Neuroscience and Biobehavioral Reviews 111 (2020) 84–94

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Mapping sign-tracking and goal-tracking onto human behaviors

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ARTICLE INFO

Keywords:
Sign-tracking
Goal-tracking
Addictive behavior
Impulse control disorders
Humans
Rodents

ABSTRACT

As evidenced through classic Pavlovian learning mechanisms, environmental cues can become incentivized and influence behavior. These stimulus-outcome associations are relevant in everyday life but may be particularly important for the development of impulse control disorders including addiction. Rodent studies have elucidated specific learning profiles termed 'sign-tracking' and 'goal-tracking' which map onto individual differences in impulsivity and other behaviors associated with impulse control disorders' etiology, course, and relapse. Whereas goal-trackers are biased toward the outcome, sign-trackers fixate on features that are associated with but not necessary for achieving an outcome; a pattern of behavior that often leads to escalation of reward-seeking that can be maladaptive. The vast majority of the sign- and goal-tracking research has been conducted using rodent models and very few have bridged this concept into the domain of human behavior. In this review, we discuss the attributes of sign- and goal-tracking profiles, how these are manifested neurobiologically, and how these distinct learning styles could be an important tool for clinical interventions in human addiction.

1. Introduction

Impulse control disorders, such as substance use, conduct, and eating disorders, are often anteceded by early development of externalizing disorders (Biederman et al., 2008). More specifically, externalizing disorders in youth increase risk for later development of: (1) major depressive, substance use, bipolar, and antisocial personality disorders; and (2) behavior problems including school suspensions/expulsions, traffic violations, early/risky sexual behaviors, crime convictions, and job terminations (Biederman et al., 2008). Although the relationship between early evidence of externalizing disorders and later risk for mental health disorders is robust, it is mostly descriptive, i.e. the underlying biobehavioral processes remain poorly understood. There is a need for translational approaches that can help to quantify individual differences in both animals and humans. Animal studies can more rigorously evaluate causal mechanisms whereas human studies are essential to determine the utility of these approaches for clinically useful predictions. The "sign-tracker/goal-tracker" (ST/GT) animal model has the potential to fill this gap. This model is based on individual differences in cue-reward learning and seems to capture a neurobehavioral endophenotype relevant to a number of psychiatric disorders (Lovic et al., 2011; Morrow et al., 2011, 2015; Robinson et al., 2014; Saunders and Robinson, 2013). This review aims to address the limited, but growing, literature attempting to translate relevant concepts, methods, and correlates of sign-tracking and goal-tracking behaviors from rodent models to human behaviors, with a particular emphasis on human addiction vulnerability. While this has been done extensively theoretically, only recently has a body of literature begun to emerge addressing the translational ability of this construct and the optimization of methodology to apply it to humans. This opens a potential avenue for the information gained from these paradigms to be an important tool for clinical screening and intervention within the context of human addiction. Here we review the theorized attributes of sign- and goal-tracking animal profiles with an emphasis on the neurobiological and behavioral profiles with the greatest relevance to human behaviors. We then discuss the limited research focusing on these constructs in humans, address some promises and pitfalls of translation, and provide suggestions regarding further validation in humans for future research. The wealth of knowledge gained from the distinct learning profiles reflected by the ST/GT animal model, including underlying neural mechanisms, lays a solid foundation for translational work that could aid our understanding of risk for substance use and other impulse control disorders.

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https://doi.org/10.1016/j.neubiorev.2020.01.018
Received 31 July 2019; Received in revised form 16 January 2020; Accepted 18 January 2020
Available online 20 January 2020

2. Learning profiles: 'sign-tracking' versus 'goal-tracking'

Cues in one's environment (e.g., sights, sounds, smells) play a significant role in learning processes because they predict positive or negative outcomes. During Pavlovian learning, or classical conditioning, stimuli or cues that repeatedly and reliably precede an event are ascribed with predictive value. For example, a neutral stimulus (e.g. bell) will become a conditioned stimulus (CS) after repeated pairing with an unconditioned stimulus (US, e.g. food). Over time, this CS prompts a conditioned response (CR), a set of automatic behaviors, even in the absence of the original US (Pavlov, 1927). Hence, the neutral stimulus is transformed into a CS once it attains predictive value. We know, however, that for some individuals the CS is also imbued with incentive motivational value. For example, when rats are exposed to a Pavlovian conditioned approach paradigm in which a lever cue (CS) always precedes the delivery of a food reward (US), the CS attains predictive value and elicits a conditioned response (CR). Populations of rats can be classified as goal-trackers (GTs; Boakes, 1977) or sign-trackers (STs; Hearst and Jenkins, 1974) based on the conditioned response that is exhibited in this scenario (Meyer et al., 2012; Robinson and Flagel, 2009). For GTs, the lever-cue is merely a predictor and elicits a conditioned response directed at the location of reward delivery; whereas for STs the lever-cue is attributed with both predictive and incentive value and thereby transformed into a "motivational magnet" (Flagel et al., 2009; Robinson and Flagel, 2009). There are three fundamental properties of an incentive stimulus: (1) it biases attention, (2) it becomes desirable, and (3) it invigorates reward-seeking behaviors (e.g., Berridge, 2001; Berridge and Robinson, 2003; Meyer et al., 2012; Saunders and Robinson, 2013). Such stimuli thereby attain the ability to elicit "wanting" and "craving" - implicit and unconscious magnetic drives that motivate behavior (Berridge, 2001; Berridge and Robinson, 2003). While much of the literature that has emerged surrounding the ST/GT animal model over the past decade has centered around the incentive salience theory, alternative accounts suggest that sign-tracking behavior may be mediated by expectancies because it is sensitive to devaluation of the US (Derman et al., 2018). Further, different types of cues (e.g. contextual 'occasion-setters') vary in their ability to elicit aberrant behavior in GTs or STs (Fraser and Holland, 2019; Saunders et al., 2014). For the scope of the current review, however, we will focus on the prevailing theory that sign-tracking is marked by the excessive attribution of incentive motivational value to the reward-cue (CS).

