's response lever. Of particular interest are arrangements where the conduit serves as the response manipulandum and, in addition, as the reward cue. Under such conditions, the conduit provides for Cue-At-Manipulandum (CAM), an
arrangement that induces the performance of sign-tracking CRs that have often been mistaken for the operant responses that induced them (Tomie, 1995, 1996).

Consider the case where the conduit is the cocktail glass employed to self-administer an alcoholic beverage. The operant alcohol drinking response is directed at the cocktail glass that serves the role of the instrumental response manipulandum. The subject must contact the cocktail glass in order to obtain alcohol's rewarding effects. The cocktail glass conduit may also serve the function of a reward cue when the cocktail glass is positively correlated with the availability of the drug's rewarding effects. Under these conditions, the cocktail glass provides for CAM and allows sign-tracking of drug-taking to develop and co-mingle with operant drug-taking. Thus, the conduit that provides for CAM induces sign-tracking that is targeted at the same location as the operant drug-taking response. In this way, the conduit serves as a tool that allows sign-tracking to masquerade as operant drug-taking.

### CAM and the Blind Spot

The animal learning literature reveals that operant procedures that provide for CAM induce sign-tracking CRs that resemble the operant responses that induced them (for reviews, see Hearst & Jenkins, 1974; Schwartz & Gamzu, 1977; Tomie, 1995, 1996). Remarkably, this resemblance was so striking to the naked eye that specifically trained scientific observers could not tell them apart (Schwartz, 1975; Schwartz, Hamilton, & Silberberg, 1975; Schwartz & Williams, 1972). In addition, during CAM procedures both response forms are directed at the same location, therefore, the induced sign-tracking CRs have been mistaken for and added to the frequency counts of operant responses (for reviews, see Hearst & Jenkins, 1974; Schwartz & Gamzu, 1977). Thus, the experimental scientific evidence reveals that when the operant response manipulandum provides for CAM, then sign-tracking CRs are masked to pass for operant responding. The masking by CAM is so effective that it was revealed only by rigorous experimental analysis in the animal learning laboratory.

For many years, learning scientists were perplexed by what was presumed
to be the excessive levels of operant responding that developed during CAM procedures. Laboratory experiments examined the effects of manipulating the location of the cue with respect to the manipulandum or, alternatively, the cue's correlation with the reward. These studies revealed that excessive operant-like responding was not observed in these non-CAM control conditions. Moreover, it was discovered that the excessive operant-like responding varied with conditions known to be conducive to the induction of sign-tracking CRs. Investigators concluded that CAM recruits sign-tracking CRs that are indistinguishable from and additive with ongoing operant responding (Hearst & Jenkins, 1974; Schwartz & Gamzu, 1977). To detect the presence of sign-tracking, innovative experimental analyses of the effects of CAM arrangements were required before scientists who study learning discovered the presence of this blind spot. In this way, scientists discovered that sign-tracking CRs had long been mistaken for voluntary operant responses, and the mistaken identity created the false impression that operant responding was being performed to excess (Tomie, Brooks, & Zito, 1989). Note that the CAM arrangements that produce this masking effect, this blind spot, are analogous to those experienced by humans during drug-taking.

Non-CAM Controls

CAM procedures produce higher rates of operant-like responding than do non-CAM control procedures (Tomie, 1995, 1996). Signal-key studies reveal that this effect is due to the induction of sign-tracking CRs which, during CAM procedures, add to frequency counts of operant responding. In signal-key studies, for example, pigeons peck an operant response key (manipulandum) for food reward. In CAM procedures, the reward cue, a green keylight, is projected onto the operant manipulandum key. Non-CAM controls receive similar procedures except the green keylight reward cue is projected onto another key (signal key) located at a distance from the operant key (Hearst & Gormley, 1976; Keller, 1974; McSweeney, Dougan, & Farmer, 1986; Schwartz, 1975). These pigeons peck the operant key, as is required to obtain the reward, but at a reduced rate, relative to the CAM group. The non-CAM controls also pecked the signal key where the green
keylight predictive of the food reward was projected. They did this even though pecking the signal key did not serve the purpose of procuring the food reward. Thus, signal-key studies reveal that when operant procedures provide for CAM, sign-tracking CRs are induced, and they are targeted at the operant response key, yielding higher rates of operant-like responding relative to non-CAM controls. The scientific literature reveals that the naked eye cannot differentiate sign-tracking CRs from operant responses, and rigorous experimental analysis in the animal learning laboratory is required to distinguish between them.

Another non-CAM control procedure is the non-differential reward training schedule (for reviews, see Dunham, 1968; Rachlin, 1973; Terrace, 1972). In these studies, pigeons peck an operant key (manipulandum) for food reward. The manipulandum key is illuminated either by a green light or a red light, which alternate sequentially. In the first phase, the non-CAM control procedures are in effect. The food reward is equally likely when pigeons peck the green keylight or the red keylight. In the second phase, the schedule in effect during the green keylight remains as before, but the red keylight now signals that an extinction schedule is in effect. The green keylight is a reward cue; therefore, CAM procedures are in effect, and the rate of responding directed at the green keylight increases dramatically.

For many years, this effect, called “positive behavioral contrast,” was interpreted as elevated operant responding, even though the higher rates of operant-like responding did not produce more food rewards. It is a well-documented property of time-based interval schedules of reward that the number of rewards delivered is largely independent of the rate of responding (Ferster & Skinner, 1957). The non-CAM control procedures favored a different interpretation of the positive behavioral contrast effect. They revealed that the excessive pecking directed at the green keylight was due to the signal value of the green keylight. This is consistent with an interpretation based on the induction of sign-tracking CRs that were simply misconstrued as operant responses. It should be noted that positive behavioral contrast during CAM procedures have also been reported in other species, including rats (Allison, 1976; Atnip, 1985; Freeman, 1971; Higa & McSweeney, 1987; Jensen & Fallon, 1973; Karpicke, Christoph, Peterson, & Hearst, 1977; Peterson, Ackil, Frommer, & Hearst, 1972) and goldfish (Bottjer, Scobie, & Wallace, 1977). These data reveal that sign-tracking CRs have often been counted as operant responses and that non-CAM control procedures have been required to distinguish between them.
Preposterous Imposters

CAM induces sign-tracking of non-instrumental performance of instrumental-like responding. This type of effect may bedevil the drug abuser who intends to refrain from drug use but is instead triggered to have yet another. In this way, CAM may induce mistake-prone, erroneous, and unintended behavior that appears to be an operant or instrumental response but is instead a sign-tracking response. The unwelcome behavior is actually a well-disguised imposter. The actions are not voluntary, they are reflexive. Some examples of the sign-tracking CR posing as an error-prone operant response include the misbehavior effect and the feature-learning effect.

The “misbehavior of organisms” was first reported by professional animal trainers, Keller and Marian Breland, who successfully applied Skinnerian reinforcement contingencies in the training of thousands of animals in a variety of tasks (K. Breland & M. Breland, 1961, 1966). They did, however, experience some rather perplexing instances where things did not go according to plan. In a typical example, raccoons were trained to pick up wooden coins and deposit them through a slot into a small metal box for food reward. Though initially things went well, with further training the raccoons began to experience problems. They seemed unable to let go of the coins, spending several minutes handling them with their forepaws and “rubbing them together in a most miserly fashion” (K. Breland & M. Breland, 1961). The raccoons often dipped the coins into the slot only to pull them out again. In the end, the coins were chewed, licked, scratched, clawed, rubbed, and washed, but rarely deposited. Remarkably, the actions of the raccoons made it appear as if they were trying to clean a morsel of food. Further training only made matters worse, until the project was reluctantly abandoned. Other abandoned projects attempted similar training with rats, pigs, squirrel monkeys, chickens, turkeys, otters, porpoises, and whales. This “misbehavior” should not be construed as the distraction of an animal that has lost interest in eating, because increasing the animal’s hunger merely intensifies this effect (K. Breland & M. Breland, 1961, 1966). For video of raccoons exhibiting misbehavior due to sign-tracking, see: https://tailoftheraccoon.com/the-integrated-reward-system/.

Procedures conducive to misbehavior provide for CAM. The coin serves as the reward cue and as the instrumental response manipulandum. Misbehavior is revealed by the development of a prohibited response that
occurs excessively and persists despite contingent non-reinforcement. Misbehavior is an instance where CAM induces mistake-prone, erroneous, and unintended behaviors that appear to be operant or instrumental responses, when, in reality, the responses are actually due to sign-tracking, the well-disguised imposter. It should be noted that the misbehaving raccoons resemble drug abusers whose intention to refrain is thwarted by their triggered actions to have yet another. They are unable to stop themselves. They are repeatedly stymied by their inability to control themselves, as they are reflexively triggered to approach, contact, and “consume” the object that has been paired with the reward.

The feature-learning effect provides another instance where the intrusion of sign-tracking induced error-prone responding during operant procedures. In a typical study, the subject responds by touching the stimulus display, which is the response manipulandum. The S+ display is a red dot on a green background. The S- display is the same, except without the red dot. This is the feature-positive discrimination, which yields excellent accuracy. The feature-negative procedure reverses the displays, so that the red dot, the distinguishing feature, is on the S-. Although the stimulus displays used in the two discrimination tasks are equally distinguishable from one another, subjects in the feature-negative condition make far more errors (Bitgood, Segrave, & Jenkins, 1976; Norton, Muldrew, & Strub, 1971; Sainsbury, 1971).

Analysis of the location of responding supports a sign-tracking interpretation (Crowell & Bernhardt, 1979; Hearst & Jenkins, 1974). Feature-positive subjects respond to the S+ display by touching the red dot, thereby recording a correct response and earning the reward. Feature-negative subjects, on the other hand, respond to their S+ display by touching the green background. Apparently, the pairing of the green display with the reward induces sign-tracking CRs, leading to incorrect responding on S- trials. Some children expressed frustration upon performing the error, because they knew better, but responded without thinking (personal communication, H. Strub). This suggests that feature-negative errors were induced by sign-tracking CRs posing as operant responses. These sign-tracking CRs are preposterous imposters that served to sabotage the intention of the subject, which was to produce accurate discrimination performance.
CAM and the Alcohol Sipper

In the animal laboratory, voluntary operant alcohol self-administration is observed when a rat drinks an alcohol solution from a sipper tube. Note that the sipper tube is the response manipulandum, a tool employed as a conduit to assist in the drinking of the alcoholic beverage. The positive contingency between the sipper tube CS and alcohol (i.e., CAM arrangement) will elicit sign-tracking CR performance of sipper CS-directed alcohol drinking, and the alcohol drinking due to sign-tracking will add to operant alcohol drinking, resulting in elevated levels of alcohol intake relative to non-CAM controls. Studies that vary the contingency between the sipper CS and alcohol US show that alcohol intake varies directly with the positive contingency between the sipper CS and alcohol US (Tomie, Gittleman, Dranoff, & Pohorecky, 2005; Tomie, Miller, Dranoff, & Pohorecky, 2006). Note that the elevated alcohol drinking, presumably due to sign-tracking, is indistinguishable from operant alcohol self-administration.

Sign-tracking CR performance is sensitive to the positive contingency between the CS and the US, which varies as a function of the ratio of the duration of the non-CS (i.e., sipper CS retraction) periods relative to the duration of the CS presentation (i.e., sipper CS insertion) periods (Balsam & Gibbon, 1988; Gallistel & Gibbon, 2000; Jenkins, Barnes & Barrera, 1981). Intermittent sipper procedures improve the covariation between the sipper CS and the alcohol US by increasing the amount of time during the daily drinking session that the sipper CS and, consequently, the alcohol US, are both absent. The CAM hypothesis predicts that elevated sign-tracking of alcohol drinking will be induced by extending the periods of time during the daily drinking session when the sipper CS is retracted from the drinking chamber. This schedule increases the contingency between the sipper and the alcohol. An intermittent schedule of availability of the alcohol sipper CS (Intermittent Sipper procedure) provides for repeated insertions and retractions of the alcohol sipper CS such that the alcohol sipper CS is removed from the drinking chamber for the majority of the drinking session. In a Continuous Sipper procedure, fixed position alcohol drinking tubes provide for continuous availability of the alcohol sipper CS during the entire duration of the drinking session. Remarkably, it has been reported in several studies that the Intermittent Sipper procedure induced more alcohol drinking than the Continuous Sipper procedure, even though the
Continuous Sipper procedure made the alcohol solution available to the rats for a much longer time (Tomie, et al., 2005; Tomie, et al., 2006).

Similar effects of intermittent sipper procedures versus continuous sipper procedures have been reported in studies of home cage alcohol drinking. Rats provided with continuous access to the alcohol sipper in their home cage drink less alcohol per day than rats deprived of access to the alcohol sipper, and consequently, access to the alcohol solution, on some of the days (Brancato, Plescia, Cavallaro, & Cannizzaro, 2016; Carnicella, Ron, & Barak, 2014; Loi et al., 2010; Peris, Rhodes, McCullough, Aramini, & Zharikova, 2015; Sabino, Kwak, Rice, & Cottone, 2013; Simms, et al., 2008; Simms, Nielsen, Li, & Bartlett, 2013; Wise, 1973). This effect has also been reported in mice (Melendez, 2011). This suggests that the effects of the contingency between sipper CS and alcohol US are evident across a broad range of alcohol drinking procedures.

CAM and Problem Drinking

STM predicts that, due to CAM-induced sign-tracking, excessive and poorly controlled alcohol drinking (i.e., problem drinking) will vary directly with the positive contingency between the conduit CS and alcohol US. Consider the following scenario. Suppose that your favorite drink is a double martini, extra dry, with two olives and an onion, served in a lead crystal cocktail glass. Suppose further that all of the alcohol that you drink is consumed in this way. Under these conditions, your alcohol drinking repertoire is extremely narrow. While this does simplify the ordering of drinks (i.e., “I’ll have the usual”), the narrow drinking repertoire is an alcohol drinking style that, according to STM will encourage problem drinking, due to the development of sign-tracking. This is because alcohol’s rewarding effects are only experienced after the cocktail glass has been experienced, making the cocktail glass an excellent cue that is highly predictive of alcohol reward. The cocktail glass will, therefore, readily elicit sign-tracking, resulting in reflexive acts of automatic and unintended alcohol drinking. Therefore, due to sign-tracking the narrow drinking repertoire will be associated with binge episodes of excessive alcohol drinking and elevated rates of problem drinking.
Addiction nosologists studying the progression into alcoholism have confirmed the longitudinal trend toward the narrowing of the drinking repertoire (Cottler, Phelps, & Compton, 1995; Jellinek, 1960; McCreary, 2002). Eventually, alcohol is consumed only in the form of a favorite alcoholic beverage that is served only in a particular form of glassware. This alcohol drinking style eventually becomes a ritual that has been noted to presage the nosological progression into more frequent episodes of excessive and poorly controlled alcohol drinking (Jellinek, 1960). The link between the narrowing of the drinking repertoire and the subsequent onset of problem drinking is consistent with the hypothesis that the CAM arrangement, and, consequently, the induction of sign-tracking, contributes to poorly controlled alcohol drinking in humans.

Additional evidence consistent with the CAM hypothesis is provided by cultural anthropologists who noted higher rates of problem drinking in Northern Europe, as compared to Mediterranean Europe, even though the per capita consumption of alcohol in those regions is comparable (de Lint, 1973; Heath, 1987). While there are many cultural aspects of alcohol drinking that may contribute to these regional disparities in problem drinking rates, it should be noted that the types of glassware used to consume alcoholic beverages differ across regions and in accordance with predictions by the CAM hypothesis. Northern European cultures have widely adopted a style of drinking alcohol almost exclusively from specialized containers, including lead crystal stemware, goblets, and flutes, as well as metal ware in the form of beer mugs and ale steins.

This style of drinking is in contrast to Mediterranean Europe, where alcohol is often consumed from common everyday glassware of the sort typically used to consume water or other non-alcoholic beverages (Levin, 1990). The common glassware is a poor alcohol cue because it is often present even though alcohol's effects are not, and, therefore, the common glassware is less likely to elicit sign-tracking. The link between specialized glassware and elevated rates of problem drinking is consistent with the hypothesis that CAM-induced sign-tracking contributes to the loss of control of alcohol drinking in humans.

If problem drinking in humans is partially due to CAM-induced sign-tracking of alcohol drinking, then an effective therapeutic remedy would be to reduce the cue value of the glassware used to consume alcoholic beverages. For example, consider the effects of pouring your favorite alcoholic beverage into a soup bowl. The soup bowl, that presumably has
never been used to drink an alcoholic beverage, will be unlikely to trigger sign-tracking of alcohol drinking, so that the alcohol consumed will be limited to that which was intended. Another remedy to correct excessive drinking would consist of using your favorite specialized alcohol glassware to drink non-alcoholic beverages, such as milk, soft drinks, fruit juice, and vegetable smoothies. This practice will reduce the cue value of that glassware as a signal for alcohol reward, making your favorite specialized alcohol glassware less effective as a trigger. In addition, by using common tools unrelated to alcohol drinking, the entire ritual of consumption would be disrupted, thereby making the process much less familiar and enjoyable. In summary, evidence from studies of cross-cultural drinking styles reveals that problem drinking rates vary directly with the cue value of the container used to consume alcoholic beverages. This is consistent with the CAM hypothesis and suggests that problem drinking in humans, that has been interpreted as voluntary alcohol drinking performed to excess, is in part due to sign-tracking of alcohol drinking. This reflexive and excessive use of alcohol is camouflaged by CAM to pass for operant alcohol self-administration. Thus, a good recipe for the induction of problem drinking in humans is CAM.

Addiction Scotoma

A visual scotoma is a blind spot in the visual field, due to a floater, a cataract, or other physical obstruction in the eye. A mental or psychological scotoma is a blind spot in our perception, in the way we view reality. It is, therefore, in a sense, a denial of reality. The denial of reality is a losing proposition that pits our perception against what is true. This is a battle that we can never win. In any dispute with reality, we must lose eventually (Paul, 2017). Such is the case with drug addiction, where turning a blind eye toward the loss of self-control can only make matters worse. The question remains, why is the addiction blind spot so prevalent? Why are we unable to realize that we are losing control of our drug-taking? Part of the problem is our tendency to see things as they were before. Early in the process, when drug use was initiated, drug-taking was strictly voluntary and intended, so that these repetitions of voluntary acts of operant drug-taking provided us with
a presented pattern. Factors related to representational momentum and
cognitive momentum favor forward projected displacements that continue
With regard to drug-taking, the repetitions of voluntary acts of operant
drug-taking clearly provide the presented pattern, so that additional
instances of drug-taking are likely to be seen as the mere continuation of
this previously established pattern. Due to cognitive momentum, the user is
biased to see drug-taking as voluntary and intended, regardless of whether
the drug-taking was an operant or a sign-tracking CR. The previously well-
established presented pattern of voluntary and intended drug-taking
influences the user to see sign-tracking but mistake it as more of the same.
We are blind to the influence of sign-tracking because of the strong
expectation formed by the previously presented pattern of voluntary drug
use.

When it comes to recognizing we are losing control of our drug-taking,
another part of the problem, is the “illusion of control,” our inclination to
overestimate our ability to exercise control over events in our lives (Chapin
& Coleman, 2009; Gouveia & Clark, 2001). The illusion of control is consistent
with a pervasive optimistic bias that fuels the ego-hypertrophic
overconfidence that causes the user to fail to internalize risk (Kendler,
Prescott, Myers, & Neale, 2003; Leyton & Stewart, 2014). The overconfident
user believes that the risk of losing control of drug-taking is something that
may happen to others, but it will never happen to them. They are in denial of
how much is at risk. The illusion of control biases the user to see themselves
as always in control of their drug-taking, and this is the case even when there
is evidence that suggests self-control failure. Due to the overconfidence
instilled by the illusion of control, the user’s perception will be biased so as
to be highly resistant to the possibility they may lose control of their drug-
taking.

To explain this overconfidence, Kahneman (2011) has introduced a concept
that he labels What You See Is All There Is (WYSIATI). According to this
theory, when the mind draws a conclusion, it deals primarily with what it
knows. These are the phenomena that the mind has already observed, that
is, Known Knowns. In the case of addiction, the Known Knowns are the
previously performed acts of drug-taking, which were uniformly voluntary
and intended. Thus, the mind concludes that acts of drug-taking are
voluntary and intended actions. The mind rarely considers Known
Unknowns, phenomena that it knows to be relevant but about which it has
no information. An example of Known Unknowns is when the mind has been warned of triggers, or has heard of addiction, but lacks understanding of how they actually work. Finally, the mind is completely oblivious to the possibility of Unknown Unknowns, which are unknown phenomena of unknown relevance, such as sign-tracking. Thus, early on, according to WYSIATI, the pattern of voluntary and intended drug-taking establishes the Known Knowns as the set of possible exemplars of drug-taking forms. It follows, therefore, that all acts of drug-taking that you witness appear to be of this sort, that is, intended and voluntary. This is so because, with respect to drug-taking, intended and voluntary drug-taking are perceived as all there is.

A psychological scotoma is a mental activity in which one locks on to one idea and excludes all others. For example, the idea that I am in control of my drug-taking is locked in, while all other possibilities are locked out. In this way, I protect what I wish to maintain as my truth, even if it is not true. The addiction blind spot, the psychological scotoma, that leads the user to be unable to recognize that they are losing control of their drug-taking, is likely to develop because many of the predisposing factors that favor the development of the scotoma are present. For example, (1) representational momentum and cognitive momentum favor forward projected displacements that continue the presented pattern of well-controlled drug-taking, and; (2) the illusion of control biases the ego-hypertrophic and overconfident user to overestimate their control of their drug-taking, while failing to internalize the risk of losing self-control, and; (3) because of WYSIATI, the user sees voluntary and intended drug-taking and concludes that, going forward, voluntary and intended drug-taking is all there is.

These psychological factors relate to the processing and filtering of the mind's representations of reality. They do not act alone. They interact with the physical properties of the drug use environment (drug rewards) that produce operant drug-taking through the use of a conduit, which, in turn, induces sign-tracking of drug-taking, so that voluntary and reflexive drug-taking responses resemble each other and are targeted at the same location (CAM). The addiction blind spot, therefore, is created by the confluence of several factors that work together to blur the acuity necessary to distinguish reflexive acts of drug-taking from those that are intended.

The blind spot increases the risk of addiction by concealing the evidence from the user that they are losing control of their drug-taking, while simultaneously, increasing their use of the drug. The remedy for this situation is to develop tools to boost the user's awareness of and ability
to recognize the loss of self-control, and how the loss of self-control of drug-taking contributes to the development of drug addiction. Levitch, Marcinkowski-Paulis, and Tomie (this volume) report that telling stories about sign-tracking is an effective tool for boosting awareness of self-control and how the loss of self-control relates to drug addiction in 9th–12th grade students. Although psychological scotoma obscures the detection of these factors, our objective is to arm the casual drug user with knowledge of sign-tracking which will reveal the stealthy aspects of the drug addiction process. By boosting awareness of the difference between voluntary operant drug-taking as opposed to reflexive sign-tracking of drug-taking, the drug user will be able to more quickly recognize the early indications that freedom of choice is slipping away and is being replaced by an automatic and reflexive form of drug use.

References


Bitgood, S., Segrave, K., & Jenkins, H. (1976). Verbal feedback and the feature-


approach and contact behavior toward signals for food or brain-stimulation reinforcement. *Science*, 177(4053), 1009–111. doi:10.1126/science.177.4053.1009.


3. The Neurobiological Mechanisms Underlying Sign-Tracking Behavior

Brittany N. Kuhn, a Paolo Campus, b Shelly B. Flagel*,a–c

aNeuroscience Graduate Program
bDepartment of Psychiatry
cMolecular and Behavioral Neuroscience Institute, the University of Michigan, Ann Arbor, MI 48109

Corresponding Author:
Shelly B. Flagel, PhD, 205 Zina Pitcher Place, Ann Arbor, Michigan, 48109-0720; e-mail: sflagel@umich.edu; phone: 734-936-2033; fax: 734-647-4130.

Abstract

Pavlovian learning processes can render cues and contexts associated with drug-taking experiences into powerful motivators, such that exposure to such stimuli can elicit drug-seeking behavior and relapse. However, there is considerable individual variation in the extent to which a reward cue can gain control over behavior. The sign-tracker (ST)/ goal-tracker (GT) animal model provides a means to capture this individual variation and study the underlying psychological and neurobiological processes. For both phenotypes, a reward cue acquires predictive value and elicits a conditioned response, but only for STs does it also acquire incentive value. That is, for STs the reward cue becomes an incentive stimulus, or a “motivational magnet.” Relative to GTs, STs are also more impulsive on tests of impulsive action, show greater motivation to work for cocaine, and show greater drug-seeking behavior during tests for cue- and cocaine-induced reinstatement. Using this model, we are able to
interrogate the neurobiological mechanisms underlying both the propensity to attribute incentive salience to reward cues and the associated addiction-related behaviors. Research thus far has shown that sign-tracking is a dopamine-dependent process that relies on subcortical circuitry, including the hypothalamic-thalamic-striatal pathway. Conversely, goal-tracking behavior is driven by cortical cognitive processes. Furthermore, differences in neurotransmitter systems, including dopamine and acetylcholine, appear to contribute to the distinct neural circuits mediating sign- and goal-tracking behavior. Taken together, we believe that an imbalance between “top-down” cortical processing relative to “bottom-up” subcortical processing is responsible for the behavioral phenotypes of sign- and goal-trackers, including addiction vulnerability and relapse propensity.

Keywords: goal-tracking; incentive salience; individual differences; motive circuit; paraventricular nucleus of the thalamus; sign-tracking; top-down control

Introduction

Associative learning strategies are often advantageous as they result in the recognition of cues in the environment that reliably predict resources needed for survival, such as food. These cue-reward associations are partially governed by Pavlovian learning processes, whereby a cue in the environment that precedes the delivery of a reward (unconditioned stimulus, US) becomes a conditioned stimulus (CS). While a CS has predictive value, it can also acquire incentive motivational value, thereby being transformed into an incentive stimulus or a “motivational magnet” (Robinson & Berridge, 1993). This process is known as incentive salience attribution and is believed to contribute to addiction (Berridge & Robinson, 2016; Robinson & Berridge, 1993). For example, cues in the environment (people, places, paraphernalia) previously associated with the drug-taking experience can become incentive stimuli and gain excessive control over behavior. Exposure to these stimuli, therefore, can elicit drug-seeking and drug-taking behavior and cause one to relapse in spite of the desire to remain abstinent. Thus, a better understanding of the neural processes underlying incentive salience
attribution may lead to more effective treatments for addiction and the prevention of relapse.

To elucidate the neurobiological mechanisms underlying incentive salience attribution, we use an animal model that allows us to dissociate the predictive value from the incentive motivational value of a reward cue. This model, known as the sign-tracker (ST)/goal-tracker (GT) model, is illustrated in Figure 3.1 and described in greater detail in Chapter 1 of this book. While STs and GTs differ in their conditioned responses (CR), both phenotypes learn their respective CRs at the same rate and consume the food reward. Additionally, compared to GTs, STs work harder for the presentation of the lever-cue in the absence of the food reward (Robinson & Flagel, 2009). Thus, while the lever-cue is a predictor and elicits a conditioned response for both STs and GTs, only for STs does it also become an incentive stimulus.

Figure 3.1. Rats undergo Pavlovian conditioned approach training whereby an illuminated lever (conditioned stimulus, CS) is inserted into the testing chamber for 8 seconds and immediately upon its retraction a food reward (unconditioned stimulus, US) is delivered to the food cup. At the conclusion of training, rats are characterized as sign-trackers (STs) or goal-trackers (GTs). (a) STs are those who are attracted to and manipulate and engage with the lever-CS during its presentation; whereas, (b) GTs are those who upon lever-CS presentation orient toward the CS, but then immediately go to the food cup to await reward delivery. While the lever-CS is a predictor and elicits a conditioned response for both STs and GTs, only for STs is it also attributed with incentive value and thereby transformed into a “motivational magnet.”
Importantly, sign-trackers attribute enhanced incentive motivational value to both food- and drug-associated cues and will sign-track to discrete cues associated with cocaine (Yager & Robinson, 2013) and opioids (Yager, Pitchers, Flagel, & Robinson, 2015). In addition, relative to GTs, STs have been found to work harder for the delivery of cocaine (Saunders & Robinson, 2011) and show greater drug- and cue-induced drug-seeking behavior, or enhanced propensity for relapse, following limited drug exposure and a period of abstinence (Saunders & Robinson, 2010; Saunders, Yager, & Robinson, 2013; see also Robinson et al., this volume). The sign-tracker/goal-tracker animal model, therefore, supports the long-standing notion that Pavlovian incentive learning processes contribute to addiction-related behaviors (Bindra, 1978; Bolles, 1972; Robinson & Berridge, 1993; Stewart, de Wit, & Eikelboom, 1984; Toates, 1981) and provides a means to parse the underlying neurobiological mechanisms. The remainder of this chapter will highlight the neural circuits and associated neural processes believed to play a role in the propensity to attribute incentive motivational value to reward cues.

Neurobiology of Motivated Behavior

The brain is structurally and functionally divided into several regions, some of which communicate directly with one another through the synaptic connections of neurons (see Figure 3.2). Neurons can become activated in response to stimuli in the outside world, such as cues that are associated with rewards, and/or in response to chemical signals released into its surrounding environment in the brain. When a neuron becomes activated, it causes a cascade of reactions within the cell such as the production of gene transcripts and proteins, which can be measured. For example, c-fos, an immediate early gene that is “immediately” produced upon neuronal activation, can be quantified in specific brain regions and used to determine the activity of said brain region in response to certain stimuli or in association with a given behavior (for review see Kovacs, 1998). Additionally, when neurons become activated, they release various chemicals that can bind to receptors on surrounding cells, thereby influencing the activity of neighboring neurons. These chemicals, such as dopamine and acetylcholine,
can be measured, and their fluctuations associated with different behaviors. Indeed, such chemicals have distinct effects in different brain regions, so examining the chemical profile of a given brain region in response to environmental stimuli can further our understanding of how that region is contributing to behavior.

Brain regions can work in concert with one another, creating a neurocircuit that mediates behavior (Figure 3.2). The “motive circuit” is a set of cortical and subcortical nuclei that integrate information regarding a motivationally salient event, such as the presentation of a reward cue, and guide subsequent behavior (Kalivas & Volkow, 2005). Cortical structures, such as the prefrontal cortex (PFC), govern executive functions in the brain (for review see Diamond, 2013; Fuster, 2001; Jurado & Rosselli, 2007; Nyberg, 2018). The PFC is believed to exert “inhibitory control,” allowing one to attend only to the most meaningful stimuli and thereby mediate goal-directed behavior (for review see Asplund, Todd, Snyder, & Marois, 2010; Mihindou, Guillem, Navailles, Vouillac, & Ahmed, 2013; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). For example, students need to rely on this “inhibitory control” exerted by the PFC in order to focus on what they are learning in class, perhaps in lieu of attending to their phone. In contrast to cortical structures, subcortical structures tend to mediate aspects of emotions such as fear and reward (for review see Baxter & Murray, 2002; Davis, 1992; Shin & Liberson, 2010), autonomic functions such as hunger and sleep (Dietrich & Horvath, 2013; for review see Salin-Pascual, Gerashchenko, Greco, Blanco-Centurion, & Shiromani, 2001) and different forms of learning (for review see Baxter & Murray, 2002; Daniel & Pollmann, 2014; Liljeholm & O’Doherty, 2012). Nuclei throughout the cortical and subcortical components of the motive circuit communicate with one another to mediate various aspects of motivated behavior, ranging from encoding the value of the reward to determining the correct behavioral output to obtain that reward (for review see Kalivas & Volkow, 2005). Thus, it is not surprising that dysregulation of this circuit contributes to addiction and relapse (Kalivas & Volkow, 2005).
Figure 3.2. A simplified schematic view of the brain circuitry involved in mediating individual variation in cue-motivated behaviors. All of the brain regions listed have been identified as part of the “reward” or “motive” circuits of the brain, and those highlighted in yellow have specifically been investigated for their role in incentive salience attribution. Dotted lines indicate known connections between brain areas and solid lines are proposed circuits regulating the behavior of goal-trackers (red) and sign-trackers (blue). The behavior of goal-trackers is thought to be mediated via “top-down” cognitive control processes; whereas that of sign-trackers is mediated via “bottom-up” subcortical processes. As indicated in the main text, we believe that it is an imbalance between the “top-down” versus “bottom-up” processes that contributes to each of the extreme phenotypes. The following references support the involvement of those nuclei highlighted in yellow (Ahrens, Meyer, Ferguson, Robinson, & Aldridge, 2016; Chang, Wheeler, & Holland, 2012; Danna, Shepard, & Elmer, 2013; DiFeliceantonio & Berridge, 2016; Fitzpatrick, Creeden, Perrine, & Morrow, 2016; Flagel, Cameron, Pickup, Watson, Akil, & Robinson, 2011a; Flagel, Clark, Robinson, Mayo, Czuj, Willuhn, Akers, Clinton, Phillips, & Akil, 2011b; Haight, Fuller, Fraser, & Flagel, 2017; Stringfield, Palmatier, Boettiger, & Robinson, 2017; Yager, Pitchers, Flagel, & Robinson, 2015).

