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Sign-Tracking and Drug Addiction

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DOI: http://dx.doi.org/10.3998/mpub.10215070

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Chapter 1: Introduction: The Role of Sign-Tracking in Drug Addiction

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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 http://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.

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