STs and GTs can be characterized according to their behavior during a Pavlovian conditioned approach paradigm (Boakes, 1977; Fitzpatrick et al., 2013; Flagel and Robinson, 2017; Flagel et al., 2007; Hearst and Jenkins, 1974; Robinson and Flagel, 2009; Robinson et al., 2014; Sarter and Phillips, 2018; for reviews of procedures and detailed characterizations of rodent phenotypes see Meyer et al., 2012). In this paradigm, rodents are placed in a testing chamber that is equipped with a food tray and a discrete, localized CS such as a retractable lever (an auditory cue does not typically elicit the same results; Meyer et al., 2014) that is reliably followed by a US, such as food (for review see Flagel et al., 2009). Each trial consists of the brief presentation of an illuminated lever and, immediately following its retraction, a food pellet is dispensed into an adjacent tray (see Fig. 1). Daily conditioning sessions consist of 25 trials and after approximately 5 sessions distinct phenotypes emerge and remain stable (e.g., Flagel and Robinson, 2017). For GTs, the lever-CS elicits approach behavior directed towards the food tray (Boakes, 1977; Flagel et al., 2008, 2007). In contrast, STs approach and interact with the lever-CS itself (Hearst and Jenkins, 1974) and do so more vigorously across training (Flagel et al., 2009) and with prolonged intervals between trials (Lee et al., 2018). As an incentive stimulus, the lever-CS becomes reinforcing, as STs will work for its presentation even in the absence of a food reward (e.g., Flagel and Robinson, 2017; Meyer et al., 2012; Robinson et al., 2014; Saunders and Robinson, 2013). A third phenotype can also be observed with this

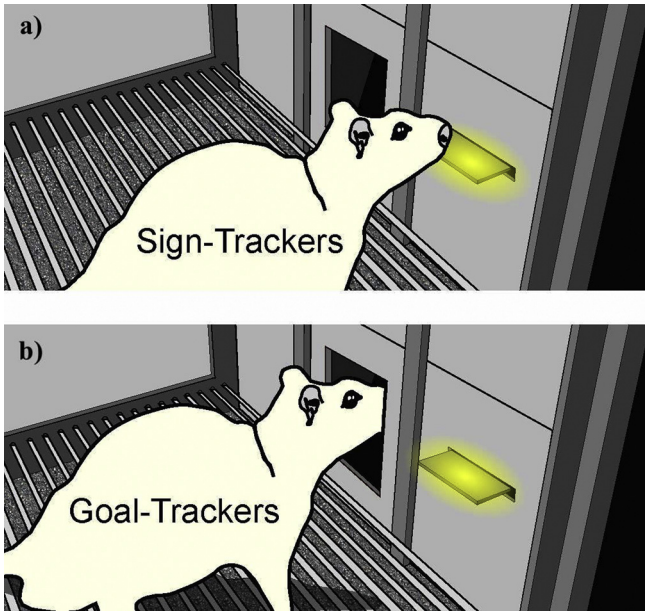

Fig. 1. Rodent Sign- and Goal-Trackers.
An example of the rodent PCA task. (a) A sign-tracking conditioned response directed toward the CS. (b) A goal-tracking conditioned response directed toward the US.

Pavlovian conditioning paradigm in which rats, characterized as intermediate responders, may demonstrate both approach to the lever-CS and the location of US delivery, and often vacillate between the two on a given trial. It is important to recognize that delivery of the food reward (US) is response-independent; yet these distinct CRs are displayed and consistently followed by retrieval of the US (e.g., Flagel et al., 2009). Typically, in rodents, these phenotypes are stable and consistent within each individual (Flagel et al., 2008).

Importantly, divergent behaviors for STs and GTs do not appear to reflect differences in learning abilities. Both groups learn the associations between the CS-US equally well, exhibit a CR, and initially orient towards the CS at similar rates; the cue is equally effective as a CS, or a predictor, in both phenotypes (Robinson and Flagel, 2009; Saunders and Robinson, 2013). However, the discrete, localized cue acquires the incentivizing and motivational properties, and can elicit 'wanting', similar to that of a US and becomes a more effective conditioned reinforcer for STs relative to GTs (Flagel et al., 2009, 2007; Robinson and Flagel, 2009; Robinson et al., 2014; Saunders and Robinson, 2013).

2.1. Pavlovian learning: transitioning from animals to humans

Although to some extent sign-tracking behavior may provide evolutionary benefits for both animals and humans (e.g., attention to stimuli signaling the presence of food or water may increase an individual's chance of survival in times of scarcity), sign-tracking can also become maladaptive, even when paired with a US that represents a valuable resource. Indeed, sign-tracking behavior is problematic when it is perseverative, inflexible, and resistant to extinction (Ahrens et al., 2016; Flagel et al., 2009; Tomie, 1996). Individuals may display a rigid response pattern that is reminiscent of addictive behaviors in humans, engaging in time-consuming reward-seeking behaviors that may persist beyond the point of the reward remaining adaptive. In that sense, sign-tracking traits have been associated with behavioral signs of impulse control deficits (Flagel and Robinson, 2017; Flagel et al., 2010; Lovic et al., 2011) and are sometimes associated with 'obsessive' or 'compulsive' behaviors. For example, ST rats will continuously gnaw on the CS and only stop once the food is presented, and raccoons will handle the CS as if it were the reward itself (chewing, licking, etc.), often

delaying receipt of the actual reward by performing these behaviors (Breland and Breland, 1961). (For a brief video example, see https://tailoftheraccoon.com/the-integrated-reward-system/). When a CS is repeatedly presented alone, in the absence of the US, the CR will typically decrease, or be extinguished; however, a sign-tracking CR is more resistant to extinction and more prone to reinstatement than a goal tracking CR (Ahrens et al., 2016; Saunders and Robinson, 2013; Yager and Robinson, 2010). That is, relative to GTs, STs exhibit enhanced responding to a Pavlovian food-paired cue during extinction (Ahrens et al., 2016; Yager and Robinson, 2010). Similarly, STs persist in their approach to the CS even if interacting with the CS begins to produce an adverse outcome or loss in reward (Chang and Smith, 2016). GTs, on the other hand, respond rapidly and with better discrimination between reward and non-reward cues than STs (Ahrens et al., 2016). Furthermore, following limited drug exposure, STs appear more vulnerable to cue-induced relapse than GTs, even after extinction (Saunders and Robinson, 2010, 2011). STs also work harder to access previously conditioned drugs (Saunders and Robinson, 2011; Yager et al., 2015) and generally react to drug cues more readily (Saunders and Robinson, 2010). This may look similar in humans, such that for some, but not all, individuals with substance use disorder, drug-related cues can instigate relapse (e.g., Grüsser et al., 2004) and stimuli previously associated with cocaine (CS) can produce a cardiovascular response (CR) akin to that evoked through the use of cocaine (US) (Cascella et al., 1989). Likewise, food-related cues can instigate cravings that lead to compulsive eating behaviors (e.g., Ferriday and Brunstrom, 2008) and create insulin responses (CR) even in the absence of a US (Stockhorst et al., 2000). Such cue-evoked responses can thereby motivate an individual to seek out food or drug (for reviews see Courtney et al., 2016; Volkow et al., 2008).