Abbreviations: ACC, anterior cingulate cortex; BLA, basolateral amygdala; CeA, central nucleus of the amygdala; CeM, central medial nucleus of the thalamus; dHPC, dorsal hippocampus; DLS, dorsolateral striatum; DMH, dorsomedial nucleus of the hypothalamus; DMS, dorsomedial striatum; DRN, dorsal raphe nucleus; IL, infralimbic cortex; IMD, intermediodorsal nucleus of the thalamus; LA, lateral amygdala; LH, lateral hypothalamus; LHb, lateral habenula; LC, locus coeruleus; MeA, medial nucleus of the amygdala;
STs and GTs differ in the extent to which they rely on the motive circuit, such that, in response to a discrete food- or drug-associated cue, STs show greater neuronal activation (i.e., c-fos expression) throughout this circuit (Flagel, Cameron, Pickup, Watson, Akil, & Robinson, 2011a; Yager, Pitchers, Flagel, & Robinson, 2015). That is, only when the reward cue is attributed with incentive salience (i.e., in STs) does it activate the cortico-striatal-thalamic motive circuit. Furthermore, when patterns of neuronal activity were examined between brain regions for a given phenotype, correlated activity was found between the cortical and subcortical areas for GTs, whereas for STs the correlated patterns of activity were restricted to subcortical regions (Flagel, Cameron, Pickup, Watson, Akil, & Robinson, 2011a). As reviewed later in the text, these data, as well as more recent findings (Flagel & Robinson, 2017; Haight, Fuller, Fraser, & Flagel, 2017; Sarter & Phillips, 2018), suggest that GTs rely on “top-down” cortical processes to inhibit the propensity to attribute incentive salience to reward cues; whereas enhanced “bottom-up” subcortical drive in STs increase that propensity.

“Top-Down” Cortical Control

Goal-trackers are believed to have greater top-down attentional control than STs, and it has been postulated that a “deficit” in this top-down control contributes to the sign-tracking phenotype (for review see Sarter & Phillips, 2018). In support, GTs perform better than STs on tasks that demand more cortical control, including those associated with impulse control (Flagel, Robinson, Clark, Clinton, Watson, Seeman, Phillips, & Akil, 2010; Lovic, Saunders, Yager, & Robinson, 2011) and sustained attention (Paolone, Angelakos, Meyer, Robinson, & Sarter, 2013). Next we will review the neurobiological mechanisms that have been associated with this proposed...
“deficit” in cortical control and attentional processing in sign-trackers and discuss the implications of these findings in regards to addiction.

Prefrontal Cortex

Role of Cortical Cholinergic Activity in Sign-Trackers and Goal-Trackers

As previously discussed, the PFC mediates top-down executive control in the brain, thereby maintaining goal-directed behaviors (Asplund, Todd, Snyder, & Marois, 2010; Mihindou, Guillem, Navailles, Vouillac, & Ahmed, 2013; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). That is, the PFC acts to selectively guide attention such that the focus is on the task at hand and not on “irrelevant” cues in the surrounding environment. The ability to maintain performance on tasks that demand sustained attention is associated with increases in acetylcholine (ACh) activity within the PFC (St Peters, Demeter, Lustig, Bruno, & Sarter, 2011). On such a task, STs show poor performance relative to GTs and concomitantly exhibit attenuated task-related increases in PFC ACh levels (Paolone, Angelakos, Meyer, Robinson, & Sarter, 2013). Furthermore, when an ACh receptor agonist is administered, thereby increasing ACh levels within the brain, STs show improvement on attentional performance (Paolone, Angelakos, Meyer, Robinson, & Sarter, 2013). Thus, it is believed that lower attentional performance in STs is due to lower levels of cortical ACh compared to GTs (Paolone, Angelakos, Meyer, Robinson, & Sarter, 2013). Importantly, however, the differences in ACh levels between STs and GTs are not apparent under baseline conditions and only evident under stimulated conditions, such as task-performance (Paolone, Angelakos, Meyer, Robinson, & Sarter, 2013). Such deficits in cortical cholinergic modulation in STs have recently been attributed to the inability to transport choline, the precursor of ACh, into the neurons that produce and release it (Koshy Cherian, Kucinski, Pitchers, Yegla, Parikh, Kim, Valuskova, Gurnani, Lindsley, Blakely, & Sarter, 2017). In support, when the transport of choline into neurons is blocked early in Pavlovian training, sign-tracking behavior increases while goal-tracking behavior decreases (Koshy
Thus, it has been suggested that the lack of top-down executive control in STs is, at least in part, driven by inefficient mechanisms at the cortical cholinergic transporter, resulting in a bias for bottom-up or stimulus-driven attention (Koshy Cherian, Kucinski, Pitchers, Yegla, Parikh, Kim, Valuskova, Gurnani, Lindsley, Blakely, & Sarter, 2017). Cortical ACh levels are also differentially affected by the presentation of a Pavlovian cocaine cue in STs versus GTs, as are cortical dopamine levels (Pitchers, Kane, Kim, Robinson, & Sarter, 2017). In STs, cocaine cue presentations elicit approach behavior and elevate dopamine levels in the PFC, while ACh levels remain unchanged. Interestingly, cue-elicited increases in dopamine levels correlate with higher levels of approach to the cocaine cue (Pitchers, Kane, Kim, Robinson, & Sarter, 2017), suggesting that cortical dopamine plays a role in encoding the incentive motivational value of the cue (but see also Ellwood, Patel, Wadia, Lee, Liptak, Bender, & Sohal, 2017). Conversely, in GTs, presentation of the cocaine cue does not elicit approach and does not affect dopamine levels but does increase ACh levels (Pitchers, Kane, Kim, Robinson, & Sarter, 2017). Importantly, PFC ACh levels are not correlated with cue-elicited behaviors. These data highlight the involvement of distinct cortical processes in regulating the behavior of STs and GTs and demonstrate a role for PFC dopamine levels in mediating the incentive motivational value of reward cues.

Conversely, the lack of cue-elicited changes in cortical dopamine levels, concurrent with increased ACh, support the notion that GTs rely on dopamine-independent cognitive processes to encode the meaning or value of reward cues (Dickinson & Belleine, 2002; Flagel, Clark, Robinson, Mayo, Czuj, Willuhn, Akers, Clinton, Phillips, & Akil, 2011b; Sarter & Phillips, 2018). That is, for GTs, as a function of enhanced cortical processing, a discrete reward cue is merely an “informational” stimulus that is relatively devoid of incentive properties (Flagel, Cameron, Pickup, Watson, Akil, & Robinson, 2011a). Thus, GTs exhibit goal-directed approach to the location of impending reward delivery if the reward cue is food and explicitly do not approach drug-associated cues when no alternative behavioral response is available (i.e., when the drug reward is delivered intravenously). Furthermore, these distinct cortical processes inherent to sign- and goal-trackers are believed to contribute to the enhanced attention to contextual cues that is characteristic of GTs (Pitchers, Phillips, Jones, Robinson, & Sarter, 2017b; Saunders, O'Donnell, Aurbach, & Robinson, 2014).
Contexts and discriminative stimuli are powerful motivators for drug relapse and are inherently more complex than a discrete cue signaling reward availability. Indeed, a context is defined as an environment where no single cue predicts reward availability but rather the compilation of cues together does so. For example, the environmental context of a bar includes the smell of alcohol, the sight of frosty mugs, the sound of music, the presence of friends, and so on. Discriminative stimuli within this context may include the flashing neon sign indicating the bar is “open”; that is, a cue that signifies whether or not the presentation of a subsequent cue will be followed by a reward. Given the complexity of such stimuli, it is perhaps not surprising that GTs seem to be more responsive to contextual cues and discriminative stimuli (Pitchers, Phillips, Jones, Robinson, & Sarter, 2017b; Saunders, O’Donnell, Aurbach, & Robinson, 2014). In fact, GTs show greater drug-seeking behavior upon exposure to drug-associated contexts (Saunders, O’Donnell, Aurbach, & Robinson, 2014) or discriminative stimuli previously associated with drug availability (Pitchers, Phillips, Jones, Robinson, & Sarter, 2017b). Moreover, when cholinergic transmission is attenuated in the PFC, GTs no longer show higher rates of drug-seeking behavior compared to STs in the presence of discriminative stimuli (Pitchers, Phillips, Jones, Robinson, & Sarter, 2017b). Thus, while elevated cortical ACh levels appear to inhibit the attribution of incentive motivational value to a cocaine cue, these same processes appear to make GTs more vulnerable to context-induced relapse. These data suggest that both STs and GTs are vulnerable to addiction (Kawa, Bentzley, & Robinson, 2016), or relapse (Kuhn, Klumpner, Covelo, Campus, & Flagel, 2017; Pitchers, Phillips, Jones, Robinson, & Sarter, 2017b; Saunders, O’Donnell, Aurbach, & Robinson, 2014; Saunders & Robinson, 2011; Saunders, Yager, & Robinson, 2013) but via different psychological and neurobiological pathways.

Role of Serotonin in Pavlovian Conditioned Approach Behavior and Incentive Motivational Learning

In addition to acetylcholine, serotonin levels in the PFC have also been shown to play a role in sign-tracking behavior (Campus, Accoto, Maiolati, Latagliata, & Orsini, 2016; Winstanley, Dalley, Theobald, & Robbins, 2004). Serotonergic neurons originate in the dorsal raphe nucleus and project
widely throughout the brain, including to the PFC (Michelsen, Prickaerts, & Steinbusch, 2008; Vertes, 1991). Serotonin has a wide range of functions within the brain, including mediating mood and appetite (for review see Mohammad-Zadeh, Moses, & Gwaltney-Brant, 2008). Increases in serotonin levels in the PFC, but not striatum, have been reported following Pavlovian training, therefore demonstrating a role of PFC serotonin in appetitive Pavlovian tasks (Tomie, Tirado, Yu, & Pohorecky, 2004). Furthermore, Pavlovian training results in an increase in the binding of serotonin to the serotonin 1a and 2a receptors within the PFC (Tomie, Di Poce, Aguado, Janes, Benjamin, & Pohorecky, 2003). When serotonin is depleted from the forebrain, rats approach a reward cue (i.e., sign-track) more often and do so faster compared to control rats (Winstanley, Dalley, Theobald, & Robbins, 2004). Additionally, when approaches to the reward cue no longer result in delivery of the food reward, rats with serotonin depletion continue to approach the reward cue to a greater extent than control rats (Winstanley, Dalley, Theobald, & Robbins, 2004). These data suggest that serotonin is not only contributing to the appetitive learning associated with Pavlovian training but also to the incentive motivational value of the reward cue. In agreement with these findings, it was found that depleting serotonin specifically within the medial PFC increases sign-tracking behaviors in mice (Campus, Accoto, Maiolati, Latagliata, & Orsini, 2016). Taken together, these data support a role of serotonin transmission within the PFC in mediating aspects of incentive motivational learning (Pentkowski, Duke, Weber, Pockros, Teer, Hamilton, Thiel, & Neisewander, 2010) and addiction-related behaviors (Anastasio, Liu, Maili, Swinford, Lane, Fox, Hamon, Nielsen, Cunningham, & Moeller, 2014; Swinford-Jackson, Anastasio, Fox, Stutz, & Cunningham, 2016).

“Bottom-Up” Subcortical Control

Whereas goal-trackers are thought to rely primarily on “top-down” cortical mechanisms to guide their goal-directed behaviors, sign-trackers are believed to have enhanced “bottom-up” processing, as a function of increased activity in subcortical regions, including the striatum, amygdala, midline thalamus, and hypothalamus (Flagel, Cameron, Pickup, Watson, Akil, ...
Moreover, cue-induced activity is correlated only between subcortical regions in sign-trackers, such that activity in midline thalamic nuclei correlates with neuronal activity in the ventral striatum (Flagel, Cameron, Pickup, Watson, Akil, & Robinson, 2011a; Haight, Fuller, Fraser, & Flagel, 2017). Next we highlight some of the subcortical regions and associated neural mechanisms that appear to play an important role in mediating the propensity to attribute incentive salience to reward cues (see also Figure 3.2).

**Striatum: Dopaminergic Regulation of Incentive Motivational Learning**

**Ventral Striatum**

The nucleus accumbens (NAc), a region within the ventral striatum, is a key component of the motive circuit (Kalivas & Volkow, 2005). The NAc receives dense dopaminergic projections from the ventral tegmental area, and this pathway, known as the mesolimbic pathway, plays an important role in reward-related processes (for review see Salamone & Correa, 2012; Volkow, Wise, & Baler, 2017). Over the course of Pavlovian learning, STs and GTs show differences in the mesolimbic dopamine system, with emergent differences in gene expression (Flagel, Watson, Robinson, & Akil, 2007) and distinct patterns of phasic dopamine release in the nucleus accumbens (Flagel, Clark, Robinson, Mayo, Czuj, Willuhn, Akers, Clinton, Phillips, & Akil, 2011b). Phasic dopamine transmission in the NAc is known to be triggered initially by the receipt of a reward-US, but then, upon learning an association between a cue-CS and reward-US, the dopamine response shifts to the predictive-cue-CS (Day, Roitman, Wightman, & Carelli, 2007; Schultz, Dayan, & Montague, 1997). This pattern of dopamine activity is believed to support the “prediction error theory”; that is, that dopamine is acting primarily to encode the discrepancy between rewards received and those predicted (Montague, Dayan, & Sejnowski, 1996; Waelti, Dickinson, & Schultz, 2001). Thus, an unpredicted reward initially elicits an increase in dopamine activity,
or positive prediction error; a fully predicted reward elicits no response to the reward itself; and the omission of a predictive reward results in a decrease in dopamine activity, or negative prediction error (Schultz, Dayan, & Montague, 1997). The prediction error theory, therefore, suggests that dopamine is used to update the predictive value of stimuli during associative learning and thereby guide cue-elicited behaviors (Balleine, Daw, & O'Doherty, 2008).

In contrast to the prediction error theory, others have long postulated that dopamine acts to encode the incentive motivational value of reward cues (Berridge, 2007; Berridge & Robinson, 1998). Until the advent of the sign-tracker/goal-tracker model, however, it was difficult to parse the processes underlying predictive versus incentive learning, as the two were confounded in the majority of studies (for review see Robinson, Yager, Cogan, & Saunders, 2014). Thus, the sign-tracker/goal-tracker model was exploited to address the long-standing debate in the field regarding the role of dopamine in reward learning. Using fast-scan cyclic voltammetry, which allowed the detection of dopamine on a sub-second time scale, Flagel, Clark and colleagues examined phasic dopamine release in the core subregion of the nucleus accumbens (NAcC) in response to cue and reward presentation in STs and GTs during Pavlovian training (Flagel, Clark, Robinson, Mayo, Czuj, Willuhn, Akers, Clinton, Phillips, & Akil, 2011b). The NAcC was examined as it is considered a central locus for the dopamine-mediated effects of Pavlovian learning (Dalley, Laane, Theobald, Armstrong, Corlett, Chudasama, & Robbins, 2005; Di Ciano, Cardinal, Cowell, Little, & Everitt, 2001; Parkinson, Dalley, Cardinal, Bamford, Fehnert, Lachenal, Rudarakanchana, Halkerston, Robbins, & Everitt, 2002; Parkinson, Olmstead, Burns, Robbins, & Everitt, 1999). Flagel, Clark, and colleagues found that the “classic” prediction-error shift in dopamine from the reward-US to the cue-CS occurs only in STs. That is, in GTs, the dopamine response does not differ between cue and reward presentation over the course of learning. Given that the reward cue (CS) is a predictor and elicits a conditioned response for both STs and GTs, these data demonstrate that the shift in phasic dopamine must be encoding the incentive value of the cue and not the predictive value (Flagel, Clark, Robinson, Mayo, Czuj, Willuhn, Akers, Clinton, Phillips, & Akil, 2011b). In support, when dopamine transmission is blocked via systemic administration of flupenthixol, a nonselective dopamine antagonist, the learning and expression of a sign-tracking response, but not goal-tracking, is attenuated (Flagel, Clark, Robinson, Mayo, Czuj, Willuhn, Akers, Clinton,
Phillips, & Akil, 2011b). A subsequent study expanded upon these findings demonstrating specifically that dopamine in the NAcC is necessary for the expression of sign-tracking and not goal-tracking behavior (Saunders & Robinson, 2012). Thus, sign-tracking is dopamine-dependent, and dopamine in the nucleus accumbens appears to be critical for incentive learning processes.

Dopamine transmission within the NAcC also plays an important role in individual variation in the propensity to relapse, or cue-induced reinstatement (Saunders, Yager, & Robinson, 2013). During a test for cue-induced reinstatement, the action (e.g., nose poke) that previously resulted in the presentation of the drug and associated drug-paired cue, now results in cue presentation without drug delivery. Thus, rats are responding based on the conditioned reinforcing properties of the drug-associated cue, which is thought to be akin to humans reporting craving in response to presentation of drug-associated images (e.g., paraphernalia; Childress, Ehrman, McLellan, & O’Brien, 1988). Indeed, it is most often exposure to such cues that elicits drug-seeking behavior and relapse in humans (Foltin & Haney, 2000; Grusser, Wrase, Klein, Hermann, Smolka, Ruf, Weber-Fahr, Flor, Mann, Braus, & Heinz, 2004; Shaham, Shalev, Lu, de Wit, & Stewart, 2003). Relative to GTs, STs exhibit increased responding during a test for cue-induced reinstatement, and blockade of dopamine transmission in the NAcC significantly attenuates responding in STs, rendering them more like GTs (Saunders, Yager, & Robinson, 2013). In contrast, when dopamine concentrations in the NAcC are increased via administration of amphetamine, drug-seeking behavior increases in both STs and GTs (Saunders, Yager, & Robinson, 2013). Taken together, these data support a role for dopamine in encoding the incentive motivational value of reward cues and specifically suggest that dopaminergic transmission within the NAcC is a critical part of the neurobiology underlying cue-induced drug-seeking behavior and the propensity to relapse.

When dopamine is released from a neuron into the extracellular space, mechanisms are in place to remove “excess” dopamine from the synapse. The longer dopamine remains in the extracellular space, the more it can interact with neighboring neurons, causing dysregulation of the system. Dopamine is removed from the synapse and relocated back into the presynaptic cell via dopamine transporters (DATs), which exist on the surface of the presynaptic neuron. Dopamine uptake from the extracellular space in the NAcC has been reported to occur more rapidly in STs compared to GTs, and this is thought
to be a result of more abundant surface DATs in STs (Singer, Guptaroy, Austin, Wohl, Lovic, Seiler, Vaughan, Gnegy, Robinson, & Aragona, 2016). Certain drugs of abuse, such as cocaine and amphetamine, increase synaptic dopamine concentrations by blocking and inhibiting DATs. Amphetamine also reverses the DATs such that more dopamine is being released into the synapse, further intensifying the effects of the drug. Thus, in individuals with more abundant DATs, amphetamine results in more dopamine being released into the synapse, without efficient removal. In support, administration of amphetamine directly into the NAcC causes slower dopamine reuptake in STs compared to GTs (Singer, Guptaroy, Austin, Wohl, Lovic, Seiler, Vaughan, Gnegy, Robinson, & Aragona, 2016). Additionally, NAcC amphetamine infusions result in an increase in sign-tracking behavior in STs, while behavior in GTs remains unaffected. Thus, the upregulation of DATs in STs compared to GTs appears to contribute to the incentive motivational value of reward cues, and certain drugs of abuse have the ability to amplify these effects. These data further support the notion that dopaminergic transmission within the NAcC contributes to sign-tracking behavior and incentive salience attribution, while goal-tracking behavior is not reliant on these processes.

Synaptic dopamine that is not taken up by the dopamine transporter acts on surrounding cells by binding to dopamine receptors. There are five different types of dopamine receptors, and these receptors can be divided into two families with different functions. The D1 family, composed of the dopamine 1 and 5 receptor, result in excitatory processes within the cell; while the D2 family, containing dopamine receptors 2–4, act in an inhibitory fashion (for review see Keeler, Pretsell, & Robbins, 2014). These receptor subtypes are known to mediate different behaviors and are found in both shared and separate circuitries throughout the brain (for review see Keeler, Pretsell, & Robbins, 2014). The D1 receptor has been associated with mediating phasic dopamine release (Dreyer, Herrik, Berg, & Hounsgaard, 2010), and systemic injection of a D1 antagonist attenuates the acquisition of sign-tracking behavior (Clark, Collins, Sanford, & Phillips, 2013). In recent years, the D3 receptor has also been implicated in motivated behaviors and addiction (Le Foll & Di Ciano, 2015) and has been specifically examined for its role in incentive salience attribution. Systemic administration of a D3 receptor antagonist has no effect on the expression of sign- or goal-tracking behavior (Fraser, Haight, Gardner, & Flagel, 2016). However, systemic administration of compounds that act at both D2 and D3 receptors, either as
agonists or antagonists, decrease the conditioned response that had already been learned, whether it is sign- or goal-tracking behavior (Fraser, Haight, Gardner, & Flagel, 2016). These data suggest that D2 receptors, but not D3 receptors, mediate sign- and goal-tracking behaviors, though the mechanism by which this occurs and exactly where in the brain they are acting is still unknown. It should be noted, however, that D2 receptor expression, in the prefrontal cortex as well as the striatum, has been associated with features of addiction in both animals (Briand, Flagel, Garcia-Fuster, Watson, Akil, Sarter, & Robinson, 2008; Flagel, Chaudhury, Waselus, Kelly, Sewani, Clinton, Thompson, Watson, & Akil, 2016) and humans (Asensio, Romero, Romero, Wong, Alia-Klein, Tomasi, Wang, Telang, Volkow, & Goldstein, 2010; Volkow, Wang, Telang, Fowler, Logan, Childress, Jayne, Ma, & Wong, 2006).

Dorsal Striatum

The dorsal striatum, comprised of the caudate and putamen, is also known to play a role in motivation and addiction-related behaviors (B. W. Balleine, Delgado, & Hikosaka, 2007; Volkow, Wang, Fowler, Logan, Jayne, Franceschi, Wong, Gatley, Gifford, Ding, & Pappas, 2002) and has been increasingly recognized for its role in habit formation (for review see Malvaez & Wassum, 2018). Multiple subregions of the dorsal striatum are activated to a greater degree in sign-trackers relative to goal-trackers after presentation of a food- or drug-associated cue (Flagel, Cameron, Pickup, Watson, Akil, & Robinson, 2011a; Yager, Pitchers, Flagel, & Robinson, 2015). One of these subregions, the dorsolateral striatum, has been investigated for its role in incentive salience attribution using the sign-tracker/goal-tracker animal model. When amphetamine is administered directly into this region, the conditioned response of both STs and GTs is amplified, and this is due to increased motivation, not habit formation (DiFeliceantonio & Berridge, 2016). In contrast, however, neither blockade of dopamine signaling within the dorsolateral striatum nor inactivation of this region affects sign-tracking behavior (Fraser & Janak, 2017). This is true with the typical amount of training (i.e., 5 sessions), and persists after prolonged (i.e., 15 sessions) training, when the ventral striatum no longer mediates sign-tracking behavior (Clark, Collins, Sanford, & Phillips, 2013). Thus, although enhanced
dopamine signaling in the dorsolateral striatum can increase the incentive motivational value of a Pavlovian cue, making it a stronger motivational magnet, such incentive motivational processes appear to be dependent on dopamine signaling in the ventral and not the dorsal striatum (Flagel, Clark, Robinson, Mayo, Czuj, Willuhn, Akers, Clinton, Phillips, & Akil, 2011b; Fraser & Janak, 2017; Saunders, Yager, & Robinson, 2013).

Midline Thalamus

Paraventricular Nucleus of the Thalamus

One region that has consistently shown the most robust differences in cue-induced neuronal activation between sign- and goal-trackers is the paraventricular nucleus of the thalamus (PVT) (Flagel, Cameron, Pickup, Watson, Akil, & Robinson, 2011a; Yager, Pitchers, Flagel, & Robinson, 2015). The PVT is a midline thalamic nucleus located in an ideal position to influence motivated behaviors, as it acts as an interface to integrate cortical, emotion, and motor networks, and relays this information to the striatum (Kelley, Baldo, Pratt, & Will, 2005). Although this nucleus has been recognized as being part of the motive circuit for over a decade (Kelley, Baldo, Pratt, & Will, 2005), only recently has it gained attention in mediating addiction-related behaviors (Hamlin, Clemens, Choi, & McNally, 2009; James, Charnley, Jones, Levi, Yeoh, Flynn, Smith, & Dayas, 2010; Kuhn, Klumpner, Covelo, Campus, & Flagel, 2017; Matzeu, Kerr, Weiss, & Martin-Fardon, 2016; Matzeu, Weiss, & Martin-Fardon, 2015). When a lesion to the PVT is made prior to Pavlovian training, effectively taking it “off-line,” sign-tracking behavior is amplified, whereas goal-tracking behavior is attenuated (Haight, Fraser, Akil, & Flagel, 2015). When the lesion is made after rats have acquired their conditioned response, the behavior of sign-trackers is not affected (likely due to a ceiling effect); but in GTs, goal-tracking behavior is decreased and sign-tracking behavior increased (Haight, Fraser, Akil, & Flagel, 2015). These data led us to postulate that the PVT may be acting as a “brake” on the attribution of incentive salience to reward cues. Thus, when the PVT is “off-line,” the incentive motivational value of a reward cue is enhanced.
In support, inactivation of the PVT prior to a test for cue-induced reinstatement significantly increases drug-seeking behavior in GTs, without affecting sign-trackers (Kuhn, Klumpner, Covelo, Campus, & Flagel, 2017). Thus, it appears that the PVT is a central node that mediates the learning and expression of incentive motivational processes and contributes to individual differences in the propensity to relapse.

Indeed, when correlated neuronal activity is considered between brain regions for each phenotype separately, the PVT is highlighted as a common locus that differentially mediates cue-induced responsivity (Flagel, Cameron, Pickup, Watson, Akil, & Robinson, 2011a; Haight & Flagel, 2014). In STs, cue-induced activity in the PVT is correlated with that in the ventral striatum; whereas in GTs, cue-induced activity in the PVT is correlated with subregions of the prefrontal cortex (Flagel, Cameron, Pickup, Watson, Akil, & Robinson, 2011a; Haight & Flagel, 2014). To further explore the PVT-circuitry that might be differentially regulating the behavior of sign- and goal-trackers, we examined cue-induced neuronal activity selectively in neurons that were directly communicating with the PVT (Haight, Fuller, Fraser, & Flagel, 2017). Relative to controls, both STs and GTs exhibit enhanced cue-induced activity in neurons in the prelimbic cortex that project to the PVT. In contrast, however, STs exhibit enhanced cue-induced activity in subcortical areas, including neurons from the lateral hypothalamus and medial amygdala that project to the PVT, and neurons in the PVT that project to the ventral striatum (Haight, Fuller, Fraser, & Flagel, 2017). These data support the notion that enhanced “bottom-up” processing largely contributes to the sign-tracking phenotype. Next we will briefly review parts of the PVT circuitry—both cortical and subcortical—that we believe are playing a critical role in incentive motivational processes.

PVT Circuitry: Cortical Connections

The prelimbic cortex (PrL) is a subregion of the prefrontal cortex that sends the most dense set of glutamatergic projections to the PVT, while receiving reciprocal glutamatergic projections from the PVT (Li & Kirouac, 2012). The PrL is known to be a critical mediator of both drug- and cue-motivated behaviors, including reinstatement of drug-seeking behavior (for review see Di Ciano, Benham-Hermetz, Fogg, & Osborne, 2007; Di Pietro, Black, &
Kantak, 2006; Moorman, James, McGlinchey, & Aston-Jones, 2015). Although cue-induced neuronal activity does not differ between STs and GTs in the PrL (Flagel, Cameron, Pickup, Watson, Akil, & Robinson, 2011a; Yager, Pitchers, Flagel, & Robinson, 2015), correlated activity between the PrL and PVT is evident only in GTs, suggesting that this structure might play a role in differentially mediating the behavioral phenotypes (Flagel, Cameron, Pickup, Watson, Akil, & Robinson, 2011a; Haight & Flagel, 2014). Indeed, these data, in combination with that reviewed earlier indicating that goal-trackers rely on dopamine-independent cognitive learning processes (Flagel, Clark, Robinson, Mayo, Czuj, Willuhn, Akers, Clinton, Phillips, & Akil, 2011b; Paolone, Angelakos, Meyer, Robinson, & Sarter, 2013; Pitchers, Kane, Kim, Robinson, & Sarter, 2017; Pitchers, Phillips, Jones, Robinson, & Sarter, 2017b), led us to hypothesize that the PrL-PVT pathway may play an important role in exerting cognitive control in GTs. Interestingly, however, we found that, in response to a food-associated cue, STs and GTs engage projections from the PrL to the PVT to the same degree (Haight, Fuller, Fraser, & Flagel, 2017). Thus, since the reward cue is a predictor (i.e., it elicits a conditioned response) for both STs and GTs, we concluded that the PrL-PVT circuit likely encodes the predictive qualities of the cue-CS, and that the enhanced subcortical activity in STs is driving the incentive motivational processes (see Figure 3.2).

**PVT Circuitry: Subcortical Connections**

As indicated earlier, we examined differences in cue-induced neuronal activity between STs and GTs in a number of subcortical brain regions that are known to project to the PVT, including subnuclei of the amygdala and multiple subregions of the hypothalamus. The medial amygdala (MeA) is one of the regions in which we found greater cue-induced neuronal activity in STs relative to controls in neurons projecting to the PVT (Haight, Fuller, Fraser, & Flagel, 2017). While little is known about the role of the MeA in appetitive-motivated behaviors, early work demonstrated that rats will bar press for electrical stimulation, or self-stimulate the MeA, suggesting that this nucleus does indeed play a role in reward processing (Kane, Coulombe, & Miliareissis, 1991). However, additional work is needed to elucidate the
function of the MeA in the circuits that appear to be mediating incentive motivational learning (see Figure 3.2).

Neurons in the lateral hypothalamus (LH) that project to the PVT also show greater cue-induced activity in STs relative to GTs and controls (Haight, Fuller, Fraser, & Flagel, 2017; Figure 3.2). The hypothalamus is known to play an important role in the motive circuit, as it is composed of multiple subregions with various key functions (Kelley, Baldo, Pratt, & Will, 2005). While the dorsomedial nucleus regulates autonomic functions such as blood pressure; the LH mediates aspects of motivation, state-dependent arousal, learning and feeding behaviors (for review see Stuber & Wise, 2016; Tyree & de Lecea, 2017). Thus, it is not surprising that the LH may play an important role in incentive motivational processes. The LH sends orexinynergic projections to the PVT (Kirouac, Parsons, & Li, 2005; E. Y. Lee & Lee, 2016; J. S. Lee, Lee, & Lee, 2015), and the role of PVT orexin signaling in addiction-related behaviors has gained increasing attention in recent years (James, Charnley, Levi, Jones, Yeoh, Smith, & Dayas, 2011; Matzeu, Kerr, Weiss, & Martin-Fardon, 2016; Yeoh, Campbell, James, Graham, & Dayas, 2014). For example, blockade of orexin signaling in the PVT prevents cocaine-seeking behavior (Matzeu, Kerr, Weiss, & Martin-Fardon, 2016). In relation, we have found that antagonism of orexin receptors in the PVT attenuates the incentive motivational value of a reward cue and decreases sign-tracking behavior (Campus, Haight, Johnson, Klumpner, Covelo, & Flagel, 2017; Haight, 2016). Thus, orexin signaling in the PVT may be a critical component of the neurobiological mechanisms underlying incentive salience attribution (Figure 3.2).

In addition to examining patterns of cue-induced neuronal activity in regions that send projections to the PVT, we were interested in examining differences in activity in neurons projecting from the PVT to the ventral striatum, a region we know is key in modulating individual differences in reward learning (Flagel, Clark, Robinson, Mayo, Czuj, Willuhn, Akers, Clinton, Phillips, & Akil, 2011b; Saunders, Yager, & Robinson, 2013). As expected, we found that, relative to controls, STs show enhanced cue-induced activity in neurons projecting from the PVT to the NAc (Haight, Fuller, Fraser, & Flagel, 2017). Importantly, the NAc is a main target of PVT projections (Dong, Li, & Kirouac, 2017), and the PVT can independently elicit dopamine release within the NAc (Parsons, Li, & Kirouac, 2007). Furthermore, this pathway from the PVT to the NAc has been implicated in several addiction-related behaviors, including context-induced reinstatement (Hamlin, Clemens, Choi,
& McNally, 2009), long-term effects of cocaine (Neumann, Wang, Yan, Wang, Ishikawa, Cui, Huang, Sesack, Schluter, & Dong, 2016), and opiate dependence (Zhu, Wienecke, Nachtrab, & Chen, 2016). Ongoing work will continue to focus on the role of this pathway in incentive salience attribution, with the hope of elucidating the mechanism by which this circuit influences addiction-related behaviors.

Taken together, the PVT seems to act as a hub that integrates cortical and subcortical information to guide behavior, but it does so to varying degrees in sign- and goal-trackers. Work thus far suggests that STs rely on enhanced hypothalamic-thalamic-striatal circuitry, whereas the behavior of GTs is primarily mediated by cortical-thalamic processes (see Figure 3.2). Our working hypothesis is that the subcortical processes in STs override the cortical control mechanisms, permitting the attribution of incentive salience to reward cues in an excessive manner.

### Hippocampus

While much attention has been focused on the contribution of striatal and thalamic regions in sign- and goal-tracking behavior, other brain regions, such as the hippocampus, have also been implicated in incentive motivational processes (Fitzpatrick, Creeden, Perrine, & Morrow, 2016; Garcia-Fuster, Parsegian, Watson, Akil, & Flagel, 2017). The hippocampus is involved in various types of memory, including that associated with spatial navigation and encoding contextual information (for review see Burgess, Maguire, & O'Keefe, 2002; Martin & Clark, 2007). The hippocampus is often divided anatomically into the ventral (vHPC) and dorsal hippocampus (dHPC), based on differences in function, connectivity, and neurochemistry. For example, it has been shown that lesions of the vHPC affect dopamine activity in the NAc (Lipska, Jaskiw, Chrapusta, Karoum, & Weinberger, 1992), whereas lesions of the dHPC do not (Lipska, Jaskiw, Karoum, Phillips, Kleinman, & Weinberger, 1991). In relation, lesions of the vHPC, but not the dHPC, affect sign-tracking behavior (Fitzpatrick, Creeden, Perrine, & Morrow, 2016). Specifically, lesions of the vHPC prevent the learning of a sign-tracking conditioned response, and concomitantly decrease concentrations of a dopamine metabolite, homovanillic acid (HVA) in the NAc (Fitzpatrick, Creeden, Perrine, & Morrow, 2016). Interestingly, lesions of the vHPC have

Sign Tracking and Drug Addiction | 55
no effect on sign-tracking behavior after the CR is acquired. Taken together, the ventral hippocampus seems to be another structure involved in incentive motivational learning, presumably via its connections to the ventral striatum (Blaha, Yang, Floresco, Barr, & Phillips, 1997; Floresco, Todd, & Grace, 2001; French & Totterdell, 2002).

Ventral Pallidum

The ventral pallidum (VP) has also been investigated for its role in incentive motivational learning, as it is considered a key component of the reward system and motive circuit (for review see Kalivas & Volkow, 2005; Kelley, Baldo, Pratt, & Will, 2005; Smith, Tindell, Aldridge, & Berridge, 2009). The VP is a primary target of NAcC projections and the mesolimbic dopamine system (Heimer & Wilson, 1975) and is thereby necessary for reward processing and motivated behaviors (Smith, Tindell, Aldridge, & Berridge, 2009). Stimulated activation of the VP causes reward and motivation enhancements (Panagis, Miliaressis, Anagnostakis, & Spyraki, 1995; Smith & Berridge, 2005); whereas lesions of this region decrease the motivation for food and drug rewards (Cromwell & Berridge, 1993; Harvey, Foster, McKay, Carroll, Seyoum, Woods, Grey, Jones, McCane, Cummings, Mason, Ma, Cook, & June, 2002; Shimura, Imaoka, & Yamamoto, 2006). Interestingly, neuronal firing in the VP appears to encode different information in STs and GTs (Ahrens, Meyer, Ferguson, Robinson, & Aldridge, 2016). Neurons in this region respond to the presentation of the cue-CS and the food-US in both phenotypes but with different patterns of activation. In GTs, neuronal activity decreases over the course of cue-CS presentation and increases upon delivery of the food reward. In contrast, in STs, neuronal activity remains high during the entire cue-CS presentation period (Ahrens, Meyer, Ferguson, Robinson, & Aldridge, 2016). Furthermore, neural activity in the VP is positively correlated with the degree of attraction to the food cue. Thus, neural activity in the VP seems to encode the incentive motivational properties of reward cues, presumably via its direct relationship with mesolimbic dopamine transmission in the NAcC (Figure 3.2).
Additional Neurobiological Differences between Sign-Trackers and Goal-Trackers

Thalamic Mast Cell Activity

In addition to specific nuclei of the brain mediating incentive motivational processes, there are also subtler neurobiological processes that appear to contribute to sign-tracking behavior. For example, active mast cells in the thalamus have been associated with sign-tracking behavior (Fitzpatrick & Morrow, 2017b). Mast cells are part of the immune system and reside in the thalamus of the brain until fully developed and functional (Goldschmidt, Hough, Glick, & Padawer, 1984). Once the cells have matured, they can be activated and release various signaling molecules, including monoamines (e.g., dopamine), that can in turn affect surrounding cells (Nautiyal, Ribeiro, Pfaff, & Silver, 2008). Compared to GTs, STs show a greater number of active mast cells in the thalamus, and infusion of a mast cell inhibitor into the lateral ventricle of the brain decreases sign-tracking behavior, without affecting goal-tracking behavior (Fitzpatrick & Morrow, 2017b). Due to the complex nature of mast cells, it is difficult to determine the exact manner by which they are regulating sign-tracking behavior. However, the fact that mast cells can directly affect levels of dopamine (Ronnberg, Calounova, & Pejler, 2012), histamine (Bugajski, Chlap, Gadek-Michalska, Borycz, & Bugajski, 1995; Chikahisa, Kodama, Soya, Sagawa, Ishimaru, Sei, & Nishino, 2013), and corticotrophin-releasing factor (involved in response to stress) (Theoharides, Donelan, Papadopoulou, Cao, Kempuraj, & Conti, 2004), suggests that there are a number of plausible mechanisms by which this might occur.

NMDA Receptors: Effects of Sub-anesthetic Ketamine on Sign-Tracking and Goal-Tracking Behaviors

The involvement of NMDA receptors in sign-tracking behavior has also been investigated through the use of ketamine, a selective NMDA antagonist.
Glutamate, one of the main excitatory chemicals in the brain, binds to NMDA receptors which are known to play a role in learning and memory (for review see Castellano, Cestari, & Ciamei, 2001). Several drugs of abuse, such as ketamine, bind to NMDA receptors. However, sub-anesthetic doses of ketamine have been investigated as a treatment for depression (aan het Rot, Collins, Murrough, Perez, Reich, Charney, & Mathew, 2010; Larkin & Beautrais, 2017; Price, Nock, Charney, & Mathew, 2009) and more recently for addiction (Dakwar, Levin, Foltin, Nunes, & Hart, 2014; Krupitsky, Burakov, Romanova, Dunaevsky, Strassman, & Grinenko, 2002). Results thus far have reported decreases in cue-induced cravings and increases in motivation to quit taking drugs in humans following treatment (Dakwar, Levin, Foltin, Nunes, & Hart, 2014; Krupitsky, Burakov, Romanova, Dunaevsky, Strassman, & Grinenko, 2002). The role of sub-anesthetic doses of ketamine in incentive motivational processes was recently investigated using the ST/GT model. Interestingly, a systemic injection of ketamine decreases sign-tracking behavior and increases goal-tracking in STs, without affecting the behavior of GTs (Fitzpatrick & Morrow, 2017a). These results could be a function of altered neurochemical signaling in the prefrontal cortex, a primary target region for ketamine's effects (Moghaddam, Adams, Verma, & Daly, 1997; Perrine, Ghoddoussi, Michaels, Sheikh, McKelvey, & Galloway, 2014). It is then likely that administration of sub-anesthetic doses of ketamine alters, and possibly strengthens, top-down cortical processes that are otherwise lacking in sign-trackers thus resulting in an increase in goal-tracking behavior (Fitzpatrick & Morrow, 2017a). In support, it was recently reported that STs exhibit an increase in the concentration of extracellular glutamate in the prelimbic cortex of the PFC, as well as in the nucleus accumbens core, during the presentation of a reward cue (Batten, Pomerleau, Quintero, Gerhardt, & Beckmann, 2018). Furthermore, administration of an NMDA receptor antagonist prior to Pavlovian training attenuates the learning of a sign-tracking conditioned response but increases goal-tracking behavior (Chow & Beckmann, 2018). These data suggest that NMDA-mediated glutamatergic transmission, and particularly that within the PFC, contributes to the propensity to attribute incentive salience to reward cues.
Conclusion

The sign-tracker/goal-tracker model not only captures individual variation in the propensity to attribute incentive motivational value to reward cues but also individual variation in addiction-related behaviors, such as relapse propensity. Using this model, we are able to dissociate the predictive from the incentive value of reward cues and explore the neurobiological mechanisms underlying these distinct associative learning strategies. To date, we know that the behavior of sign-trackers is dopamine-dependent and seemingly reliant on subcortical hypothalamic-thalamic (PVT)-striatal pathways; whereas that of goal-trackers is dependent on cortical cognitive processes. Taken together, we believe it is the imbalance between “top-down” versus “bottom-up” processing that drives the extreme behaviors inherent to each of the phenotypes, including deficits in attentional processing, impulsive behavior (see Meyer and Tripi, this volume) and increased propensity to relapse that are characteristic of sign-trackers.

Acknowledgments

We would like to thank past and present members of the Flagel Lab who have contributed greatly to a number of studies, conclusions, and hypotheses put forth in this chapter. The work included from the Flagel Lab was supported largely by a grant from the National Institute on Drug Abuse (R01DA038599) and training grants (T32DA007821 and T32DA007268).

References


alternative to response reinforcement *Behavior and Brain Sciences* (1), 41–91.


Differential involvement of NMDA, AMPA/kainate, and dopamine receptors in the nucleus accumbens core in the acquisition and performance of pavlovian approach behavior. *Journal of Neuroscience*, 21(23), 9471–9477.


Heimer, L., & Wilson, R. D. (1975). The subcortical projections of allocortex similarities in the neural associations of the hippocampus, the periform cortex and the neocortex.


Nyberg, L. (2018). Cognitive control in the prefrontal cortex: A central or


4. The Propensity to Attribute Incentive Salience to Drug Cues and Poor Cognitive Control Combine to Render Sign-Trackers Susceptible to Addiction

Terry E. Robinson*, Crystal Carr, and Alex B. Kawa

Department of Psychology (Biopsychology), the University of Michigan

Corresponding Author:
Terry E. Robinson, PhD, East Hall, University of Michigan, 530 Church St., Ann Arbor, Michigan 48109; e-mail: ter@umich.edu; phone: (734) 358-8055.

Abstract

There are at least two major psychological factors thought to contribute to the development of problematic drug use and addiction. On one hand, drugs and drug cues acquire pathological motivational value, which leads to excessive drug “wanting” and a high propensity to relapse, especially in the presence of drug cues. On the other hand, poor cognitive/attentional control over behavior can result in impulsivity and difficulty in inhibiting drug-seeking and taking behavior when faced with temptations. The former psychological process—incentive salience attribution—is mediated by “bottom-up” dopamine-dependent neural systems, whereas cognitive control involves the activity of “top-down” acetylcholine-dependent neural systems. In this chapter, we
discuss how individual variation in these neuropsychological processes combine and interact to influence vulnerability to addiction. It is suggested that animals that are especially prone to attribute incentive salience to drug cues (“sign-trackers”) also have relatively weak cognitive/attentional control over their behavior, and this “double-whammy” results in an endophenotype with a high propensity to transition from experimental/recreational patterns of drug use to those that define addiction.

Keywords: acetylcholine; addiction; attention; autoshaping; dopamine; goal-tracking; incentive salience; motivation; Pavlovian learning; prefrontal cortex; sensitization; sign-tracking

Introduction

Each day we are constantly faced with choices concerning what goals to pursue in a given moment. Some choices may be adaptive, promoting our welfare (e.g., obtaining food), and others, although desired in the moment, may be maladaptive (taking drugs). Some choices may be conscious and deliberative and others made quickly, without much awareness (Kahneman, 2011). The choices we make are influenced to a considerable degree by cues in the environment that in the past have been associated with different outcomes, even if we are unaware of their influence on our behavior (Johansson et al., 2006; Childress et al., 2008). Indeed, cues that predict the receipt or availability of biologically important objects, such as food, can come to acquire some of the properties formally associated only with the biologically important object. This form of learning, which guides us toward objects of desire and away from those that may harm us, is called Pavlovian learning, named after the famous Russian scientist who conducted the first systematic studies on this topic (Pavlov, 1927). The biologically important object is called the unconditioned stimulus (US) and the cue associated with it is called the conditioned stimulus (CS). In the case of Pavlov's seminal studies presentation of the US (meat) caused dogs to salivate (an unconditioned response, UR), and presentation of a sound initially did not. However, if presentation of the sound (CS) came to reliably predict receipt of the US, the CS itself began to evoke salivation (the conditioned response,
CR). Although Pavlov mostly studied relatively reflexive CRs, such as salivation, it is now known that Pavlovian learning has far more profound effects on behavior and psychological function than this. As put by the American learning theorist, Robert Rescorla (1988), Pavlovian conditioning involves “the learning of relations among events so as to allow the organism to represent its environment” (p. 151), and it “is intimately involved in the control of central psychological processes, such as emotions and motivations” (p. 157).

Pavlovian Conditioned Motivation

Indeed, Pavlovian CSs do not only evoke simple CRs, but they can come to generate complex emotional and motivational states that can exert considerable control over our behavior, if CSs are attributed with incentive salience and thus additionally acquire the properties of an incentive stimulus (Berridge, 2001; Bindra, 1978; Lajoie and Bindra, 1976; Rescorla, 1988). An incentive is defined as “something that arouses feeling, or incites to action; an exciting cause or motive; an incitement, provocation, spur” (Oxford English Dictionary). Importantly, a Pavlovian CS, capable of evoking a CR, does not always additionally acquire the motivational properties of an incentive stimulus; that is, a perfectly effective CS does not necessarily function as an incentive stimulus. It turns out that there is a great deal of individual variation in the extent to which CSs are attributed with incentive salience (for reviews see Saunders and Robinson, 2013; Robinson et al., 2014; and other chapters in this book).

How does one tell if a CS also has incentive motivational properties in a nonhuman animal? Barry Everitt and his colleagues (Everitt et al., 2001; Cardinal et al., 2002; Milton and Everitt, 2010) have nicely defined the three fundamental properties of an incentive stimulus and procedures that can be used to assess if a stimulus has these properties. An incentive stimulus has three defining properties. One, it is attention-grabbing (e.g., Hickey and Peelen, 2015) and attractive, which can promote approach into close proximity with it. In nonhuman animals approach is typically measured using procedure in which presentation of a discrete cue (CS, often a lever) predicts food delivery at a different location. The extent to which the lever-CS (“sign”)
produces approach and engagement with it is taken as an indicator that the lever-CS is attractive and thus has acquired incentive value. Interestingly, when a group of animals are tested using this procedure, some animals do indeed begin to approach and engage a lever-CS, that is, they develop what is called a sign-tracking (ST) CR. However, other animals do not, but instead, when the lever-CS is presented, they move toward the location where food will soon be delivered. This is called a goal-tracking (GT) CR. Yet other animals are ambivalent, making both ST and GT CRs (Boakes, 1977; Zener, 1937). Thus, only in some animals (STs) does a cue acquire this property of an incentive stimulus (Flagel et al., 2009).

The second defining property of an incentive stimulus is that it becomes an object of desire itself, in the sense that animals will work to obtain just the reward-associated cue (CS), even in the absence of the reward. That is, the cue comes to act as what is called a conditioned or secondary reinforcer (the food reward is called the primary reinforcer). Thus, in a conditioned reinforcement test one assesses the extent to which animals will work for a CS, or even learn new actions to get it. The ability of a CS to act as a conditioned reinforcer is another measure of the extent to which the cue functions as an incentive stimulus.

Third, an incentive stimulus can generate a conditioned motivational state whereby it instigates or invigorates seeking for the associated reward. This “craving” state (which can operate outside conscious awareness) can be quantified by assessing the extent to which a Pavlovian cue reinstates seeking behavior or energizes ongoing instrumental responding (so-called Pavlovian to Instrumental Transfer [PIT] effects).

If a CS acquires these properties, as in the case of STs, it is considered to not only act as a CS, evoking a CR, but also an incentive stimulus that has emotional and motivational value. Importantly, although these three properties collectively define an incentive stimulus, they are themselves psychologically and neurobiologically dissociable (Cardinal et al., 2002).

**Individual Variation in Incentive Salience Attribution**

As alluded earlier, animals vary considerably in the extent to which a food
cue (a lever-CS) comes to act as an incentive stimulus when it is paired with delivery of a food reward (US), based on the three measures discussed earlier. In a series of studies we have quantified Pavlovian conditioned approach behavior in a very large sample of rats (over 6,000). With this procedure, an animal is classed as a sign-tracker (ST) if it makes twice as many ST CRs as GT CRs and as a goal-tracker (GT) if this is reversed. The rest of the animals, which vacillate between making ST and GT CRs, are called Intermediates (INs). In this large sample about 1/3 of the rats were STs, 1/3 GTs, and 1/3 INs, indicating that in only about 1/3 of the population does the CS acquire strong motivational properties—although this is a continuous distribution from a high to low propensity to attribute incentive salience to a food cue. There are not marked sex differences in approach behavior, although on average, female rats are biased toward sign-tracking (Pitchers et al., 2015). The idea that STs preferentially attribute incentive salience to a food cue is further supported by studies showing that a food cue is also a more effective conditioned reinforcer in STs than GTs and is also more effective in instigating seeking behavior (Robinson and Flagel, 2009; Yager and Robinson, 2010; Flagel et al., 2011). In summary, there is now considerable evidence that many species (including humans; Mahler and de Wit, 2010; Styn et al., 2013; Garofalo and di Pellegrino, 2015) vary in the extent to which cues that are fully predictive of reward, and act as effective CSs, also acquire the properties of an incentive stimulus, and thus the ability to arouse feelings, incite to action, provoke, spur and motivate behavior (Robinson et al., 2014; Flagel and Robinson, 2017; Pitchers et al., 2018; and other chapters in this book).

Of course, if cues that predict rewards act as incentives, this will increase the probability one will be motivated to approach and obtain them, and given they are necessary for survival, as in the case of obtaining food or a mate, this will often be advantageous. However, such cues can in some situations lead to maladaptive behavior. For example, our modern environment is laden with cues signaling the availability of high calorie, high fat foods, and when they generate excessive motivation for them this can lead to overeating, which may be a contributing factor to obesity (e.g., Berridge et al., 2010).
Dopamine, Drug Cues, and Incentive Motivation

Another situation where reward cues may contribute to maladaptive behavior is when cues predict the availability of drugs of abuse. Indeed, the importance of drug cues in maintaining drug-taking behavior and in producing relapse in otherwise abstinent drug users has long been recognized. As put by Jane Stewart and colleagues in 1984, “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” (p. 251). They went on to state that 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. 256) (Stewart et al., 1984; also see Robinson and Berridge, 1993). However, given the large individual variation in the extent to which food cues acquire motivational properties, as described earlier, an obvious question is whether there is similar variation in the extent to which drug cues come to act as incentive stimuli, as this could contribute to vulnerability to addiction (Flagel et al., 2009). That is the topic of the remainder of this chapter. We first address the question: to what extent does the propensity to attribute incentive salience to a food cue predict the extent to which drug cues acquire motivational value?

The way we have approached this issue is to ask whether STs and GTs differ in the extent to which they attribute a drug cue with each of the defining properties of an incentive stimulus, as described earlier. As put by Milton and Everitt, (2010) the features of an incentive stimulus provide “three routes to relapse,” as each feature can contribute to relapse, individually, or they can combine. The ability of an incentive stimulus to attract attention to it, and to elicit approach behavior, could draw an addict into close proximity to places where drugs are to be found, or to devices used to administer drugs. The ability of a drug cue to act as a conditioned reinforcer can maintain high levels of drug-seeking behavior even in the absence of the drug. And lastly, the ability of drug cues to generate conditioned motivational craving states can instigate drug-seeking and relapse (Epstein et al., 2009; Preston et al., 2009), and such cues may be especially potent under stressful conditions (Preston et al., 2018). Therefore, we will discuss each of these features in turn.
Conditioned Approach

The first studies showing that rats would approach a cue associated with a drug, that is, show a ST CR, used alcohol as the US (Tomie, 2001; Krank, 2003; Tomie et al., 2003; Krank et al., 2008; Srey et al., 2015). More recently, Kruse et al. (2017) reported that exposure to alcohol in adolescence also increases the probability that rats later develop a ST CR to a food cue. Although these initial studies noted there was considerable individual variation in the degree to which rats would approach an alcohol cue, they did not explicitly compare STs and GTs. However, more recently, Villaruel and Chaudhri (2016) have reported that an alcohol cue is more attractive and a more effective conditioned reinforcer in STs than GTs.

In studies with alcohol, the drug is administered orally, but for many other drugs of abuse addicts prefer routes of administration that result in drugs reaching the brain very rapidly, such as intravenous injection or smoking (Samaha and Robinson, 2005; Allain et al., 2015). The first report that rats would come to approach a cue that signaled an intravenous injection of a drug, cocaine, was by Uslaner et al. (2006). More recently, Reilly et al. (2016) reported that rhesus monkeys trained to self-administer cocaine also come to avidly approach a light cue associated with cocaine delivery—touching and biting it. This behavior was seen in the absence of any response-drug contingency, and so presumably represented a Pavlovian ST CR, although it occurred at even higher levels when cocaine delivery was made contingent upon a response, as emphasized by Tomie (1996). These initial studies did not examine STs and GTs, but there are now a number of reports that STs approach a discrete cocaine cue (e.g., a light or a lever) much more avidly than GTs (Flagel et al., 2010; Yager and Robinson, 2013; Pitchers et al., 2017c). Using a different procedure, Meyer et al. (2012b) reported that STs were also more likely to approach a tactile cue associated with cocaine and made more positive ultrasonic vocalizations (USVs) in the presence of this cue. Interestingly, cocaine administration produces more positive USVs in STs and with repeated administration this sensitizes (Tripi et al., 2017). Furthermore, individuals showing the greatest number of USVs when initially exposed to cocaine are most likely to be later identified as STs (Tripi et al., 2017; also see Meyer and Tripi, this book). Finally, Yager et al. (2015) reported that STs are also more likely than GTs to approach a cue that predicts the intravenous delivery of an opioid drug, remifentanil.
Of course, when intravenous drug is used as a US there is no “goal” (e.g., food cup) to approach, so one cannot see GT CRs. This raises the possibility that GTs do not approach a drug cue because they fail to learn the CS-US association, rather than because the CS does not acquire sufficient motivational value to attract GTs toward it. However, in addition to quantifying sign-tracking, Yager and Robinson (2013) and Yager et al. (2015) also measured the extent to which rats learned a conditioned orienting response to a drug cue, and they found that both STs and GTs learned this CR equally well, as is also the case when food is used as the US (Zener, 1937; Yager and Robinson, 2013). This dissociation between conditioned approach and conditioned orienting, which was recently replicated by Pitchers et al. (2017a), establishes that GTs in fact learned the CS-US(drug) association. This supports the interpretation that the reason GTs did not approach a cocaine or opioid cue was because it lacked sufficient incentive value to act as a “motivational magnet,” drawing them into close proximity to it, not because they failed to learn the CS-US association.

**Conditioned Reinforcement**

There are a number of studies showing that STs will work more avidly than GTs for presentation of a food cue; that is, a food cue is a more effective conditioned reinforcer in STs than GTs (e.g., Robinson and Flagel, 2009; Yager and Robinson, 2010; Lomanowska et al., 2011; Meyer et al., 2012b). The question here is whether this is also the case for drug cues. This question has been approached using a number of different procedures. In some experiments, rats were allowed to self-administer a drug, and thus presentation of both the drug and the cue were contingent on the animal making an instrumental action, such as a nose poke. In other experiments, Pavlovian procedures were used and drug injections were given independent of the animal’s behavior and were paired with presentation of a cue. The test for whether the drug cue acquired conditioned reinforcing properties was conducted by determining whether rats would work for the cue alone, sometimes using traditional extinction-reinstatement (conditioned reinforcement) procedures (e.g., Shaham et al., 2003). A cue associated with cocaine (Saunders and Robinson, 2010; Yager and Robinson, 2013), with nicotine (Yager and Robinson, 2015; Versaggi et al., 2016), with alcohol
(Villaruel and Chaudhri, 2016), or with remifentanil (Yager et al., 2015) is a more effective conditioned reinforcer in STs than GTs. Furthermore, during cocaine self-administration omission of the cue attenuates self-administration behavior to a greater extent in STs than GTs (Saunders and Robinson, 2010). Importantly, in all these studies the drug cue consisted of either a discrete light or a lever-CS. In contrast, a tone-CS is reported to reinstate cocaine-seeking behavior to the same extent in STs and GTs (Pitchers et al., 2017c). A tone-CS also does not attract rats to it and functions as a relatively weak incentive stimulus (Meyer et al., 2014; Beckmann and Chow, 2015; Chow et al., 2016; Singer et al., 2016a; also see Holland et al., 2014). Compared to levers and lights a tone CS is also relatively ineffective in engaging brain motive circuits (Singer et al., 2016a; Cogan et al., 2018), indicating that the form of the CS is an important determinant of its ability to acquire incentive motivational properties.

**Conditioned Motivation**

In addition to eliciting approach behavior and acting as a conditioned reinforcer, the third “route to relapse” described by Milton and Everitt (2010) refers to the ability of reward cues to generate Pavlovian conditioned motivational states that then influence instrumental actions (Rescorla and Solomon, 1967; Bindra, 1968; Berridge, 2001). This is Bindra’s (1968) “central motive state,” which can influence ongoing behavior implicitly, outside of conscious awareness (e.g., Childress et al., 2008), or, if it rises to the level of conscious awareness, it is perceived as a state of desire. The former is akin to what Robinson and Berridge (1993) have termed “wanting” (in quotation marks) and the latter to wanting (without quotation marks), or craving. This action of a Pavlovian cue is typically measured by assessing its ability to instigate reward-seeking behavior and/or to invigorate ongoing-seeking behavior; that is, to produce so-called Pavlovian to instrumental (PIT) action effects (Estes, 1943; Lovibond, 1983; Holmes et al., 2010). Typically, in a test for PIT, a cue (usually a tone) is paired with receipt of a reward in some sessions (the Pavlovian part), while in other sessions an animal is trained to make an instrumental action (lever press or nose poke) to receive a reward (the instrumental part). On the test day, usually conducted under extinction conditions, the Pavlovian cue is periodically presented. If
the Pavlovian cue increases the rate of instrumental responding, it indicates that it was able to generate a burst of motivation for the associated reward, as reflected by its influence on seeking behavior.

Although there are many studies of PIT using a food reward, there are very few that have used this procedure to assess the extent to which a drug cue generates a Pavlovian conditioned motivational state, and most of these used alcohol as the US (e.g., Krank et al., 2008b; Lamb et al., 2016b). However, in one study using cocaine, LeBlanc et al. (2012) reported that presentation of a cocaine cue did increase the rate of ongoing self-administration behavior, both during the “seeking” and “taking” phases of the self-administration schedule. Such PIT effects have been associated with a surge in DA in the core of the nucleus accumbens (Ito et al., 2000; Wassum et al., 2013; Aitken et al., 2016). Nevertheless, as pointed out by Lamb et al. (2016), evidence for PIT effects using Pavlovian drug cues is scarce, and there are a number of procedural difficulties in conducting such studies.

We are not aware of any studies using a traditional PIT procedure to ask whether STs and GTs differ in the ability of a drug cue to energize an ongoing instrumental action, perhaps because the design of such a study is fraught with problems. In PIT studies typically an auditory stimulus is used as the Pavlovian cue, and it is presented while animals are making an instrumental response. However, as reviewed earlier, in rats, an auditory stimulus is not attributed with incentive salience to the same degree as a light or lever. Furthermore, if a localizable stimulus were used as the Pavlovian cue it could elicit approach toward it, as has been described by Krank (Krank, 2003; Krank et al., 2008), and presumably this would be most pronounced in STs. Indeed, in tests of conditioned reinforcement, in which STs make an action for presentation of a lever-CS, we have frequently seen that as soon as the lever is presented they disengage from the instrumental manipulandum (nose port) and run to the lever-CS and engage with it, even when it is presented for only 2 sec (Robinson and Flagel, 2009; Fraser et al., 2016). Obviously, this competes with performance of the instrumental response and would thus interfere with the ability to see a PIT effect.

Nevertheless, there are studies suggesting that a Pavlovian cue does generate greater conditioned motivation in STs than GTs. To circumvent the problem with traditional PIT procedures described earlier, Saunders et al. (2013) modified a protocol developed by Cooper et al. (2007) to examine the ability of a cocaine cue (a light) to instigate an instrumental action (rather than energize an ongoing action). With this procedure, after rats
acquired stable cocaine self-administration behavior, the front two-thirds of
the chamber (where the nose port was located) was electrified, such that rats
had to walk across the electrified floor to take drug. The current was initially
very weak, but it was increased each day, until a point where animals stopped
taking drug—they became abstinent because of the negative consequences
of continuing to take drug. On the test day, the light cue was periodically
flashed to see if it created a motivational state sufficient to compel the rats
to cross the still electrified floor to seek drug, although no drug was available
during this test. It did so, but more effectively in STs than GTs. In addition,
the degree to which the rats approached the food cue when they were
screened for sign-tracking and goal-tracking predicted the ability of the
cocaine cue to reinstate self-administration behavior (r²=0.253). Saunders
et al. (2013) argued that this effect was due to the cocaine cue generating
a conditioned motivational state, and not to Pavlovian attraction (see the
paper for discussion), and also showed that it was blocked by injection of a
DA antagonist into the core of the nucleus accumbens. One shortcoming of
this study is that the cocaine cue acquired its motivational properties in the
instrumental (self-administration) setting, and it would be good to know if a
similar effect were seen with a Pavlovian-trained cue.

Another line of evidence that suggests drug cues produce greater
conditioned motivation for drug in STs than GTs comes from studies on
the effects of exposure to the drug itself. It has long been known that
the drug itself (a “taste” of drug) can evoke craving and relapse in addicts
(e.g., Jaffe et al., 1989; de Wit and Chutuape, 1993), and in animals a drug
“prime” can reinstate drug-seeking behavior following extinction of self-
administration behavior (de Wit and Stewart, 1981; Venniro et al., 2016 for
review). One interpretation of this effect is that the drug produces a variety
of interoceptive effects, and with experience some of these become
associated with the unconditioned motivational effects of the drug, such that
even a small dose of drug can produce a conditioned motivational state that
promotes further drug-seeking behavior.