The traditional view of distinct vulnerability of ST over GT animals as it relates to addictive behavior has recently been revised. In particular, it appears that the degree of access to the drug moderates addiction vulnerability. For example, GTs will develop addiction-related behaviors similar to those observed for STs following prolonged access to drug (Kawa et al., 2016). Moreover, GTs are more sensitive to the ability of complex, situational, or contextual cues (i.e. “occasion setters”) to motivate and control their drug-seeking behaviors (Pitchers et al., 2017b; Saunders et al., 2014). Together, these findings suggest that some cues acquire incentive salience for GTs as well as STs, which may reflect an alternate pathway to addiction (Fraser and Janak, 2019; Robinson et al., 2014). It appears that STs and GTs are motivated by and sensitive to different classes of cues that can lead to addiction-related behaviors and relapse. As extant research robustly shows that the ST endophenotype captures many behavioral characteristics that overlap with human addiction, including greater impulsivity and deficits in attentional control (discussed below), we continue to discuss STs as those with enhanced vulnerability to addiction; with the important caveat that this represents just one of many paths to this disorder (Belin et al., 2016; Flagel et al., 2009; Tomie et al., 2008, 2018; Tomie and Morrow, 2018).

Despite extensive work relating the ST phenotype with enhanced addiction vulnerability, very little translational work has been done in this regard. Therefore, it will be beneficial to examine individual differences in incentive salience attribution in human models in order to 1) assess translational utility and whether the ST/GT model is relevant to the development of psychopathology and 2) examine whether the same brain mechanisms unveiled in rats are relevant to human endophenotypes. Thus, this review will discuss the current knowledge regarding these individual differences mainly in rodent models and highlight how these differences could be an important tool for clinical interventions in human addiction. We also review brain and behavioral characteristics that have emerged from the ST/GT animal model and relate them to psychological characteristics in humans, many of which are associated with symptoms of psychiatric disorders.

3. Sign-tracking and goal-tracking biobehavioral characteristics

Beyond their namesake behaviors, STs and GTs differ on a number of behaviors. Below is a summary of some of the relevant overlapping constructs between rodent sign-tracking traits and human addiction (Belin et al., 2016; Flagel et al., 2010; for reviews see Robinson et al., 2014; Tomie et al., 2008; Tomie and Morrow, 2018).

3.1. Attention

Relative to GTs, STs display deficits in attentional control (Koshy Cherian et al., 2017; Paolone et al., 2013; Pitchers et al., 2017c). For example, STs tend to perform poorly in a sustained attention task (SAT), which requires individuals to repeatedly respond to a cue in the presence of distractors (e.g., flashing lights). In this situation, a stronger degree of sign-tracking behavior (higher Pavlovian conditioned approach scores) is associated with poorer task performance (Paolone et al., 2013). In fact, the behavior exhibited by STs never recovers to pre-distractor levels, as does that of GTs (see Sarter and Phillips, 2018). This response pattern in the rodent model is indicative of poor top-down control that appears to be driven, at least in part, by deficits in cortical cholinergic regulation (Koshy Cherian et al., 2017; Paolone et al., 2013; Pitchers et al., 2017a; Sarter and Phillips, 2018). Similarly, in humans, attentional bias to cues has been related to sign-tracking-like behaviors (e.g., Le Pelley et al., 2015 discussed below) and implicated in impulse control disorders, including substance use (Frodl, 2010).

3.2. Novelty seeking and risk-taking

Rats that are selectively bred based on locomotor response to novelty also differ in their propensity to attribute incentive value to reward cues. Selectively bred high-responder rats (bHRs) are STs, and selectively bred low-responder rats (bLRs) are primarily GTs (Flagel et al., 2010). In fact, bHR rats, with high reactivity to novelty and the tendency to sign-track, exhibit a number of addiction-related behaviors (Kuhn et al., 2018a), including aggressive behavior, impulsivity, increased motivation for drug reward, and an increased propensity for relapse (Flagel et al., 2016, 2010; Flagel et al., 2014; Kerman et al., 2011). While these traits all seem to be related in the selectively bred rats, it is clear that from other studies using outbred rats that novelty-seeking traits and sign- and goal-tracking traits are *uncorrelated* (Hughson et al., 2019; Robinson and Flagel, 2009), suggesting that novelty seeking provides only a partial genetic explanation in sign- and goal-tracking traits. As with attentional bias, novelty-seeking has also been implicated in impulse control disorders in humans (Wingo et al., 2016), reemphasizing the potential for translational links between rodent sign-tracking behaviors and human psychopathology.

3.3. Impulsivity

Impulsivity is a heterogeneous construct (Dalley and Robbins, 2017), but can be broadly defined as a lack of behavioral inhibition that may lead to unplanned, premature, and often risky behaviors (Belin et al., 2016; de Wit, 2009d). Relative to GTs, rats and humans that sign-track demonstrate more impulsive behaviors (Flagel et al., 2009, 2010; Flagel et al., 2008; Garofalo and di Pellegrino, 2015; Robinson and Flagel, 2009; Tomie et al., 2000). For example, selectively bred bHR rats show a diminished ability to inhibit behaviors (faster and more frequent pursuit of the lever) and to withhold responding for a reward compared to bLR rats (Flagel et al., 2010). Additionally, outbred ST rats demonstrate more impulsive *actions* (measured by a reaction time task) but no differences in impulsive *choice* (measured by a delay discounting choice procedure) compared to GTs (Lovic et al., 2011), and mice with a reduced availability of the serotonin transporter 5-HT show both sign-tracking behaviors and impulsive actions (Campus et al., 2016). Again,

in humans, impulsivity is not only related to sign-tracking behaviors (see discussion below; Garofalo and di Pellegrino, 2015), but it has also been implicated in externalizing and substance use disorders both behaviorally and neurobiologically (e.g., Castellanos-Ryan et al., 2014; Verdejo-Garcia et al., 2007) (for reviews see de Wit, 2009d; Meyer and Tripi, 2018). Together, the propensity for both sign-tracking behaviors and impulsivity may increase an individual's vulnerability to developing these disorders.

3.4. Neurobiology

Cortical and subcortical networks communicate with each other to integrate information regarding one's internal and external environment and, in turn, guide motivated behavior. STs and GTs engage different circuitry in response to reward cues (for reviews see Flagel and Robinson, 2017; Kuhn et al., 2018a), and the pattern of cue-induced activation suggests that only for STs is the classic cortico-thalamic-striatal "motive circuitry" engaged (Flagel et al., 2011a). When a "functional connectivity" approach was used to further examine patterns of cue-induced activation in STs and GTs, it appeared that GTs relied on top-down cortical engagement; whereas the behavior of STs was dependent primarily on subcortical processes (Flagel et al., 2011a). More recent studies support this notion, suggesting that top-down cortical control mechanisms are intact in GTs, but deficient in STs (Haight et al., 2017; for a detailed reviews see Kuhn et al., 2018a; Sarter and Phillips, 2018). In relation, inhibition of a top-down cortico-thalamic circuit enhances the tendency to sign-track in rats that are inherently GTs; whereas activation of the same circuit appears to elicit behavioral control over STs and decreases the incentive value of a reward cue for these animals (Campus et al., 2019).