The first experiment to ask whether the interoceptive effects of cocaine
have different motivational value in STs and GTs was by Saunders and
Robinson (2011), who assessed motivation for drug using a progressive ratio
(PR) schedule and by the ability of a drug prime to reinstate drug-seeking
behavior. To better isolate the motivational effects of the drug itself, no
environmental cue (CS; e.g., light or tone) was explicitly paired with drug
injections, either during self-administration training, the PR test or the
reinstatement test. It was found that STs were more motivated to self-administer cocaine than GTs, as they had higher breakpoints on the PR schedule, and the drug prime reinstated more drug-seeking in STs than GTs during the reinstatement test. Consistent with this, STs also choose cocaine over a food reward more frequently than GTs (Tunstall and Kearns, 2015). Kawa et al. (2016) recently confirmed that, at least after relatively limited drug experience, STs are more motivated to self-administer cocaine than GTs. Kawa et al. (2016) used a behavioral economic “threshold” procedure in which the “price” (responses/mg) required to obtain cocaine was progressively increased. It was found that STs were willing to pay a higher price for cocaine (in effort) than GTs—they had a higher Pmax—and the cocaine demand curve was less elastic in STs (they had a lower alpha than GTs). Interestingly, STs and GTs did not differ on Qo, which is a measure of the preferred level of drug consumption when cost is negligible, and may reflect the hedonic effects of the drug. If that is true, it suggests that interoceptive cocaine cues may have greater incentive motivational value in STs than GTs, at least when animals have had only limited drug experience (see sections below for more discussion of this issue), but cocaine produces similar hedonic effects in STs and GTs, consistent with the notion that “wanting” and “liking” are dissociable processes (Robinson and Berridge, 1993; Berridge et al., 2009; Olney et al., 2018).

In summary, as with food cues, there is now considerable evidence that cues associated with drugs of abuse are attributed with greater motivational value in STs than GTs, which could predispose STs to addiction (see sections below for more discussion of this issue).

Acetylcholine and Variation in the Top-Down Executive Control over Behavior

Earlier we have emphasized that the greater drug cue reactivity of STs may make them vulnerable to addiction and relapse, but there is a general consensus that this is only one of a number of “vulnerability factors,” as stressed by so-called dual-systems formulations of behavioral control. One system is often referred to as an automatic, impulsive system in which behavior is strongly controlled by incentive stimuli, in the moment; what
Sarter and Phillips (2018) refer to as a “bottom-up, cue-driven cognitive-motivational style.” The other system is described as a more deliberative, executive (cognitive) control system that allows for inhibitory control over behavior (e.g., Jentsch and Taylor, 1999; McClure and Bickel, 2014; Bickel et al., 2016); what Sarter and Phillips (2018) refer to as a “top-down goal-driven attentional control” system. Although everyone possesses both of these behavioral control systems, they may compete with one another, and one or the other may dominate in any given individual. Thus, addictive behavior is thought to not only be promoted by hyperreactivity to drugs and drug cues but also relatively poor executive (attentional) control over behavior, especially in the presence of reward cues. It is important to emphasize, therefore, that not only are STs more prone than GTs to attribute incentive salience to drug cues, but they also have relatively poor top-down executive control over their behavior (Flagel et al., 2009; Meyer et al., 2012a; Haight et al., 2015, 2017; Sarter and Phillips, 2018), which may account for the fact that they are impulsive (Lovic et al., 2011).

Martin Sarter and his colleagues have conducted an extensive series of studies on the neural systems involved in executive/attentional control over behavior, using a Sustained Attention Task (SAT) designed to tax such processes, in both rats and humans (Sarter and Paolone, 2011). Paolone et al. (2013) used the SAT to assess executive/attentional control in STs and GTs and found that STs performed poorly on this task, relative to GTs. STs could perform the task, and at times performed as well as GTs, but their performance was highly variable, fluctuating between periods of good performance and periods of very poor performance. This is thought to reflect “relatively poor cognitive or ‘top-down’ control of attention in STs, including a relatively lower capacity for maintaining task rules and behavioral goals in working memory (or ‘on-line’),” as well as, “poorer levels of performance monitoring, specifically error monitoring” (Paolone et al., 2013, p. 8332). In addition, the performance of STs on the SAT is slower to recover after disruption by a distractor (Sarter and Phillips, 2018).

The idea that STs have relatively poor top-down control over their behavior is also supported by studies using stimuli that indicate what rules are operative at any given time. For example, stimuli that signal reward availability can “set the occasion” for appropriate responding and this is thought to require cognitive control to override the tendency to unthinkably respond to a CS. STs are relatively insensitive to such stimuli, compared to GTs, and are slow to modify their behavior in an appropriate fashion.
as circumstances change. Thus, STs may be biased to respond impulsively to cues, even when it is no longer appropriate, because they have poor cognitive control over attention, which is required to “suppress prepotent responses,” “to maintain task rules,” “to monitor performance and weigh outcomes,” and to “filter distractors” (see Sarter and Paolone, 2011). Ahrens et al. (2016b) demonstrated the inflexibility of STs by alternating periods of reward and non-reward. In the presence of a signal of non-reward GTs immediately modified their behavior, by ceasing conditioned responding (goal-tracking). However, it took several days before STs discriminated between periods of reward versus non-reward, as they persisted in approaching a food cue (sign-tracking) even during periods of non-reward, and it was difficult to extinguish this response to the cue, relative to GTs.

Changes in context also often provide information about whether a reward is available or not, and animals thus modify their behavior according to the context they find themselves. For example, if rats are trained to self-administer a drug in one context (context A) but then undergo extinction training in a different context (context B), during which time their previously reinforced action no longer produces drug, they stop self-administering in context B. However, if, after extinction, they are placed back into context A they immediately resume drug-seeking behavior, in part because that context still signals drug availability (Crombag et al., 2008). The processing of such higher-order signals of reward availability or non-availability is thought to require the executive (cognitive) control system that dominates in GTs, as described earlier. It is interesting, therefore, that when placed back into a context that was previously associated with cocaine self-administration GTs reinstate cocaine-seeking behavior more avidly than STs (Saunders et al., 2014). That is, they more readily modify their behavior depending on the context they find themselves in (also see Morrow et al., 2011).

Stimuli that signal reward availability (occasion-setters or discriminative stimuli) are thought to share many properties of contextual stimuli (Weiss, 2005; Trask et al., 2017). Consistent with this, Pitchers et al. (2017b) reported that a discriminative stimulus that signaled cocaine availability evoked greater cocaine-seeking behavior in GTs than STs. It appears, therefore, that cues that control behavior by more “top-down” hierarchical processes (Rescorla, 1988) are more influential in GTs than STs. It is still not entirely clear how to interpret these findings (see additional discussion in sections below), but it is consistent with the idea that different learning/cognitive processes dominate control of behavior in STs and GTs. That is, STs are more

88 | Jonathan Morrow and Arthur Tomie
susceptible to control by bottom-up, cue-driven processes whereas GTs are more likely to employ top-down executive (cognitive) control processes that allow them to more readily adapt their behavior as circumstances change (Flagel et al., 2009; Clark et al., 2012; Meyer et al., 2012a; Haight et al., 2015, 2017; Sarter and Phillips, 2018).

Research on which ascending neuromodulatory neurotransmitter systems dominate in STs and GTs supports this kind of distinction. Studies by Sarter and colleagues (e.g., Sarter and Paolone, 2011; also see Kuhn et al., this book) have established that the high levels of attentional control necessary for optimal performance on the SAT require increased acetylcholine (ACh) neurotransmission in the prefrontal cortex while performing the task. However, during performance on the SAT prefrontal extracellular ACh levels, assessed with microdialysis, rise much less in STs than GTs. This may account for their relatively poor performance because “systemic administration of the partial nAChR agonist ABT-089 improved SAT performance in STs and abolished the difference between SAT-associated ACh levels in STs and GTs” (Paolone et al., 2013). This difference between STs and GTs may be because in STs the choline transporter, which is required to elevate ACh under demanding conditions, is remarkably unresponsive (Koshy Cherian et al., 2017). Interestingly, inhibition of choline transport, which limits stimulated ACh release in the cortex, also shifts behavior away from goal-tracking and toward sign-tracking (Koshy Cherian et al., 2017). In addition, the ability of a discriminative stimulus that signals cocaine availability to preferentially reinstate drug-seeking behavior in GTs (relative to STs) is abolished by an immunotoxic lesion of the basal forebrain that decreases cortical ACh levels (Pitchers et al., 2017b). Finally, there is a double dissociation in the effects of presentation of a cue previously paired with an IV injection of cocaine on DA and ACh in the prefrontal cortex. A cocaine cue (CS) increases extracellular DA (but not ACh) in the prefrontal cortex of STs, and the magnitude of this effect predicts how avidly STs approach the cue. This cue did not increase DA in GTs, nor did they approach the cue (although they oriented to it). On the other hand, the cocaine cue increased prefrontal ACh in GTs, but not STs. This double dissociation is consistent with the idea that the top-down executive control system, which requires ACh neurotransmission in the prefrontal cortex, may dominate in GTs, whereas in STs a dopaminergic incentive system dominates (Pitchers et al., 2017a; Sarter and Phillips, 2018).
Susceptibility to Addiction

As reviewed earlier, there is now considerable evidence indicating that STs and GTs represent the extremes of two complex endophenotypes that differ on a number of behavioral/psychological dimensions, such that different “cognitive-motivational styles” (Sarter and Phillips, 2018) dominate control of behavior in STs and GTs (Flagel et al., 2009; Clark et al., 2012; Robinson et al., 2014; Beckmann and Chow, 2015). Although these endophenotypes are labeled by the terms ST and GT, this should not be confused with a ST or GT CR, which narrowly refers to the tendency to approach the CS or the location of reward delivery in a Pavlovian conditioned approach task, respectively. As described earlier, the ST and GT endophenotypes involve much more complex and multifaceted constellations of interacting traits.

We originally hypothesized that STs are more susceptible to addiction than GTs, based primarily on their propensity to attribute incentive salience to discrete drug cues (Flagel et al., 2009; Saunders and Robinson, 2013). We still think the ST endophenotype represents a vulnerability factor for addiction, although, as described next, more recent research has forced a reevaluation as to how this is conceptualized (Robinson et al., 2014; Kawa et al., 2016; Pitchers et al., 2018). Dual-systems models postulate that addiction and relapse result from an interaction between: (1) hyperreactive “bottom-up” neural systems that attribute incentive motivational value to reward cues, resulting in a hypersensitivity to drugs and drug cues, and, (2) hypoactive “top-down” neural systems that confer executive (cognitive) control over behavior, resulting in poor inhibitory control, especially in the presence of drugs and drug cues (e.g., Jentsch and Taylor, 1999; Mcclure and Bickel, 2014; Bickel et al., 2016; Sarter and Phillips, 2018). By this formulation, STs suffer a “double-whammy,” in that they are not only especially prone to attribute undue incentive salience to drugs and drug cues, but they also have relatively poor executive or attentional control over behavior, which can, of course, contribute to why they are biased toward cues in the first place (Robinson et al., 2014; Flagel and Robinson, 2017; Sarter and Phillips, 2018; Pitchers et al., 2018). We hypothesize, therefore, that individuals with a ST endophenotype may be more vulnerable to undergo a transition from recreational/casual patterns of drug use to addiction for the following reasons (also see Kuhn et al., this book).
Upon initial use the interoceptive effects of cocaine are more motivating in STs than GTs (Saunders and Robinson, 2011).

STs are especially susceptible to the motivating effects of discrete drug cues (Saunders and Robinson, 2010; Saunders et al., 2013).

STs are more impulsive than GTs (Tomie et al., 2008; Lovic et al., 2011).

The motivational effects of Pavlovian reward cues are more difficult to extinguish in STs than GTs (Beckmann and Chow, 2015; Ahrens et al., 2016b).

Relative to GTs, STs are more likely to choose drug (cocaine) over a non-drug reward (Tunstall and Kearns, 2015).

Reward (including drug) cues more effectively engage brain systems that confer incentive motivational value to such cues in STs than GTs (Flagel et al., 2011; Yager et al., 2015; Ahrens et al., 2016a; Singer et al., 2016b; Flagel and Robinson, 2017, for review).

STs have relatively poor executive (attentional) control over behavior, which is due, at least in part, to unresponsive cortical choline transporters, which limits their ability to increase acetylcholine neurotransmission under cognitively demanding conditions (Paolone et al., 2013; Sarter and Phillips, 2018, for review).

As put by Kawa et al. (2016), “All of these characteristics would increase the probability that individuals with a ST phenotype, after initial casual drug use, continue to use drugs, which would eventually expose them to incentive-sensitization and addiction (Robinson and Berridge, 1993).”

Context

The interpretation of individual variation in the motivational properties of context cues and discriminative stimuli requires special comment. As noted earlier, studies using reinstatement procedures have found that context cues and discriminative stimuli reinstate cocaine-seeking behavior more effectively in GTs than STs (Saunders et al., 2014; Pitchers et al., 2017b). One interpretation of these findings was provided by Robinson et al. (2014), who said: “different individuals may be sensitive to different ‘triggers’ capable of motivating behavior and producing relapse. That is, STs and GTs may process motivationally salient information in quite different ways, and thus vary in their sensitivity to different classes of drug-associated stimuli. It may be,
therefore, that STs are not more susceptible to addiction than GTs, but that for different individuals there are different pathways to addiction.”

However, the recent studies by Martin Sarter and his colleagues on attentional control in STs and GTs (Sarter and Phillips, 2018, for review) suggest a very different interpretation. The ability to appropriately modify behavior based on the information provided by higher-order cues that signal the availability (or non-availability) of reward, such as context cues and discriminative stimuli, is much more cognitively demanding than the processing of CSs. Thus, the greater reinstatement produced by such cues in GTs may reflect their superior ability to appropriately incorporate such information in guiding their behavior, and conversely, the ability of STs to do this is compromised because of their limited capacity for executive (cognitive) control. Indeed, this may also be why GTs are less impulsive than STs. By this interpretation, the effects of context cues in GTs could be interpreted as reflecting better “top-down” executive control, which could be protective in terms of susceptibility to addiction. Conversely, the fact that STs have difficulty incorporating such information to appropriately modulate their behavior represents another risk factor that increases the probability they transition from casual drug use to problematic use and eventually addiction. This issue will clearly require further study.

Individual Variation in Incentive-Sensitization

Earlier we itemize the features of the ST endophenotype that may render them more likely than GTs to transition from casual drug use to addiction. However, Robinson and Berridge (1993, 2008; Berridge and Robinson, 2016) have argued that the repeated intermittent exposure to drugs of abuse can change brain reward systems in ways that render animals hypersensitive to drugs and drug cues, and that this process of incentive-sensitization is both central in the transition from casual patterns of drug use to those that characterize addiction, as well as maintaining pathological motivation for drugs in addicts, contributing to high rates of relapse, even after long periods of abstinence. An important question, therefore, is whether STs and GTs differ in their susceptibility to incentive sensitization. The GT endophenotype may be protective in that it decreases the probability that
initial use will lead to more sustained use that could then result in escalation of intake and the adoption of routes of drug administration with greater addiction liability, such as intravenous administration or smoking (e.g., Allain et al., 2015). But what if, for any reason, individuals with a GT endophenotype do progress to problematic patterns of drug use? Will they be protected from incentive-sensitization? There is one study that suggests perhaps not (Kawa et al., 2016).

Kawa et al. (2016) first assessed motivation for cocaine in STs and GTs using behavioral economic measures of cocaine demand and found that after limited drug experience STs showed greater motivation for cocaine than GTs, consistent with earlier studies using different measures (Saunders and Robinson, 2010, 2011). However, after this, all rats were allowed to self-administer cocaine over 36 days using an Intermittent Access (IntA) schedule, which has been shown to promote the development of addiction-like behavior (Zimmer et al., 2012; Allain et al., 2015, 2017; Singer et al., 2018), and during this time cocaine demand was periodically reassessed. As predicted, there was a progressive development of addiction-like behavior as a function of IntA experience, including escalation of intake, increasing motivation for drug, increasing willingness to endure an adverse consequence to procure drug and very robust cue-induced reinstatement of drug-seeking behavior. Importantly, both STs and GTs underwent this process of incentive-sensitization such that after IntA self-administration experience they no longer differed on any measure of addiction-like behavior. Furthermore, in such a situation sustained exposure to drugs may also impair frontal cortical function, diminishing cognitive control, even in GTs (Briand et al., 2008). Thus, although having a GT endophenotype may be protective in that it could decrease the probability of continued drug use following initial experimentation with drugs, should such an individual in fact continue to use drugs they may be just as susceptible to incentive-sensitization, and addiction, as those with a ST endophenotype. In addition, female rats appear to undergo incentive-sensitization more readily than males (Kawa and Robinson, 2017), consistent with reports that female humans escalate to problematic drug use more quickly than males (Becker and Koob, 2016, for review).
Conclusion

The behavior of animals with a ST versus GT endophenotype is dominated by very different “cognitive-motivational styles” (Sarter and Phillips, 2018) (see Fig. 4.1). STs are very sensitive to the influence of reward cues processed by bottom-up, cue-driven, dopamine-dependent incentive motivational systems, and they have relative poor executive (attentional) control over their behavior, and thus they have difficulty resisting such cues. GTs, on the other hand, are less susceptible to the motivational properties of reward cues and also have greater executive (attentional) control over behavior, mediated in part by prefrontal cortical cholinergic signaling, and therefore are better able to resist such cues. It is hypothesized, therefore, that a ST endophenotype will increase the likelihood that an individual will progress from casual/experimental patterns of drug use to patterns characteristic of addiction, relative individuals with a GT endophenotype (see other chapters in this book). However, although much more research is required, the available evidence suggests that should, for any reason, drug use escalate, a GT endophenotype may not protect from incentive-sensitization (Kawa et al., 2016), or drug-induced alterations in frontal cortical function (e.g., Jentsch and Taylor, 1999). Thus, under conditions of continued and escalating drug use both STs and GTs may undergo a transition to addiction.

Acknowledgments

We thank all the former members of the Robinson lab who contributed to many of the studies discussed herein, as well as members of the Sarter lab for their studies on ACh and cognitive control. The research was supported by grants from the National Institute on Drug Abuse to TER (PO1 DA031656 and T32 DA007281).
Figure 4.1. A highly simplified graphic illustration of two endophenotypes, sign-trackers and goal-trackers, in which different neuromodulatory systems and psychological processes dominate in the control of behavior. The width of the arrows represent the relative strength of functional, not anatomical, relationships (see text). Left. “Sign-Trackers” (STs) are animals in which bottom-up, dopamine (DA)-mediated incentive salience motivational processes dominate control of behavior (red arrows), as indicated by a propensity to attribute incentive salience to discrete reward cues, and by strong functional activity in dopaminergic projections from the ventral tegmental area (VTA) to the prefrontal cortex (PFC) and nucleus accumbens (NAc; ventral striatum), and between the NAc and its main target, the ventral pallidum (VP). In these animals, the activity of cholinergic inputs to the PFC under conditions of attentional demand is relatively muted. Under such conditions, increased cholinergic activity in the PFC is required for strong top-down cognitive (attentional) control over behavior, which is presumably one reason that STs have poor cognitive control over their behavior (blue arrows). The PFC projects to many brain regions that participate in cognitive control (as indicated by the dashed lines), including projections back to the VTA, NAc and basal forebrain, and many others (see Kuhn et al., this volume; Haight and Flagel, 2014; Haight et al., 2017; Sarter and Phillips, 2018). How these different brain regions interact to reciprocally modulate one another in the control of behavior is not well understood. Right. “Goal-Trackers” (GTs) are animals in which functional activity in dopaminergic projections from the VTA to PFC and NAc, and between the NAc and VP, are weaker than in STs, which is presumably why they are less prone to attribute incentive salience to discrete reward cues than STs. In contrast, GTs show greater ACh activity in the PFC in response to reward cues and under conditions that tax attentional processes, which presumably contributes to their superior cognitive (attentional) control over behavior, and diminished impulsivity. See the text for
references to studies that support these assertions. Finally, the term “Basal Forebrain” is used here narrowly, to refer to the brain regions where cholinergic neurons that project to the cortex are located, which includes the nucleus basalis of Meynert, substantia innominata, and the horizontal limb of the diagonal band.

References


Cogan, E. S., Shapses, M. A., Robinson, T. E., & Tronson, N. C. (May 3, 2018). Disrupting reconsolidation in rats: Memory erasure or blunting of
emotional/motivational value? Neuropsychopharmacology. doi: 10.1038/s41386-018-0082-0. [Epub ahead of print].


Kawa, A. B., Bentzley, B. S., & Robinson, T. E. (2016). Less is more: Prolonged intermittent access cocaine self-administration produces incentive-
sensitization and addiction-like behavior. Psychopharmacology (Berl) 233, 3587–3602.


Gambling Hijacks an Ancestral Motivational System Shaped by Natural Selection

Patrick Anselme

Corresponding Author:
Patrick Anselme, Faculty of Psychology, Department of Biopsychology, University of Bochum, Universitätsstraße 150, D-44801 Bochum, Germany; e-mail: Patrick.Anselme@rub.de; phone: +49 (234) 32 21628; fax: +49 (234) 32 14377.

Abstract

Gambling is a desirable and pleasurable activity for many people throughout the world. Why do we find attractive and fun engaging in an activity that, for sure, will cause greater monetary losses than gains? And why does this activity sometimes acquire addictive properties to such a point that its practice may become uncontrollable and destroy the gambler’s life? Reward uncertainty, a major component of gambling situations, is known to invigorate food seeking and food consumption in birds and mammals, including humans, exposed to natural and artificial settings. It is argued that behavioral invigoration is an adaptive strategy against the risk of starvation when food availability is unpredictable, and that this effect results from motivational excitement for possible good news when bad news are likely—that is, the “hope” for upcoming rewards. Incentive hope, a concept not reducible to that of incentive salience, is thought to motivate seeking behavior when rewards are unguaranteed. Although reward uncertainty is unlikely to be a source of addiction in itself, it is suggested that gambling hijacks incentive hope as an ancestral motivational system adapted to the search of food in the wild, leading to addictive behaviors.
in vulnerable human individuals exposed to overstimulating environments such as casinos.

Keywords: adaptation; dopamine; gambling; incentive hope; incentive salience; motivation; pathological behavior; reward uncertainty

**Why Do We Gamble?**

People gamble on many occasions, at casinos but also simply buying lottery tickets and scratch cards. In the United Kingdom, for example, around 70% of people gambled in the past 12 months according to a 1999 (72%) and a 2007 (68%) survey (Wardle et al., 2007). Gambling activity is not new; prehistoric dice consisting of objects such as pebbles and bones as old as 8,000 years have been identified (Schwartz, 2006). The first dice throwers were shamans who used *astragalus* for divination (the practice of telling the future), not for gambling in its modern form, but this was already a way of wagering on uncertain outcomes. The line between divination and gambling is blurred in our ancestors, but it is a fact that gambling-like activity has always been a crucial part of the human experience (Schwartz, 2006).

Why do people gamble in our modern societies? Griffiths (1990) reported that a large majority (90%) of individuals start to gamble for fun, and that this factor remains the most common reason invoked (84%) to continue this activity thereafter (see also Nower & Blaszczynski, 2010). A smaller number of individuals start to gamble to win money (70%), and this reason is then less frequently given to justify continuation of the activity (48%). Why is it so attractive and fun engaging in an activity that, for sure, will cause greater monetary losses than gains? And why do many people repeat this activity again and again to such a point that gambling behavior may turn pathological and destroy the gambler’s family, social, and professional lives? Here, I defend the hypothesis that gambling is attractive and fun, irrespective of its possible deleterious modern consequences, because natural selection favored organisms for which reward uncertainty enhances reward-seeking motivation. (The word “organism” refers to our human ancestors but also to our nonhuman ancestors and to many other animal species that are not directly related to humankind.) I am not trying to say that individuals seek and like uncertainty in itself. Instead, the relatively
random distribution of resources (especially food) in the environment is a challenge for survival. Food is globally predictable but locally unpredictable; whether an attempt to get food will be rewarded or not cannot be determined in advance. Individuals with a higher motivation to seek food items in this gambling-like situation—time and energy must be spent without any guarantee of positive outcomes—increase their chance of finding them in sufficient amounts and hence their chance of survival and of reproduction (Anselme, 2013; Anselme & Robinson, 2013; Anselme et al., 2017).

In this perspective, gambling is attractive and fun because we tend to find desirable and pleasant the activities we are adapted for. For example, we want and like to consume sweet and salty nutrients due to their favorable metabolic implications, but we are less hungry for bitter and sour foods—two tastes often associated with toxins and fermentation in nature (Panksepp, 1998). Similarly, people prefer to live in savanna-like environments relative to other alternatives such as deserts and different forest types (Falk & Balling, 2010; Orians & Heerwagen, 1992), suggesting that we want and like the environments in which our hunter-gatherer ancestors lived and evolved during the Pleistocene—a period of approximately 2.5 MY (Pinker, 1997). In other words, gambling would be attractive and fun because this activity hijacks an ancestral motivational system shaped by natural selection to optimize food seeking in uncertain environments.

In this chapter, I aim to go further in the analysis of this motivational system. Specifically, I target the implications of previous theoretical developments (see Anselme 2015, 2016) for the understanding of the motivational origins of gambling behavior. First, it is shown that reward uncertainty enhances foraging behavior in animals (and humans) exposed to natural and artificial settings, indicating that this represents quite a general process. Second, it is argued that a good candidate to explain the behavioral invigoration observed under uncertainty is to say that animals “hope” for rewards when they are not guaranteed. Incentive hope—or the motivational excitement for possible good news when bad news are likely—is believed to be a product of natural selection, because it may act against the risk of starvation (Anselme et al., 2017). It is explained how incentive hope can be distinguished from conscious hope, the former denoting the core psychological underpinning of the latter, and also partly from incentive salience (Berridge & Robinson, 1998). Third, I suggest that our modern societies provide well-designed environments, such as casinos, in which
incentive hope is hijacked and may lead to maladaptive behaviors in the most vulnerable individuals.

**Reward Uncertainty Boosts Foraging Activity**

Researchers working with animals have long noted that the uncertainty of obtaining a reward invigorates seeking behavior. This phenomenon is well documented in two distinct research fields: the ecology of energy management and Pavlovian autoshaping. Here, I briefly review the uncertainty situations under which behavioral invigoration can be observed and emphasize the adaptiveness of this process.

**Energy Management in Unfavorable Environments**

In the wild, animals have to face multiple sources of risk, especially predation and starvation. The risk of starvation is particularly important for small-sized individuals, such as found in many passerine bird species (e.g., robins, starlings, blackbirds), because their unfavorable surface/volume ratio causes a rapid loss of their internal heat. In summer, when food is abundant, small birds spend 40–60% of the day time seeking food and tend to reject opportunities to eat in order to reduce the risk of predation—the leaner an individual, the faster and the more agile it is to escape from predatory attacks. But in winter, when food is scarcer, they may spend up to 85–95% of the day time seeking food, and they eat as many food items as they can find out in order to reduce the risk of starvation, despite a higher risk of predation. Cold is only partly responsible for this increase in foraging time, because individuals kept under low temperatures in the lab do not necessarily increase food consumption (e.g., Pravosudov & Grubb, 1998). In fact, small birds eat and/or hoard more food items when the resources are unpredictable—that is, potentially unavailable on some days (Bauer et al., 2011; Dolnik, 1967; Haftorn, 1976; King & Farner, 1965; Pravosudov, 2003; Pravosudov & Grubb, 1997; van Balen, 1980). Invigoration of seeking behavior in winter has the adaptive consequence that, if food remains in sufficient
amounts in the environment, this process may increase the fat reserves of birds—and therefore their chance to survive the unlucky days (for computer simulations, see Anselme et al., 2017). It is important to note that humans exposed to limited, irregular resources also eat more and become attracted by high-calorie food items (Cheon & Hong, 2017; Laran & Salerno, 2013; Nettle et al., 2017; Swaffield & Roberts, 2015). The fact that people—for whom starvation risk is low within modern Occidental societies—exhibit the same kind of behavioral responses to food unpredictability as wild birds do is an indication that invigoration of seeking behavior is genetically determined here, shaped by natural selection as an anti-starvation strategy.

Finally, it must be emphasized that winter is only one cause of food unpredictability in the wild, other factors contribute to render access to food difficult. Some individuals have an unpredictable access to food because they are poor foragers (Cresswell, 2003), or because dominant individuals prevent them from reaching the richest-food sites (Krams, 2000), or because of intraspecific competition. Indeed, a food site contains a limited number of edible items. The presence of competitors on this site reduces the opportunities to eat for a given individual. As in the case of poor foragers and of subordinate individuals, competitors tend to invigorate foraging rate and foraging effort in general (Chakravarti & Cotton, 2014; Fernandez-Juricic et al., 2004; Keeling & Hurnik, 1996; Plowright & Redmond, 1996; Xin et al., 2017).

Sign-Tracking Behavior under Partial Reinforcement

The brief presentation of a conditioned stimulus (CS, such as a lever for rats), followed by automatic delivery of some food pellets, may lead animals—after repeated trials—to approach and interact with the CS (sign-tracking) or to inspect the food dish during the CS presentation (goal-tracking). For detailed information on the behavioral and neurobiological analyses of sign- and goal-tracking behaviors, see Kuhn et al. (this volume), Meyer & Tripi (this volume), and Robinson et al. (this volume). In this experimental procedure (Pavlovian autoshaping), sign-tracking appears irrational because this behavior occurs without necessity—the animal is rewarded on each trial, irrespective of its interaction with the CS (Tomie et al., 2016).

Interestingly, when only half of the trials are randomly rewarded (the CS is ambiguous, predicting food or no food), sign-tracking behavior increases
in comparison with a situation of continuous reinforcement (where the CS is nonambiguous, predicting food consistently; Anselme et al., 2013; Boakes, 1977; Collins & Pearce, 1985; Gottlieb, 2004). Accordingly, goal-tracking behavior is decreased, and there is evidence that food uncertainty converts potential goal-trackers into sign-trackers (Robinson et al., 2015). The invigoration of the sign-tracking responses appears even more irrational here in that reward rate is reduced (partial reinforcement) compared to what it could be (continuous reinforcement). But is this irrationality? After all, we saw previously that foraging effort is increased when resources are scarce, and that this adaptive strategy consists of an insurance against starvation. To understand the stimulating effect of partial reinforcement on sign-tracking behavior, we have to ask a simple question: why did Pavlov's dog salivate to the sound of a bell? The answer is: because salivation is useful to the digestion of the upcoming food. Animals learn to respond to a CS only if the conditioned response helps them cope with—is relevant to—the unconditioned stimulus or UCS (Domjan, 2016, p. 100). For example, Garcia and Koelling (1966) found that the number of lick responses to an audiovisual CS decreased when the UCS was shock but not when the UCS was sickness. In contrast, the lick responses to a taste CS decreased when the UCS was sickness but not when the UCS was shock. The rationale behind these results is that, in nature, the auditory or visual detection of a stimulus can potentially predict injury (e.g., predatory attack) but not illness, while the taste of an ingested food can potentially predict illness (e.g., spoiled nutrient) but not injury. The evolutionary established relationships between CSs and UCSs could also explain the higher response rates to an unreliable than to a reliable CS in Pavlovian autoshaping; animals would respond more to unreliability because, in nature, the distribution of food items is basically random and many CSs are imperfect predictors of food (a seed husk may be empty, a mulberry may have no fruits, etc.). Animals are simply prepared to work harder when part of the attempts to get food is non-rewarded. In other words, avidly responding to the CS presentations in uncertainty autoshaping is similar to avidly checking the available CSs in a poor-food environment; this schedule-induced behavior is the signature of a neurobehavioral adaptation—aimed to minimize the risk of starvation in a natural setting.

Incentive Hope: A Common Response to
Unpredictable, Significant Events

I have suggested that animals increase their responses to signals of uncertain food because this contributes to reduce the risk of starvation, but how this adaptive behavior is produced remains unclear. What is the psychological process responsible for behavioral invigoration here? Elsewhere, I showed that learning and frustration cannot satisfactorily account for invigoration (Anselme 2015, 2016)—the arguments will not be repeated due to space limitation. Instead, as previously, I focus on the importance of incentive salience (or incentive motivation or “wanting”) in the process-controlling invigoration, while showing that this phenomenon is only part of the full explanation. It is suggested that behavioral invigoration under uncertainty comes from the motivational excitement animals develop for possible good news when bad news are likely—a psychological state referred to as incentive hope (Anselme 2015, 2016). How incentive hope can motivate gambling will be considered.

Incentive Salience and Beyond

The incentive salience hypothesis (Berridge & Robinson, 1998) relies on a body of evidence showing that (a) motivated behavior is strongly correlated with the release of dopamine in the ventral striatum, and (b) motivated behavior is produced unconsciously rather than by means of conscious decisions. The hypothesis suggests that mesolimbic dopamine transforms the neutral perception/representation of a stimulus in an appetizing reward (Berridge, 2007). For example, dopamine controls the fact that a high-calorie dessert is attractive when hungry and aversive when full, and cognition is ineffective in modulating this effect. The neurophysiological underpinnings of this phenomenon is adaptive, informing the individual of what should or should not be done (e.g., eat or don't eat) without having to think about it. Thus, incentive salience easily explains why a CS predictive of reward is avidly approached and physically contacted in hyperdopaminergic mutant mice (Peciña et al., 2003), while food itself is ignored in dopamine-deficient mice (Cannon & Bseikri, 2004).

At first sight, incentive salience could also easily explain why reward
uncertainty invigorates behavioral responses; uncertainty could be viewed as a factor contributing to “wanting.” Indeed, reward uncertainty enhances dopamine production in the ventral tegmental area, which directly projects to the ventral striatum (D’Souza & Duvauchelle, 2008; Fiorillo et al., 2003; Hart et al., 2015), and reward uncertainty interacts in a complementary fashion with dopaminergic drugs (Robinson et al., 2015; Singer et al., 2012; Zack et al., 2014). Also, there is evidence that pathological gamblers show higher striatal dopamine levels than healthy controls (Joutsa et al., 2012), especially when they are experiencing uncertainty (Linnet et al., 2012). For sure, incentive salience is involved in the processing of reward uncertainty, but there are two good reasons to believe that it is only part of the whole story:

1. The incentive salience hypothesis does not make any prediction relative to the behavioral effects of reward uncertainty. The attribution of incentive salience to a CS is independent of the predictive value of the CS—that is, of the reliability of the CS-UCS association (Flagel et al., 2007; Robinson & Flagel, 2009). A 100% reward-predictive CS is attractive, but the hypothesis does not tell us whether a 50% reward-predictive CS should be more or less attractive. Intuitively, we may have the feeling that the hypothesis would predict a decrease (rather than an increase) in response rates under a 50% (relative to a 100%) probability of reward, because a 0% reward-predictive (random) CS is unattractive (e.g., Rescorla, 1968). But the incentive salience hypothesis provides no theoretical justification for this interpretation.

2. If incentive salience fully controlled behavioral invigoration under uncertainty, animals exposed to a free choice should prefer an ambiguous CS (50% predictive of food) to a nonambiguous CS (100% predictive of food). But such a preference is not observed, except perhaps under the influence of some dopaminergic agonists (Tremblay et al., 2017). In probabilistic choices, animals avoid CS ambiguity when possible (McDevitt et al., 2016). They may prefer one option that provides food or no food over another option that provides food with more certainty but only if the former is associated with nonambiguous CSs (e.g., if the white key turns red—> 80% chance of reward, if the white key turns green—> 0% chance of reward) and the latter with ambiguous CSs (e.g., if the white key turns blue or yellow—> 100% chance of reward). In other words, animals exposed to free choices
In summary, explaining how reward uncertainty invigorates response rates—whether in the wild or in serial autoshaping—amounts to understanding how uncertainty alters the animal's motivation to respond. The role of dopamine in this phenomenon suggests that incentive salience is required, but more is needed to fully capture how reward motivation interacts with uncertainty itself.

**Motivational Excitement for Possible Good News**

How can animals become motivated to seek unpredictable reward sources? In fact, the more unpredictable a food source, the more motivated an animal should be to optimize its chance of survival (Anselme, 2013). As discussed earlier, this is what they do; animals behave as if they were excited by possible good news—that is, finding what they seek—when the environmental conditions indicate that bad news—not finding what they seek—are likely. This is the incentive hope hypothesis (Anselme, 2015, 2016). The word “hope” refers to the fact that an individual “wants” a reward that is not guaranteed; and “incentive” refers to the fact that this psychological state is subcognitive—its occurrence does not require any form of knowledge or consciousness. Importantly, incentive hope is viewed as the unconscious core psychological underpinning of conscious hopes but does not require the perception of an introspective self—there is an “I” who hope for future reward. Conscious hopes involve the ability to have a concept of self as a stable entity that existed in the past (yesterday) and will continue to exist in the future (tomorrow). However, current findings suggest that this ability is specific to humans (Tulving, 2005). Incentive hope simply means that animals behave as if they consciously hoped for reward. Similarly, incentive salience—“wanting” that food—is likely to be the unconscious core psychological underpinning of conscious desires (Anselme and Robinson, 2016) but does not imply that there is an “I” who want that food. Thus, the concept of incentive hope encompasses that of “wanting,” since incentive hope is assumed to be a dopamine-dependent process. But it is not reducible to that of incentive salience, and incentive hope may recruit brain regions
not specifically involved in the control of incentive salience such as the dorsomedial striatum (Torres et al., 2016).

Now, we have a theoretical framework compatible with the incentive salience hypothesis that can overcome the two limits described in the previous section. First, our view predicts that reward uncertainty invigorates response rates to an ambiguous CS because of the animal's motivational excitement. Second, and this is important, incentive hope implies that an ambiguous CS invigorates responding only if uncertainty is unavoidable (like in serial autoshaping or in the wild), not that an ambiguous CS should be preferred to a nonambiguous CS. Behavioral invigoration does not denote preference but survival requirement. The incentive hope hypothesis predicts that ambiguity cannot be preferred to nonambiguity because developing hope for something you can obtain for sure is superfluous. It could be argued that a number of experiments show a preference for reward uncertainty in choice procedures (e.g., Belke & Spetch, 1994; Dunn & Spetch, 1990; Gipson et al., 2009; Mazur 1991; Spetch et al., 1990; Stagner & Zentall, 2010; Vasconcelos et al., 2015). But, as noted earlier, uncertainty is not sought for itself in these experiments; the animals are just tracking the nonambiguous CSs associated with it. For example, Chow et al. (2017) tested the preference of rats for a discriminative option consisting of two nonambiguous CSs with 50:50 odds (one predicted 0% and the other 100% chance of reward) and a non-discriminative option consisting of one ambiguous CS that predicted reward or non-reward with 50:50 odds. Thus, the overall probability of reinforcement was 50% with each option. They observed an increasing preference for the discriminative alternative with training, indicating that animals do not prefer ambiguity. These authors argued that this result contradicts a major prediction of the incentive hope hypothesis, which suggests that uncertainty-induced hope for rewards adds some motivational value to normal “wanting” for those rewards (Anselme, 2015, 2016; Anselme et al., 2013). For them, incentive hope should be minimal in the discriminative option because reward probabilities are known for each CS (0% and 100%), while it should be maximal in the non-discriminative option due to the predictive inaccuracy of the CS (50%). However, there is misinterpretation about the definition of the incentive hope hypothesis here; the hypothesis posits that unavoidable reward uncertainty associated with CS ambiguity enhances conditioned responding (e.g., serial autoshaping), not that animals prefer this configuration. In their procedure, the rats were undoubtedly attracted by the nonambiguous 100% chance of reward associated with one
of the CSs in the terminal link of the discriminative option. Probabilistic choice behavior is a consequence of incentive salience without incentive hope.

In summary, we showed that animals increase their response rates to stimuli that ambiguously and unavoidably predict the presence or the absence of rewards—especially food—in natural and artificial settings. This phenomenon appears to be an adaptive strategy shaped by natural selection to minimize the risk of starvation. We suggested that the core psychological state underpinning behavioral invigoration in this context is incentive hope. If correct, this means that incentive hope is likely to play a determining role in human gambling. For example, the idea that hopes for future success develop among gamblers experiencing near misses—that is, failures that are close to being successful—was briefly proposed by Parke and Griffiths (2004). Indeed, near misses are perceived as encouraging signs that confirm the effectiveness of the gambler's strategy, leading to continued gambling. In addition, the motivational effects of near misses are evidenced by the higher dopamine levels correlated with their occurrence (Chase and Clark, 2010; Clark et al., 2009; Kassinove and Schare, 2001). More generally, let's see how gambling environments may contribute to recruit incentive hope.

**Casinos Act as Supernormal Configurations of Stimuli**

In this section, it is argued that gambling hijacks an ancestral motivational system (incentive hope) shaped by natural selection to promote survival in the wild—just as serial autoshaping does. The idea that some behaviors exploit cognitive/perceptual systems designed for independent evolutionary purposes is not new: reading, writing, enjoying music, and even believing in God have no adaptive function in themselves, they are all by-products of the toolkits of our complex adapted brain (Pinker, 1997). For the same reason, we have no adaptation to specifically enjoy eating hamburgers, but hamburgers contain a number of ingredients (fat, salt, proteins) for which high-selective pressures existed among our hunter-gatherer ancestors—these ingredients were both rare and necessary for survival. The individuals who could find them out had a better chance of survival than
those who could not, and had consequently a better chance of transmitting their good genes to the next generation, and so forth. Today, hamburgers act as supernormal configurations of stimuli because they bring all these ingredients together, stimulating incentive salience ("wanting") more than many other foods. Similarly, I think that gambling hijacks incentive hope, because casinos act as supernormal configurations of stimuli:

1. **Casinos are confined environments in which any outcome is uncertain.** In a sense, monetary rewards in casinos are comparable to the scarce food items that an animal seeks midwinter: reward uncertainty is unavoidable and successful foraging behavior is not guaranteed, irrespective of the cognitive strategy that is used. One major difference, however, is that the person may leave the casino any time. The opportunity to express an activity we are adapted for (seeking under uncertainty) while having the option to quit before things are going bad might be part of the pleasure to gamble.

2. **Casinos contain multiple potent, ambiguous CSs.** Sounds, lights, the tokens used for slot machines, and money itself, are very powerful CSs that contribute to motivate people to play games and persist in this activity. Griffiths (1990) reported that, among other factors, the flashing lights and/or the music and noise are attractive qualities for 60% of the players. More specifically, Mentzoni et al. (2014) found that low-tempo music increases gambling persistence (more bets placed), while high-tempo music increases gambling impulsivity (faster reaction time per placed bet). Tokens, sometimes in metal like real money, may become strong CSs for people going to a casino repeatedly. All these CSs are ambiguous: a token is placed in a slot machine and many lights/sounds arise before the outcome—win or loss—is known.

3. **Casinos simulate intraspecific competition for resources.** When the amount of a resource is limited, the presence of competitors necessarily reduces the availability of that resource for each individual. Competition-induced scarcity increases foraging effort, as shown earlier in animals. The same principle might apply to casinos, which are full of people trying to get (foraging on) the same rare resource—money (Kohn, 1992). In a sense, the competition also exists between the gambler and the casino owner.

4. **Availability of such environments.** Countries that offer many gambling opportunities have higher prevalence rates of pathological gambling
It is interesting to note that not all forms of gambling are good predictors of pathological behavior, and that the best six predictors—pull-tabs, casino, bingo, cards, lottery, and sport betting—have little in common (Welte et al., 2004). However, the two riskiest types—pull-tabs and casino—have high-event frequencies, compared to the least risky types—lottery and sport betting (Welte et al., 2004). Pathological gambling obeys the same logic as other addictions, such as overeating in junk-food societies or hypersexuality induced by free pornography on the Internet.

Together, these situational factors may generate a context that favors the expression of human foraging activity, just as similar features/qualities enhance foraging effort in nonhuman animals. But if gambling recruits an ancestral motivational system established for other evolutionary purposes, why does only a small portion of the population (1–2%) develop pathological gambling (Shaffer et al., 1999; Wardle et al., 2007)? The presence of many casinos in our modern Western societies should attract most people and cause severe addiction to gambling. In fact, the presence of favorable environments is certainly insufficient in itself to induce addictive behaviors—similarly, animals forage more intensively in winter than in summer, but they do not become addicted to food seeking. Important factors to consider here are related to the personality traits (Forbush et al., 2008) and lifestyle of gamblers (Ledgerwood & Petry, 2006). Individual vulnerability contributes to explain why problem gambling remains relatively marginal relative to the significant proportion of individuals who gamble in the general population (e.g., Wardle et al., 2007).

Why Are We Not All Pathological Gamblers?

What is an addiction? Take the example of drug addiction (for details, see Morrow, this volume; Robinson et al., this volume; Tomie et al., this volume). Repeated use of a drug abuse (cocaine, heroin, alcohol, etc.) has deleterious effects on health and other dimensions of the drug user’s life. Drug addicts may be fully aware of that, expressing their firm intention to stop their consumption and partaking sometimes in treatment programs. However, a
drug rehab removes the withdrawal symptoms associated with the early phase of abstinence but has no action on the long-lasting sensitization of dopamine neurons caused by repeated drug administration (Robinson & Berridge, 1993). Even long after the withdrawal symptoms have disappeared, a significant number of individuals relapse to drug taking (Hunt et al., 1971), and the probability to relapse is higher for those who developed neuronal sensitization (Bartlett et al., 1997). This means that mesolimbic dopamine plays a determining role in addictive behavior, independently of the individual's cognitive intention to remain abstinent. In fact, any kind of addiction—including problematic gambling activity—is a consequence of this same process. And any kind of addiction is susceptible to develop only in the most vulnerable individuals. Many persons cannot stop smoking, while others quit easily. The most probable reason for this is that the former have an addiction to nicotine and the latter do not. The same is true of gambling. For example, Parkinson's disease patients are often treated with dopaminergic drugs—such as pramipexole and ropinirole—to alleviate their symptoms (Dodd et al., 2005; Voon et al., 2011). However, only a minority of them (13.6%) develop addictions, which may include compulsive shopping and pathological gambling (Weintraub et al., 2010; see also Crockford et al., 2008).

There are no strict causes of problem gambling activity, but a series of risk factors have been identified (for extensive reviews, see Goudriaan et al., 2004; van den Bos et al., 2013; van Holst et al., 2010). For example, impulsivity—the tendency to prefer small immediate rewards over larger delayed rewards—is a major factor to consider. The inability to wait for gratifications leads problem gamblers to try to obtain the jackpot at a casino rather than saving a little amount of money every week. Given that young individuals have lower levels of self-control than older ones, they are more susceptible to gambling addiction (Johansson et al., 2009), a feature also observed between young and older rats with respect to drug self-administration (Adriani et al., 2002; Quoilin et al., 2010; Spear & Varlinskaya, 2010). Competitiveness is also correlated with pathological gambling, because competitive people are less likely to give up after a loss than noncompetitive people (Parke et al., 2004). Thus, competitive individuals are more prone to chasing behavior, which is also a risk factor in the development of problem gambling. Problem gambling is more frequent among people experiencing a lack of rewarding events in life: slot machine players typically gamble to escape stressful situations, while horse race and
casino gamblers attempt to replace feelings of boredom with higher levels of arousal (van Holst et al., 2010). Finally, social and environmental stresses make individuals more vulnerable to the addictive properties of drugs of abuse and also more prone to attribute motivational salience to CSs (Beckmann & Bardo, 2012; Diaz et al., 2013; Lomanowska et al., 2011; Nader et al., 2012; Pattison et al., 2013). This may certainly contribute to enhance the attractive power of the CSs present in casinos or on the screen of a computer for people who gamble online at home. Other factors have been reported, such as the illusion of control and the presence of drug addictions (e.g., Johansson et al., 2009).

Thus, vulnerability to gambling addiction results from a combination of external and internal factors, explaining why many people do not have to struggle against gambling problems. But it must be realized that gambling addiction is only possible because we have a motivation to perform this kind of activity. Impulsivity, competitiveness, boredom, and stress can lead individuals to gamble only because they have an attraction for money (incentive salience) and are motivationally aroused by possible good news (incentive hope). Incentive salience is sufficient to explain drug addiction, because drugs directly act at a neurobiological level and have immediate reinforcing effects. Incentive salience is also crucial in gambling and represents the motivational basis for money attraction. But incentive hope is necessary to explain why unlikely monetary CSs are so avidly chased, just as why a rat respond more to an unreliable than to a reliable metal lever CS. Original predictions can be proposed on this basis. For example, the incentive hope hypothesis predicts that the hope for money is higher than a negative emotion such as frustration before a trial, especially in problem gamblers because their motivation to earn money is higher than in non-gamblers (Nower & Blaszczynski, 2010). The hypothesis also predicts that the perception of economic insecurity is correlated with this form of addiction. It is already known that problem gamblers are more frequent among people with low socioeconomic status (e.g., Johansson et al., 2009). But it is here argued that people without money problems who perceive themselves in a situation of potential economic insecurity (because of unstable working activities) might be a population at risk as well.

In conclusion, incentive hope is hypothesized to be at the very origin of gambling addiction, even though maladaptive behavior depends on a combination of many other factors that is found only in a small proportion of the general population. But it is paradoxically this motivational system that
perhaps allowed all our ancestors to survive for hundreds of thousands of years.

Acknowledgments

This study was funded by the Deutsche Forschungsgemeinschaft through An1067/1–1.

References


Kassinove, J. I., & Schare, M. L. (2001). Effects of the “near miss” and the “big win” on persistence at slot machine gambling. *Psychology of Addictive Behavior, 15*, 155–158.


Krams, I. (2000). Length of feeding day and body weight of great tits in


128 | Jonathan Morrow and Arthur Tomie
Individual variation in sign- and goal-tracking during Pavlovian conditioned approach (PavCA) is thought to reflect a psychological trait that we refer to as the tendency to attribute incentive value (incentive salience) to reward cues. But is incentive salience attribution truly a personality trait that reflects temperament, like impulsivity or sensation seeking? An alternative explanation is that these subgroups of rats differ in general learning processes. For example, the initial value placed on the unconditioned stimulus (US) may explain the differences in the development of sign- and goal-tracking and some of the correlated traits associated with these behaviors. However, while many findings can be explained by such differences in general learning processes, some, such as cocaine-induced vocalizations, cannot. In this chapter we review examples of behaviors in other paradigms that are associated with sign-tracking and goal-tracking, focusing on (1) the deficits in response inhibition and enhanced impulsivity that are apparent in sign-trackers, and (2) the seemingly disparate association of sign-tracking with drug-induced vocalizations. In integrating these findings, we suggest that sign-tracking is...
associated with poor inhibitory control that leads to increased impulsivity and enhanced responsivity to conditioned stimuli (CSs)\(^1\) associated with rewards. Further, once this learning has occurred, CSs can have enduring influences upon behavior that depend on their acquired incentive properties, but that can also be updated as the value of the US changes.

Keywords: attention; autoshaping; cocaine; devaluation; goal-tracking; impulsivity; incentive salience; omission; sensitization; sign-tracking; suboptimal choice; ultrasonic vocalizations

**Introduction**

A classic study by Breland and Breland (1961), while not explicitly measuring sign-tracking, showed abnormal attachment to food-associated stimuli. When they trained raccoons to deposit coins into a receptacle to earn food, they reported that “Not only could [the raccoon] not let go of the coins, but he spent seconds, even minutes, rubbing them together (in a most miserly fashion), and dipping them into the container. He carried on this behavior to such an extent that the practical application we had in mind—a display featuring a raccoon putting money in a piggy bank—simply was not feasible. The rubbing behavior became worse and worse as time went on, in spite of nonreinforcement.” This may be better described as an extreme example of conditioned reinforcement, because these raccoons were trained in an operant and not a Pavlovian paradigm. In fact, as discussed later in the text, studies with sign- and goal-trackers suggest that the persistent behavior that occurs during instrumental conditioning is different than that which occurs during Pavlovian conditioning. However, it is an early demonstration of how excessive attribution of incentive salience to a reward cue can lead to maladaptive behavior.

In her 1982 review, Karen Hollis describes her “prefiguring” hypothesis, in

\(^1\) Here we use the term “cue” to refer to reward-related stimuli generally, while reserving “conditioned stimulus” (CS) for discussions involving Pavlovian conditioning.
which sign-tracking is an adaptive response in that it enables “the animal to optimize interaction with the forthcoming biologically important event (US) [which] allows the animal to better deal with the US event, and as such, the [conditioned response] is essentially preparatory” (Hollis 1982). Hollis says that it is irrelevant to her functional argument that the CS and US are separated in the laboratory, essentially because this separation rarely occurs in the real world. Yet, these laboratory experiments demonstrate that sign-tracking is a poorly controlled conditioned response and is related to poor response inhibition in animal models of impulsivity (Tomie 1996). This has translational impact, because modern human environments frequently accomplish exactly what Hollis deemed irrelevant by separating the CS and US, and is a common factor among many disorders, including drug addiction, obsessive-compulsive disorder, and other cue-controlled disorders such as problem gambling and post-traumatic stress disorder (Anselme this volume; Morrow this volume; Robinson et al. this volume; Tomie et al. this volume). For these disorders, the cues are often far-removed from the primary reinforcer (e.g., the drug or money). Thus, even though sign-tracking may have evolved as an adaptive behavior, understanding how sign-tracking can lead to maladaptive behavior in modern environments is a key goal from basic learning and translational perspectives. In the next two sections, we provide several examples of sign-tracking being a poorly controlled response, and how individuals predisposed to sign-track engage in other putatively maladaptive behaviors.

2. It is worth mentioning the distinction between studies of sign-tracking versus sign-trackers (and goal-tracking/trackers). Sign-tracking refers to the degree of sign-tracking within a group, while sign-trackers refers to the subgroup of rats that preferentially sign-track or are predisposed to sign-track. This is important, because the purpose of an experiment differs depending on whether an entire group (i.e., including sign-trackers, goal-trackers, and intermediates) is being studied, or sign-trackers and goal-trackers are being explicitly compared. In the former case, the objective is to understand the brain and behavioral mechanisms that underlie sign-tracking, while in the
Omission studies are particularly interesting because they impose a negative contingency on the subjects' behavior. Specifically, if the subject makes a sign-tracking response, the reward is not delivered. Adding this instrumental contingency would be expected to decrease sign-tracking rapidly, because in doing so the number of rewards would be maximized. Yet, several studies suggest that under omission conditions, sign-tracking is reduced only slowly and does not completely disappear (Herrnstein and Loveland 1972; Hollis 1982; Moore 1973; Williams and Williams 1969). This is particularly evident in studies with pigeons (Williams and Williams 1969) but can be seen in rat studies as well. For example, an early study with rats (Davey et al. 1981) found that, while lever pressing was reduced by omission, rats still approached and investigated the lever. This “nosing” behavior increased as a result of the omission contingency. In our own studies, we trained rats in a PavCA paradigm, and after five days of training, switched to an omission contingency in which either a sign-tracking or a goal-tracking response resulted in the non-delivery of the food pellet. As can be seen in Figure 6.1, lever-presses declined throughout training (as did goal-tracking, not shown in the figure). However, during this experiment we equipped the levers and their surrounding faceplates with contact detectors, which enable the detection of approach that does not result in a lever press. We found that there was no effect of omission on this measure of sign-tracking. Thus, as in Davey et al. (1981) and in other studies (Chang and Smith 2016; Locurto et al. 1976; Stiers and Silberberg 1974) we found that sign-tracking was still present, although the topography of the response had been altered. These findings suggest that sign-tracking is not completely independent of the US latter case the objective is to determine the vulnerability factors that render particular individuals more likely to become sign-trackers and engage in other related behaviors.
such that it cannot be modified, but also that the incentive properties of the CS remain intact despite the negative behavioral contingency.

**Extinction**

Subsequent studies using Pavlovian conditioning have demonstrated a similar phenomenon regarding poorly controlled sign-tracking in the face of non-reinforcement. In the extinction paradigm, the food reward is simply withheld while the CS continues to be presented. When this is done in a Pavlovian paradigm, the conditioned response (in our case sign-tracking and goal-tracking) decreases in frequency and eventually ceases. For example, Stringfield et al. (2018) removed the US (a sucrose solution) during a single extinction session and observed a reduction in goal-tracking, but not sign-tracking. In a study by Beckmann and Chow (2015), sign- and goal-tracking were conditioned to separate stimuli, and they showed that sign-tracking was more resistant to extinction as well. This 2-CS model is useful for determining learning mechanisms of conditioned approach behaviors, because it allows the simultaneous assessment of sign- and goal-tracking in the same individual. However, for this same reason, it is not ideal for studies targeted toward determining whether individual vulnerabilities render certain subjects resistant to extinction.
Ahrens et al. (2016) compared extinction rates in sign- and goal-trackers and demonstrated that sign-tracking extinguishes more slowly than goal-tracking. However, there were no apparent differences between sign- and goal-trackers in the extinction of instrumental responses, for example, nose-poke responding for either food or cocaine (Ahrens et al. 2016; Saunders and Robinson 2011; Yager and Robinson 2010). This instrumental versus Pavlovian distinction is important for two reasons. First, instrumental extinction typically occurs in the absence of any cues, while the CS is present during Pavlovian extinction. Thus, the presence of the CS during Pavlovian extinction is the key distinguishing factor underlying sign- and goal-tracker differences in these two paradigms. Second, it suggests sign- and goal-trackers do not differ in this form of inhibitory learning generally, because only Pavlovian, and not instrumental, extinction is different between these two subgroups.
Outcome Devaluation

A third way to study the persistence of sign-tracking is through outcome devaluation. Instead of omitting the US, subjects can be US-satiated, that is, they are given a large quantity of the US before testing, thus reducing the relative value of the US. For example, a recent study in humans (De Tommaso et al. 2017) found that a water-paired CS biased attention in thirsty subjects even after they were allowed to drink. Alternatively, the US can be replaced with something less valued, aversive (e.g., quinine), or paired with an illness-inducing drug such as lithium chloride. This latter method is ideal, because the US-illness pairing occurs in the absence of the CS, and thus changes in sign- and goal-tracking cannot be attributed to alterations of learning (Colwill and Motzkin 1994; Holland and Straub 1979). The idea is that any reduction in sign-tracking or goal-tracking observed after devaluation provides evidence that these responses are driven by the ability of the CS to evoke an internal representation of the US. Alternatively, if the devaluation does not cause a change in sign- or goal-tracking, that suggests the incentive value of the CS and its ability to evoke a response controls behavior independently of the US.

Morrison et al. (2015), after establishing sign- and goal-trackers in a group of rats, gave injections of lithium chloride after being allowed to consume the US (liquid sucrose) in the home cage for 20 minutes. They found that sign-tracking was enhanced after this treatment, while goal-tracking was reduced. Further, by examining sign-trackers and goal-trackers separately, they found that most of these changes were due to changes in goal-trackers, but not sign-trackers. A study by Nasser et al. (2015) showed a similar result using a slightly different procedure. They first paired a light stimulus with a food pellet (which elicited only goal-tracking in all rats), and then paired the food pellet with lithium chloride. The effectiveness of the devaluation was measured by examining the response to the light CS. Then, after this test, PavCA was conducted to determine which rats were sign- or goal-trackers. The authors found a positive correlation between the response to the light CS and the magnitude sign-tracking during PavCA. Like Morrison et al. (2015), this indicates that sign-trackers, relative to goal-trackers (Nasser grouped goal-trackers and intermediates together in this study), are relatively insensitive to the US devaluation. They also performed a second order conditioning task, in which a second stimulus was paired with their
light CS, but there was no relationship between the response to this second stimulus and sign-tracking. However, this does raise an interesting experimental idea: would the lever CS from PavCA support greater second-order conditioning in sign-trackers versus goal-trackers? If so, this would provide further evidence that the CS supports conditioning independent of the US. While this study has not been done, one might predict this outcome based on the experiments showing that the CS serves as a better conditioned reinforcer in sign-trackers relative to goal-trackers (Meyer et al. 2014; Robinson and Flagel 2009).

However, other studies have found that US devaluation does alter the sign-tracking response. For example, Cleland and Davey (Cleland and Davey 1982; Davey and Cleland 1984) devalued the US in rats both by satiation and using lithium chloride. They found that sign-tracking and goal-tracking were reduced similarly by both of these methods. Interestingly, rats oriented more to the lever and the goal following devaluation. The authors argued that satiation had weakened a response chain consisting of orient-approach-contact, with the latter components of this chain preferentially weakened by satiation and thus making it more likely to observe the orientation component. Another study using lithium chloride devaluation (Derman and Delamater 2014) found a similar effect and also demonstrated that an already learned goal-tracking response inhibits the development of a sign-tracking response, and vice-versa.3

**Increasing US Value**

Together, these studies show that the sign-tracking response is influenced by the value of the US. Perhaps the strongest evidence of this includes

3. However, another study found that an auditory CS did not block the sign-tracking response to a lever CS, suggesting that these different CSs engage different learning processes (Holland et al. 2013). While this does not rule out a role of the US, it does suggest that the lever CS is more prone to acquire incentive salience than auditory CSs (Meyer et al. 2014).
experiments where increasing the value of the US increases the sign-tracking response (Robinson and Berridge 2013). In this experiment, pairing a concentrated salt solution with a lever CS evoked low levels of sign-tracking, but once the rats were tested in a salt-deprived state, rats approached the CS immediately, even before additional learning had occurred. Thus, changing the value of the US in this experiment had powerful and instantaneous effect on the incentive value of the CS. Davey and Cleland (1984) also showed that (1) giving rats food that was not paired with the CS or (2) presenting rats with a food-paired auditory CS both increased sign-tracking. This suggests that the enhanced probability of “extra” USs occurring in these two conditions, whether or not the extra USs were actually presented, enhanced the degree of sign-tracking.

Impulsivity

Given the evidence that CSs acquire incentive salience and lead to poorly controlled sign-tracking responses, several studies have examined whether sign-tracking is related to other maladaptive responses. For example, impulse-control disorders are characterized by failure to resist temptation or urges. Generally speaking, these disorders can be defined by poor inhibitory control and self-regulation. However, impulsivity can be further subdivided into two subcategories, including impulsive choice and impulsive action. Classic laboratory models of these subcategories include the delay discounting task and choice reaction time tasks, respectively. Theoretically, both of these tests should be affected by overvaluing of the US, but they could also be affected by temperament, in the sense that an impulsive individual may exhibit behavioral responses in these tasks. In this section, we will discuss how impulsivity is implied experimentally and describe how it appears that sign-trackers are more impulsive than goal-trackers.

Choice Impulsivity

In delay discounting, the subject must make one of two responses, one which
results the delivery of a smaller immediate reward, while the other results in a delayed, albeit larger, reward. Either the amount of, or the delay to, the larger reward is varied, and from the subjects' responses an “indifference point” is calculated. The indifference point is the amount or delay at which the subject chooses the larger reward 50% of the time. Thus the larger this value, the less impulsive the subject is said to be (Bickel et al. 1999; de Wit and Richards 2004; Richards et al. 2012; Richards et al. 1997).

The relationship to sign-tracking in animal models of discounting is mixed, and may depend on genetic background. For example, the Lewis strain of rats have lower indifference points (Anderson and Woolverton 2005) and also learn to sign-track faster and to a larger degree compared to Fischer rats (Kearns et al. 2006). There is also some evidence from neurobiological studies that suggest that the mechanism underlying sign-tracking overlaps at least partially with that underlying impulsive choice. For example, lesions of the subthalamic nucleus decreased impulsive choice and impaired sign-tracking, and depletion of forebrain serotonin increased sign-tracking and the conditioned locomotor response to food (Winstanley et al. 2005; Winstanley et al. 2004). In another study, Long-Evans rats were tested in a PavCA paradigm and then tested under delay discounting conditions where the small reward was 1–2 pellets and the large reward was 5–10 pellets. The delays were 0, 10, 20, 40, and 60 seconds (Tomie et al. 1998). When tested in this manner, two subpopulations of rats emerged: “Sensitive” rats responded more for the large reward at the 0 and 10 second delays compared to “Insensitive” rats that were not affected by the delay and mostly chose the small reward. Interestingly, Sensitive rats sign-tracked 6 to 9-fold more than Insensitive rats, although it is not known if there was a difference in goal-tracking among these rats. Together these studies suggest a link between sign-tracking and choice impulsivity.

A study that explicitly compared sign- and goal-trackers assessed preference for a large (4 sucrose pellets) versus small (1 pellet) reward at 0, 3, 6, 12, and 24 second delays (Lovic et al. 2011) provided contrasting results. Relative to goal-trackers, sign-trackers preferred the large reward at the 12 and 24 second delay, although the effect size was marginal. Additionally, in another study using rats selectively bred for locomotor response to novelty, sign-trackers were less impulsive in a delay discounting task, which is opposite to what one might hypothesize (Flagel et al. 2010). Yet, it is worth noting that some phenotypic differences in these lines may be a by-product of genetic drift. Nevertheless, in our own work using a large sample of
heterogeneous stock rats, we have not observed a relationship between sign-tracking and delay discounting measures of impulsivity but have reported differences in action impulsivity (King et al. 2016).