As evidenced by both animal and human research, dopaminergic activity in the mesolimbic pathway, particularly the ventral striatum or the nucleus accumbens (NAc), plays an important role in bottom-up motivational processing and reward learning. In humans, multiple neuroimaging studies indicate structural and functional differences in impulse control and externalizing disorders during reward processing (Castellanos-Ryan et al., 2014; Raschle et al., 2015). Specifically, structural deficits in frontostriatal regions (orbital and dorsolateral prefrontal cortex and anterior cingulate) implicated in reward processing and inhibition (Castellanos-Ryan et al., 2014; Raschle et al., 2015; Yang and Raine, 2009), and functional deficits in the dorsal/ventral striatum (caudate nucleus and nucleus accumbens) during reward processing and goal-directed tasks (Cope et al., 2019) are characteristic of impulse control disorders. In rodents, although the exact role of dopamine in reward processing is still under debate (e.g., Berke, 2018; Schultz, 2019), the ST/GT model has been used to demonstrate that dopamine encodes the incentive value of a reward cue, not the predictive value (Flagel et al., 2011b; Saunders and Robinson, 2013). That is, dopamine plays a primary role in rendering reward-cues into "motivational magnets" that are capable of eliciting irresistible urge and desire (Berridge and Robinson, 2011). It is not surprising, therefore, that dopamine activity has, on a broad level, been correlated with impulsive behavior and, more specifically, shown to play a critical role in drug addiction (Moeller and Paulus, 2018; Saunders and Robinson, 2013; Volkow et al., 2010).

Specific to sign- and goal-tracking behaviors, rodent models have elucidated that dopamine, D1 and D2 receptors in particular (Fraser et al., 2016), in the NAc are integral in the attribution of incentive salience to reward cues and the expression of sign-tracking behavior (Chow et al., 2016; Dalley et al., 2005; Scülfort et al., 2016). After Pavlovian conditioned approach training and the establishment of a stable conditioned response, STs differ in their dopamine receptor gene expression (Flagel et al., 2007) and have higher levels of dopamine in the NAc and PFC, which, in turn, appears to be directly related to the strength of sign-tracking behaviors (more vigorous engagement with the cue; Pitchers et al., 2017a; Tomie et al., 2000). Indeed, sign-tracking, but not goal-tracking, is attenuated following administration of a dopamine antagonist in the NAc core (Saunders and Robinson, 2012). Furthermore, Flagel et al. (2010) demonstrated that selectively bred bHR rats (STs) are more sensitive in their responses to dopamine agonists and have a greater proportion of $D2^{high}$ receptors in the striatum than bLR rats (GTs), characteristics which suggest overlap with human externalizing and addictive behaviors. Goal-tracking behavior, on the other hand, seems to be associated more with cholinergic activity; such that presentation of a previously paired cue increases acetylcholine, but not dopamine, levels in GTs and not STs (Pitchers et al., 2017a). Taken together, these findings implicate the role of dopamine in subcortical circuits in response to reward cues for STs, which supports the bottom-up, stimulus-driven control theory of sign-tracking behavior (e.g., Campus et al., 2019; Haight et al., 2017; Kuhn et al., 2018a).

In concert with the striatum/NAc influencing sign-tracking behaviors are the paraventricular nucleus of the thalamus (PVT), basolateral amygdala (BLA), and ventral pallidum (VP; Saunders and Robinson, 2013). Specifically, cue-induced neuronal activity is correlated between the PVT and the ventral striatum in STs, but not GTs (Flagel et al., 2011b; Flagel and Robinson, 2017; Haight and Flagel, 2014). Further, lesions to the PVT generally enhance sign-tracking behaviors (Flagel and Robinson, 2017; Haight et al., 2015), and cue-induced drug seeking behavior is increased in GTs following inactivation of the PVT (Kuhn et al., 2018b). Together, these data demonstrate a significant role for the PVT in encoding the incentive value of drug cues. Neuronal activity in the VP, a primary destination for dopaminergic output, has also been associated with the attribution of incentive salience to reward cues. Relative to GTs, STs demonstrate robust changes in the VP neural activity compared to GTs after training (Ahrens et al., 2018), and chemogenetic disruption of the VP (mainly inhibitory) during Pavlovian conditioning impacts sign- but not goal-tracking behaviors (Chang et al., 2015). Finally, lesions to the BLA and disruptions in the BLA to NAc connectivity decrease sign-tracking behavior (Chang et al., 2012).

Integrating these results with other data, we postulate that hyperactive subcortical processes that are able to override top-down control mechanisms underlie the behavioral endophenotype of STs. In contrast, top-down inhibition of subcortical motivational processes promotes the goal-tracking phenotype (Campus et al., 2019; Haight et al., 2017; Kuhn et al., 2018a). Although more research is necessary to fully delineate the neural circuits and neurobiological mechanisms contributing to these two phenotypes, data collected thus far in the animal model provides a solid foundation from which we can build to identify the neural underpinnings of behavioral correlates in the human model.

4. Environmental and developmental influences

While the behavioral profiles are often consistent, not every individual with sign-tracking or impulsive tendencies develops maladaptive behaviors, indicating that there are other underlying risk factors and traits contributing to vulnerabilities toward substance use disorders. One in particular, environmental stress, especially in early life, impacts long-term behaviors through epigenetic changes that can contribute to maladaptive tendencies. For example, higher rates of externalizing and impulse control disorders are evidenced in children experiencing inconsistent and harsh parenting, whereas positive, supportive parenting serves as a protective factor against these disorders (Samek and Hicks, 2014).