**Action Impulsivity**

Another domain of impulsivity is action impulsivity, in which subjects fail to withhold a response at appropriate times. Several studies have demonstrated a link between sign-tracking and action impulsivity, as measured by tasks that require a response to be withheld in order for a reward to be delivered. For example, in the DRL (differential reinforcement of low rates of responding) task (Richards et al. 1993), subjects are only reinforced if they withhold a response for a predetermined period of time before responding. While there were no differences in overall responding or total reinforcers earned, sign-trackers, compared to goal-trackers, were less efficient in that they made more premature responses that did not result in reinforcement, which is consistent with a more impulsive phenotype (Lovic et al. 2011).

Another, more complicated test that measures impulsive action in addition to attention, is the serial reaction time test, also known as the choice reaction time task. In this task, rats must pay attention to multiple holes on a wall and enter the one that is illuminated very briefly with a small light in the hole. Correct responses are rewarded, while incorrect responses are not and result in a time-out period before the next trial. The task requires the subject to pay close attention so as not to miss which hole is illuminated. Thus, correct and incorrect responses can be measured and are thought to reflect deficits in attention (Robbins 2002). In addition, rats must refrain from entering the hole before the stimulus light appears, otherwise a time-out ensues and a premature response is recorded. These premature responses are the operational measure of impulsivity. In their study, Lovic et al. (2011) found that sign-trackers made more premature responses than goal-trackers but did not differ in the number of correct or incorrect responses. In our own work with Jerry Richards, we used a variant of this task in which rats must hold their snout in a center hole before responding and found a similar increase in premature responses (snout withdrawal) in sign-trackers compared to goal-trackers (King et al. 2016). We also did not observe any differences in correct or incorrect responses, nor did we see
differences in reaction times, which are another measure of attention in this task. Together, these studies suggest that sign-tracking is associated with increased impulsive responding but not with attentional deficits. However, Martin Sarter and colleagues have reported attentional deficits in sign-trackers (discussed later) using more rigorous tests of attentional function (Koshy Cherian et al. 2017; Paolone et al. 2013; Pitchers et al. 2017).

In summary, most reports reveal that sign-trackers are more impulsive than goal-trackers. It may seem initially paradoxical that while sign-trackers are not different than goal-trackers during extinction of instrumental responses, there is a difference in instrumental responding when the rats must withhold responding. Why is this? First, during Pavlovian extinction, the CS is present, while during instrumental extinction there is no stimulus. Second, during the choice reaction time task, DRL, and devaluation tasks, while the Pavlovian CS is not present during the test trials, the unconditioned stimulus is. Thus, the presence of either the CS or the US is key in determining whether there are differences between sign- and goal-trackers. Indeed, when sign- and goal-trackers that had undergone instrumental extinction were presented with the CS anew, the food-seeking behavior of sign-trackers reinstated to a greater degree than goal-trackers (Yager and Robinson 2010).

**Uncertainty and Suboptimal Choice**

Because of the link between sign-tracking and impulsive behavior indicated earlier, others have suggested a link between sign-tracking and gambling-like behavior. A key feature of gambling scenarios is that rewards (i.e., money) are delivered intermittently and with varying magnitude. This is readily modeled in animals by replacing money with food as the reward. For example, in a set of studies, rats were presented with a CS that was followed by a US only half the time, and the number of sucrose pellets delivered varied such that one, two, or three pellets was delivered. This led to substantial increases in sign-tracking compared to the control group that got two pellets on 100% of the conditioning trials (Anselme et al. 2013; Davey et al. 1982; Robinson et al. 2014a; Robinson et al. 2015). Anselme (2016) points out that this cannot be accounted for by most theories of learning that rely on the CS-US contiguity as a key factor leading to increases in conditioned
responding. Instead he argues that the magnitude and form (i.e., sign- versus goal-tracking) of the response are determined by motivational factors. To oversimplify his “incentive hope” model (Anselme this volume), rewards obtained during uncertain conditions make those rewards more motivationally relevant and valued, and thus conditioned responding is increased due to the reward’s enhanced incentive salience. This is also consistent with work summarized by Hearst and Jenkins (Brown and Jenkins 1968; Hearst and Jenkins 1974) showing that manipulations that decrease the frequency of CS-US presentations (e.g., long intertrial intervals) also increase the magnitude and/or acquisition of sign-tracking.

One prediction based on this idea is that sign-trackers will make risky decisions in animal models of gambling-like behavior. One such model is the suboptimal choice procedure, in which rats must choose between two alternatives, one that leads to an infrequent reward that is preceded a by CS 100% of the time, the other that leads to a frequent reward that preceded by a CS half the time. Suboptimal choice, akin to gambling, is demonstrated when the rats choose the perfectly predicted but infrequent reward (Smith et al. 2016). A recent study tested the hypothesis that sign-trackers would be more sensitive to suboptimal choice (Lopez et al. 2018). First, sign- and goal-trackers were identified using standard techniques and then tested in the suboptimal choice procedure. The authors found that both sign- and goal-trackers exhibited a preference for the poorly predicted but frequent reward, thus behaving optimally. However, while these findings indicate that vulnerability to sign-tracking does not overlap with vulnerability to suboptimal choice, other studies suggest that incentive salience, as measured by sign-tracking behavior, is a mechanism that promotes suboptimal choice. Specifically, Chow et al. (2017) presented a lever (that could be sign-tracked) as the CS in one group and compared responding to a separate group where a light (that elicited only goal-tracking) was the CS. The lever promoted suboptimal choice behavior in this experiment, thus showing that a CS that has acquired incentive value can promote risky, gambling-like behavior. Interestingly, like Lopez et al. (2018), they did not observe an association between the magnitude of sign-tracking and choice behavior. While this may seem paradoxical, the mechanism underlying sign-tracking may not be the same as the predisposing factors that render an individual more likely to become a sign-tracker.

Sign Tracking and Drug Addiction | 141
Discussion

What is particularly interesting is that, unlike PavCA, during delay discounting, omission, and the suboptimal choice task, the measures of action impulsivity occur during a period in which there is no stimulus immediately present. Therefore, the activation of the motivated response must be driven by (or poorly controlled by) an internal force, rather than being a conditioned response to an external stimulus. In other words, explanations for enhanced impulsivity in sign-trackers include (1) sign-trackers value the US more than goal-trackers and as a result are more likely to make premature responses, or (2) sign-trackers have poor inhibitory control despite valuing the US similarly compared to goal-tracking. One might expect that, if the US had enhanced value for sign-trackers, rats would have enhanced attention in tasks such as the choice reaction time task, but no study has demonstrated such an attentional enhancement. In fact, Paolone et al. (2013) demonstrated attentional deficits in sign-trackers trained in the sustained attention task, a cue-detection task that involves extended testing. Sign-trackers did poorly as this testing progressed, relative to goal-trackers, and fluctuated between periods of good and near-chance performance. Further, this poor attentional control was associated with lower levels of cortical acetylcholine levels. In a later paper (Koshy Cherian et al. 2017), they manipulated the acetylcholine system and demonstrated that experimental reductions of cortical acetylcholine increased the degree of sign-tracking. The authors concluded that this neurochemical deficit in sign-trackers causes a deficit in executive control over behavior, effectively unmasking motivated behaviors driven by CSs and/or USs (see Pitchers et al. 2017 for further discussion). This latter finding is somewhat at odds with other papers showing that nicotinic acetylcholine receptor agonists (such as nicotine itself) increase sign-tracking (Palmatier et al. 2013; Versaggi et al. 2016), although this is likely due to these manipulations affecting non-cortical areas of the brain. Regardless, these studies demonstrate that sign-tracking is associated with high levels of action impulsivity that are accompanied by poor attention, which, loosely speaking, could be conceptualized as another manifestation of poor self-regulation.

Thus far, we have reviewed findings that suggest sign-tracking reflects a trait associated with impulsivity, but that is also partially influenced by the current value of a given US. However, up until this point we have ignored
drug USs, which are interesting for several reasons. First, drugs are a different class of US that are not present in the Pavlovian conditioned approach test at all. Second, sign-trackers prefer a cocaine US over a food US (Tunstall and Kearns 2015). Finally, the unconditioned vocalization response to cocaine is enormously different in sign- and goal trackers (Tripi et al. 2017). In the next section we will discuss these drug-induced vocalizations, how they are different in sign- and goal-trackers, and how they provide insight on the underlying nature of the differences between sign- and goal-trackers.

Ultrasonic Vocalizations

The correlated responses discussed in this section reveal several behavioral distinctions between sign- and goal-trackers, and other chapters in this volume suggest a strong link between sign-tracking, goal-tracking, and addiction-related behaviors (Levitch et al. this volume; Robinson et al. this volume; Tomie et al. this volume). However, all of the tasks previously described involve some form of learning, and there are few measures of unconditioned responsivity to rewards that have been thoroughly investigated. As such, this provides limited information regarding what predisposing factors lead to differences in sign- and goal-tracking. In the case of drugs of abuse, some have suggested that the locomotor response to reward presentation is a simple measure of the unconditioned response to rewards (Wise and Bozarth 1987). However, there are several dissociations between drug-induced locomotion and motivation, and studies have reported subtle differences or no differences in drug-induced locomotion between sign- and goal-trackers (Beckmann et al. 2011; Flagel et al. 2008; Tripi et al. 2017). Thus, the locomotor response to reward presentation may not necessarily reflect the motivational response to a given US. Alternatively, reward presentation evokes other unconditioned responses in rodents, including the production of ultrasonic vocalizations (USVs).
Relevance to Motivation

USVs are complex vocal responses produced by rodents occurring at a frequency above the upper limit of human hearing (> 20 kHz). Adult rats produce a repertoire of USVs that can be classified in two distinct categories based on their mean frequencies: 22 kHz (18–28 kHz) and 50 kHz calls (30–80 kHz) (Portfors 2007; Wohr and Schwarting 2013). Both of these categories of USVs have been proposed to serve a communicative function and may represent distinct motivational and affective states in response to different social and nonsocial situations (Knutson et al. 2002). Specifically, 22 kHz USVs are primarily produced in response to aversive contexts such as electric shock (van der Poel et al. 1989), intermale aggression (Sales 1972; Thomas et al. 1983), stress (Knapp and Pohorecky 1995), and drug withdrawal (Berger et al. 2013; Vivian and Miczek 1991). On the other hand, 50 kHz USVs predominate in positive contexts involving appetitive or reinforcing stimuli including mating (Burgdorf et al. 2008), play (Knutson et al. 1998), exploration (Blanchard et al. 1993) and also in response to abused drugs and their associated cues (Meyer et al. 2012). Thus, researchers in the field have proposed USVs as potential objective measures of negative and positive emotional states in preclinical models. Further, this measure has been suggested as a preclinical analogue to human “self-report” of subjective states that include both physiological and motivational changes in the organism (Brudzynski 2007; Mahler et al. 2013; Panksepp et al. 2002).

Importantly, the production of USVs can occur in both unconditioned and conditioned contexts. Unconditioned responding constitutes reflexive behaviors that occur naturally due to a given stimulus, and unconditioned USVs have been shown to be elicited by acute exposure to various manipulations, including those previously listed. USVs occurring prior to learning may reflect the initial subjective experience to a given stimulus. On the other hand, conditioned USV responding implies that some learning about the stimulus and its relationship to cues in the external and/or internal environment has occurred, and thus has come to elicit an affective response. Evidence for the production of conditioned USVs has been demonstrated by the ability of reward-paired cues alone to instigate vocalizations. For example, environments paired with drugs of abuse have been shown to produce USVs in the absence of the drug (Burgdorf et al. 2007; Knutson et al. 1998; Meyer et al. 2012), and 50 kHz USVs have been
proposed to reflect anticipation of reward and reward-related cues (Brenes and Schwarting 2014; Ma et al. 2010).

Several rodent studies measuring both spontaneous and stimuli-induced USVs have confirmed stable individual differences in 50 kHz vocalizations, with some subjects exhibiting high USV rates and others exhibiting low USV rates (Ahrens et al. 2013; Mallo et al. 2007; Taracha et al. 2012). This bidirectional affective response, reflected by USV production, can be selectively bred for. Thus, natural variability of this measure can be used to study the neuroanatomical and pharmacological basis of individual differences in aspects of motivation and emotion (Brudzynski et al. 2011). In fact, according to Dickinson and Balleine (2002), the incentive value of rewards and their related stimuli are largely determined by the affective experience that results from consuming a reward. This perspective is supported by clinical studies in which positive responses to a drug during its initial use was associated with shorter latency for second use and increased willingness to take the drug in subsequent sessions (de Wit et al. 1986; Kollins et al. 2001; Volkow et al. 1999). Browning et al. (2011) demonstrated this relationship in rats by measuring cocaine-induced USVs. In this study, high rates of USVs on the first day of acquisition were positively correlated with the speed at which cocaine self-administration was acquired. Taken together, these studies provide evidence that assessing the individual differences in the initial subjective experience in response to rewards, particularly drug rewards, may reveal insight into future conditioned reward-direct behaviors.

Relationship to Sign- and Goal-Tracking

Previous work has assessed the relationship between incentive motivation and the production of conditioned USVs in response to both food and drug. In a study conducted by Brenes and Schwarting (2015), subjects learned to enter a runway maze to gain access to a food reward in a connected cage. In this, sign-tracking was characterized by repeated returns to the food-associated runway during the food access period and results indicated that subjects exhibiting high levels of sign-tracking also showed heightened conditioned 50 kHz USVs. They concluded that the reward-paired maze cue had been imbued with incentive salience by these individuals and its
increased motivational value triggered appetitive USVs. In Tripi et al. (2017), we measured USV production in sign- and goal-trackers before, during, and after the presentation of a food-paired lever cues on the last day of PavCA (Day 5). Results of this study indicated only marginal differences in USV production at any point during the task, and this lack of differences may have been due to low cue-induced USVs in general. Although not specifically associated with cue or reward presentation, the only USV differences between sign- and goal-trackers occurred during the first 5 minutes of the task, indicating moderate differences in the conditioned affective response to reward-associated environments between these rats.

Differences between sign- and goal-trackers have also been observed in the conditioned and unconditioned USV response to drugs of abuse. For example, Meyer et al. (2012) measured USVs in a cocaine conditioned place preference (CPP) paradigm. They demonstrated that cocaine-treated sign-trackers produced more 50 kHz USVs compared to cocaine-treated goal-trackers for all cocaine-pairing sessions. Additionally, during the post-test (during which no drug was given), sign-trackers, unlike goal-trackers, exhibited preference for the cocaine-paired floor and also produced significantly more USVs than goal-trackers at this time. This finding was the first to suggest that sign-tracking individuals may have heightened sensitivity to the reinforcing effects of Pavlovian cocaine cues, and that the subjective value of the drug may facilitate this difference.

Differences in cocaine-induced USVs can also be observed in paradigms that do not require reward learning. We conducted a study in which sign- and goal-trackers were treated with 10 mg/kg (i.p.) cocaine and placed into a locomotor chamber (Tripi et al. 2017). On the first day of drug administration, sign-trackers produced significantly more 50 kHz USVs compared to goal-trackers, illustrating an inherent difference in the unconditioned affective response to cocaine. Notably, this response sensitized across repeated administration and also following a seven-day drug-free period in sign-trackers alone (see Figure 6.2). These findings substantiate a relationship between sign-tracking and cocaine-induced vocalizations, suggesting that the two may function through overlapping neural mechanisms. In fact, the more robust cocaine-induced USV rate observed in sign-trackers may reflect an increased sensitivity to the motivational properties of cocaine, and thus begin to explain previously reported variation between sign- and goal-trackers in drug seeking and taking behaviors.
Indexing Differences in the Subjective Response to Cocaine

The individual differences in cocaine-induced 50 kHz USVs between sign- and goal-trackers suggest different subjective responses to the drug unconditioned stimulus (US). Whereas it is unclear which aspects of cocaine's subjective effects are promoting this difference or what the mechanism is, there is some other evidence that informs these gaps in knowledge. Appetitive 50 kHz USVs in response to drugs of abuse, including cocaine, have been proposed to reflect positive hedonic states including euphoria (Burgdorf et al. 2011). Under this interpretation, sign-trackers would be more sensitive to pleasurable properties of cocaine, compared to goal-trackers. In this same vein, initial positive subjective responses to cocaine have been closely tied to subsequent drug-seeking and taking
behaviors in both preclinical and clinical models. According to Barker et al. (2014) the presence or absence of a hedonic response to drug treatment may indicate differences in neural physiology that are responsible for differences in learning and even in the transition for drug use to dependence in humans. Thus, increased 50 kHz cocaine-induced USVs could serve as a predictor for these addiction-like behaviors. Interestingly, this interpretation fits well with previous findings regarding variation between sign- and goal-trackers in other cocaine paradigms. For example, although both sign- and goal-trackers will acquire cocaine self-administration at the same rate, when tested under progressive ratio, sign-trackers will work nearly twice as hard as goal-trackers for a single cocaine infusion (Saunders and Robinson 2011). This increased willingness to work could be facilitated by a more pronounced positive evaluation of the drug by sign-trackers during learning. In support of this, a study by Tunstall and Kearns (2015) similarly supports this notion of differential evaluation of cocaine. In this, subjects previously characterized and sign- and goal-trackers were trained to lever press for a food pellet and cocaine infusion. When given a choice to administer either, sign-trackers chose cocaine over food significantly more than goal-trackers. Further, Robinson et al. (2014b) suggested that tendency to sign-track may be reflective of an underlying trait to globally attribute incentive salience to reward stimuli, including interoceptive stimuli. Thus, sign-trackers may not only be more sensitive to the initial subjective effects of cocaine, but also may come to attribute incentive salience to the internal state associated with cocaine and thus be more likely to take and seek drug in the future.

Mechanisms of Individual Differences in Subjective Response to Cocaine

The individual variation in cocaine-induced USVs between sign- and goal-trackers may rely upon differences in the mesolimbic dopamine system, specifically in how rewards and their related cues are encoded. Previous reports have demonstrated that unlike goal-tracking, sign-tracking is dopamine-dependent and the acquired conditioned response can be blocked by DA antagonism (Flagel et al. 2011; Kuhn et al. this volume). Additionally, mesolimbic dopamine firing appears to be critical for the initiation of positive affect and the production of 50 kHz USVs (Hori et
Thus, dopamine neurotransmission is a likely contributor to the differences in the affective response to cocaine among sign- and goal-trackers. For example, dopamine firing may be differentially affecting the initial reinforcing action of the drug and, with continued exposure, may affect variation in learning during drug conditioning. Importantly, it has been shown that cocaine-induced USVs sensitize in sign-trackers alone indicating unique alterations in the mesolimbic dopamine system through repeated cocaine administration (Burgdorf et al. 2001; Tripi et al. 2017; Willuhn et al. 2014).

The behavioral effects of cocaine are also mediated by other neurotransmitter systems that may play a role in the individual differences observed in sign- and goal-trackers. For example, the noradrenergic system has been shown to play a role in both sign-tracking and the production of stimulant-induced USVs. Activation of this system in the prefrontal cortex has been shown to increase during the pairing of a lever cue with a food reward (Tomie et al. 2004), suggesting that the increase has an underlying role in the development of the sign-tracking response. Additionally, antagonism of this system inhibits sign-tracking behavior in PavCA (Pasquariello et al. 2018). Similarly, stimulant-induced USVs are not completely abolished by DA antagonism and, additionally, hedonic responses in general may be DA independent (Berridge 2009; Wright et al. 2013), implying a contribution of additional neurochemical mechanisms. Wright et al. (2012) demonstrated that, along with dopamine, noradrenergic neurotransmission plays a critical role in stimulant-induced 50 kHz USVs. In fact, antagonism of the alpha-1 adrenergic receptor reliably attenuates 50 kHz USVs in rodents and has been reported to decrease the subjective effects of cocaine in humans (Newton et al. 2012).

Serving as a “self-report” of affective state, CS- and US-induced USVs may provide a reliable measure to index distinct aspects of reward sensitivity in rodent models. In fact, the robust relationship between sign-tracking and cocaine-induced 50 kHz USVs is particularly profound because of its implications as not only a predictive marker for sign-tracking and its correlated behaviors but also as an indicator of the underlying mechanisms that make sign- and goal-trackers distinct. The differential cocaine-induced USVs suggest that the sign- and goal-trackers differ in their initial subjective response to reward (whether that be the physical reward of the internal and external cues related to the reward), and this in turn may facilitate a divergence in reward-directed behavior in both food and drug paradigms.
Conclusion and the Potential Role of the US

In summary, the just discussed studies suggest that sign-tracking is persistent, albeit not entirely inflexible in the sense non-reinforcement can lead to a change in the topography of the response. This demonstrates that once the CS-US association is learned, the current value of the US can still influence the response to the CS in sign-trackers and goal-trackers. This does not seem to be due to enhanced motivation for the US, because there are no systematic differences between sign- and goal-trackers in tests that should be affected by the value of the US, including food self-administration. In fact, sign-trackers have attentional deficits, which is the opposite one might predict if they valued the US more than goal-trackers. Thus, especially considering that sign-trackers are more impulsive than goal-trackers in several paradigms, the most parsimonious explanation is that sign-tracking and goal-tracking reflect individual differences in a trait characterized by poor self-regulation that unmasks extreme incentive salience attribution to CSs. Still, because all of the tasks that involve assessing the value of the US involve learning, one cannot definitively conclude that sign- and goal-trackers do not differ in their response to USs.

A recent study by Patitucci et al. (2016) asserted that differences in sign- and goal-tracking arise “from the interaction between the palatability or value of the reinforcer and processes of association as opposed to dispositional differences (e.g., in sensory processes, ‘temperament,’ or response repertoire)”. Their support for this assertion is that (1) in their experiments, the sign-tracking response to two different CSs, associated with either a food pellet or sucrose solution, were unrelated, and (2) the palatability of the reinforcer, as measured lick cluster size, was related to sign-tracking. These findings suggest that the US is initially more valued in sign-trackers than goal-trackers. There is some indirect evidence from other studies that sign-trackers may indeed value food and drug USs more. First, when sign- and goal-trackers self-administered food pellets on an FR1 schedule, sign-trackers did so at a faster rate, especially early in training (Yager and Robinson 2010), although the opposite effect was seen when a discriminative stimulus signaled food availability (Ahrens et al. 2016). Second, in rats selectively bred for high (HR) or low (LR) locomotor response to novelty, HR rats (who also exclusively sign-track) had more US-evoked dopamine compared to their goal-tracking LR counterparts, but there was
no difference in outbred Sprague-Dawley rats (Flagel et al. 2011, see the session 1 US responses in Figures 2 and 3). Third, for cocaine, sign-trackers respond more in a PR test in the absence of cues (see Figure 4 in Saunders and Robinson 2011), and we found that one injection of cocaine induces many more ultrasonic vocalizations in sign-trackers compared to goal-trackers, and that this difference was further increased after repeated cocaine injections (Tripi et al. 2017). Finally, when considered in conjunction with the finding that larger reward magnitudes promote sign-tracking (e.g. Kasties et al. 2016), it seems there is ample evidence that the US initially has more incentive value in sign-trackers compared to goal-trackers, and this may explain why the CS acquires more incentive value in these subjects during Pavlovian paradigms. Data from action impulsivity studies are also consistent with this idea, because enhanced reinforcer value could explain increased impulsive responding. Surprisingly, there are no studies that test this idea directly. For example, a simple experiment would be to compare responding on a progressive ratio of reinforcement, which measure how hard subjects are willing to work for the reinforcer, in sign-trackers and goal-trackers. As it stands, a potential unconditioned response or behavioral “biomarker” that reliably predicts sign- and goal-tracking remains elusive.

References


Anselme, P. (this volume). Gambling hijacks an ancestral motivational system.


stimulus can influence the degree to which it acquires incentive motivational properties. PLoS one 9, e98163.


7. Relevance of Sign-Tracking to Co-Occurring Psychiatric Disorders

Jonathan D. Morrow\textsuperscript{a,b}

\textsuperscript{a} Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109
\textsuperscript{b} Neuroscience Graduate Program, University of Michigan, Ann Arbor, MI 48109

Corresponding Author:
Jonathan D. Morrow, M.D., Ph.D, 4250 Plymouth Rd. SPC 5767, Ann Arbor, Michigan 48109–2700; e-mail: jonmorro@umich.edu; phone: (734) 764–4283; fax: (734) 232–0244.

Abstract

Sign-tracking is a behavior that reflects Pavlovian learning. Sign-tracking and its complementary behavior, goal-tracking, are often discussed in terms of their relevance to substance use disorders, but emotional learning is a fundamental part of several other neuropsychiatric disorders. The overlapping neurobiology of sign-tracking, addiction, and other psychiatric disorders suggest that individual variation in incentive-motivational processes may contribute to specific patterns of psychiatric comorbidity. Targeting transdiagnostic traits such as this could lead to more effective treatments than can be achieved by focusing on individual disorders. Here, the phenomenology and neurobiology that links sign-tracking to a wide range of disorders is discussed.

Keywords: addiction; comorbidity; dual-diagnosis; individual
Introduction

Addiction is a complex disorder and is often deeply intertwined with other neuropsychiatric disorders. Studies of patients in treatment for substance use disorders (SUDs) routinely find very high rates of psychiatric comorbidities, typically with >80% of patients meeting criteria for an identified psychiatric disorder. Such studies may overestimate the prevalence of comorbidity in the general population because those who enter treatment tend to be the most functionally impaired (Sackett, 1979). However, epidemiological studies of community samples largely avoid such bias, and they consistently find co-occurring mental health disorders in more than half of people with SUDs (Grant et al., 2016; Kessler et al., 1996; Regier et al., 1990). Understanding and addressing these comorbidities is essential because co-occurring psychiatric illness makes SUDs more severe and difficult to treat, leading to more hospitalizations, more interpersonal problems, and worse physical health (Ritsher, McKellar, Finney, Ottingam, & Moos, 2002; Schaar & Ojehagen, 2001). Patients tend to believe their own disorders are functionally related and prefer concurrent, integrated treatment (Brown, Stout, & Gannon-Rowley, 1998).

Several potential reasons have been proposed to explain why SUDs are so commonly complicated by the presence of comorbid psychiatric disorders. One category of explanation is essentially that SUDs play a causal role in the development of other psychiatric disorders. For example, the prolonged use of drugs and alcohol can damage sensitive brain structures like the prefrontal cortex, which in turn can contribute to the development of other psychiatric disorders (Lyvers, 2000). This is particularly relevant in the adolescent and teenage years, when substance use can lead to impaired cognitive and social development, resulting in increased risk of psychiatric disorders later in life. Another potential explanation for the link between SUDs and psychiatric comorbidities is that psychiatric disorders in some way cause addiction, and this process is most commonly framed in terms of “self-medication” (Khantzian, 1985). While there is evidence to support both these types of causal relationships, there is also evidence of common factors such as genetic variants or early life experiences that can predispose toward both addiction and other psychiatric disorders (Kendler, Prescott, Myers, &
Neale, 2003). This type of shared risk is thought to be largely mediated by personality or behavioral traits such as impulsivity and neuroticism (Kotov, Gamez, Schmidt, & Watson, 2010; Verdejo-Garcia, Lawrence, & Clark, 2008). Sign-tracking behavior may be an index of one such trait that can contribute to multiple psychiatric disorders.

As Tomie outlined in the introductory chapter of this book, sign-tracking is a type of learned attraction to cues that predict reward. Sign-tracking is often distinguished from goal-tracking, which is a learned, cue-triggered approach toward the location of impending reward delivery. Sign-tracking, as opposed to goal-tracking, is difficult to restrain and may contribute significantly to cue-induced relapse and other problematic features of SUDs. The neurobiology of sign-tracking behavior corresponds almost exactly to the neurobiology of motivated behavior in general. For example, sign-tracking appears largely dependent on dopaminergic activity within the nucleus accumbens (Flagel, Clark, et al., 2011; Fraser & Janak, 2017; Saunders & Robinson, 2012). The nucleus accumbens is part of a larger system, often referred to as the limbic system, whose overall function seems to be translating thoughts, perceptions, and emotions into behavior (Mogenson, Jones, & Yim, 1980; Salamone & Correa, 2012). Because mental illness by definition involves difficulties with generating appropriate emotional, cognitive, and behavioral responses to the environment, it should come as no surprise that limbic circuitry has been implicated in practically all psychiatric disorders. Because sign-tracking behavior reflects a particular bias within this limbic emotional-motivational system, we might expect sign-tracking to be involved in a large number of motivational and emotional abnormalities. In this chapter, we will touch on some of the ways sign-tracking intersects with neuropsychiatric conditions other than drug addiction.

Impulse Control Disorders

SUDs are most closely related to a group of diagnoses known as “behavioral addictions,” including both well-accepted disorders such as pathological gambling and more controversial conditions such as compulsive sexual behavior and Internet gaming disorder. The neurobiology of behavioral addictions overlaps considerably with that of SUDs (Leeman & Potenza,
Behavioral addictions and SUDs are highly comorbid, have a shared genetic basis, and cross-sensitize with one another. Though there have been few attempts to measure sign-tracking behavior per se in human subjects, a related trait known as “cue-reactivity” is predictive of problematic substance use (Carter & Tiffany, 1999). Cue-reactivity refers to measurable emotional, motivational, and physiological responses (i.e., cravings) in response to drug-associated versus neutral cues. Several studies have documented heightened cue-reactivity to specific reward-related stimuli among patients with behavioral addictions (Goudriaan, de Ruiter, van den Brink, Oosterlaan, & Veltman, 2010; Jansen et al., 2003; Ko et al., 2009; Thalemann, Wolfling, & Grusser, 2007; Voon et al., 2014). In Chapter 5 of this volume, Patrick Anselme outlined several ways in which gambling games and casinos employ reward-cue configurations that are known to maximize sign-tracking behavior, and many online games use similar tactics to keep users engaged. Given the lack of restraint and seeming irrationality that is so characteristic of sign-tracking, it is possible that behavioral addictions actually represent an extreme, almost pure form of sign-tracking behavior.

SUDs and behavioral addictions both fall under a larger umbrella of disorders related to a lack of impulse control. Impulsivity has been more clearly and consistently associated with addiction than any other personality trait. More specifically, the inability to withhold a pre-potent response predicts escalation of drug use in both animals and humans (Belin, Mar, Dalley, Robbins, & Everitt, 2008; Dalley, Everitt, & Robbins, 2011; Verdejo-Garcia et al., 2008). Precisely this type of “impulsive action” has been associated with sign-tracking behavior in rats (Lovlic, Saunders, Yager, & Robinson, 2011). Impulsive action results from a lack of prefrontal cortical control over subcortical impulses (Davis et al., 2013; Schmaal, Goudriaan, van der Meer, van den Brink, & Veltman, 2012), and sign-tracking rats show the same pattern of decreased functional connectivity between cortical and subcortical regions (Flagel, Cameron, et al., 2011). Attention-deficit hyperactivity disorder (ADHD) is one example of an impulse control disorder that may have mechanistic commonalities with sign-tracking. As implied by the name, attentional deficits are a defining feature of ADHD, and sign-tracking rats also have difficulty sustaining attention over time and in the presence of distractors (Paolone, Angelakos, Meyer, Robinson, & Sarter, 2013). The attentional deficits in sign-trackers appear to be due to a relatively unresponsive choline transporter and a consequently reduced capacity to mobilize acetylcholine in the prefrontal cortex during sign-tracking.
attentionally demanding tasks (Koshy Cherian et al., 2017; Pitchers, Kane, Kim, Robinson, & Sarter, 2017). A human genetic polymorphism of the choline transporter gene mimics some of the functional deficits seen in sign-tracking rats, and this polymorphism is associated with ADHD (English et al., 2009). Impulse control disorders can also include abnormalities in patterned motor outputs, for example, Tourette’s disorder. Intriguingly, recent experiments have shown abnormalities in complex motor control tasks among sign-trackers, indicating a possible relevance of the sign-tracking phenotype to a range of neuropsychiatric movement disorders (Kucinski, Kim, Lustig, & Sarter, 2018).

**Personality Disorders**

Impulse control disorders are often placed within an even broader group of “externalizing disorders,” including conduct disorder, antisocial personality disorder, and borderline personality disorder, all of which are associated with high rates of SUDs. In addition to impulsivity, the association with SUDs and externalizing disorders is thought to be mediated by other traits such as sensation-seeking (Dick et al., 2013; Hicks, Foster, Iacono, & McGue, 2013; Pingault et al., 2013). Interestingly, in outbred rats, sensation-seeking does not correlate with sign-tracking behavior in the way impulsivity does (Beckmann, Marusich, Gipson, & Bardo, 2011; Robinson & Flagel, 2009; Vanhille, Belin-Rauscent, Mar, Ducret, & Belin, 2015). The sensation-seeking trait seems to specifically predispose individuals to initiation of drug use and to using high doses of drug but does not directly hasten the transition from casual to dysregulated drug use patterns (Belin et al., 2008; Deroche-Gamonet, Belin, & Piazza, 2004; Ersche et al., 2013; Piazza, Deminiere, Le Moal, & Simon, 1989). Thus, sign-tracking may be more specifically involved in predisposing individuals with externalizing disorders to addiction, as opposed to just drug taking. Borderline personality is a particularly interesting disorder in this regard, because it is characterized in part by a combination of neuroticism, impulsivity, and cue-reactivity, all of which are associated with increased risk for SUDs. Many borderline patients suffer from a particular type of emotional instability characterized by exaggerated emotional responses to seemingly innocuous cues. Though sign-tracking
has not been studied in this population, the strong cue-induced motivated behaviors seen in sign trackers are presumably accompanied by equally strong cue-induced emotional responses. Indeed, studies of ultrasonic vocalizations indicate that sign-trackers derive more intense pleasure from Pavlovian conditioned approach procedures than do goal-trackers (Meyer, Ma, & Robinson, 2012). This raises the possibility that sign-tracking, or a closely related psychological process, may be a major contributor to the functional impairment seen in borderline personality disorder.

Anxiety Disorders

The affective instability of borderline personality involves disproportionate emotional responses to stimuli associated with positive, rewarding experiences and also to stimuli associated with negative, aversive experiences. This fact raises the question of whether sign-tracking is specific to reward learning, or whether a similar process may be at work in all types of emotional learning. Pavlovian fear conditioning involves generating a fear response to a neutral cue that has been paired with an aversive experience, for example, a mild electrical shock to the foot. The fear conditioning process is very similar to Pavlovian conditioned approach procedures that produce sign-tracking. The main difference is that conditioned fear learning is supported by an aversive outcome, while conditioned approach is supported by an appetitive reward. There are significant individual differences in the amount of fear expressed after a classic Pavlovian fear conditioning paradigm, and sign-trackers express more fear to discrete shock-associated cues than goal-trackers (Morrow, Maren, & Robinson, 2011). This suggests that the increased emotional and motivational value that sign-trackers attribute to cues is not limited to reward. Fear learning is a central part of several anxiety disorders, including post-traumatic stress disorder (PTSD) and specific phobias. Much like addiction, in which craving is triggered by drug-related cues, PTSD and phobias involve excessive fear states that are triggered by trauma-related cues. Indeed, sign-trackers are more susceptible to developing PTSD-like abnormal fear responses that “incubate,” or increase instead of staying stable or decreasing over time (Morrow, Saunders, Maren, & Robinson, 2015). If
sign-tracking is a process common to both addiction and PTSD, this may help to explain some of the high rates of co-occurrence of these two disorders found in patient populations (Cottler, Compton, Mager, Spitznagel, & Janca, 1992; Kulka et al., 1990).

Another important feature held in common between sign-trackers and PTSD patients is difficulty with processing and integrating contextual information. A context is a particular combination of stable cues that together comprise the setting in which an event occurs. In behavioral experiments, distinct contexts are intentionally created by using different configurations of odors, background lighting, background noise, floor textures, and color patterns on the walls of the testing chamber. The brain processes information about contexts differently from discrete cues; for example, contextual learning is highly dependent on hippocampal activity, whereas discrete cue learning depends more on the amygdala (Marschner, Kalisch, Vervliet, Vansteenkoven, & Buchel, 2008; Phillips & LeDoux, 1992; Selden, Everitt, Jarrard, & Robbins, 1991). Interestingly, hippocampal dysfunction is one of the most consistent findings among PTSD patients (Abdallah et al., 2017; Gilbertson et al., 2002; Logue et al., 2018; Smith, 2005), and there is evidence of differential hippocampal involvement in sign- versus goal-tracking (Fitzpatrick, Creeden, Perrine, & Morrow, 2016; Fitzpatrick, Perrine, Ghoddoussi, Galloway, & Morrow, 2016; Ito, Everitt, & Robbins, 2005). Impaired contextual fear learning has been demonstrated in PTSD patients and is now hypothesized to be a central feature of the disorder (Garfinkel et al., 2014; Maren, Phan, & Liberzon, 2013; Rougemont-Bucking et al., 2011). Sign-tracking rats also show deficits in contextual fear learning (Morrow et al., 2011). In addition, contextual cues are less effective at triggering relapse-like drug-seeking behavior in sign trackers as compared to goal-trackers (Pitchers, Phillips, Jones, Robinson, & Sarter, 2017; Saunders, O'Donnell, Aurbach, & Robinson, 2014). Thus, if an individual is predisposed toward sign-tracking behavior, that individual will likely have strong emotional and motivational responses to any cue that is paired with an emotionally salient event. In addition, these cue-triggered responses will be relatively immune from any contextual modulation. A sign-tracker will tend to react strongly to cues regardless of the time, place, or social situation in which the cue is encountered. For example, a military veteran who has experienced a roadside bomb attack may feel intense fear and start driving with a dangerous level of aggression at the sight of a pile of garbage close to the road. That would be an entirely appropriate response in the context of
an active military operation in Afghanistan, but it is a pathological response in the context of driving home from a child’s birthday party in a Michigan suburb. In a similar vein, using psychoactive drugs such as alcohol and marijuana is a normal human behavior and can be appropriate in certain social contexts like celebrations or religious ceremonies. However, over the course of addiction drug use begins to occur in increasingly inappropriate contexts, for example, at work, before driving, or while caring for children. A decreased ability to limit the expression of emotional and motivational responses to their appropriate contexts may be a common thread that links sign-tracking, addiction, PTSD, and other related disorders.

Psychotic Disorders

Dopamine signaling is critical for the transformation of neutral cues into motivationally relevant stimuli. As mentioned previously, blocking dopamine transmission prevents sign-tracking behavior (Danna & Elmer, 2010; Flagel, Clark, et al., 2011). However, increasing dopamine transmission by direct injection of amphetamine can also inhibit sign-tracking under some circumstances (Holden & Peoples, 2010; Simon, Mendez, & Setlow, 2009). This apparent dichotomy may be due to the fact that dopamine’s effects on the motivational properties of a given cue are critically dependent on the relative timing of the cue, the associated outcome, and the dopamine signal (Chang et al., 2016; Sharpe et al., 2017; Steinberg et al., 2013). Reward learning is best supported by transient dopamine signals that occur in close temporal proximity to both the cue and the reward. Dopamine transients outside of that time window may actually reduce the motivational connections between the cue and the reward. This timing effect may help to explain why route of administration can have such a profound effect on the addictive properties of drugs. Generally speaking, the faster a drug causes dopamine levels to spike in the brain, the more efficient that drug will be at inducing and maintaining addictive behavior (Allain, Minogianis, Roberts, & Samaha, 2015; Samaha, Li, & Robinson, 2002). For example, smoking crack cocaine is more addictive than snorting powdered cocaine because inhaling cocaine delivers the drug to the brain faster than absorbing it through the nasal mucosa. The consequent dopamine release will then presumably strengthen
associations with cues that are in closer proximity to the act of smoking crack than it will to cues that accompany snorting cocaine.

Dysfunction within the dopaminergic system is a prominent feature of many psychiatric disorders, some of which have already been discussed in this chapter. In particular, schizophrenia and other psychotic disorders are thought to result in part from excessive, inappropriately timed dopaminergic activity (Kapur, Mizrahi, & Li, 2005). The general applicability of this hypothesis is attested by the efficacy of dopamine receptor blockade in reducing the symptoms of psychosis (Kapur & Mamo, 2003) and by the prominence of psychotic symptoms as side effects of dopaminergic drugs (Cummings, 1991; Goetz, Tanner, & Klawans, 1982). It is specifically the positive symptoms of schizophrenia, such as hallucinations and delusions, that seem to be mediated by aberrant dopamine signals. Psychotic delusions typically start out as “overvalued ideas,” which refers to a thought that feels so important to the individual that it begins to drown out all other considerations (McKenna, 1984). Such ideas become delusional when seemingly random and unconnected perceptions, such as television ads or even cloud formations, start to acquire new, typically self-referential meaning, for example, “the United Nations is altering weather patterns in order to send me personal messages in the clouds.” In the example just given, the delusional thought might have crystallized due to a random surge of dopamine that happened to coincide with looking at a particular cloud. The same process that gives drug-associated cues the motivational value to produce approach behaviors like sign-tracking may be at play in psychotic disorders, driving random thoughts and perceptions to a place of prominence in the mind because of the dopamine-driven sense that they are connected and personally relevant. Once that feeling of importance is established, the details of the delusional content are filled in by “top-down” cognitive processes based on the individual’s unique life experiences. Like sign-tracking behavior, delusional thoughts are typically very difficult to restrain, and depending on the severity of the illness patients may struggle with “knowing” their delusion is not true without being able to reconcile the “feeling” that it is both true and extremely important. Addiction patients have a similar, biologically driven relationship with drug use, and in treatment circles this internal struggle is commonly referred to as “ambivalence.”
Disorders of Over-Control

When considering the relevance of sign-tracking to psychopathology, it is important to remember that sign-tracking is a normal behavior. All individuals are capable of both sign-tracking and goal-tracking, but the sensory features of the cue, the proximity of the cue to the reward in both space and time, and other such testing parameters can influence the likelihood that a given individual will employ one strategy or the other (Burns & Domjan, 2001; Christie, 1996; Gallistel & Gibbon, 2000; Meyer, Cogan, & Robinson, 2014). Sign-tracking evidently has a long evolutionary history. A great deal of recent sign-tracking studies have used rats, but sign-tracking behavior has been reported in a wide variety of organisms including primates, horses, birds, and fish (Bullock & Myers, 2009; Burns & Domjan, 1996; Miyashita, Nakajima, & Imada, 1999; Nilsson, Kristiansen, Fosseidengen, Ferno, & van den Bos, 2008). In fact, sign-tracking has been observed among invertebrate species such as insects and cephalopods, whose common ancestors with humans likely did not even have a brain (Purdy, Roberts, & Garcia, 1999; Zhang, Bartsch, & Srinivasan, 1996). The ubiquity of sign-tracking throughout the animal kingdom suggests that it must be an adaptive behavioral strategy and may even be a required feature for organisms that use complex behaviors to navigate the real world. However, if either a propensity toward sign-tracking or a propensity toward goal-tracking were always advantageous, only one of these traits would exist because natural selection pressures would quickly cull the other out of the population. The persistence of both sign- and goal-tracking suggests that there must be an evolutionary trade-off of some kind, such that each trait has advantages over the other depending on the different life circumstances that an individual may face (Wolf, van Doorn, Leimar, & Weissing, 2007). For example, sign-tracking may provide a faster, more stereotyped way to pursue rewards, whereas goal-tracking may be a slower but more flexible response pattern. In that case, sign-tracking would be more advantageous in environments with scarce, unpredictable access to resources. In contrast, goal-tracking would be the more suitable strategy in stable environments with a relative abundance of resources. In modern, civilized societies, and especially those parts of society that value academic achievement, the disadvantages of externalizing traits like sign-tracking are often emphasized, while traits like prudence and patience are almost universally extolled as virtues. However,
just as a lack of prefrontal control over subcortical impulses can contribute to psychopathology, an overabundance of prefrontal control can also lead to functional impairment.

Obsessive-compulsive personality disorder (OCPD) is a relatively straightforward example of how excessive cognitive control can become almost paralyzing and interfere with daily life. These patients spend so much time planning, checking, and attending to every little detail that it is very difficult for them to complete even simple tasks. Because very few data exist that address the functional neuroanatomy of OCPD or goal-tracking, it is difficult to draw parallels between them based on pathophysiology. However, based on phenomenology and their inverse correlations with externalizing disorders and sign-tracking, we could reasonably speculate that OCPD patients and extreme goal-trackers may have some biological similarities.

Obsessive-compulsive disorder (OCD) is closely related but distinct from OCPD. Whereas OCPD is characterized by an intense need for control and orderliness, OCD is defined by intrusive thoughts or action patterns that are repeated over and over, such as counting or excessive handwashing, even though they serve no practical purpose. Researchers often highlight phenomenological similarities between addiction and OCD because drug-taking often involves stereotyped rituals, and cravings can be described as intrusive, repetitive thoughts. A multitude of evidence, much of it derived from animal studies, suggests that over time drug use becomes more “habitual” and concurrently shifts from being dependent on ventral striatal structures to more dorsolateral areas of the striatum (Everitt & Robbins, 2016). However, some of this evidence has recently been challenged on the grounds that it could be an artifact of the stereotyped way in which animal subjects are required to use drugs in most controlled studies (Singer, Fadanelli, Kawa, & Robinson, 2018). The preponderance of neuroimaging evidence from OCD patients indicates hyperactivity of prefrontal cortical structures that participate in cortico-striatal loops, a pattern that is largely opposite of that observed in addiction patients (Menzies et al., 2008; Nakao, Okada, & Kanba, 2014). OCPD shares some traits with anorexia, particularly perfectionism, behavioral rigidity, high impulse control, and emotional restraint (Halmi et al., 2005; Young, Rhodes, Touyz, & Hay, 2013). The imaging data that are available for anorexia are not always consistent from one study to the next, but overall they also paint a picture of hyperconnectivity between cortical and subcortical regions of the limbic system (Frank, Shott, Riederer, & Pryor, 2016). The functional circuitry of anorexia might therefore
be expected to reduce sign-tracking responses and presumably increase goal-tracking, though a specific test of this hypothesis has not yet been conducted. Clinically, comorbid anorexia and addiction can be particularly challenging because psychotherapies for addiction are generally designed to increase cognitive control over subcortical urges, while psychotherapies for anorexia essentially aim to do the opposite. It is common for symptoms of one disorder to worsen while the other improves, making it essential to monitor both disordered eating behaviors and substance use throughout the course of treatment.

**Depression**

Despite very high rates of comorbidity between addiction and mood disorders, there have been almost no attempts to relate sign-tracking behavior to either depression or bipolar disorder. Depression comes in many forms, and the clinical definition of depression may in fact encompass more than one biological disorder (Ostergaard, Jensen, & Bech, 2011; Zimmerman, Ellison, Young, Chelminski, & Dalrymple, 2015). Much like the related personality trait of neuroticism, depression can include features consistent with cognitive undercontrol, such as impulsivity, as well as features that might indicate cognitive overcontrol such as the repetitive negative thoughts or worries known as “ruminations.” Because of this heterogeneity, sign- and goal-tracking behavior might not correlate with depression in a straightforward way. However, sign-tracking might prove useful for understanding anhedonia, which is a deficit in reward-related behavior common in depression and several other psychiatric disorders. Anhedonia is typically conceptualized as a reduced capacity for pleasure, but several lines of evidence have suggested that “anhedonia” in many cases is actually a lack of motivation that is mistakenly interpreted by both patients and clinicians as a lack of pleasure (Myin-Germeys, Delespaul, & deVries, 2000; Treadway & Zald, 2013). Based on the known neurobiology of sign-tracking behavior, a deficit in dopaminergic activity might be expected to result in a specific deficit in cue-directed motivation, which might in turn be interpreted as anhedonia. Indeed some recent experiments have suggested that severe
stressors can cause deficits in both dopamine-signaling and sign-tracking behavior (Fitzpatrick et al., 2018).

Conclusions

As might be expected based on the strong relationship between addiction and other psychiatric disorders, sign-tracking has relevance to many conditions beyond just substance use disorders. It fits within a rubric of externalizing disorders that seem to share common neurobiological features including diminished capacity for prefrontal cortical regions to provide contextual modulation and cognitive control over subcortical motivational impulses. This general trait of unrestrained emotional and motivational responses to cues can apply not only to rewards but also to aversive experiences. Disorders of excessive cognitive control such as eating disorders and OCPD may also relate to sign- and goal-tracking behavior, though little research has been done to explore such a hypothesis. Disrupted timing of dopamine signaling in the limbic system can lead to both a loss of motivation toward natural rewards and to pathological increases in responding to irrelevant stimuli. Because multiple psychological functions are coordinated and interconnected within the limbic system, symptoms resulting from disruption to this system can take the form of emotional, motivational, and/or cognitive preoccupation. Current psychiatric classification systems might give a patient with such symptoms multiple diagnoses, even though the fundamental neurobiology is the same. If sign-tracking more directly reflects the neurobiology common to all these disorders, it might be used in the future to more efficiently diagnose and treat patients with multiple psychiatric comorbidities, rather than focusing on each individual disorder.

Acknowledgments

I would like to acknowledge Rachel Atkinson for her contributions to an early
draft of this manuscript. This work was made possible in part by financial support from the National Institute on Drug Abuse (K08 DA037912–04).

References


Jansen, A., Theunissen, N., Slechten, K., Nederkoorn, C., Boon, B., Mulkens,


Meyer, P. J., Ma, S. T., & Robinson, T. E. (2012). A cocaine cue is more preferred and evokes more frequency-modulated 50-kHz ultrasonic vocalizations


Sign Tracking and Drug Addiction | 183


Zimmerman, M., Ellison, W., Young, D., Chelminski, I., & Dalrymple, K. (2015). How many different ways do patients meet the diagnostic criteria for...
8. Telling Stories about Sign-Tracking Boosts Awareness of Loss of Self-Control Related to Drug Use

Emily Ann Levitch,\textsuperscript{a,b} Stacey Elizabeth Marcinkowski-Paulis,\textsuperscript{c} and Arthur Tomie \textsuperscript{*},\textsuperscript{a,b}

\textsuperscript{a} Department of Psychology, Rutgers University, New Brunswick, NJ 08903
\textsuperscript{b} Center of Alcohol Studies, Rutgers University, New Brunswick, NJ 08903
\textsuperscript{c} East Mountain School, Carrier Clinic, Belle Meade, NJ 08502

Corresponding Author:
Arthur Tomie, PhD, Department of Psychology and Center of Alcohol Studies, Rutgers–The State University of New Jersey, New Brunswick, NJ 08903; e-mail: tomie@psych.rutgers.edu; phone: (848) 445-8885; fax: (848) 445-3500.

Abstract

In the United States, there are ongoing epidemics of drug addiction and drug overdose deaths, accompanied by an alarming increase in the number of young victims. Unfortunately, the epidemics reveal that primary prevention programs developed to stop drug addiction before it starts have been largely ineffective. A new primary prevention tool is needed. This chapter describes two experiments that employ storytelling to deliver scientific lessons about the loss of self-control due to the Pavlovian conditioning of sign-tracking. In experiment 1, the experimental group read the scientific short story, The Tail of the Raccoon: Secrets of Addiction (Illustrated), while the control group read Where the Buffaloes Begin. Survey 1 was administered before and after each
group read their story. Analysis of Survey 1 responses revealed no evidence of group differences in awareness of self-control and no evidence of an increase in awareness of self-control as a result of reading the story. In experiment 2, the experimental group read the scientific short story, The Tail of the Raccoon, Part II: Touching the Invisible (Illustrated), while the control group read The Call of the Wild. Survey 2 was administered to each group before and after reading their story. Analysis of Survey 2 responses revealed that the experimental group, relative to the control group, provided significantly higher post-treatment ratings of self-control awareness, as well as significantly elevated ratings of their understanding of how loss of self-control can lead to drug addiction. These group differences were not observed for survey questions that did not pertain to self-control. The results provide evidence that reading The Tail of the Raccoon: Secrets of Addiction (Illustrated) and then reading The Tail of the Raccoon, Part II: Touching the Invisible (Illustrated) boosted awareness of the loss of self-control and, in addition, improved understanding of how the loss of self-control contributes to drug addiction.

Keywords: drug addiction; prevention; self-control; sign-tracking; storytelling; survey

Introduction

Drug abuse is one of the most destructive health problems in American society. From March 2016–March 2017, 65,094 people lost their lives because of a drug overdose, up from 54,786 the previous year (Ahmad, Rossen, Spencer, & Sutton, 2017). Because of the rising prevalence of opioid abuse, President Trump has recently deemed the epidemic a national health emergency. The consequences of abusing drugs not only have devastating effects on the individual but also have an enormous negative impact on society at large. In 2007, the societal costs of drug abuse overall have been estimated at $200 billion in legal costs, healthcare costs, lost production in the workplace, and criminal justice fees (National Drug Intelligence Center, 2011). With drug overdose now the leading cause of death among the American population under the age of 50 (Kaplan, 2017), effective drug
prevention programs are essential in reducing drug abuse. Unfortunately, the majority of programs used today have failed to decrease the prevalence of usage.

One of the most well-known drug addiction prevention programs is Drug Abuse Resistance Education (DARE). The DARE program has been widely employed in schools since 1983. DARE police officers undergo 80 hours of training to teach 17 lessons each lasting for about 45–60 minutes. The DARE program’s mission is to reduce use of illicit drugs, improve psychosocial behaviors including social skills and self-esteem, and build community relationships through lectures and role-playing activities (Pan & Haiyan, 2009). Unfortunately, DARE has no reliable short-term or long-term impact on students’ drug use nor does it have any significant positive effects on social and psychological risk factors (Ennett, Rosenbaum, Flewelling, Bieler, Ringwalt, & Bailey, 1994; Dukes, Ullman, & Stein, 1997; Hansen & McNeal, 1997).

DARE’s lack of efficacy may be due to the brevity of the program itself, which takes only a few weeks to complete. The lessons of an effective drug program should be reinforced in multiple sessions ideally spanning the course of a few years (Engs & Stuart, 1988). This allows the program to progress with students as they reach various situations that correspond with increasing age. Also, with constant reinforcement over the years, lessons are remembered better. The role-playing scenarios point to another problem with DARE. In a classroom setting, a role-playing exercise does not arouse the same feelings of anxiousness and the desire to fit in, which are prominent characteristics of a peer pressure experience. Practicing how to act in a classroom might not adequately prepare a student for the real thing. Moreover, students use drugs for reasons other than peer pressure, such as self-medicating, rebellion, curiosity, genetic predisposition, and/or emulating a parental figure or role model (Engs & Stuart, 1988). Due to the backlash, DARE reconstructed their curriculum and combined forces with the prevention program Keepin’ It Real. But, once again, this new adaptation was still shown to be ineffective at reducing drug use (Caputi & McLellan, 2017).

Another way of delivering the anti-drug message to young people is through fear appeal. Scare tactics often impact attitudes and future intentions but have no reliable effect on changing that individual’s behavior (Witte & Allen, 2000; Hastings, Stead, & Webb, 2004). Instead of managing the fear of the danger to their health, people tend to manage their fear by
claiming this could never happen to them (Witte & Allen, 2000; Hastings, Stead, & Webb, 2004) or the outcome is unlikely (Goldberg, Halpern-Felsher, & Millstein, 2002). Initially, people may have an emotional reaction after seeing the scare tactic, but after repeated exposure, that emotional reaction diminishes or disappears (Goldberg, Halpern-Felsher, & Millstein, 2002).

A new drug prevention tool is needed. The scientific short stories, The Tail of the Raccoon: Secrets of Addiction (Illustrated) and The Tail of the Raccoon, Part II: Touching the Invisible (Illustrated), lend themselves to a storytelling approach to deliver a message to young people about the loss of self-control that is induced by sign-tracking. From the beginning of time, storytelling of fables, allegories, and anecdotes has been passed from generation to generation as a way of teaching life's lessons to young people (Goodman-Scott, Carlisle, Clark, & Burgess, 2016). Storytelling is especially effective in teaching lessons to special needs populations (Olçay Gül, 2016) and has a broad range of effective applications, even increasing language skills in non-native English speakers (Kalantari & Mahmood, 2015). The success of storytelling with children and youth suggests that delivering scientific messages regarding self-control and sign-tracking via the storytelling vehicle may increase their awareness of the drug addiction process. In this regard, several studies have already shown that storytelling is an effective way to educate youth about drug addiction (Arthur & Nelson, 2003; Metzger & Janet, 1992).

Sign-tracking is an animal learning model of the clinical psychopathology of drug addiction. Drug-taking by humans typically provides experience with a pairing of an object (e.g., a cocktail glass) with a reward (e.g., the pleasurable effects of alcohol). Repeated acts of drug-taking lead to what scientists call “sign-tracking,” the automatic, reflexive inclination to approach and contact and “consume” the object that predicts the reward (Tomie, Badawy, & Rutyna, 2016; Tomie & Sharma, 2014). Sign-tracking is triggered by the object and the performance of sign-tracking is poorly controlled by the subject, even when the action serves no purpose or is counterproductive or maladaptive. The tendency to develop sign-tracking is well established as a behavioral marker of an individual's subsequent vulnerability to addiction (Flagel, Watson, Robinson, & Akil, 2007; Hirschman, 1992; Tunstall & Kearns, 2015). Although sign-tracking may lead to maladaptive behavior, it is nevertheless widely exhibited in many animals, including humans (Joyner, Gearhardt, & Flagel, 2018; Reilly, Berndt, & Woods, 2016; Srey, Maddux, & Chaudhri, 2015; Tomie, Badawy, & Rutyna, 2016; Tomie
The objective of reading the scientific short stories is to equip the reader with an understanding of how object-reward pairings may induce the loss of self-control due to sign-tracking that leads to the development of addictive behaviors. In this way, the reader of the story will better understand that reflexive actions may occur even though they were not intended. The chapter by Tomie, Jeffers, and Zito (this volume) shows that the addiction blind spot, the widespread inability of the user to recognize the loss of self-control of drug-taking, contributes greatly to their demise, as they continue to assume that quitting drug use is simply a matter of deciding to do it. When they finally attempt to quit and discover that they can't, it is telling that many complain that they were blindsided and never saw their loss of self-control coming. The better informed reader is more likely to develop vigilance enabling them to identify these unintended acts of drug-taking much earlier in the drug addiction process. The goal is to enhance awareness of the loss of self-control earlier in the drug addiction process to allow the individual to prevent the downward spiral into drug addiction. Tomie, Jeffers, and Zito (this volume) provide a sign-tracking account of the addiction blind spot. The failure to recognize the loss of self-control is a key feature of the drug addiction process because it allows the downward spiral into the pit of drug addiction. The results of the present paper offer a possible way to address the blind spot problem. We report that using scientific short stories about sign-tracking and drug addiction, as an educational tool in 9th–12th grade students, is effective in boosting their awareness of the loss of self-control and the relationship between loss of self-control and drug addiction.

The scientific phenomenon of sign-tracking was exhibited in the first story, *The Tail of the Raccoon: Secrets of Addiction (Illustrated)*, when a raccoon, later named Sign Tracker, was instructed to bring wood to Mapache, a blind Native American warrior, in exchange for a delicious food reward. After repeated pairings of the wood and the food, the raccoon began to behave strangely. He started behaving toward the wood as though it were the food. Eventually, he spent all his time obsessively handling wood, which he gnawed and chewed, and dragged into the lake to be cleaned. He brought very little of this damp and shredded wood to Mapache and received few food rewards. This cycle of obsessively chewing and cleaning wood continued to spiral out of control, until finally help intervened. Note that the raccoon's behavior was maladaptive and makes no sense, because gnawing...
the wood resulted in the loss of the real food reward. The raccoon’s behavior revealed the loss of self-control, the lack of connection between his action and his intention. The action of the raccoon was to gnaw the wood, which interfered with his intention, which was to deliver the wood to Mapache, to get the delicious food rewards. To regain self-control, the raccoon had to leave that spot in the woods and relocate to the other side of the Great Lake, away from the dark forest of the kindling wood that triggered the raccoon to exhibit sign-tracking behavior.

In the second story, *The Tail of the Raccoon, Part II: Touching the Invisible (Illustrated)*, sign-tracking was exhibited by a young raccoon, Sign Tracker’s son, named Lepus. In the nearby woods, a spider named Alatro offered Lepus a vial of her potion in exchange for goods stolen from the Native Americans. Lepus enjoyed drinking the potion from the vial, and Lepus agreed to steal the goods to exchange for a vial of potion. Right away, Lepus enjoyed the intoxicating effects of the spider’s potion, and so he quickly developed a routine of stealing the goods to trade for the vial of potion. Before long, after many pairings of the vial and the potion’s effects, Lepus lost control over his actions. The mere sight of the vial triggered an automatic, irresistible reflex to drink from the vial. In the presence of the vial, Lepus ingested the potion repeatedly, to the point of excess, and beyond what he had intended. Eventually, after repeated episodes of intoxication, his family had to step in to save him.

The story emphasizes an important aspect of the drug addiction process that is typically overlooked. Note that the actions of sign-tracking closely resemble the actions of voluntary drug-taking. Therefore, sign-tracking is likely to pass for voluntary drug-taking. For further discussion of this issue see the chapter by Tomie, Jeffers, and Zito (this volume), titled “Sign-Tracking Model of the Addiction Blind Spot.” When Lepus saw the vial, he was triggered reflexively to reach out and drink from it, causing him to ingest the potion. But, while the action was neither intended nor voluntary, the triggered reflex was readily mistaken and misconstrued as a routine voluntary act of drug-taking. A casual observer, and even Lepus himself, would likely conclude that Lepus simply needs to make better decisions, when, in fact, Lepus actually was acting reflexively and had no control over his actions. The purpose of the story is to introduce the reader to the existence of reflexive sign-tracking. In this way, students will be better able to see how Lepus lost control of his drug-taking, and how this occurred due
to pairings of the vial and potion that induced sign-tracking of reflexively triggered drug-taking.

Loss of self-control is a central theme in both of The Tail of the Raccoon stories. Self-control is an important protective factor when it comes to addiction (National Institute on Drug Abuse, 2003). The goal is to raise students’ awareness of self-control, to strengthen the students’ will power and their ability to resist drug use. Our hypothesis is that these stories will be an effective means of delivering a drug prevention message by increasing the students’ understanding of the process of losing self-control and how this can lead to drug addiction.

Methods

Participants. Our population consisted of a total of 51 students enrolled in grades 9–12 of East Mountain School (EMS) of Carrier Clinic. The Educational Program provides a structured setting, with both Community Day students and Residential students. EMS is an alternative school located on the grounds of Carrier Clinic and is considered a division of the facility. The school program emphasizes the individual’s growth and improvement, focusing on the development of appropriate academic and social skills, as delineated per each student’s Individualized Education Plan (IEP).

Each classroom ranges in age from 13 to 18, divided appropriately to foster learning. Students of EMS enter the program throughout the school year, upon placement from their home school district. The members of the school staff are adapted to facilitate the rolling admissions of the student population. Some of the students are referred to the residential program, East Mountain Youth Lodge. The Lodge and school work in cooperation to set goals in both academic and behavioral areas. Finally, other students, usually requiring some interventions and accommodations, also attend EMS as Community Day students, commuting to EMS from their home district.

EMS is divided into three unique subprograms. Each subprogram within the school specializes in their own particular approach to addressing students with interfering behaviors. All students remain in their specific sub-school and do not usually interact with students in any of the other sub-schools. The students in sub-school #1 are usually classified as having
intense behavioral issues, including, for some students, conduct disorders or defiance disorders. The students in sub-school #2 have the greatest challenges. Most of these students learn to navigate school, while developing coping skills for various issues, such as panic attacks, clinical depression, self-injurious behaviors, and ideation. The students enrolled in sub-school #3 may present with behavioral and anxiety issues. Students from any of the sub-schools may come from a foster home environment, or from an abusive family environment, or from a low-income family environment. Students from any of the sub-schools may be familiar with drug addiction, based on their prior experience of sharing a home with an addicted family figure or from their prior firsthand experience with using addictive drugs.

**Procedures**

The Human Subjects Institutional Review Board of Rutgers University approved this study. Several weeks before the study began, parental consent letters explaining the study were mailed to the home address of each student's parents. The parents then signed and mailed back the parental consent letter giving permission for their child, under the age of 18, to participate in the study. Each student for whom parental consent was obtained was then given the minor assent form. The minor assent form explained the study and requested the approval of the minor to participate. All students who signed the minor assent form were eligible to participate in the study.