Because cortisol directly influences dopamine in the brain's reward pathways (Piazza and Le Moal, 1996), stress in early life, such as residential instability, maltreatment, family adversity, or domestic violence, has long-term effects on the dopaminergic system and reward-motivated behaviors that may, consequentially, increase vulnerabilities for reward-seeking and substance use behaviors (Buu et al., 2009; Otten et al., 2018; Teixeira et al., 2017; Wakeford et al., 2018). Additionally, the hypothalamic-pituitary-adrenal (HPA) stress axis is believed to

directly influence sign- and goal-tracking behaviors, as corticosterone release is higher in rodents following Pavlovian autoshaping (Tomie et al., 2002, 2004) and greater in STs relative to GTs following a single session of Pavlovian conditioning (Beckmann and Bardo, 2012; Flagel et al., 2009; Tomie et al., 2000). Rats reared in a socially isolated environment (isolated from both the mother and littermates) demonstrated more sign-tracking behavior than control rats that were maternally reared (Lomanowska et al., 2011). Additionally, socially isolated peri-adolescent rats showed more locomotor reactivity to novelty (characteristic of sign-tracking behaviors in selectively bred rats; Dalley et al., 2002), a stronger motivation to seek and use drugs (Baarendse et al., 2014), increased alcohol use (Lesscher et al., 2015), and both structural and neurochemical changes in the PFC and dopaminergic changes in the striatum (Fone and Porkess, 2008; Hall et al., 1997). Finally, relative to adult rats, adolescent rats, whose behavior includes minimal sign-tracking tendencies (Anderson et al., 2013; Anderson and Spear, 2011; Doremus-Fitzwater and Spear, 2011), were significantly more sensitive to the effects of isolated or food-restricted environments and displayed increased sign-tracking behaviors in response to stress (Anderson et al., 2013). On the other hand, environmental enrichment and positive social interactions can act as protective factors against maladaptive behaviors, resulting in reduction in HPA axis activity and a decrease in cue-elicited responses and sign-tracking behaviors (Beckmann and Bardo, 2012). Furthermore, rats reared in large, social spaces with access to novel objects are less likely to self-administer drugs, more resistant to responding to reward cues, and attribute less incentive salience to reward-paired cues - thus resembling behavioral characteristics of GTs (Bardo et al., 2001; Beckmann and Bardo, 2012; Gipson et al., 2011). In sum, enriched early environments appear to dampen HPA stress reactivity and lessen reward-cue incentive salience, thereby decreasing sign-tracking behaviors; whereas exposure to stress, particularly in early life, appears to increase reward-cue incentive salience, and thereby increase sign-tracking behaviors.

Prior work regarding the impact of early life stress on these behaviors has almost exclusively been addressed using rodent models. There are, however, many parallels to human early life stress research and its impact on addiction vulnerability. The biobehavioral impacts of early stress and enrichment is evident in human populations in which much of the research points to increased sensitivity of the neural reward pathway in response to chronic stressors, such as higher ventral striatal dopamine responses to stimulants in those with histories of early life stress (Oswald et al., 2014). A recent report of a longitudinal study following high risk children revealed that greater NAc activation in response to reward anticipation in childhood (preclinical) is predictive of substance use in adolescence, beyond what was predicted by youth externalizing behaviors and parental substance use (Cope et al., 2019). These stress-related neurobiological risk factors may create vulnerabilities that could increase the potential for reward-seeking behaviors such as substance use (Roos et al., 2018; Wakeford et al., 2018). Both human and rodent findings emphasize the environmental and epigenetic impact, particularly in early life, on the expression of reward-seeking behaviors and their potential contribution to addiction vulnerabilities.

Much work still needs to be done to delineate the developmental trajectory of sign- and goal-tracking behaviors in humans and in rodents. So far, the results regarding developmental timing of sign- and goal-tracking are mixed and seem to depend on specific genetic strains (Campus et al., 2016; DeAngeli et al., 2017). For instance, when compared to adolescents of the same genetic strain, adult rats display more sign-tracking behaviors by making faster and more frequent contacts with the CS (Doremus-Fitzwater and Spear, 2011). Adolescent rats are characterized by lower basal dopamine levels in the NAc compared to adults (Anderson and Gazzara, 1993), and such attenuations may lead to decreased incentive salience and therefore less sign-tracking behavior. More recently, however, it was reported that sign-tracking was greater in adolescents particularly when under stress (social deprivation or food restriction; DeAngeli et al., 2017) and that, once learned, these sign-tracking traits persist into adulthood (Anderson and Spear, 2011; DeAngeli et al., 2017).

In humans, stages of cortical development impacting cognitive control abilities suggest that sign-tracking behavior may be more evident in children and adolescents. In children, frontal regions are not yet fully developed, resulting in reduced cognitive control abilities (e.g., planning, attentional control, inhibitory control) compared to adults (Casey et al., 2000), a skill which seems integral to goal-tracking behaviors in particular. Similarly, in adolescence, reward-related regions are faster to develop when compared to frontal regions (Casey and Jones, 2010). Thus, adolescence is characterized by a marked development of the subcortical reward system that is off balance with the slower-developing cognitive control systems. This may indicate that children and adolescents are prone to be more highly influenced by rewarding stimuli, and with less top down control (Casey et al., 2008), similar to STs. More research is necessary to elucidate the developmental trajectory of sign- and goal-tracking behaviors in humans and to determine whether such trajectories can be predictive of adult learning profiles and ultimately of individual variations in vulnerability to impulse control and substance use disorders. The combination of neurodevelopmental stages, the effects of stress on sign- and goal-tracking behaviors, and the hypersensitivity of children and adolescents to stress indicates that early life is an opportune time to address vulnerabilities toward substance use disorders and discover potential preventative interventions.

5. Mapping animal learning profiles onto human psychopathology

The disparities between STs and GTs are well-established in rodent models but the translation to humans remains unclear, with no validated consensus on appropriate methodologies. Replicating and extending findings from animals to humans can be a daunting task and should be approached with both caution and well-developed theoretical foundations (Stephens et al., 2013). In addition to behavioral and brain responses present in both STs and GTs, we must also consider a multitude of psychological constructs in humans that may map onto sign- and goal-tracking learning profiles and could convolute translation efforts. However, looking closer at parallels to human behaviors may lend to their predictive qualities for modeling risk for engaging in maladaptive compulsive behaviors and provide insights for future interventions. Below we discuss the few existing studies that have attempted this translation to human populations. Although the methodology varies between studies, we attempt to compare results, identify commonalities, and discuss considerations for an optimal paradigm moving forward.

5.1. Human sign-trackers and goal-trackers

There is preliminary evidence that sign-tracking and goal-tracking behaviors can be measured in humans (e.g., Garofalo and di Pellegrino, 2015), providing a unique opportunity for the translational study of risk factors for the development of impulse control deficits and addictive behaviors. Many human studies assess individual variation in behaviors that are related to, but technically different than sign- and goal-tracking, such as cue-reactivity or reward seeking (for reviews see Field and Cox, 2008; Jasinska et al., 2014; Saunders and Robinson, 2013). Perhaps more directly comparable to sign- and goal-tracking behaviors, recent studies have addressed the measurement of incentive salience attribution in humans through attentional bias to reward-paired stimuli (for a review of incentive salience sensitization in alcohol use disorder see Cofresi et al., 2019). As the classification of STs and GTs depends on attentional bias to one stimulus or another, in humans, eye-tracking may be a promising place to start. As such, Garofalo and di Pellegrino (2015) measured eye gaze in a Pavlovian instrumental transfer paradigm (PIT; the process by which a Pavlovian cue is used to elicit

instrumental responding for rewards) to classify human STs and GTs during a monetary reward conditioning task. Participants were first trained that an instrumental response was followed by a reward, and then taught that a previously neutral, task-irrelevant visual cue (CS) was associated with this same reward (US). During this Pavlovian conditioning, participants' eye movements toward the sign (CS) or the goal (US) were tracked in order to categorize individuals as STs or GTs. Finally, researchers tested PIT by assessing how the CS impacted behavior on the previous instrumental task which no longer resulted in reward presentation. Relative to GTs, STs demonstrated a greater likelihood to respond to the task-irrelevant CS even after the US was unavailable. Importantly, STs self-reported higher levels of impulsivity than GTs, which is consistent with behavioral patterns seen in animal models.

Similarly, another group of researchers have used eye-tracking to measure the level of interaction with a response-dependent, reward-paired CS (Anderson, 2016; Failing et al., 2015; Le Pelley et al., 2016, 2015; Pearson et al., 2015, 2016). In one variation, termed value-modulated attentional capture (VMAC), researchers measured attentional capture by reward cues as an index of incentive salience attribution. As in traditional ST/GT animal models, a visual distractor cue indicating reward (here, distinct colors represent either a high or low value) was presented but was irrelevant to the task itself. Divergent from animal models, however, the task was response-dependent and if participants looked toward the distractor first in a trial, the reward was omitted; thus, responses must be suppressed in order to gain the reward. Nevertheless, adults often looked toward the distractors, especially if the distractors indicated a high-value reward (Failing et al., 2015; Le Pelley et al., 2015; Pearson et al., 2015, 2016). This effect was exaggerated when participants were under high memory load (Watson et al., 2019) and held when both high- and low-value distractors were presented concurrently (Pearson et al., 2016). The effect was also apparent when all stimuli (not just the distractors) were different colors (Failing et al., 2015), and regardless of the participants' knowledge of reward omission (Pearson et al., 2015). These findings suggest that the effect of reward on attentional capture (VMAC) reflects an automatic response outside volitional control and reliant on cognitive capacity. Further, in these reports, the VMAC effect was not dependent on physical salience. The increased distractor-driven attention in these studies implies reward-motivated responding and incentive salience. Therefore, individual differences in VMAC have been argued to be translatable as a dimensional analogue of sign-tracking and thus, a potential indicator of risk for addiction-related psychopathology. In fact, higher levels of illicit drug use have been associated with higher attentional capture especially for those with low cognitive control (Albertella et al., 2017). Similarly, performance on a reward-only variant of the VMAC task (participants were not punished for incorrect responses) was positively associated with both impulsivity and compulsion-related behaviors across addictive- and obsessive-compulsive-related symptoms in subclinical adults (Albertella et al., 2019a). Just as ST animals engage with reward-paired signals even if the approach omits the reward or initiates punishment (Chang and Smith, 2016), human participants were more likely to have their attention captured by high-reward signals, even though this capture was at the expense of receiving the reward. In comparative animal studies, similar 'misbehavior' is considered maladaptive, possibly compulsive in nature (Breland and Breland, 1961), and mediated by the attribution of incentive salience to reward cues. In humans, this implies that individual differences in reward-related attentional capture (i.e., incentive salience) may reflect various impulse control deficits and promote stimulus-driven maladaptive behaviors. Notably, in each of these studies the variability of symptom presentation or substance use was limited by non-clinical samples as well as a cross-sectional approach, making it difficult to draw firm conclusions.

These findings are noteworthy and suggest that individual differences in substance use lie partially with attentional biases to reward and are impacted by cognitive control. However, a major distinction should be noted between VMAC and rodent ST/GT models before strong conclusions are made. In all of these reported studies, rewards were response-dependent, as only correct responses to the target elicited reward delivery, whereas response-*independence* in rodent models is crucial for measuring sign- and goal-tracking phenotypes. One group, however, measured VMAC in adults using a Pavlovian conditioning task in which reward-paired stimuli were both task-irrelevant and response-independent. In this variant, stimuli indicated high- and low-value rewards that were automatically allocated with no participant response necessary (Bucker and Theeuwes, 2017a,b), providing a closer representation of the rodent models. A non-reward test phase following training showed that adults were still more likely to attend to the reward, particularly of high value, suggesting that simply the co-occurrence of stimuli and rewards in Pavlovian conditioning was sufficient to draw attention to a reward-paired cue. Although this paradigm does not address individual differences in responding, further exploration of this variant of the VMAC task may offer insight to the expansion of sign- and goal-tracking research to the human population.

Extending translation efforts to address underlying neural mechanisms, a recent study aimed to measure sign- and goal-tracking in humans within the context of model-based and model-free reinforcement learning (Schad et al., 2019). In model-based learning, an organism creates an internal model of how states of the world may change depending on different possible actions, and uses that model to select actions expected to lead to the most rewarding states. In that sense, it is thought to underlie goal-directed behaviors and be driven by the integration of state prediction errors, or the difference between the actual and expected state based on previous experiences (Glascher et al., 2010). In model-free learning, on the other hand, an organism learns values for different action choices and uses those to maximize reward. Model-free learning is thought to underlie habitual behaviors and integrate reward prediction errors, or the difference between the actual and predicted value of a US (Glascher et al., 2010). Schad and colleagues hypothesized that healthy human adult STs would demonstrate model-free learning and GTs would demonstrate model-based learning (see also Derman et al., 2018). Participants completed tasks including instrumental conditioning, response-independent Pavlovian conditioning, and PIT, the latter two during functional magnetic resonance imaging (fMRI). In the Pavlovian conditioning task - which included a visual-auditory CS paired with various monetary rewards/losses - sign- and goal-tracking behaviors were defined as the difference between the proportion of time visually fixated on the CS and the proportion of time they instead fixated on the US location (which was then regressed onto the value of each CS). As in animal models (e.g., Robinson and Flagel, 2009), all participants showed evidence of learning the CS-US association. There were also multiple indicators that STs relied more on model-free learning and GTs on model-based learning. Specifically, fMRI signals of model-free learning (trial-by-trial temporal differences in signals interpreted as reflecting reward prediction-errors at CS and US onsets) were measured during Pavlovian conditioning in the ventral striatum for STs, but were not detectable in GTs. GTs instead demonstrated stronger indicators of model-based learning (trial-by-trial signals interpreted as reflecting state prediction-errors at US onset) in the intraparietal sulcus and lateral PFC; regions previously associated with model-free and model-based learning, respectively (Glascher et al., 2010). Furthermore, in STs, pupil dilation in response to reward anticipation was driven by model-free CS value, whereas for GTs it was driven by model-based uncertainty. Finally, consistent with prior reports (Garofalo and di Pellegrino, 2015), behavioral PIT effects were stronger in STs than GTs, suggesting that the CS acquired more incentive salience and elicited more approach behaviors for STs. This study is the first to address the simultaneous behavioral and neurobiological representations of sign- and goal-tracking in a human population. While these findings indicate a potential relationship between sign-tracking and goal-tracking behavior with model-free and model-based learning, respectively, the animal literature suggest that the

relationship is not this simple and that there are likely more factors involved (e.g., Flagel et al., 2011b; Lesaint et al., 2014). Thus, additional research is needed to fully delineate this relationship and to determine if the findings from the human studies are based on the same sign- and goal-tracking processes evident in animal models.