In the weeks prior to initiating the study, Professor Tomie and his research assistant, Emily Levitch conducted three individual one-hour orientation sessions attended by the EMS administrators and teachers. Each orientation session consisted of a PowerPoint slide show and video materials that explained the science of sign-tracking and how sign-tracking relates to the loss of self-control of drug-taking. In addition, the orientation introduced the audience to the scientific raccoon short stories (*The Tail of the Raccoon: Secrets of Addiction [Illustrated]* and *The Tail of the Raccoon, Part II: Touching the Invisible [Illustrated]*)). These scientific short stories would be used in the classroom with the intention of boosting awareness of the loss of self-control and how the loss of self-control contributes to drug addiction. The
orientation also introduced the audience to the many formats in which these stories could be used in the classroom, including having individual students each read the illustrated books themselves; having an instructor read-aloud to the class, while also providing each student with an individual binder copy of abbreviated versions of the illustrated books; providing each student with an iPad digital e-book text-only speech-enabled version of the book, to be used in conjunction with the binder copies of abbreviated versions of the illustrated books; and, for group participation and for purposes of review, projecting the iPad digital e-book onto a screen in the classroom, to be used in conjunction with the binder copies of abbreviated versions of the illustrated books. Also introduced to the audience were the control stories (Where the Buffaloes Begin and The Call of the Wild). The control stories were similar in content, length, reading level, and illustration quality, to the scientific short stories, but the content of the control stories did not pertain to self-control.

Prior to the start of the study, students from each sub-school were divided into two groups. One group was assigned the scientific short story, The Tail of the Raccoon: Secrets of Addiction (Illustrated) (hereafter referred to as “Tail I”), while the other group was assigned a different short story, Where the Buffaloes Begin (hereafter referred to as “Buffaloes”). For each sub-school, there were three students randomly assigned to the Tail I group for each one student randomly assigned to the Buffaloes group. Prior to reading the stories, all students were asked to fill out Survey 1-Pre (see Table 8.1) to assess their pretreatment baseline awareness of self-control. For purposes of analysis, the seven questions were organized into two clusters. Questions 2, 4, and 6 (Target Questions) specifically pertain to self-control, while Questions 1, 3, 5, and 7 (Non-Target Questions) do not pertain to self-control. Each student was asked to rate their agreement with each Survey question by selecting the best alternative provided by a 5-point scale, where 1 = “Poor,” 2 = “Below Average,” 3 = “Average,” 4 = “Above Average,” and 5 = “Excellent.” The mean pretreatment baseline ratings of the “Tail I” group and the “Buffaloes” group were assessed by Survey 1-Pre prior to reading their assigned stories in order to determine the presence of preexisting group mean differences.
To help us meet our goal to help students and educators please complete this survey.

<table>
<thead>
<tr>
<th>Statements</th>
<th>Poor</th>
<th>Below Average</th>
<th>Average</th>
<th>Above Average</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The illustrations inside this book are . . .</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. My understanding of what causes an individual to lose self-control is . .</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Relative to three years ago, the improvement in my reading skills is . .</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. My understanding of how the loss of self-control leads to drug addiction is . .</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. The illustrations that accompany this story are . .</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. My understanding of what it means to lose self-control is . .</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. The quality of this story is . .</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments:

After completion of Survey 1-Pre, all students were provided with access to their assigned story using one or more of the methods described earlier. For all students in sub-school #1 during the first week, the teacher read the story aloud to the class, who were each provided with a binder copy of an abbreviated version of the illustrated books. After the first week, slower readers and students who were absent during parts of the first week were allowed to catch up using an iPad digital e-book text-only speech-enabled version of the book and also available were the binders of illustrations described earlier. For all students in sub-school #3, the teachers read the stories aloud to the class, who were each provided with a binder copy of
an abbreviated version of the illustrated books. All students in sub-school 
#2 were given the choice of engaging the story in the way that they found 
most suitable, and they were free to change methods at any time. Upon 
completion of the reading of their assigned story, each student in the Tail 
I group and in the Buffaloes group was asked to fill out Survey 1-Post, 
which was identical to Survey 1-Pre. The purpose of Survey 1-Post was to 
assess the students in each group their posttreatment awareness of self-
control after they had completed the reading of their assigned story. Our 
hypothesis was that the Tail I group, which had read a story introducing 
them to the loss of self-control due to sign-tracking would score higher 
on the Target Questions (2, 4, and 6) related to self-control, relative to the 
Buffaloes group, which had read a story unrelated to the loss of self-control. 
In addition, our hypothesis was that the groups would not differ on the Non-
Target Questions (1, 3, 5, and 7) that did not pertain to self-control. Forty-six 
students completed Survey 1-Pre, and 51 students completed Survey 1-Post.

Data Analysis

For each subject, a self-report of their awareness of self-control was 
assessed using paper-and-pencil surveys that were administered 
immediately before and after the subject read each story. Each survey 
response was entered into an Excel spreadsheet with the identity of the 
subject encrypted by code. For each group and for each subject and for each 
survey, the mean, standard deviation, and standard error of the mean were 
derived. For each subject, the mean of the survey scores for questions 2, 4, 
and 6 were derived for each survey. For each subject, the mean of the survey 
scores for questions 1, 3, 5, and 7 were derived for each survey.

Between-Groups Effects: The effect of groups (The Tail of the Raccoon: 
Secrets of Addiction (Illustrated ) [Tail I] versus Where the Buffaloes Begin 
[Buffaloes]) on mean responses to each of the seven survey questions 
(Questions 1, 2, 3, 4, 5, 6, or 7) was assessed by separate one-way univariate 
analysis of variance (ANOVA) using Systat Inferential Statistical Analysis 
Software (San Jose, California), with an alpha level of 0.05, two-tailed.

Repeated-Measures Effects: The effect of groups on mean responses to 
each cluster of questions pertaining to self-control was evaluated by
comparing each individual subject’s mean responses to all Target Questions (Questions 2, 4, and 6) and all Non-Target Questions (Questions 1 and 3), as assessed by mixed-design 2 × 2 two-way ANOVA, with two levels of groups (Tail I versus Buffaloes) and two levels of cluster (Target Questions versus Non-Target Questions). Effects of groups on mean survey (Pre-Story versus Post-Story) scores was assessed by repeated-measures, mixed-design 2 × 2 ANOVA with two levels of group (Tail I versus Buffaloes) and two levels of survey (Pre-Story versus Post-Story).

Results, Experiment 1

Survey 1-Pre, Between-Groups Effects: Survey 1 was given prior to reading the first story and was administered to assess any preexisting baseline differences between the groups. For Survey 1, students were told not to answer questions 5 and 7 because these questions asked for their opinions of the story, which they had not read at that point. For each of the five remaining questions for Survey 1, one-way ANOVA revealed no significant mean differences between the groups, (all F’s < 1).

Survey 1-Pre, Repeated-Measures Cluster Effects: On Survey 1-Pre for the “Tail I” group, the mean ratings for the Target Cluster questions (2, 4, and 6), n = 37, and the Non-Target Cluster Questions (1 and 3), n = 37, were 3.42 ± 0.15 and 3.39 ± 0.15, respectively, and this difference was not significant, (F < 1). Similarly, on Survey 1-Pre for the “Buffaloes” group, n = 9, the mean ratings for the Target Cluster questions (2, 4, and 6) and the Non-Target Cluster Questions (1 and 3), were 3.35 ± 0.41 and 3.54 ± 0.36, respectively, and this difference was not significant, (F < 1). To confirm the results of the one-way analysis, a 2 × 2 mixed-design, repeated-measures ANOVA was conducted. This analysis revealed no significant main effect of groups (F < 1), no significant main effects of cluster (F < 1), and no significant interaction effect between groups and cluster, (F < 1). See Figure 8.1.

Survey 1-Post, Between-Groups Effects: For each of the seven individual questions for Survey 1-Post, one-way ANOVA revealed no significant mean differences between the groups, (all p’s > 0.10). One-way ANOVAs also revealed no significant mean differences between the groups on mean
ratings for Target Cluster questions (2, 4, and 6), $F < 1$, or on mean ratings for Non-Target Cluster Questions (1, 3, 5, and 7), $F < 1$. See Figure 8.2.

Survey 1-Post Repeated-Measures Cluster Effects: On Survey 1-Post for the “Tail I” group, the mean ratings for the Target Cluster questions (2, 4, and 6), $n = 37$, and the Non-Target Cluster Questions (1, 3, 5 and 7), $n = 37$, did not differ significantly, $F < 1$. Similarly, on Survey 1-Post for the “Buffaloes” group, $n = 9$, the mean ratings for the Target Cluster questions (2, 4, and 6), $n = 9$, and the Non-Target Cluster Questions (1 and 3), $n = 9$, did not differ significantly, $F < 1$.

Repeated-Measures Surveys and Cluster: For Survey 1-Pre and Survey 1-Post, mixed-design $2 \times 2 \times 2$, three-way ANOVA revealed no significant main effect of groups, ($F < 1$) and no significant main effect of cluster, ($F < 1$), and no significant main effect of survey, ($F < 1$). There was no significant two-way interaction between groups and cluster, ($F < 1$). There was a significant two-way interaction between groups and surveys, $F (1, 35) = 4.70$, $p = 0.04$, indicating that irrespective of groups, ratings on Survey 1-Pre were significantly higher than on Survey 1-Post. There was no significant three-way interaction between groups, cluster, and survey, ($F < 1$). See Figure 8.3.

Discussion, Experiment 1

The results of Experiment 1 provided no reliable evidence that reading “Tail I” enhanced awareness of loss of self-control. There were no significant effects of groups on Survey 1-Post on mean ratings of Target Cluster Questions pertaining to self-control (Questions 2, 4, and 6) or for Non-Target Cluster Questions that did not pertain to self-control (Questions 1, 3, 5, and 7). Comparing across surveys (Survey 1-Pre versus Survey 1-Post) for each individual question provided no evidence of improvement in awareness of self-control in either group. Reading “Tail I” did not produce an increase in the ratings for Target Cluster questions and this was also the case for Non-Target Cluster Questions, and, in addition, this was also the case for both Target Cluster and Non-Target Cluster questions for the “Buffaloes” group. This may be due, at least in part, to the overall trend toward lower ratings across surveys. For the “Buffaloes” group, mean responses to Survey 1-Post for Non-Target Questions (1 and 3) were 0.50 lower than for Survey 1-Pre,
indicating an overall deterioration in ratings of questions that did not pertain to self-control. This overall trend toward lower ratings would decrease the likelihood of observing improvement in ratings of questions pertaining to self-control.

Methods, Experiment 2

Participants: The subjects were the same students that had participated in Experiment 1. For Experiment 2, all subjects were assigned to the same groups to which they had been previously assigned for Experiment 1.

Procedures: Upon completion of Survey 1-Post, all student were asked to fill out Survey 2-Pre (see Table 8.2), which was identical to Survey 1-Post, except that the Target Questions (2, 4, and 6) pertained to self-control as it related to drug addiction, and students were asked to answer questions 5 and 7 on Survey 2-Pre and Survey 2-Post. Upon completion of Survey 2-Pre, all students began reading their second assigned story. One group was assigned the scientific short story, *The Tail of the Raccoon, Part II: Touching the Invisible (Illustrated)* (hereafter referred to as “Tail II”), while the other group was assigned a different short story, *The Call of the Wild* (hereafter referred to as “Call”). All students were provided with access to their second assigned story using one or more of the methods described earlier. For Experiment 2, all students in sub-school #1 were provided with an iPad digital e-book text-only speech-enabled version of the book, and, also available were the binders of illustrations described earlier. For all students in sub-school #3, the teachers read the stories aloud to the class, who were each provided with a binder copy of an abbreviated version of the illustrated books. All students in sub-school #2 were given the choice of engaging the story in the way that they found most suitable, and they were free to change methods at any time.
Table 8.2: The Tail of the Raccoon, Part II: Touching the Invisible
Survey 2

To help us meet our goal to help students and educators, please complete this survey.

<table>
<thead>
<tr>
<th>Statements:</th>
<th>Poor</th>
<th>Below Average</th>
<th>Average</th>
<th>Above Average</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My level of interest in reading stories is . . .</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. My understanding of what causes an individual to lose their self-control of their drug-taking is . . .</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Relative to three years ago, the improvement of my reading skills is . . .</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. My understanding of why the loss of self-control is difficult to recognize is . . .</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. The illustrations that accompany this story are . . .</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. My understanding of what I can do to prevent the loss of self-control is . . .</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Based on the cover illustration of this book, I predict that the story inside is . . .</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments:

Upon completion of the reading of their second assigned stories, each student in the Tail II Group and in the Call Group was asked to fill out Survey 2-Post, which was identical to Survey 2-Pre, to assess their awareness of self-control after they had competed the reading of their second assigned story. With respect to Survey 2, 48 students completed Survey 2-Pre, and 47 students completed Survey 2-Post.
Data Analysis, Experiment 2: Same as Experiment 1

Results, Experiment 2

Survey 2-Pre, Between-Groups Effects: Survey 2-Pre was administered prior to reading the second story. For each of the seven questions for Survey 2-Pre, one-way ANOVA revealed no significant main effect of group, (all F’s < 1). The mean rating for Target Cluster Questions (2, 4, and 6) for each student and the mean rating for Non-Target Cluster Questions (1, 3, 5, and 7) for each student were derived. The group means for Target Cluster Questions did not differ significantly, (F < 1), and the group means for Non-Target Questions did not differ significantly, (F < 1). See Figure 8.4.

Survey 2-Pre, Repeated-Measures Cluster Effects: On Survey 2-Pre for both groups, there were no significant differences in mean ratings for the Target Cluster Questions (2, 4, and 6) compared to the Non-Target Cluster Questions (1, 3, 5 and 7), (both F’s < 1). To confirm the results of the one-way analysis, a 2 × 2, mixed-design, repeated-measures ANOVA was conducted. Both groups, “Tail II” and “Call,” for Survey 2-Pre for the repeated measures analysis 2 × 2 ANOVA revealed a similar pattern of results, as there was no significant main effect of groups, (F < 1), no significant main effect of cluster, F (1, 46) = 3.16, p > 0.05, and no significant interaction effect between groups and cluster, (F < 1).

Survey 2-Post, Between-Groups Effects on Self-Control Questions: Target Cluster Questions: The mean rating for Question 2 for the “Tail II” group, n = 32, and the “Call” group, n = 15, was 3.28+/−0.23 and 2.93+/−0.26, respectively, and this difference was not significant, (F < 1). The mean rating for Question 4 for the “Tail II” group, n = 31, and the “Call” group, n = 13, was 3.42+/−0.22 and 2.54+/−0.28, respectively, and this difference was significant, F (1, 42) = 4.76, p = 0.04. The effect size is 0.72. The mean rating for Question 6 for the “Tail II” group, n = 31, and the “Call” group, n = 15, was 3.71+/−0.18 and 2.73+/−0.35, respectively, and this difference was significant, F (1, 44) = 7.15, p = 0.01. The effect size is 0.84. See Figure 8.5.

Non-Target Cluster Questions: The mean rating for Question 1 for the “Tail II” group, n = 28, and the “Call” group, n = 13, was 2.82+/−0.21 and
The mean rating for Question 3 for the “Tail II” group, \( n = 31 \), and the “Call” group, \( n = 13 \), was 3.32+/−0.24 and 3.54+/−0.26, respectively, and this difference was not significant, \( F < 1 \). The mean rating for Question 5 for the “Tail II” group, \( n = 31 \), and the “Call” group, \( n = 15 \), was 3.26+/−0.22 and 2.80+/−0.27, respectively, and this difference was not significant, \( F (1, 44) = 1.45, p = 0.24 \). The mean rating for Question 7 for the “Tail II” group, \( n = 32 \), and the “Call” group, \( n = 15 \), was 2.97+/−0.15 and 2.47+/−0.31, respectively, and this difference was not significant, \( F (1, 45) = 2.59, p = 0.11 \). See Figure 8.6.

Survey 2-Post Effects of Groups on Cluster: The mean rating for Target Cluster Questions (2, 4, and 6) for each student was derived, and the mean rating for Non-Target Cluster Questions (1, 3, 5, and 7) for each student was derived. The group means for Target Cluster Questions for the “Tail II” group, \( n = 32 \), and the “Call” group, \( n = 15 \), were 3.46+/−0.19 and 2.79+/−0.25, respectively, and this difference was significant, \( F (1, 45) = 4.31, p = 0.04 \). The effect size is 1.05. The group means for the Non-Target Cluster Questions for the “Tail II” group, \( n = 32 \), and the “Call” group, \( n = 15 \), were 3.09+/−0.16 and 2.93+/−0.21, respectively, and this difference was not significant, \( F < 1 \). To further evaluate, a 2 × 2, mixed-design, repeated-measures ANOVA was conducted. This analysis revealed no significant main effect of groups, \( F (1, 45) = 2.56, p = 0.12 \), and no significant main effect of cluster \( (F < 1) \), but there was a marginally significant interaction effect between groups and cluster, \( F (1, 45) = 2.85, p < 0.10 \). Fisher’s LSD revealed that on Survey 2-Post for the Target Cluster Questions, the ratings of the “Tail II” group were significantly higher than the ratings of the “Call” group, \( p < 0.05 \). See Figure 8.7.

Repeated-Measures Surveys and Cluster Effects: For Survey 2-Pre, there were no significant effects of groups on ratings of Target Cluster Questions, \( (F < 1) \). For Survey 2-Post, the “Tail II” group, \( n = 24 \), provided significantly higher ratings for the Target Cluster Questions than the “Call” group, \( n = 10 \), \( F (1, 32) = 7.54, p = 0.01 \). The effect size was 1.04. There was no significant two-way interaction between groups and cluster, \( F = (1, 32) = 1.48, p > 0.20 \). There was no significant two-way interaction between groups and surveys, \( (F < 1) \). There was a significant three-way interaction between groups, cluster, and survey, \( F (1, 32) = 6.51, p = 0.02 \). Fisher’s LSD revealed that on Survey 2-Post for Target Cluster Questions (2, 4, and 6) the “Tail II” group provided higher mean ratings relative to the mean ratings of the “Call” group, \( p < 0.05 \). See Figure 8.8. This effect was not observed for Non-Target Cluster Questions.
(F < 1), which revealed no main effect of groups, no main effect of survey, and no interactions between groups and survey, (F’s < 1). See Figure 8.9.

Repeated-Measures Surveys 2-Pre and 2-Post: For each of the seven questions, mean ratings for “Tail II” group, for Survey 2-Pre and Survey 2-Post were compared by separate one-way ANOVAs. In all cases, the effects of survey were not statistically significant, (all p’s > 0.05). For each of the seven questions, mean ratings for “Call” group, for Survey 2-Pre and Survey 2-Post were compared by separate one-way ANOVAs. In all cases, the effects of Survey were not statistically significant, (all p’s > 0.05).

Discussion, Experiment 2

All subjects participating in Experiment 2 had previously participated in Experiment 1 and remained in their assigned group for both experiments. The results of Experiment 2 provided consistent evidence that reading “Tail II” after reading “Tail I” enhanced awareness of loss of self-control and, in addition, enhanced awareness of how the loss of self-control contributed to drug addiction. This conclusion is supported by several lines of convergent evidence. Note that the experimental design included several controls to allow for more precise specification of the factors responsible for our effects. For example, the control group read “Buffaloes” and “Call” that were comparable to “Tail I” and “Tail II” in reading level, number of pages, quality of illustrations, and general story time, but “Buffaloes” and “Call” differed from “Tail I” and “Tail II” in that “Buffaloes” and “Call” were not stories about losing self-control. Therefore, the group differences in ratings to questions specifically related to self-control were unlikely due to nonspecific extra-experimental factors such as distractions related to reading, or the schedule of completing assignments, or to interactions among students or instructors.

The mean rating for Cluster Target Question #4 was significantly higher for the “Tail II” group, relative to the “Call” group, indicating that reading “Tail II” significantly elevated ratings of their understanding of why the loss of self-control is difficult to recognize. The effect size was 0.72, indicating that the significance level is not an artifact of group size. In addition, for the “Tail II” group, relative to the “Call” group, the mean rating for Cluster Target Question #6 was significantly higher, indicating significantly elevated
ratings of their understanding of what they can do to prevent the loss of self-control. The statistical significance is confirmed by calculation of the effect size which was 0.84 for Question 6, indicating that the difference in group means was large in relation to the within group variances. On Survey 2-Post for the “Tail II” group, relative to the “Call” group, the mean rating for Cluster Target Questions (2, 4, and 6) that pertain to the loss of self-control was significantly higher, indicating significantly elevated rating of the general understanding of the loss of self-control. This significance is confirmed with an effect size of 1.05. Finally, it should be noted that although the self-control Question 2 produced group mean rating differences that failed to achieve statistical significance, the mean was higher for the “Tail II” group than for the “Call” group, indicating that for all of the self-control questions, the pattern of group mean differences were similar.

The experimental design also included control questions in the form of Cluster Non-Target Questions that did not pertain to self-control. This allowed more precise specification of the beneficial effects of reading the stories. The beneficial effect of reading “Tail II” relative to reading “Call” was specific to self-control awareness, as significant group differences were not observed in mean Non-Target Cluster Questions (1, 3, 5, and 7) scores, indicating that the reading of “Tail I” then “Tail II” enhanced awareness of the loss of self-control more than reading “Buffaloes” and then “Call,” and this beneficial effect was specific to self-control awareness and was not due to extraneous factors that boosted rating of all questions including those that did not pertain to self-control.

The experimental design included repeated testing by administering the survey before and after reading the stories. The Survey 2-Pre data obtained before reading the second stories revealed that the groups did not differ on any of the questions, indicating that the pre-story baselines for the two groups were comparable. This shows that the groups did not differ in their awareness of self-control before reading the stories, but the groups did differ significantly in their awareness of self-control after reading the stories. Therefore, the post-story differences cannot be due to preexisting baseline differences between the groups.

Survey 2-Post scores were generally lower than Survey 2-Pre scores, for the “Call” group. Mean responses to Survey 2-Post for Non-Target Questions (1, 3, 5, and 7) were 0.15 lower than for Survey 2-Pre, indicating that there was an overall deterioration in ratings of questions across surveys that did not pertain to self-control. This deterioration effect across surveys was
also observed for Cluster Target Questions as well as Cluster Non-Target Questions. The notable exception was Question 6, which for the “Tail II” group increased mean ratings from Survey 2-Pre to Survey 2-Post, and this effect was significant, \( p < 0.05 \). This reveals that “Tail II” improved the understanding of what the students can do to prevent the loss of self-control, and this improvement between Survey 2-Pre and Survey 2-Post was observed despite the overall deterioration in ratings across surveys.

This deterioration effect was quite prevalent and was noted previously in Experiment 1, where Survey 1-Post scores were overall, across all questions, 0.50 points lower than Survey 1-Pre scores. The reason for the decrease in scores across surveys may be due to the students’ reaction to being asked to repeatedly answer the same or similar questions. Another factor could be due to the mere passing of days and weeks since the beginning of the school session, combined with the monotony of the daily regimen of reading the stories day after day. This suggests that a general within-semester fatigue effect may have developed amongst the students.

It should also be noted that this study was conducted under a number of challenging circumstances. The students were attending EMS, which is an alternative, out-of-district school, located on the grounds Carrier Clinic. Many of the students are challenged with interfering behaviors or troublesome childhood histories. Students may be diagnosed with social adjustment problems or are in need of clinical services. There is usually a component of poor academic performance as well. For many of the students, their reading skill levels were several grades below their mean age-appropriate reading skill levels, and, consequently, it may be that many of the students did not particularly enjoy reading stories or filling out surveys. These factors may have contributed to the overall decline in ratings across surveys, as the students became fatigued by daily readings, as the semester wore on. Whatever the cause, the decline in scores was observed across all questions, irrespective of their relevance to self-control, and this created a headwind for the hypothesis of post-story improvement in awareness of self-control. Nevertheless, despite the headwind, significantly improved ratings were obtained for Question 6 for the “Tail II” group.

The finding that “Tail II” significantly improved knowledge of self-control through a storytelling format is consistent with previous findings on the success of storytelling to deliver a message (Goodman-Scott, Carlisle, Clark, & Burgess, 2016). Storytelling is especially useful in populations with intellectual disabilities (Olcay Gül, 2016), who are particularly vulnerable to
substance use disorders (Arthur & Nelson, 2003; Metzger & Janet, 1992). The results of the present studies indicate that storytelling about sign-tracking is effective in boosting awareness of the loss of self-control, and this, in turn, suggests that both “Tail I” and “Tail II” may be effectively employed as part of a drug prevention education program in schools.

The loss of self-control of drug-taking is stealthy, sneaking up on the unsuspecting, largely because reflexively triggered involuntary acts of sign-tracking of drug-taking closely resemble voluntary and intended acts of drug-taking (see chapter in this volume “Sign-Tracking Model of the Addiction Blind Spot” by Tomie, Jeffers, & Zito). For this reason, for all drug users, the early instances of the loss of self-control of drug-taking are readily ignored or misconstrued as a poor decision, allowing additional repetitions of drug-taking to strengthen further the reflexive actions that presage full-blown drug addiction. The remedy is to increase awareness of this problem, to enhance vigilance of what might otherwise be overlooked. The present studies reveal that storytelling about sign-tracking can significantly increase awareness of the loss of self-control and improve understanding of how the loss of self-control contributes to the development of drug addiction. The present findings suggest that reading these stories about the science of sign-tracking and the loss of self-control may provide an early education tool for the primary prevention of drug addiction.

With regard to future research, the results of the present study revealed a significant effect of reading the “Tail I”-“Tail II” sequence on awareness of the loss of self-control. It remains unclear, however, the degree to which this effect was dependent upon reading “Tail I” since surveys showed no between-groups differences in the ratings of the self-control questions after reading “Tail I.” Future research will address the possibility that reading only “Tail II” may be sufficient to provide the improvement in awareness of self-control, or, alternatively, if the additional dosing of the focus on self-control provided by “Tail I” is necessary for “Tail II” to produce its significant effects.

With regard to design flaws of the present study, it should be acknowledged that in the present study, the teachers were not blind to the experimental conditions. All teachers attended all training seminars given prior to the initiation of the experiments. They were then assigned to their groups. It is possible that their knowing the experimental conditions may have influenced their behavior during the course of the study. Along the same lines, it should also be acknowledged that in the present study, students within a sub-school intermingled during the study. Some students
in each sub-school were in the “Tail I and II” group, while others were in the control group, and students in one of the groups may have talked about the stories to students in the other group. Another factor that should be acknowledged is the student population. This study was conducted in an out-of-district school. Many of the subjects had conduct disorders or behavioral issues that could have affected their ability to absorb the story and learn more about self-control. There were many students who missed school days and had to catch up, and student turnover during the semester was considerable, as students dropped out of the program. This created missing data issues that impacted the number of students in our populations of repeated-measures assessments. Future research projects are planned at more traditional school settings where presumably less daily volatility in the classroom could be more conducive to reading stories and providing more consistent within-subjects survey data.

Further longitudinal follow-up studies are required to assess if a student’s increased awareness of the loss of self-control predicts that student’s subsequent resistance to drug use. We need to ascertain if the messages of these books regarding the loss of self-control are helpful to the students later in life when confronted with the opportunity to engage in drug use. A longitudinal study consisting of students who read “Tail I” and “Tail II” compared to students who read control stories, who were then assessed for their subsequent drug habits years later would provide the crucial test of the effectiveness of the stories in actually preventing drug use. Currently in development are additional scientific short stories on sign-tracking. These illustrated stories are intended to extend the range of application for this drug prevention tool from the 3rd grade through the 9th grade.

Acknowledgments

Authors thank the teaching staff of East Mountain School, including Tom Discafani, Barbara Wojtowicz, Lawrence Booth, Bonnie Kole, Chris Saponara, Charles Sumners, Erika Witkowski, and Eric Olsen. Authors also thank the East Mountain School administrators Dr. Stephen Bender, PhD., DD; Dr. Angela DiDolce, ND; and Mr. Russel Hudson for their guidance and assistance during this project. In addition, authors thank Ayon Iwasaki and Collin A.
Brown for their assistance with statistical analyses. This research was supported by the Center of Alcohol Studies at Rutgers University, New Brunswick, New Jersey, and the Carrier Clinic, Belle Meade, New Jersey.

References


**Figure 8.1.** Mean Survey 1 (Pre-Story) ratings to the Target Cluster of Questions 2, 4, and 6 and to the Non-Target Cluster of Questions 1 and 3 for subjects in the Tail I Group and the Buffaloes Group. The vertical bars represent the standard error of the mean (S.E.M.). The Target Cluster of Questions 2, 4, and 6 pertain to self-control. The Non-Target Cluster of Questions 1 and 3 do not pertain to self-control. Subjects in the Tail I Group were assigned The Tail of the Raccoon: Secrets of Addiction. Subjects in the Buffaloes Group were assigned Where the Buffaloes Begin.
Figure 8.2. Mean Survey 2 (Pre-Story) ratings to the Target Cluster of Questions 2, 4, and 6 and to the Non-Target Cluster of Questions 1, 3, 5, and 7 for subjects in the Tail I Group and the Buffaloes Group. The vertical bars represent the standard error of the mean (S.E.M.). The Target Cluster of Questions 2, 4, and 6 pertain to self-control. The Non-Target Cluster of Questions 1, 3, 5, and 7 do not pertain to self-control. Subjects in the Tail I Group were assigned The Tail of the Raccoon: Secrets of Addiction. Subjects in the Buffaloes Group were assigned Where the Buffaloes Begin.
Figure 8.3. Mean Survey 1 (Pre-Story) and Survey 2 (Post-Story) ratings to Non-Target Cluster Questions 1, 3, 5, and 7 for subjects in the Tail I Group and the Buffaloes Group. The vertical bars represent the standard error of the mean (S.E.M.). Subjects in the Tail I Group were assigned The Tail of the Raccoon: Secrets of Addiction. Subjects in the Buffaloes Group were assigned Where the Buffaloes Begin.
Figure 8.4. Mean Survey 3 (Pre-Story) ratings to the Target Cluster of Questions 2, 4, and 6 and to the Non-Target Cluster of Questions 1, 3, 5, and 7 for subjects in the Tail II Group and the Call Group. The vertical bars represent the standard error of the mean (S.E.M.). The Target Cluster of Questions 2, 4, and 6 pertain to self-control. The Non-Target Cluster of Questions 1, 3, 5, and 7 do not pertain to self-control. Subjects in the Tail II Group were assigned *The Tail of the Raccoon, Part II: Touching the Invisible*. Subjects in the Call Group were assigned *The Call of the Wild*. 
Figure 8.5. Mean Survey 4 (Post-Story) ratings to Questions 2, 4, and 6 for subjects in the Tail II Group and the Call Group. The vertical bars represent the standard error of the mean (S.E.M.). Subjects in the Tail II Group were assigned The Tail of the Raccoon, Part II: Touching the Invisible. Subjects in the Call Group were assigned The Call of the Wild. The single asterisk (*) indicates that the adjacent columns differ significantly, $p < 0.05$. The double asterisk (**) indicates that the adjacent columns differ significantly, $p < 0.01$. 
Figure 8.6. Mean Survey 4 (Post-Story) ratings to Questions 1, 3, 5, and 7 for subjects in the Tail II Group and the Call Group. The vertical bars represent the standard error of the mean (S.E.M.). Subjects in the Tail II Group were assigned The Tail of the Raccoon, Part II: Touching the Invisible. Subjects in the Call Group were assigned The Call of the Wild.
Figure 8.7. Mean Survey 4 (Post-Story) ratings to the Target Cluster of Questions 2, 4, and 6 and to the Non-Target Cluster of Questions 1, 3, 5, and 7 for subjects in the Tail II Group and the Call Group. The vertical bars represent the standard error of the mean (S.E.M.). The Target Cluster of Questions 2, 4, and 6 pertain to self-control. The Non-Target Cluster of Questions 1, 3, 5, and 7 do not pertain to self-control. Subjects in the Tail II Group were assigned The Tail of the Raccoon, Part II: Touching the Invisible. Subjects in the Call Group were assigned The Call of the Wild. The single asterisk (*) indicates that the adjacent columns differ significantly, p < 0.05.
Figure 8.8. Mean Survey 3 (Pre-Story) and Survey 4 (Post-Story) ratings to the Target Cluster of Questions 2, 4, and 6 for subjects in the Tail II Group and the Call Group. The vertical bars represent the standard error of the mean (S.E.M.). Subjects in the Tail II Group were assigned The Tail of the Raccoon, Part II: Touching the Invisible. Subjects in the Call Group were assigned The Call of the Wild. The double asterisks (**) indicates that the adjacent columns differ significantly, p < 0.01.
Figure 8.9. Mean Survey 3 (Pre-Story) and Survey 4 (Post-Story) ratings to the Non-Target Cluster of Questions 1, 3, 5, and 7 for subjects in the Tail II Group and the Call Group. The vertical bars represent the standard error of the mean (S.E.M.). Subjects in the Tail II Group were assigned The Tail of the Raccoon, Part II: Touching the Invisible. Subjects in the Call Group were assigned The Call of the Wild.