Other attempts to capture sign-tracking-related behaviors in humans have also yielded interesting and informative findings. In a study assessing PIT in adults (Garbusow et al., 2014), those with alcohol use disorder were more likely to show stronger PIT effects than healthy controls to aversive, not appetitive, stimuli, suggesting sign-tracking-related behaviors may be stronger in those with substance use issues for both positive and negative valence CS. Related to food-motivated behaviors, Versace et al. (2016) employed electroencephalography (EEG) to compare lean and obese individuals on the degree of motivational salience to food cues as measured by late positive potential (LPP) signal amplitude (a measure of cortical activity related to motivational and perceptual circuits). STs and GTs were classified, not by goal-directed behaviors or attentional bias, but based on brain activity patterns in response to food and other pleasant stimuli. Specifically, participants were classified as STs if they had both high LPP responses to food-related stimuli and blunted LPP responses to other positive stimuli compared to GTs. Findings demonstrated that, within STs, food cues (CS) and appetitive/aversive emotionally arousing stimuli (US) elicit similar LPP amplitudes, whereas for GTs, food cues elicit similar LPP responses to neutral stimuli. Although there were significantly more STs who were obese than lean in this study, groups were comprised of individuals with both body types, indicating that other systems - genetics, biological predispositions, or trait behaviors - may also be associated with sign- and goal-tracking behaviors. More recently, this group (Versace et al., 2019) expanded these results by measuring incentive salience differences relating to food cues through LPP and found that, regardless of BMI, individuals with larger LPP responses to food cues than other positive arousing stimuli were more disposed to cue-induced eating than those with the opposite LPP pattern. These results may reflect the rodent literature in suggesting specific endophenotypes characterized by differential neurological and behavioral responses to reward *cues*, i.e., the attribution of higher levels of incentive salience, that are linked to an increased susceptibility to maladaptive behaviors in response to cues (Versace et al., 2019). It should be noted, however, that STs and GTs were not classified based on goal-directed behaviors and Pavlovian conditioning was not utilized in these studies. Thus, without evidence of a learned association, direct comparison between these results and rodent STs and GTs is not possible. While they are notable findings regarding food cue reactivity, this protocol divergence calls into question whether these designs offer a valid measure of sign- or goal-tracking behaviors, emphasizing the need for a consensus regarding methodologies in these translational studies.

More closely replicating the rodent protocols, Joyner et al. (2018) extended both rodent and human sign- and goal-tracking work by modeling their paradigm directly after the rodent PCA tasks and measuring behavioral responses in children aged 5–7 years. In this study, two boxes were presented to the participants: one with a response-independent lever used as the cue (CS), and another with a candy dispenser used as the reward (US; see Fig. 2) and children were allowed to freely interact with both. As in rodent studies, the lever was presented at random times and retraction of the lever was always followed by dispensed candy. While the methods for this study are available (Joyner et al., 2018) the findings are yet unpublished at the time of this review so conclusions cannot yet be addressed. Importantly, however, they report successful measurement of distinct behaviors between STs and GTs. Identifying behavioral phenotypes via a direct translation could shed light on many of the remaining questions regarding the ease with which these behaviors, and their implications, can be translated, and attempting this translation with children could be particularly useful to help facilitate early intervention efforts.

It should also be noted that other recent studies examining sign- and goal-tracking-related behaviors as markers of addiction risk in humans have yielded mixed results. Wardle and colleagues (Wardle et al., 2018), for example, discuss the potential pitfalls of translating this paradigm to humans. They paired neutral photo cues with food in an appetitive conditioned response paradigm in healthy young adults. Of multiple measures of appetitive responses, only one physiological indicator of attentional bias (measured through eye-gaze) correlated with impulsivity. These various paradigms offer promise of non-invasive, behavioral approaches that may be useful in examining sign- and goal-tracking behaviors in humans (adults and children) as a precursor to or predictor of externalizing and impulse control disorders in humans. However, the wide variability in these studies emphasizes the need for more targeted research to establish and fine-tune the translational validity from animal models to humans (see also Stephens et al., 2010) if we are to inform personalized prevention efforts.

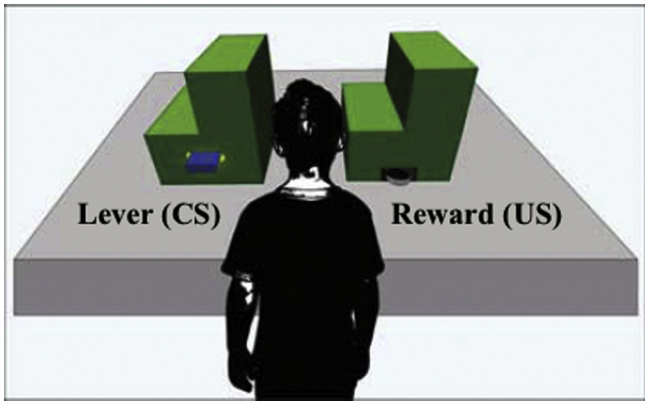

Fig. 2. Human Sign- and Goal-Tracking Apparatus.
One methodological example of the rodent PCA task adapted for use in humans. Lever (conditioned stimulus, CS) response box shown on the left. Food cup (unconditioned stimulus, US) reward box shown on the right.
Adapted with permission from Joyner, M. A., Gearhardt, A. N., & Flagel, S. B. (2018). A translational model to assess sign-tracking and goal-tracking behavior in children. *Neuropsychopharmacology,* Vol. 43, No. 1, 228-229. Published by Springer Nature.

The absence of a widely accepted or validated method for adequately measuring sign- and goal-tracking in humans likely stems from the translation efforts being a relatively new endeavor. As outlined above, while there are a handful of studies addressing sign- and goal-tracking in humans, the findings are mixed and both the methodologies and populations are vastly different. Importantly, the classification methods for determining STs and GTs are also remarkably diverse, making it difficult to extrapolate consistent conclusions or assume that any one human paradigm is truly capturing sign- and goal-tracking behaviors. In fact, with the widely divergent approaches for assessing the ST/GT phenotype in humans and the lack of replications, it is unknown whether the individual paradigms are ultimately measuring sign- and goal- tracking or slightly different constructs. Thus, replications and further exploration will be necessary in the future to address the uncertainties still lingering. Despite the methodological differences, some similarities have emerged including the distinction of behavioral groups (albeit with various definitions) and the promising use of eye-tracking to classify STs and GTs or related behaviors (e.g., Garofalo and di Pellegrino, 2015; Le Pelley et al., 2015; Schad et al., 2019). With few exceptions, the above studies assessed healthy samples which limits the ability to detect riskier phenotypes that are expected to be associated with sign-tracking behaviors. Thus, a more diverse range of clinical severity in the populations tested for sign- and goal-tracking would increase specificity in measuring both appetitive/sign-tracking responses and impulsivity. Deeper exploration toward a valid and reliable measure in humans is needed. In moving toward the use of this paradigm as a possible classification tool for phenotypic addiction risk (and

the potential for intervention strategies; Levitch et al., 2018), it will be especially important to carefully consider the context of new findings in light of these methodological and population/species differences (see Wardle et al., 2018 for further discussion).

6. Unknowns in mapping sign-tracking and goal-tracking rodent behaviors to humans

Many questions still remain to realize the translational potential of ST/GT for the development of interventions and treatments. Translating from rodents to humans involves not only methodological considerations but also a theoretical shift to reflect the influence of cognitive and psychopathological mechanisms contributing to these behaviors. In addition, at various developmental stages, the symptomatic phenotypes of sign-tracking in humans may look very diverse and thus should be measured and addressed differently. As is often the case, the answer likely lies in multiple mechanisms such that the outcome (sign- or goal-tracking or addictive behaviors) can stem from varying pathways. Building on the incentive salience model (Berridge, 2001), the evidence presented above offers conceptual explanations for the disparity between STs and GTs behaviorally, neurobiologically, and cognitively; however, while it is in the process of clarification (e.g., Schad et al., 2019), the concrete evidence in humans is yet unclear.

Though it should be done with caution, one can conceptually extrapolate hypotheses from animal studies to human behaviors. The consideration of human cognition, prefrontal control, and psychopathologies can muddle the behavioral profiles of sign- or goal-tracking. For instance, an individual may not engage or approach the CS due to high anxiety or anhedonia, looking deceptively like GTs. Likewise, one might overly engage with the CS out of superstitious behavior or hyperactivity, looking like a ST. In traditional sign- and goal-tracking paradigms, an individual must first learn the association between the CS and US, and there is evidence from studies with rodents (Robinson and Flagel, 2009; Saunders and Robinson, 2013) and humans (Schad et al., 2019) that both STs and GTs achieve this. An individual explores the association and eventually may realize the response-independence of the reward delivery and inhibit response behaviors. Arriving at this conclusion from the previous Pavlovian conditioning experience involves exploration and experimentation. For humans, this would require not only approach behaviors but also cognitive flexibility and inhibitory control, each of which have considerable individual variation (for review see Diamond, 2013) and may be the primary cognitive processes driving a propensity for sign- or goal-tracking. Evidence of this in humans is still emerging and the principal support currently lies in a number of studies from the animal literature suggesting that the neurobehavioral endophenotype of goal-trackers is characterized by excessive engagement of top-down cognitive control systems (Campus et al., 2019; Kuhn et al., 2018a; Sarter and Phillips, 2018). Thus, once response-independence is learned, GTs may actively inhibit engagement with the CS to economize their behaviors. In contrast, STs lack top-down inhibitory control (Paolone et al., 2013; Sarter and Phillips, 2018), are driven by "bottom-up" dopamine-dependent reward processes (e.g., Flagel et al., 2011b; Saunders and Robinson, 2012), and are characteristically more impulsive (Lovic et al., 2011) and unduly attracted to reward-associated cues. While still growing in number and clarity, studies from the human literature are beginning to offer preliminary evidence of similar characteristics, for instance, the model-free learning apparent in STs (Schad et al., 2019), the impact of cognitive control and awareness on the related VMAC effect (e.g., Albertella et al., 2017), and greater measures of impulsivity in STs (e.g., Garofalo and di Pellegrino, 2015). We postulate that in humans, at the junction between sign- or goal-tracking behaviors, an individual may question whether their actions are impacting the outcome and subsequently decide to engage or not. The degree to which an individual asks this question can impact risky decision making and the possibility for behavioral change. Future translation, measurement, and intervention efforts would therefore benefit from focusing on this angle.

While it appears that sign- and goal-tracking behaviors are measurable in humans, it is yet unknown the optimal methodologies for measuring these behaviors and whether these tendencies are temporary states, consistent life-long traits, or if they develop over time. Rodent research indicates strong genetic and epigenetic influences suggesting that sign- and goal-tracking may be inherent traits and not random, but also not experientially predetermined (Beckmann and Bardo, 2012). Instead there are likely several mechanisms, genetic and experiential, that interact to generate a propensity for sign-tracking or goal-tracking. We can conclude, then, that the behaviors are not random, but also, if these behaviors are developed over time and are somewhat dependent on one's environment, perhaps they are malleable within an individual. This possibility could open the door to interventions for both preclinical individuals with addiction vulnerability traits and those with substance use disorders. We know that the expression of these traits in rodents are malleable through pharmacological and other manipulations however, the flexibility of these traits is still uncertain in humans. Therefore, these questions would be imperative to address if sign- and goal-tracking behaviors in humans are to inform future intervention developments.

7. Conclusion

Many characteristics of STs (bottom-up cognitive processing, poor attentional and impulse control, and increased sensitivity within neural "reward" and stress systems) overlap with the neurobehavioral characteristics often associated with vulnerability to and/or presence of substance use disorders (Tomie et al., 2000; Tomie and Morrow, 2018). Thus, STs may be considered at greater risk for addiction-related traits (Robinson et al., 2014; Saunders and Robinson, 2013). This potential increased risk of addiction-related behaviors is evident in both rodent (Flagel et al., 2011b, 2007; Robinson and Flagel, 2009) and human models (e.g., Albertella et al., 2019b; Garofalo and di Pellegrino, 2015). Based on the associations between maladaptive tendencies and sign-tracking behaviors within the animal literature, the ability to reliably measure sign- and goal-tracking behaviors in humans would open the door to researching addiction vulnerability in light of these distinct learning trajectories and the potential malleability of these patterns. More research is needed to examine the extent, if any, of predictive qualities sign- and goal-tracking behaviors have for the development of impulse control disorders in humans and if this process can be modified to minimize vulnerability and/or alleviate symptoms.

Declaration of Competing Interest

None.

Acknowledgement

This work has been supported in part by The William K. Warren Foundation and the National Institute of General Medical Sciences Center Grant Award Number P20GM121312. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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